Introduction:

The Petitioner's/Declarant's Ground 1, 4, 7 arguments regarding the obviousness of '813's independent claims are completely illogical and are generated by two "types" of "hindsight arguments." The first of these "types," which involves the Ground 1 argument, is "reasoned forward" from a point in time over several decades ago while completely disregarding the art related to the use of stimulants, particularly amphetamines, in treatment of obesity over those several decades. The second of these "types," which involves the Ground 4/7 arguments, is "reasoned backward" from the time of the invention over several decades while completely disregarding the art related to the treatment of Bulimia Nervosa over those several decades. Lastly, the Petitioner's Ground 1, 4 and 7 arguments can be seen for both their frank irrationality and hindsight construction in view of the "art of stimulants, specifically LDX," as it would have been understood by a POSA at the time of the invention.

Regarding Ground 1:

Petitioner's/Declarant's Ground 1 argument rests on the premise featured in Appolinario's line of reasoning, namely, that a POSA at the time of the invention would have been motivated to apply Appolinario's teaching of "centrally-acting anti-obesity agents" in the treatment of BED to "other centrally-acting anti-obesity agents" and would have had a "reasonable expectation of success" in the treatment of BED by doing so. After all, all seven the RCTs featured in Appolinario involved "overweight" or "obesity" patients, two of which specifically involved treatment with "anti-obesity agents" (i.e., d-fenfluramine, sibutramine) -- and, at the time of the invention, it was self-evident to anyone in the art of eating disorders that one of the most common features of BED (though ***not*** *a* DSM-IV-TR criteria/symptom in its diagnosis) was its strong association with obesity. It bears mention that from the perspective a POSA at the time of the invention, BED's relationship to obesity was practically inextricable, as prominently evidenced in Petitioner's/Declarant's Exhibits as briefly highlighted below, which speaks to a key motivational driver for why a POSA would have regarded an "anti-obesity agent" as a reasonable "starting place" for considering treatment in the first place, but especially in view of Appolinario's characterization of d-fenfluramine (vis-à-vis Stunkard, Exhibit 1044) and sibutramine (vis-à-vis his own clinical trial, Exhibit 1046):

1) 1995 Marrazi's "**Binge Eating Disorder:** response to naltrexone" (Exhibit 1024, p. 2, - first two sentences of abstract), *"**Binge Eating Disorder (BED)** is characterized by a bulimic binge eating pattern without compensatory behaviors of purging or laxative abuse. It is **often associated with obesity**."*

2) 1996 Stunkard's d-fenfluramine Treatment of **Binge Eating Disorder** (Exhibit 1044, p. 2. Col. 1, second paragraph), *"Most patients with **binge eating disorder** are **obese**, and it has been reported that the disorder affects as many as 30% of patients entering weight reduction programs…"*

3) 1999 Brewerton's "**Binge Eating Disorder**: Diagnosis and Treatment Options" (Exhibit 1037; abstract, p. 1), *"The chronic, recurrent binging associated with **BED** is thought to **typically lead** to **obesity** and its **accompanying morbidity and mortality**."*

4) 2002 Arnold's "A Placebo-Controlled, Randomized Trial of Fluoxetine in the **Treatment of Binge Eating Disorder**" (Exhibit 1030, p. 2. Col. 1, first parag), *"**Binge eating disorder** is **frequently associated** with **obesity** and psychiatric comorbidity, most commonly major depressive disorder."*

5) 2002 Malhorta's "Venlafaxine Treatment of **Binge Eating Disorder** Associated with Obesity: A Series of 35 Patients" (Exhibit 1949, p. 2, second sentence of "Background"), *"**It [Binge Eating Disorder] commonly co-occurs** with **overweight and obesity.**"*

6) 2002 Appolinario's "An Open-Label Trial of Sibutramine in **Obese** Patients with **Binge Eating Disorder**" (Exhibit 1021, p. 2, Col 1, "background"), "***Binge Eating Disorder** is a **common diagnosis** among patients who seek **treatment** for **obesity**. There are scant data about the efficacy of **novel anti-obesity agents** for **binge eating disorder**."*

7) 2003 Carter's Pharmacologic Treatment of Binge Eating Disorder (Exhibit 1054, p. 1, "Introduction" – first two sentences), *"**Binge Eating Disorder (BED),** the most common eating disorder, is associated with significant morbidity. Individuals with **BED** are often **overweight or obese**."*

8) 2003 Appolinrio's "A Randomized, Double Blind, Placebo-Controlled Study of Sibutramine in the Treatment of **Binge Eating Disorder**" (Exhibit 1046, p. 2, first parag), *"Although BED is not limited to **obese** individuals, it is a **common diagnosis in this group**, especially among patients **seeking treatment for obesity**."*

9) 2004 Appolinario's "Pharmacological Approaches in the Treatment of **Binge Eating Disorder**" (Exhibit 1020, p. 1 – second sentences of abstract), ***"BED** is **usually associated with overweight or obesity** and psychopathology. "*

10) 2005 Milano's "Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment **of Binge Eating Disorder**" (Exhibit 1022, p. 1 - abstract), *"**Binge Eating Disorder**, which is characterized by repeated episodes of uncontrolled eating, is **common in obese patients** and is often accompanied by comorbid psychiatric disorders, **especially depression**. ..... Sibutramine, a new serotonin and norepinephrine reuptake inhibitor, has shown in the short and long term to be effective in **promoting and maintaining weight loss** in **obese patients** who **have binge eating disorder**."*

11) 2006 The APA's 2006 "Treatment of Patients with Eating Disorders" (Exhibit 1031, p. 73), *"**Binge Eating Disorder** occurs in about 2% of community cohorts and is **common among patients seeking treatment for obesity** at hospital-affiliated programs (1.3%-30.1 prevalence)…."*

As it places BED and obesity in their clinical context ***historically***, Stunkard's 1959 "Eating Patterns and Obesity" discussed *"certain theoretical and clinical aspects of the problem of overeating and obesity" (Exhibit 1040, p. 12).* And 33 years later, in 1992, Spitzer's "Binge Eating Disorder: Its Further Validation in a Multisite Study" evaluated patients from weight loss programs, about a 1/3 of which met diagnostic criteria for BED as defined by proposed criteria for the DSM-IV (p. 137, Abstract; p. 139, Table 1). Spitzer writes, *"BED was strongly associated with severe obesity and a history of unstable weight….." (p. 139).* One year after Spitzer's study but one year before Binge Eating Disorder formally entered the DSM-IV (with its own specific diagnostic criteria, as in Exhibit 1026, p. 11), Yanovski's "Binge Eating Disorder: Current Knowledge and Future Directions" (published in "Obesity Research") writes, "*While relative uncommon in the general community, BED becomes more prevalent with increasing obesity." (p. 306, Abstract).* Thus, BED's historical trajectory locates its place in the art alongside obesity, an important feature of the art as it relates to the art of treating patients with stimulants, particularly amphetamines.

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Comment [1]:
REFERENCE 1
Spitzer's "Binge Eating Disorder: Its Further Validation in a Multisite Study"

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REFERENCE 2
Yanovski's "Binge Eating Disorder: Current Knowledge and Future Directions"

In view of the art of stimulant drugs, of which amphetamines (and therefore LDX dimesylate would have been a part), and the art of obesity treatment which self-evidently bears on BED as evidenced in Appolinario's line of reasoning, it would have been bizarre for a POSA at the time of the invention to even draw on Mickle's art in the first place, as the Ground 1 argument describes. The simple reason is that amphetamines, including drugs whose active ingredient is "d-amphetamine" (like LDX dimesylate), would have been long been disregarded in the collective consciousness of the broad medical community as suitable treatments for obesity, and particularly in the individual consciousness of a POSA such as that characterized by Petitioner/Declarant. At the time of the invention, stimulants would have long been known in the art ***to be avoided*** as "anti-obesity agents" because of their significant risks despite their use as such for decades (1930s-1960s). In this respect, the Petitioner's/Declarant's "hindsight argument" is premised on a "state of the art" of "pharmacologically managing obesity" as it would have existed sometime in the temporal vicinity of, perhaps, the 1960s or earlier. As a result, the Petitioner's line of reasoning to get to the "obviousness of '813's independent claims" takes a "reasoning forward approach" that establishes its "state of the art" quite far back in time and then dismisses over several decades of medical advancement between that time and '813's filing.

The best way to establish this, and therefore to demonstrate the shear irrationality of the Petitioner's/Declarant's Ground 1 obviousness argument, is to simply look at "the art of amphetamines as anti-obesity agents" in view of "the art treating obesity." Of course, one could simply look at the Declarant's/Petitioner's prior art of

Ioannides-Demos, "Pharmacotherapy of Obesity" (Exhibit 1011) which explicitly indicates that *"amphetamines; dexamphetamine [active ingredient of LDX dimesylate]; methamphetamine"* were *"banned, restricted or discouraged because of dependency and abuse potential, cardiovascular effects" (p. 4, Table 1)* as a pharmacologic treatment of obesity. Or one could simply consider Ioannides-Demos' "state of the art teaching" from 2005 that *"the use of amphetamines has been severely restricted [as a 'therapeutic treatment for weight loss and obesity'] because of their addictive and psychosis-inducing potential" (Exhibit 1011, p. 4)* in view of the Declarant's 1997 Medscape publication "Binge Eating Disorder: Recognition, Diagnosis, and Treatment" wherein he writes, "*There are no published reports on the use of psychostimulants in the treatment of BED. Even though acutely administered stimulants suppress binge eating, the risks of addiction and the possible induction of affective and psychotic symptomatology make this agent class undesirable as a therapeutic tool." (p. 8).* But it is the medical history, already built into the most basic assumptions on which a POSA at the time of the invention would have reasoned to treat patients with agents such as LDX dimesylate, that reveals just how illogical the Petitioner's/Declarant's Ground 1 obviousness argument actually is, so it is recorded here for posterity. The art learns as much from its failures as it does from its successes. And, to be sure, nowhere is this better evidenced in the art than in the use of amphetamines for the treatment of obesity.

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Reference 3

Brewerton's 1997 "Binge Eating Disorder: Recognition, Diagnosis, and Treatment"

Coleman's 2005 "Anorectics on Trial: A Half Century of Federal Regulations of Prescription Appetite Suppressants" chronicles the use of amphetamines in the treatment of obesity, including the FDA's regulatory climate across many decades dating as far back as 1938. In particular, Coleman highlights the 1970s as representing a time when the FDA reconsidered the widespread use of "amphetamines" and "amphetamine congeners" for the treatment of obesity, in view of their risks. He also highlights how, by the mid-1990s, the FDA's position "transition[ed] to [a] long-term treatment of obesity," as obesity itself had been increasingly appreciated in the medical community as a chronic condition associated with chronic medical comorbidties (p. 382, Col. 2, p. 383, Col. 1). It is this temporal period, in particular, that establishes the proper context for understanding what Appolinario meant when he regarded d-fenfluramine and sibutramine as "anti-obesity agents," as BED was taking its own stage diagnostically in the DSM-IV and in strong association with obesity. Coleman details the history of d-fenfluramine and sibutramine, their clinical profiles, and their FDA approvals for the treatment of obesity (p. 382, Cols. 1-12). And, needless to say, there is no mention of stimulants such as those used to treat ADHD (i.e., amphetamines, methylphenidate) in the treatment of obesity since that period of the 1970s, itself testimony to their clinical place in the collective and individual consciousness of those who would have prescribed such drugs as "anti-obesity agents."

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Reference 4

Coleman's 2005 Anorectics on Trial: A Half Century of Federal Regulations of Prescription Appetite Suppressants"

The prevalence of "amphetamines" as "weight loss drugs" until the 1970s is also featured in Rasmussen's 2008 "America's First Amphetamine Epidemic 1929-1971." Rasmussen characterizes the "mainly iatrogenic amphetamine epidemic" in the United States from the 1940s through the 1960s, including its shifted in the opposite

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Comment [5]: Reference

Reference 5

Rasmussen's 2008"America's First Amphetamine Epidemic 1929-1971"

direction in the 1970s when *"the FDA was narrowing legitimate uses of amphetamines, retroactively declaring the drugs to be unproven efficacy in obesity and depression" (p. 980, Col. 1).* Coleman's "FDA Regulation of Obesity Drugs: 1938-1999" slide presentation, as identified for the FDA's "Endocrinology and Metabolic Drugs Advisory Committee" meeting of September 8, 2004, provides a bullet-point historical overview of "amphetamines as anti-obesity agents" including a *"1979 Federal Register notice calling for removal of the obesity indication of amphetamines." (Slide 15).* Simply from a regulatory and medical liability perspective, a POSA's motivation to prescribe, ***specifically, an "amphetamine drug" for the "treatment of obesity,"*** would have been severely dampened as early as the early 1970s though perhaps fully extirpated by 1980.

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REFERENCE 6

Coleman's 2004 Slide Presentation "FDA Regulation of Obesity Drugs: 1938-1999"

Coleman's 2012 "Food and Drug Administration's Obesity Drug Guidance Document: A Short History" and Hutchinson's "Obesity Pharmacotherapy from a Regulatory Perspective: Overview and Key Challenges" both highlight the "1996 FDA Draft Guidance for the Clinical Evaluation of Weight-Control Drugs" that was to characterize the "art of obesity pharmacotherapy" (i.e., "the art of 'anti-obesity agents'") for the decade preceding '813's filing with, as would be expected, certain modifications along the way. Particularly, the 1996 FDA Obesity Drug Guidance called for the "treatment population" to be moderately to markedly obese with BMI>30 kg/m2 or >27 k/m2 if accompanied with weight-related comorbidities such as hypertension, dyslipidemia, and type 2 diabetes (Hutchinson, p. 756, Col. 2; Coleman p. 2157, Col. 2). With respect to Petitioner's Ground 1 argument, the BMI parameters can be appreciated in view of Petitioner's/Declarant's reference of Appolinario which features "obesity" with "BMI>30" in the RCTs that established sibutramine and d-fenfluramine as successful drugs in treating BED (Exhibit 1020, p. 5, See Table 1 "Diagnosis" and explanatory comments under table). Additionally, FDA guidance for anti-obesity drugs included one year of clinical trial efficacy in randomized controlled studies with open-label drug exposure during a second year (Hutchinson, p. 757, Col. 1; Coleman p. 2157, Col. 2). Clearly, the medical and regulatory community was converging in their view of "obesity" as a "chronic disease" with safety considerations paramount in the use of "anti-obesity agents" for its treatment, itself something that can be appreciated all the more as the anti-obesity drug d-fenfluramine was withdrawn from the market in 1997 because of cardiac toxicity/pulmonary hypertension concerns. The drug had only been approved by the FDA in 1996. These medical developments were thus being built into the assumptions and reasoning upon which, and through which, POSAs would be motivated to use an "anti-obesity agent" from a time well-before '813's filing.

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Reference 7

Coleman's 2012 "Food and Drug Administration's Obesity Guidance Document: A Short History"

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Reference 8

Hutchinson's 2007 "Obesity Pharmacotherapy from a Regulatory Perspective: Overview and Key Challenges"

As any reasonable person familiar with art of "anti-obesity agents" would appreciate in view of its plainly written history, the shift in regulatory climate "away from" ***specifically "amphetamines"*** as a treatment of obesity was concurrent with "art of obesity management" that increasingly taught to its risks. It would not have taken a POSA at the time of the invention to understand that the primary risks of "amphetamines" in the treatment of obesity that discouraged their use as such were two-fold: 1) abuse and/or dependence risk and 2) cardiovascular risk. But for the

written record, it is worth noting that his is perhaps most succinctly stated in Petitioner's/Declarant's cited art of Ioannides-Demos article on the "Pharmacotherapy of Obesity" wherein *"amphetamines; dexamphetamine; methamphetamine"* are *"banned, restricted or discouraged because of dependency and abuse potential, cardiovascular effects" (Exhibit 1011, p. 4, Table 1).* But the history bears comment. At the time of the FDA's 1996 draft guidance on "anti-obesity drugs," the National Task Force on the Prevention and Treatment of Obesity published "Long Term Pharmacotherapy in the Management of Obesity" in the prestigious journal JAMA in 1996, writing, *"Amphetamines and closely related compounds are not recommended for the treatment by most experts because of their high potential for abuse." (p. 1908, Col. 2).* The sentiment was echoed in the 2004 (updated 2007) publication "Prescription Medications for the Treatment of Obesity" from the HHS/NIH/NIDDK that specifically cautioned, *"NOTE: Amphetamines are a type of appetite suppressant. However, amphetamines are not recommended for use in the treatment of obesity due to their strong potential for abuse and dependence." (p. 3).* Notably, the HHS/NIH/NIDDK document identifies drugs that "may be prescribed for weight loss" including those that are "FDA approved" or "not approved." (p. 2, Table 1). Self-evidently, "Schedule II" drugs like amphetamines (including d-amphetamine as in LDX dimesylate) and methylphenidate, which have high abuse/dependence potential, are nowhere featured, something that any POSA as defined by the Petitioner/Declarant at the time of the invention would have understood -- simply because of their risk and the how that risk determination already would have been built into the way they would have reasoned at the time of the invention.

The same characterization of "anti-obesity drugs" can be found in Ryan's chapter on "Pharmacological Agents in the Treatment of Obesity" in "Obesity and Mental Disorders"(2006) which, not surprisingly, features many of the same "anti-obesity agents" as the HHS/NIH/NIDDK document and also identifies their DEA Schedules. Of course, there are no Schedule II drugs listed such as would be in the "class of drugs" widely known as "stimulants" that, at the time of the invention, any M.D./psychiatrist would have understood to be broadly validated for the treatment of ADHD. Ryan even identifies the troubled history of anti-obesity drugs saying what any M.D., regardless of their specialty, would have said at the time of the invention, *"Thus, caution must be used in accepting any new drugs for the treatment of obesity, unless the safety profile would make it acceptable for almost everyone." (p. 262).* With respect to "amphetamines" -- and "d-amphetamine" in particular -- Bays perhaps sums it up most comprehensively in his art of "Current and Investigational Antiobesity Agents and Obesity Therapeutic Treatment Targets," published in the journal Obesity Research in August 2004, when he writes, "*Amphetamines (dextroamphetamine) have been used as antiobesity drugs, but can cause unacceptable tachychardia and hypertension. They also have a high rate of abuse potential and do not have a US Food and Drug Administration indication for the treatment of obesity." (p. 1198, Col. 1).*

With these rudimentary features of the art view, any reasonable person can

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Comment [9]:

Reference 9

National Task Force on the Prevention and Treatment of Obesity published "Long Term Pharmacotherapy in the Management of Obesity"

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Reference 10

HHS/NIH/NIDDK "Prescription Medications for the Treatment of Obesity," from the

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Comment [11]:

Reference 11

Ryan's chapter on "Pharmacological Agents in the Treatment of Obesity" in "Obesity and Mental Disorders"(2006)

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Comment [12]:

Reference 12

Bays' "Current and Investigational Antiobesity Agents

appreciate how the Petitioner's/Declarant's Ground 1 argument is established through a "circa 1960s and earlier state of the art lens" for the "treatment of obesity with amphetamine drugs." And it also serves to further clarify just how irrational the Petitioner's/Declarant's Ground 1 argument is as it would have been understood particularly by a POSA at the time of the invention. Beginning with "CV risk" in the "treatment of obesity," a POSA at the time of the invention would have appreciated the clinical profile of the kind of patient who would have been taking an "anti-obesity drug" like Appolinario's sibutramine in the first. Borders-Hempill's FDA utilization analysis of sibutramine, which looks at the clinical profile of patients who would have been prescribed siburtramine at the time of the invention (because her analysis is based on such patients wherein sibutramine has been prescribed), reveals the obvious. There are concurrent cardiovascular diseases and risk factors for CV disease. The "concurrency" of CV disease/risk factors in patients receiving sibutramine is featured in Slide 13 with comorbid HTN (65%) leading the list, followed by lipid disorders (63%), diabetes (26%), ischemic heart disease (11%), arrhythmia (9%), and congestive heart failure (3%). Of course, a POSA at the time of the invention would have also recognized that such a profile is essentially the same as that of a patient with BED, as the Declarant highlighted in his 1999 "Binge Eating Disorder: Diagnosis and Treatment Options" (Exhibit 1037), *"Medical conditions associated with BED are essentially the same medical conditions associated with obesity, including higher mortality and morbidty of adult-onset (type 2) diabetes, hyperlipidemias, cardiovascular diseases, several cancers and sleep apnea." (p. 3, Col. 1; p. 4. Col. 1).* Or as the Declarant highlighted in his 1997 Medscape publication "Binge Eating Disorder: Recognition, Diagnosis, and Treatment" wherein he writes, *"The medical comorbidity associated with BED is essentially the same as that associated with obesity, including increased morbidity and mortality from cardiovascular disease, hyperlipidemia, adult-onset diabetes mellitus, and certain cancers, such as endometrial and breast cancers. This risk increases linearly as weight or body mass index (BMI; weight divided by height squared, or kg/m^2) increases." (p. 3)* Notably, Borders-Hempill's analysis provides a breakdown of BMI in these sibutramine patients across age and, not surprisingly, regardless of age BMI>30 ("obese") in the vast majority (i.e., >70% across all ages, slide 8).

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Reference 13

Borders-Hempill's FDA utilization analysis of Sibutramine "Meridia"

Across many lines of evidence, any reasonable person in view of basic features of the art's teachings would see that a POSA at the time of the invention would have simply regarded a d-amphetamine-based drug like LDX dimesylate as too high risk to use as an "anti-obesity agent" for the treatment of BED wherein "obesity" was clinically regarded as the "rule rather than the exception" in BED. Appolinario's "logic," as applied to Mickle, would have actually strongly dissuaded a POSA at the time of the invention to apply Mickle's teaching of LDX dimesylate as an "anti-obesity agent" for the treatment of BED, which sheds light on just how arbitrarily and illogically reasoned the Petitioner's/Declarant's Ground 1 argument actually is. But the deep flaws in Petitioner's/Declarant's Ground 1 argument are made even more obvious in view of LDX dimesyslate's drug label at the time of the invention (Exhibit 1002, as referenced specifically below). Considering the "CV risk reason," as Bays identifies for the disfavored status of "amphetamines" in the treatment of

obesity, at the time of the invention LDX dimesylate's drug label featured:

1) a "black box warning" specifically warning on its CV risk, **"MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS"** (Exhibit 1002; p. 756, Caps and bold per drug label),
2) a section on **"CONTRAINDICATIONS"** that explicitly writes, "Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension…." (Exhibit 1002, p. 759, caps/bold per drug label), and
3) a **"WARNINGS"** section that features "**Serious Cardiovascular Events"** and "**Sudden Death and Pre-existing Structural Abnormalities or Other Serious Heart Problems"** in children and adults, as well as **"Hypertension and other Cardiovascular Conditions"** (Exhibit 1002, p. 760, caps/bold per drug label).

Surely, it doesn't take a POSA to realize that a POSA, at the time of the invention, would not have relied on Mickle's patent, as characterized in the Ground 1 argument, for information about LDX dimesylate's clinical/(safety) profile and its potential application as an "anti-obesity agent." A POSA at the time of the invention would have considered LDX dimesylate in view of its proper clinical context, its proper therapeutic application, its active drug ingredient d-amphetamine and, importantly, its drug label, particularly as LDX dimesylate was new drug on the market at the time of the invention with very little art behind it. Yet the Petitioner's/Declarant's Ground 1 argument is premised on a POSA's strong motivation to ***completely disregard*** LDX dimesylate's drug label which explicitly features the kinds of "CV risk warnings" that would have strongly discouraged a POSA to use LDX dimesylate as an "anti-obesity agent" in patients with a disorder prominently associated with obesity.

The Petitioner's/Declarant's Ground 1 argument can also be appreciated for its irrationality and "reasoning forward blind to several decades of art" hindsight construction on the basis of the decades-long history strongly discouraging the use of amphetamines, including d-amphetamine, as a treatment of obesity because of their abuse/dependence risk. Regardless of Mickle's characterization of LDX as having "***less abuse*** potential" ***in view of other stimulants*** at the time of the invention, the fact of the matter is that LDX dimesylate's active ingredient is d-amphetamine. This is how the drug works in the brain and on dopamine/norepinephrine receptors in particular, though particularly on dopamine as it regards addictive potential. This is characterized in LDX dimesylate's drug label, as it would have been expected of an amphetamine (or any stimulant drug for that matter) at the time of the invention. Specifically there is a prominent "black box warning" that "introduces" the contents of the drug label, **"AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINSITRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE."** (Exhibit 1002, p. 756, caps/bold per drug label). This is what a POSA would have relied on in considering the drug for its clinical use in patients, not on what could be

considered an obscure patent application written even before LDX dimesylate was FDA-approved for its commercial use by clinicians for the treatment of ADHD. The DEA classified LDX dimesylate as a "Schedule II" drug for reasons that any reasonable person would understand, not just a POSA. Of course, a POSA at the time of the invention would have recognized that the Schedule II classification for LDX dimesylate was expected at the time of FDA-approval simply because all stimulants until the time of the invention were classified as such, as further characterized below for its relevance to the Petitioner's/Declarant's obviousness arguments.

Additionally, LDX dimesylate's drug label at the time of the invention featured a section on **"DRUG ABUSE AND DEPENDENCE"** (Exhibit 1002, p. 767-768, bold/cap per drug label). Therein, the LDX's drug label indicated (p. 768):

1) "Controlled Substance class"
2) "Vyvanse is classified as a Schedule II controlled substance."
3) "Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred."
4) "In animal studies, lisdexamfetamine produced behavioral effects qualitatively similar to those of the CNS stimulant d-amphetamine."

That LDX dimesylate might have had a less of a "subjective drug liking effect" than d-amphetamine immediate release at comparable doses taken by mouth or intravenously, as its drug label indicates (Exhibit 1002; p. 768) and which is the basis the Petitioner/Declarant argue its ***"less abuse potential"*** as a motivation for its use in BED, would have been understood by a POSA in its obvious clinical context. That context, of course, is that the active ingredient in LDX dimesylate is "d-amphetamine" which itself carries a high potential of abuse and dependence, as the drug label highlights, ***particularly in view*** that its **"DRUG ABUSE AND DEPENDENCE"** section identifies that "drug liking effects" were indeed present (versus placebo) and, at doses of 150 mg for instance, were statistically indistinguishable from 40 mg oral amphetamine and 200 mg of diethylpropion (a Schedule IV drug). Even the "Medication Guide," which a POSA would have recognized for its application of educating patients, highlights in its own black box warning, **"Vyvanse is a federally controlled substance (CII) because it can be abused or lead to dependence."** (Exhibit 1002, p. 771, Col. 2, bold/caps per medication guide). The message, whether for a "POSA" or "any reasonable person" at the time of the invention, could not have been any clearer. Nor could the Declarant when he identified this as a key reason why the ***class of stimulant drugs*** should be disfavored for the treatment of BED (in his 1997 Medscape paper of "Binge Eating Disorder: Diagnosis, Recognition and Treatment"), *"there are no published reports on the use of psychostimulants in the treatment of BED. Even though acutely administered stimulants suppress binge eating, the risks of addiction and the possible induction of affective and psychotic symptomatology make this agent class undesirable as a therapeutic tool." (p. 8).* As a POSA would have appreciated at the time of the invention, this is ***precisely why*** the Petitioner/Declarant, despite citing a plethora of prior art they consider "relevant" to '813's, still have yet to identify any

"published reports on the use of psychostimulants in the treatment of BED," whether amphetamine or methylphenidate, except those cases featured in '813's disclosures. The reason for this, of course, whether from the perspective of a POSA at the time of the invention or "any reasonable person" in view of the invention and the art, is obvious.

Regarding Ground 4/7:

The Petitioner's/Declarant's Ground 4/7 arguments are extraordinary for their mischaracterization of the art and their illogicality but for a reason one might consider as rather different than their Ground 1 argument. Unlike their Ground 1 argument, which completely disregards the plainly obvious features of the art known for decades (i.e., amphetamines and their risks in the treatment of obesity) and perhaps more broadly recognized for its historical relevance by "any reasonable persons" old enough to have lived through times of widespread amphetamine use for obesity and weight loss, Petitioner's/Declarant's Ground 4/7 argument is based on a gross mischaracterization of a very obscure aspect of the art hardly enough to generate but a small handful of cases over several decades. Yet even so, the Petitioner/Declarant succeeds in completely disregarding the cumulative understanding of decades of prior art in the "pharmacologic treatment of Bulimia Nervosa," as it would have been understood by a POSA (as characterized by Petitioner/Declarant) at the time of the invention. In this respect, the Petitioner's/Declarant' Ground 4/7 "hindsight argument" can be appreciated as taking the very small of art of "stimulants in BN treatment" and "reasoning backward through time" as they take everything out of its proper clinical context and completely disregard the entire history of BN treatment. The line of reasoning established in the Petitioner's/Declarant's Ground 4/7 would have necessarily required one to have ***no knowledge whatsoever*** of diagnosing and treating eating disorders, ***specifically Bulimia Nervosa***, ***except for*** the Petitioner's/Declarant's cited prior art of *Ong (Exhibit 1017/Ground 4), Dukarm (Exhibit 1019/Ground 7), Schweickert (Exhibit 1042), Drimmer (Exhibit 1016), Sokol (Exhibit 1018), and Messner (Exhibit 1041),* as featured in two tables in Declaration (Exhibit 1009, p. 26 and pp. 78-79). And, to then illogically apply that very narrow and woefully lacking knowledge of art of treating BN to the treatment of BED. This is the foundational problem of the Petitioner's/Declarant's Ground 4/7 arguments.

The best way to understand just how irrational the Petitioner's Ground 4/7 arguments is to place them in their proper diagnostic and therapeutic context, namely, the art BN treatment and the role of stimulants therein. This is how a POSA at the time of the invention would have recognized them. First, Ong (Ground 4) and Dukarm (Ground 7) exclusively feature patients with BN. Thus, they are used as "entry points" in Petitioner's/Declarant's line of reasoning for the use of "stimulants" in eating disorders more generally, as BN is a different disorder than BED, and a POSA at the time of the invention would have unmistakably made that most basic distinction. The Petitioner/Declarant argue that LDX would have offered advantages over methylamphetamine (Ong) and d-amphetamine (Dukarm) in the

treatment of "binge eating in BN" and, therefore, could be cross-applied successfully to the treatment of BED. This argument can be shown for its error without even addressing the Petitioner's/Declarant's conflation of "binge eating in BN" and "binge eating in BED" because its line of reasoning "goes bad" before that point. And that is because a POSA at the time of the invention, such as that characterized by the Petitioner/Declarant, would have ***clearly understood*** that stimulants were strongly disfavored for use in the treatment of BN unless there was concurrent ADHD. The understanding would have been rudimentary among M.D./psychiatrists who "diagnose and treat eating disorders" as well as M.D./psychiatrists who "diagnose and treat ADHD," as further characterized below.

To best appreciate the role (or lack of a role) of stimulants in the treatment of BN it helps to first understand the kinds of drug treatments that were considered by POSAs (such as that characterized by the Petitioner/Declarant) for BN treatment at the time of the invention. The 2006 APA Practice Guidelines for the Treatment of Patients with Eating Disorders identifies a number of "sub-classes" of "antidepressants" (i.e., "SSRIs," "TCAs," and "MAOIs") in different "BN-specific clinical contexts," along with a number of specific antidepressant drugs in each class, among them fluoxetine, sertraline, trazodone, imipramine, desipramine, amitriptyline, phenelzine isocarboxazid. (Exhibit 1031, pp. 83-85). Notably, certain "sub-classes of antidepressants" are featured for certain specific drugs in view of which ones work for BN and which don't [i.e.,*"the SSRIs fluoxetine and sertraline but not fluvoxamine; and several MAOIs, including phenelzine and isocarboxazid but not moclobemide." (Exhibit 1031, p. 83)].* Thus, there is no "reasonable expectation of success" for the treatment of BN ***even from within the "same sub-class of antidepressants" (i.e., SSRIs, MAOIs)*** wherein one or more drugs may be considered generally helpful but one or more others are not. Additionally, the APA guidelines teach that dosing drugs in the treatment of BN can be tricky, as fluoxetine requires higher doses in BN than for major depression. Other medications featured in the treatment of BN include Lithium for co-occurring conditions, the opiate antagonist naltrexone for treating concurrent narcotic addition and preventing alcohol-relapse in patients, the anticonvulsant topiramate, and the anti-nausea drug ondansteron (a 5-HT3 antagonist).

The same general characterization of BN treatment is featured in the Declarant's 2004 "Pharmacotherapy for Patients with Eating Disorders" (p. 3-4). In particular, antidepressant drugs featured for the treatment of BN include, most notably, the "sub-class" of antidepressants known as "SSRIs" but with mention of drugs like desipramine and imipramine that a POSA at the time of the invention would have understood to be within the "sub-class" of antidepressants known as "TCAs." Importantly, the Declarant indicates that there are *"no known studies using non-SSRI newer generation agents such as nefazodone, mirtazapine and venlafaxine."* As in the 2006 APA treatment guidelines for the treatment of BN, Declarant highlights that *"unlike treatment for major depression or anxiety disorders, one cannot generalize from one SSRI to another because not all of them have been studied in BN, and available evidence suggests that they are not equally effective. The only SSRIs that*

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Comment [14]:

Reference 14

Brewerton 2004 "Pharmacotherapy for Patients with Eating Disorders"

have been seriously studied in BN using randomized controlled trials are fluoxetine and fluvoxamine (Luvox)." (p. 3). Declarant adds, *"fluoxetine at 60 mg/day, but not 20 mg/day, was superior to placebo in reducing both binge and purge frequencies (Romano et al., 2002), so it is important that clinicians treating BN realize that higher doses (40 mg/day to 80 mg/day) are generally required for an effective antibulimic response (similar to OCD)." (p. 3).* Declarant, like the 2006 APA guidelines for BN treatment, similarly identifies the anti-emetic ondansteron including its 5-HT3 antagonist action, the anti-convulsant topiramate, and the opioid antagonist naltrexone including its preferential use in comorbid alcoholism and self-injurious behavior as the APA guidelines indicate. The art of BN treatment, as featured in the 2006 APA guidelines and Declarant's 2004 "Pharmacotherapy for Patients with Eating Disorders," is consistent with the 2004 "Clinical Handbook of Eating Disorders: An Integrated Approach, " Chapter 21, "Psychopharmacology of AN, BN and BED" (pp. 489-508), a book edited by the Declarant. Further, Eisikovits' 2002 meta-analysis of pharmacotherapy for BN, which only included empirically validated treatments, identified various drugs and drug classes that nearly exclusively involved the "class of antidepressants," including the sub-classes of "SSRIs," "TCAs," "MAOIs" and "atypical anti-depressants." (p. 202). One study included in the meta-analysis featured Lithium and another d-fenfluramine (p. 198). In this respect, the art of treating BN -- among those who would have taught on its pharmacological management at the time of the invention -- was remarkably consistent for its teachings.

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Reference 15

Edited by T. Brewerton. 2004. "Clinical Handbook of Eating Disorders: An Integrated Approach, " Chapter 21, Psychopharmacology of AN, BN and BED" Pp. 489-508.

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Reference 16

Eisikovits' 2002 "A Multi-Dimensional Meta-Analysis for Bulimia Nervosa: Summarizing the Range of Outcomes in Controlled Clinical Trials."

Nowhere in any of these "state of the art treatment recommendations for BN" are stimulants, such as amphetamines (like LDX dimesylate, Adderall XR, Dexedrine) and methylphenidate (such as Ritalin, Concerta) which are used to treat ADHD, featured for their use in BN treatment, whether "successful" or not. Rather, though, the 2006 APA Practice Guidelines for the Treatment of Patients with Eating Disorders specifically writes, *"Case reports indicate that methylphenidate may be helpful for bulimia nervosa patients with concurrent attention-deficit/hyperactivity disorder (ADHD) [III], **but it should be used only for patients who have a very clear diagnosis of ADHD [I]."** (Exhibit 1031, p. 20).* The ***"[I]"*** is the strongest level of guidance, *"Recommended with substantial clinical confidence" (p. 11).* The APA guidelines also add, *"Several case reports indicate that methylphenidate may be helpful for bulimia nervosa patients with concurrent ADHD (247–249). In these situations, particular attention should be given to a range of potential adverse effects, including abuse." (Exhibit 1031, p. 54).* These several case reports (i.e, references "247," "248," and "249") cited in the APA guidelines are Petitioner's/Declarant's Exhibits of Schweickert (Exhibit 1042), Drimmer (Exhibit 1016), and Sokol (Exhibit 1018). Thus, it couldn't be any clearer "at the time of the invention" that stimulants were strongly disfavored for the treatment of BN ***except*** in such instances where there would be comorbid ADHD, which itself puts Dukarm's case series in its proper diagnostic and therapeutic perspective as all 6 patients had comorbid ADHD and BN. It also puts into perspective the art Dukarm cites as a rationale for performing her study, art which features Schweickert, Drimmer, Sokol - and Ong (Exhibit 1017) and Messner (Exhibit 1041). That Ong wasn't included in the 2006 APA guidelines for

this ***very very small*** art of treating comorbid BN/ADHD with stimulants may have been because, as a POSA at the time of the invention would have likely concluded, Ong used an IV stimulant on a one-time basis and, needless to say, IV stimulants were neither available for clinical use at the time of the invention nor would they have been recommended for use regardless of the clinical situation, even on a one-time basis – at least not in the mind of a POSA as characterized by Petitioner/Declarant.

So the question is, how is that the Petitioner/Declarant even reasoned to use the art of *Ong (Exhibit 1017/Ground 4), Dukarm (Exhibit 1019/Ground 7), Schweickert (Exhibit 1042), Drimmer (Exhibit 1016), Sokol (Exhibit 1018), Messner (Exhibit 1041),* as featured in the Declaration (Exhibit 1009, p. 26 and pp. 78-79), to "establish stimulants as a class of drugs" for the "successful treatment" of, ***specifically, BN,*** much less reason to their use as a "class of drugs" that a POSA at the time of the invention would have been motivated to use in any way for the treatment of, ***specifically, BN,*** absent its comorbidity with ADHD***?*** After all, there couldn't be any clearer representation in the art of treating BN that disfavored their use, except in such cases where there was comorbid ADHD – and even that was open to question. If a POSA wouldn't have been motivated to use stimulants (such as LDX dimesylate) to treat BN in the first place, then the entire premise of the Petitioner's/Declarant's Ground 4/7 arguments is proved wrong. And, therefore, it is proved wrong, as regarded above by the APA guideline's strongest clinical recommendation. But that still leaves open the question as to how Petitioner's/Declarant's Ground 4/7 reasoning could so "so wrong" even before actually "beginning."

Sukarm's 2006 "Association Between Attention-Deficit/Hyperactivity Disorder and Bulimia Nervosa: Analysis of 4 Case-Control Studies," published in the Journal of Clinical Psychiatry, clarifies the answer. Importantly, Sukarm speaks from the "ADHD side of things" as he is affiliated with the Adult ADHD Research Program at Massachusetts General Hospital. (p. 351). His expertise, thus, is not "eating disorders," per se, but he – like any other competent M.D./psychiatrist at the time of the invention – would have understood that *"…bulimia nervosa and ADHD* ***require different pharmacologic*** *and nonpharmacologic* ***approaches****…" (p. 353, Col. 2).* The broad success of stimulants of the amphetamine/methylphenidate kind for the treatment of ADHD have been well-recognized in the psychiatric community for decades, in direct contradistinction to their disfavored use in BN treatment except in such cases where there would be comorbid ADHD.

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Reference 17

Sukarm's 2006 "Association Between Attention-Deficit/Hyperactivity Disorder and Bulimia Nervosa: Analysis of 4 Case-Control Studies."

Sumarn's introductory comments put the Petitioner's/Declarant's Ground 4/7 arguments into complete perspective, as a POSA at the time of the invention would have appreciated them. He writes, *"There are* ***scant reports*** *in the medical literature of adults suffering from both* ***ADHD-like symptoms*** *and* ***bulimia nervosa****." (p. 352, Col. 1).* In this respect, coming from a POSA who would have had expertise in treating ADHD – and therefore using many different kinds of stimulant drugs in all kinds of clinical contexts including comorbid ones (with eating disorders, among others) – there just wasn't a lot of art on BN/ADHD/stimulants. But there was

enough art, ***"scant"*** as it was, for Sukarm to wonder if there might be something new to discover about BN, ADHD and stimulants in view of the treatment of BN with stimulants. The ***"scant reports in the medical literature of adults suffering from both ADHD-like symptoms and bulimia nervosa"*** Surman identifies are prominently featured in his introductory discussion and, not surprisingly, they include the ***majority of the total prior art*** submitted by Petitioner/Declarant ***to establish stimulants as "successful treatments" in BN***. They include (as cited in Surman, p. 352, Col. 1, references "11,""12," "14," and "15"):

1) Schweickert's "Efficacy of methylphenidate in bulimia nervosa comorbid with attention-deficit hyerpactivity disorder: a case report" (Petitioner's/Declarant's **Exibit 1042**),
2) Sokol's "Methylphenidate treatment for bulimia nervosa associated with cluster B personality disorder" (Petitioner's/Declarant's **Exhibit 1018**),
3) Drimmer's "Stimulant treatment of bulimia nervosa with and without attention-deficit disorder: three case reports" (Petitioner's/Declarant's **Exhibit 1016**), and
4) Dukarm's "Bulimia Nervosa and attention-deficit/hyperactivity disorder: a possible role for stimulant medication" (Petitioner's/Declarant's **Exhibit 1019**).

After all, what Surman recognized – as just about any psychiatrist/M.D. at the time of the invention would have understood – is that *"…bulimia nervosa and ADHD **require** **different pharmacologic** and nonpharmacologic **approaches…"** (Surman, p. 353, Col. 2),* which is why Surman writes, "*A better understanding of the putative association between ADHD and bulimia nervosa has important clinical implications. Considering that **ADHD and bulimia nervosa respond to different pharmacologic and nonpharmacologic treatments,** diagnosing ADHD in subjects with bulimia nervosa could lead to new therapeutic opportunities for this debilitating and life-threatening disorder." (p. 352, Col. 1).* Surman is writing this in ***March 2006***, which puts into perspective – from a temporal standpoint – how this art was ***actually being considered*** in the vicinity of '813's filing for its uniqueness and therapeutic implications, namely, ***for the treatment of, specifically, BN and ADHD together.*** In 2 adult samples of patients with ADHD and those without, Surman did indeed identify a significantly greater rate of BN in the ADHD group (12% vs 3%; 11% vs 1%, p. 351, "Results"). Surman acknowledges these findings are *"preliminary and require further confirmation"* but *"suggest that ADHD may be associated with BN in some women." (*p. 351, Conclusion). And, ***"if confirmed**, this association between bulimia nervosa and ADHD **could have** important clinical and therapeutic implications." (p. 351, Conclusion).* However, by the Petitioner's/Declarant's line of reasoning for both its Ground 4/7 arguments, Surman ***should have been saying*** in 2006, the year before '813's filing, ***"this finding is irrelevant because the treatment success of stimulants for 'binge eating in BN' has already been confirmed and has obvious clinical and therapeutic implications for the treatment of BED."*** Which helps underscore just how illogical the

Petitioner's/Declarant's Ground 4/7 arguments are reasoned "backward through time" as they ignore everything ***actually relevant*** to their own cited prior art of *Ong (Exhibit 1017/Ground 4), Dukarm (Exhibit 1019/Ground 7), Schweickert (Exhibit 1042), Drimmer (Exhibit 1016), Sokol (Exhibit 1018), Messner (Exhibit 1041)* – ***even before getting to BED treatment.***

Surman's paper provides the ***"proper diagnostic and therapeutic context"*** for ***every single prior art reference*** cited by the Petitioner/Declarant for establishing their "first step of reasoning" for their Ground 4/7 arguments, which itself helps put into perspective just how egregiously Petitioner/Declarant ***misrepresent the art.*** And this is best featured in Surman's Discussion wherein here writes, "***Eleven case reports*** *documenting* ***bulimia nervosa with comorbid ADHD traits*** *that were revealed in our literature search describe* ***reduction of bulimic behavior with stimulant treatment****, providing* ***tentative support*** *for the* ***hypothesis*** *that treatment of ADHD-related impulsivity could improve outcome in bulimic patients. Patients with* ***bulimia nervosa who are not identified as having ADHD*** *have also described improvement in bulimic symptoms with stimulant treatment." (p. 353, Col 2).* The ***"eleven case reports"*** of ***"BN with comorbid ADHD traits"*** are, as previously identified from Surman's introductory comments, the Declarant's/Petitioner's prior art of *Schweickert (Exhibit 1042)*, *Drimmer (Exhibit 1016)*, *Dukarm (Exhibit 1019/Ground 7),* and *Sokol (Exhibit 1018).* And Sumarn's *"patients with* ***BN who are not identified as having ADHD"*** come from two publications, Ong's "Suppression of Bulimic Symptoms with Methylamphetamine" (Petitioner's/Declarant's Exhibit 1017) and Messner's "Methylphenidate Treatment of Bulimia Nervosa After Surgery" (Petitioner's/Declarant's Exhibit 1041).

Thus, it can be seen how the Petitioner/Declarant have selectively chosen the "scant" 6 publications in ***all*** of "BN treatment-specific art (wherein stimulants have been used)," that themselves (as Surman notes) speak to how this art was barely recognized for its diagnostic and therapeutic implications ***in BN*** (much less "confirmed" for its findings), and to then ***grossly misrepresent the diagnostic and clinical context*** of that art to reason toward the obviousness of '813. It is remarkable that even Messner, one of two case reports cited in Surman wherein BN was not associated with ADHD (Ong being the other), writes, *"The possibility of Ms. J's brother may have suffered from hyerpactivity invites questions about an association between BN and ADHD, at least in some individuals for families. The mechanisms of action of MPT may be similar in both disorders. (Exhibit 1041, p. 5)."* And, not surprisingly, the Declarant/Petitioner fail to say anything about Sokol's art, which involved a BN patient with ADHD-like traits, that concluded *"given the potential risks, treatment with this agent [stimulant methylphenidate] is not recommended [for BN]." (Exhibit 1018, p. 6).* To be sure, any reasonable person in view of Surman and the Petitioner's/Declarant's Ground 4/7 arguments would recognize that the very art cited by the Petitioner/Declarant to establish their line of reasoning proves the non-obviousness of '813's independent claims as well as the obviousness of the Petitioner's/Declarant's willful misrepresentation of the art to self-servingly argue the obviousness of '813's independent claims.

The Petitioner's/Declarant's willful misrepresentation of the art as it would have been understood at the time of the invention ***is actually affirmed*** in view of Biederman's **August 2007** publication "Are Girls with ADHD at Risk for Eating Disorders? Results from a Controlled, Five-year Prospective Study," published in the Journal of Developmental and Behavioral Pediatrics and on which Surman was a co-author. This is evidenced in Biederman's rationale for conducting the study in the first place, "*Whether an association exists between ADHD and eating disorders has important implications. Considering that ADHD and eating disorders respond to different pharmacological treatments, diagnosing ADHD in patients with eating disorders could lead to new therapeutic opportunities." (p. 302, Col. 1).* And also in his findings, which are like Surman's, *"we found that adolescent females with ADHD were at elevated risk of developing an eating disorder, with a particular risk for developing bulimia nervosa." (p. 305, Col. 1).* (The other eating disorder evaluated was anorexia).

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Reference 18

Biederman's 2007 "Are Girls with ADHD at Risk for Eating Disorders? Results from a Controlled, Five-year Prospective Study"

In other words, ***the month before '813's filing*** Surman's preliminary finding of an increased risk of BN in ADHD patients is only "being first confirmed," which means that the ***therapeutic implications of this finding in, specifically, BN patients,*** is only at this time making its way into the art --- again, from the "ADHD side of things." Even Biederman writes, "*To the best of our knowledge, this is the first evaluation of the association between ADHD and eating disorders in a pediatric sample followed prospectively into adolescents." (p. 302, Col. 2).* Importantly, Biederman himself identifies his own art in its ***proper diagnostic context*** in his opening two sentences, *"Recent work by Surman et. al. suggested an association between attention-deficit/hyperactivity disorder (ADHD) and eating disorders. Several case reports describe women with* ***bulimia nervosa*** *and* ***ADHD-like symptoms.*** *[citations include art of Sokol, Schweickert, Drimer]." (p. 302).* And he speaks to his art's ***proper therapeutic context*** in view of its ***proper diagnostic context,*** *"Eating Disorders and ADHD require different pharmacological treatment approaches and therefore, clinical evaluations of females with eating disorders may benefit from systematic identification of ADHD and vice versa.* ***Among individuals with comorbid ADHD and bulimia nervosa****, the* ***impulsivity of ADHD might contribute to the severity of eating disordered behavior. Patients with bulimia nervosa and ADHD may benefit from treatments commonly used to treat ADHD****." (p. 306, Col. 2).* Biederman's study proves the Petitioner's/Declarant's willful mischaracterization of the art ***in order to*** argue the obviousness of '813's independent claims in its Ground 4/7 arguments. In this respect, the Petitioner would have been far better served for an accurate representation of the art at the time of the invention had Dr. Biederman, as further featured below for his contributions to the art, ***acted as the Declarant.*** But in such an instance, as "any reasonable person" would clearly understand in view of the plainly stated and transparently disclosed teachings from the time of the invention, Dr. Biederman's Declaration would have only proven the non-obviousness of '813's independent claims.

THE LAST AND FINAL ARGUMENT:

Now that it is clear how the Petitioner/Declarant willfully mischaracterized the art for their Ground 1/4/7 arguments by beginning with the assumption of '813's obviousness and then "reasoning forward through time" from a point decades before the invention (per Ground 1) as well as "reasoning backward through time" from a point at the time of the invention (per Ground 7) – all while ignoring every relevant aspect of the art over those decades in their line of reasoning -- it is now time to accurately characterize the art which proves the non-obviousness of 813's independent claims. Putting aside the virtual statistical impossibility that a POSA at the time of the invention could have even put together the references the Petitioner/Declarant use for their Ground 1/4/7 obviousness arguments, this last and final argument is intended to show the virtual statistical impossibility of '813 even being filed as it was in the first place with disclosures that teach on the successful treatment of BED with LDX dimesylate. Which, for the purpose of this "last and final argument," is to establish on the written record and for posterity the non-obviousness of '813's independent claims.

Fourth Quarter 2006.

On October 18, 2006, Dr. Louis Sanfilippo, the inventor of '813, publicly analyzed a press release issued by Shire Pharmaceuticals ("Shire")/New River Pharmaceuticals ("NRP") on the investigational drug NRP104 (ldx dimesylate) for the treatment of ADHD in his role as a consultant for the Gerson Lehrman Group ("GLG"), an "intermediary" between professionals of various sectors/industries (i.e., healthcare, energy, etc…) and the investment community (i.e., managers/analysts of hedge funds, mutual funds, etc…). The analysis was entitled *"NRP104: The Next Psychiatric Blockbuster Drug?"* and ***publicly posted*** on the GLG website, ***as are all the others that follow below***, particularly for investment professionals to read. (GLG, p. 46). His analysis commented on LDX's comparable efficacy to other stimulants on the market for the treatment of ADHD, as based on clinical trials. (GLG, pp. 46-47). At that point in time, as any reasonable person would appreciate in view of "the art of LDX dimesylate," LDX had yet to be FDA-approved and, therefore, could not yet be commercially marketed for clinical use by doctors who would prescribe it. Further, Dr. Sanfilippo identified its DEA classification as a potentially significant market driver though added that, until that time, all stimulants had been classified as *"Schedule II drugs (high potential for abuse which may lead to severe psychological or physical dependence)."* (GLG, pp. 46). The next month, on November 7 NRP publicly stated in their third quarter results announcement their anticipated launch of LDX in Q2 2007 for ADHD treatment in children, in collaboration with Shire Pharmaceuticals, and highlighted their "FDA approvable letter" for the indication. (p. 2)

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Reference 19: GLG POSTS, L. Sanfilippo

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REFERENCE 20

NRP 11.7.06 Press release

First Quarter 2007.

On January 10, 2007, Dr. Sanfilippo commented on the implications of the FDA's "second approvable letter" for LDX as a treatment of ADHD, which involved a *"request for 'routine' data,"* as well as the FDA's recommendation *"to the DEA that Vyvanse receive a Schedule II status (high abuse potential; severe dependence liability) rather than the less stringent classifications of III or IV, hoped for by its collaborators Shire and NRP." (GLG, p. 46).* Dr. Sanfilippo commented on the clinical implications of LDX in the ADHD treatment landscape noting, in particular, that its *"anticipated Schedule II status will likely link it to all the others [stimulants] unless head-to-head studies show greater efficacy than other stimulants." (p. 46).* Dr. Sanfilippo also wrote in the same analysis, *"there is some question as to whether clinicians and patients (and parents), despite its scheduling status, might find its novel prodrug mechanism of action as favorable for certain sub-groups of patients and co-morbidities (ie, adolescents and college students prone to abusing stimulants; substance abusers)." (p. 46).* These were, self-evidently, speculations based on Dr. Sanfilippo's knowledge of how the drug was designed to work differently, pharmacokinetically (as described in Mickle), than other stimulant drugs, and its prospective application to the treatment of ***specifically ADHD*** based on these properties from published studies as the drug was not yet even commercially available for use. To be sure, these were the kinds of features that would have been important in motivating a POSA to use LDX over other well-recognized safe stimulant drugs, including long-acting ones, for the ***specific treatment of ADHD***.

On February 20, 2007, Shire agreed to acquire NRP for an all cash transaction of $2.6 billion. As the Shire Press release writes, *"Shire Chief Executive Officer, Matthew Emmens, said: 'This is an important and complementary acquisition that gives us full control of VYVANSE, a novel drug. We are confident and expect that the* ***final labeling*** *will provide patients and physicians with real benefits that* ***differentiate this compound from other ADHD products****. It will enable us to drive the launch and future development of VYVANSE and gain the full economic benefits of the drug. Based on VYVANSE's expected profile, we believe it has the potential to be the* ***next generation stimulant product to ADDERALL XR****.'"* In this respect, CEO Emmens speaks to how Vyvanse is "in the midst of its pre-market differentiation" from other stimulants in the treatment of ADHD. Still, at this point in time, LDX has yet to receive its "final labeling" by the FDA, much less be prescribed by POSAs in the treatment of ADHD. Thus, LDX still had a way to go before its clinical nuances – its "POSA-based clinical differentiation" -- could be appreciated in the medical community by those who treat, ***specifically, ADHD***. A publicly available slide deck from Shire and its CEO Emmens of February 20, 2007 identifies the rationale for the NRP acquisition, *" 'future flagship ADHD product….logical strategic move, innovative drug – the next generation ADHD treatment, attractiveness of the ADHD market." (slides, 5-6).* In the slide deck, CEO Emmens reviews the ADHD market including its prevalence/treatment predominantly in "pediatric patients" (age 4-17) over adults (Slide 11) and highlights LDX's clinical trial efficacy *"throughout the day"* (Slide 10). Shire's ***main ADHD stimulant product***, Adderall XR, is also featured in the slide deck for *"leading US marketshare"* (slide 34), with 2006 sales at *"$836.6 million"* (slide 24). Sales of Adderall XR are shown to be far in excess of Shire's less successful

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2.20.07 Shire slide deck

(commercially) ADHD stimulant product, the transdermal (i.e., skin) methylphenidate patch known in the art as *"Daytrana,"* which had 2006 sales at *"$25.1 million"* (slide 24).

On February 21, 2007, Thomas Ginberg of the Philadelphia Inquirer writes on the anticipated launch of LDX as an ADHD treatment, *"Vyvanse has been billed as an improved ADHD medication whose method of action makes its harder to abuse. The company says it has the same safety profile of Adderall XR."* Thus, Mr. Ginsberg reports on a drug in view of its claimed prospective advantages in ADHD treatment and its anticipated launch, as well in view of its "intra-company stimulant competition." Two days later on February 23, Shire and NRP announce the FDA's approval of LDX for the treatment of pediatric ADHD, with CEO Emmens saying, *" ' The FDA approval of VYVANSE is exciting news for Shire as well as for patients, their families, and healthcare providers as it's an important,* ***novel approach for the treatment of ADHD****,' said Matthew Emmens, Shire Chief Executive Officer…. 'Beginning with product launch in Q2 2007, Shire will make VYVANSE* ***our top promotional priority within our ADHD portfolio****.' " (p. 1).* Shire's February 23 press release identifies Dr. Biederman (per 2007 ADHD/BN referenced previously) as the director of Pediatric Psychopharmacology at Massachusetts General Hospital and as the lead investigator on the pivotal clinical studies for LDX in the ADHD trial. He is quoted as saying, *"Our studies showed that this next-generation stimulant medication's unique chemical profile* ***offers an option*** *for physicians and patients in the treatment of ADHD, with outstanding efficacy and duration of actions." (p. 2).* A POSA at the time of the invention would have recognized that there would have been few people in the entire world who understood LDX's clinical properties as well as Dr. Biederman, whose Phase III trial of LDX in pediatric ADHD (which helped LDX get its FDA-approval) ***at that moment in time*** still had yet to be published, though was slated for online publication in the journal Clinical Therapeutics for March 13, 2007 (Exhibit 1002, p. 654-667).

On March 1, 2007, Shire General Counsel Tatjana May filed a 10-k filed with the SEC on behalf of the company. The 10-k provides an overview of the ADHD market among competitor stimulants, including among its own three brands of stimulant preparations – Daytrana (MPH), Adderall XR (mixed AMPH salts) and Vyvanse (d-AMPH prodrug). Featured among the stimulant competition in the ***"ADHD marketplace"*** are four long-acting once daily methylphenidate brands (ie, Concerta, Metadate CD, Ritalin LA, and Focalin XR) along with their respective ADHD marketshare, ranging from 2.8% with Ritalin LA, to 22% with Concerta. (p. 24). To be sure, the stimulant market for ADHD, including the "long-acting stimulant class," was indeed crowded, even arguably from within Shire's own ADHD "long acting stimulant drug" portfolio. As a POSA (with fairly substantial clinical experience in the treatment of ADHD with stimulants) would have appreciated at the time of the invention, Weissler's 2007 "Review of long-acting stimulants in the treatment of ADHD," published in Expert Opinions in Pharmacotherapy, provides a clinical overview of the four MPH-based "long-acting stimulants" and the three AMPH-based "long acting stimulants" at the time of the invention, including LDX. As any reasonable person would appreciate in view of the art, these "long-acting stimulants" can also be seen as "one group" of stimulants among the broader stimulant landscape for the treatment of ADHD

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2.21.07 Ginsburg Philadelphia Inquirer

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2.23.07 Shire press release

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Reference 25
3.1.07 Shire 10-k filed by Shire General Counsel Tajana May

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Reference 26

Weissler's 2007 "Review of long-acting stimulants in the treatment of ADHD"

which also at the time featured "short acting stimulants" and "intermediate acting stimulants." This "stimulant landscape" at the time of the invention is nicely featured in the 2007 AACAP (American Academy of Child and Adolescent Psychiatry) "Practice Parameters for the Assessment and Treatment of Children and Adolescents with ADHD" (Table 2, Medications Approved for the Treatment for ADHD, p. 905). The

Second Quarter 2007.

A brief analysis of the AACAP's Treatment Guidelines for ADHD is featured in Dr. Sanfilippo's April 2, 2007 GLG analysis. He writes, *"there is probably not much new here to those diagnosing and treating ADHD but international promulgation of the report will serve to heighten awareness of the disorder. The ADHD 'market' has grown considerably in the past decade, especially with many popularized books, on-line courses and self-help forums, and ADHD coaches." (GLG, p. 43).* On April 17, Dr. Sanfilippo writes on *"Switching from Strattera to Stimulants Common"* in reference to a study showing children with ADHD who start on Strattera are more likely to change therapies. (GLG, p. 42). Less than one week later, on April 23, Dr. Sanfilippo's GLG news analysis *"The Complicated Web of ADHD and Substance Abuse"* outlines clinical management issues related to ADHD/substance abuse disorders ("SUDs"). He comments specifically on the art of ADHD pharmacotherapy in patients with comorbid SUDs, *"short acting stimulants (of the Adderall or Ritalin kind) can be especially problematic....with somewhat less liability for longer acting forms (Adderall XR and Concerta) which have specialized delivery systems and aren't typically inhaled." (p. 39).* In this respect, Dr. Sanfilippo is pointing out that long-acting stimulants like Adderall XR and Concerta were, at that time, already addressing "abuse issues" by those who were prescribing them for treatment of ADHD. Dr. Sanfilippo speaks cautiously on LDX's clinical differentiating features as the drug is yet untested by POSAs who are skilled in treating ADHD with stimulants, but he does comment on how LDX may be received in the medical community with respect to treating ADHD with comorbid substance abuse *"While likely to be listed as a Schedule II drug by the DEA (to my latest knowledge), which would impact its perception among clinicians as a drug with 'high abuse potential,' knowledge of its pharmacokinetic profile might lend itself to being considered a 'first-line stimulant' for those with substance abuse histories, indeed a significant market. I suspect how the drug will be marketed, obvious FDA/legal implications, will have a role in the drug's 'clinician perception" and hence use in this population." (p. 39).* This comment can be seen in view that already, the art of ADHD treatment had recognized that "long-acting" stimulant drugs were preferable to "short-acting" ones in comorbid ADHD/substance abuse patients. This is evidenced in Upadhyaya's 2006 "Management ADHD in the Presence of Substance Use Disorder," "*Clinical recommendations for treating this dual diagnosis include using nonstimulant agents or extended-release stimulant formations in conjunction with psychosocial therapies to treat both the ADHD and SUD." (p. 23, summary).* And Farone's 2007 "Effect of Stimulant Medications for ADHD on Later Substance Use and the Potential for Stimulant Misuse, Abuse and Diversion" writes, *"Long-acting stimulants may be less likely to be misused or diverted" (p. 15, summary).*

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Reference 27

AACAP's 2007 "Practice Parameters for the Assessment and Treatment of Children and Adolescents with ADHD"

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Reference 28

Upadhyaya's 2006 "Management ADHD in the Presence of Substance Use Disorder"

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Reference 29

Farone's 2007 "Effect of Stimulant Medications for ADHD on Later Substance Use and the Potential for Stimulant Misuse, Abuse and Diversion"

Two days after Dr. Sanfilippo's April 23 GLG posting, FirstWorld Pharma reported on Shire's Q1 net income nearly doubling on account of Adderall XR's sales of $249 million, adding *" 'the key issue for Shire in 2007 is the switch from Adderall XR to (ADHD drug) Vyvanse,' Lehman Brothers analyst Kerry Holford recently commented."* The parenthetical introduction of LDX as an "ADHD drug" is revealing of its place in the consciousness of even of those savvy with new developments in the pharmaceutical markets. One might say Vyvanse, at this point in time, was in a place "diametrically opposite" that that of "amphetamines" at their peak during their "epidemic use as anti-obesity agents" some forty or fifty years earlier. Two days after FirstWorld Pharma's report, Dr. Sanfilippo posted on April 27 an analysis regarding a New England Journal of Medicine article "*Paying for Drug Approvals – Who's Using Whom."* Notably, he pointed out (among other examples) that within the regulatory/FDA landscape, safety issues were increasingly regarded as important in the prior years, including particularly ADHD stimulant drugs and cardiovascular risk; he also comments on conflicts of interests from FDA advisory board members receiving *"consulting fees from the very pharmaceutical companies whose drugs they are evaluating." (p. 34).* A POSA (familiar with prescribing stimulants) at that time would have appreciated various US/FDA-based as well as internationally-based concerns arising over the prior handful of years specific to the use of stimulants and CV risk, notably for long-acting amphetamine-based ones.

On May 3, 2007, Shire publicly announced the DEA classified LDX as "Schedule II." According to Shire's press release, CEO Matthew Emmens said, "*The **decision by the DEA was anticipated**. **All ADHD stimulant medications have historically been classified as Schedule II controlled substances**."* He also added, *"Vyvanse is the first ADHD stimulant to have the results of abuse liability studies reflected in its product label. Shire **plans to continue to build the body of evidence in support** of a **lower abuse potential profile**."* Dr. Sanfilippo posted publicly on this particular press release on May 4, writing, *"Though Vyvanse may not be the blockbuster drug it was once touted to be, there will likely be a good place for it in the ADHD market. The prodrug concept is appealing for patients with a substance abuse history (in remission) that may need stimulant treatment after other options such as Straterra (Ely Lily) or Wellbutrin (as an off-label treatment) have failed to be effective….**Stimulant treatment for ADHD is often a trial-and-error process**, with multiple dose and schedule options for the clinician to utilize, and given the pharmacokinetic profile of Vyvanse, its duration of action **may be a plus for a subset of patients.**" (p. 31).*

Eleven days later, on May 15, Dr. Sanfilippo's GLG analysis featured *"Shire's Broad ADHD platform"* and included the investigational drug SPD465, a super long-acting stimulant (greater than Adderall XR/Concerta); he also commented on LDX in the same light as prior GLG posts. (GLG, p. 28). He added that Adderall/Adderall XR are *"both very good drugs,"* as their safety and efficacy had been established in the treatment of ADHD and which their commercial sales only reinforced. On May 18, Reuters reported on a recent survey of 54 pediatricians and psychiatrists conducted by Anian, a Rueters company that tracks industry trends for institutional investors. The Anian survey found doctors *"were likely to try Vyvanse but were unconvinced it had advantages over current therapies"* and *"suggested [Vyvanse] could initially capture roughly 20 market share from Adderall XR."* Here,

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4.25.07 First Wolrd Pharma on Shire Q1

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Reference 31
5.2.07 Shire Press release

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Reference 32
5.18.07 Reuters report

Vyvanse/LDX can be seen for its general place in the consciousness of the medical community – by those most likely to prescribe it. That place from the outset, even before a POSA could prescribe it for the treatment of ADHD, was self-evidently recognized by clinicians, investors, reports and the broader community-at-large ***in view of its "block-buster long-acting mixed amphetamine-salt sister stimulant"*** Adderall XR. As any reasonable person would understand in view of the publicly available information that tells the story, everyone who had any knowledge or interest in LDX ***at this time*** was simply trying to understand how the drug would actually be clinically different than the many other stimulants on the market, particularly the long-acting ones, and including with respect to its touted "decreased abuse risk." After all, it is the clinical differences of a drug that motivates POSAs to prescribe it in the first place and that, as a consequence, is what drives sales. And that is why investment professionals, at least some of them, were interested in hearing what Dr. Sanfilippo had to say on his GLG posts about the ADHD marketplace and LDX's anticipated place within it.

The following month, on June 27, Dr. Sanfilippo publicly posted an analysis on GLG's website regarding Shire's recent approvable letter from the FDA for INTUNIV (Guanfacine) extended release, a non-stimulant treatment for ADHD. (GLG, p. 26). Then two days later, on June 29, Dr. Sanfilippo's posted a news analysis entitled *"Vyvanse, Concerta and Adderall XR: How Will it Sort Out?"* in reference to a Reuter's investment article entitled *"Shire showcases new drug Vyvanse to wary doctors." (GLG, p. 25).* Indeed, "as any reasonable person" would see in view of just the headlines themselves at the time, the picture for Vyvanse in its "pre-market differentiation" from other stimulants become clear. In this particular analysis, Dr. Sanfilippo characterized the challenges of treating patients with stimulants in his "implications" section, *"Finding a 'superior product' above others is inherently challenging for these reasons and while Vyvanse seems to offer some potentially strong positive features (ie, less euphorogenic poperties, maybe longer duration of action, less overdose risk), it faces an uphill battle to overtake medications like Concerta and Adderall XR that have a good track record and clinician comfort for many ADHD patients. I don't suspect wholesale preference of Vyvanse over Adderall XR or Concerta….." (p. 25).* His conclusion is what "any reasonable POSA" familiar with ADHD market place and LDX's "pre-market differentiation" would have concluded, *"Unless clinicians' find a visibly compelling and strongly favorably clinical profile of the drug for their patients, I think Vyvanse will develop a decent marketshare but not overshadow the other longer acting stimulants. Patients (and clinician's) may view certain features like it's slower onset of action, for instance, as both a pro and con over Concerta and Adderall XR, making it less than universally acceptable over its counterparts. There is definitely solid room here clinically and in the market for Vyvanse but it will be competing against drugs that have been proven quite valuable." (p. 25).*

Third Quarter 2007.

On July 9, as FirstWorld Pharma reported, JP Morgan downgraded Shire's rating *"over concerns that fewer patients than expected would switch to the company's new attention-deficit hyperactivity disorder treatment, Vyvanse, from its older ADHD product, Adderall XR."* In the article, JP Morgan analyst Alistair Campell is quoted as saying, *"Although Shire has an excellent track record in the attention-*

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7.9.07 First World Pharma report

deficit hyperactivity disorder market, we see real risk that the Vyvanse switch will undershoot expectations…." The sentiment is echoed in a different light and with some literary flavor from the "clinician side of things" in "The Carlat Psychiatry Blog" on July 12 by Dr. Daniel Carlat, a recognized psychopharmacologist who authored a psychopharmacology report for psychiatrists beginning in 2003 (http://www.thecarlatreport.com/archives) and whose website now provides CME training for physicians. Dr. Carlat writes,

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7.12.07The Carlat Psychiatry Blog

> *"I don't know a huge amount about Vyvanse yet. I do know that Vyvanse is the molecule dextroamphetamine (trade names Dexedrine and Dextrostat) attached to the amino acid lysine. Shire cleverly calls it 'lisdexamfetamine,' presumably on the theory that using an 'f' instead of 'ph' in the chemical name will make it less obvious that Vyvanse is simply a fancified version of good old Dexedrine, a mainstay of ADHD treatment of decades.*
>
> *At any rate, Vyvanse is an inactive "pro-drug" which has no pharmacologic effect until after it is absorbed through the GI tract into the bloodstream, when liver and gut enzymes cleave off the lysine portion and produce the active drug d-amphetamine. The requirement that lysine be lopped off delays the peak concentration of d-amphetamine, but not by very much. To give you a sense of the scale that we are talking about, Dexedrine, which is pure dexamfetamine (I'm using Shire's Newspell here) reaches its peak concentration at 3 hours after administration (see Dexedrine prescribing information, accessed at http://www.fda.gov/cder/foi/label/2006/017078s040lbl.pdf). Vyvanse reaches its peak concentration at 3.5 hours, a delay of 30 minutes. While classified as a Schedule II controlled substance like existing stimulants, Vyvanse produces no high if snorted, and a 100 mg dose made drug abusers less buzzed than a 40 mg dose of Dexedrine. However, at 150 mg of Vyvanse there were no differences between the two on the "drug likeability scale." (See the manufacturer's Web site at http://www.vyvanse.com/.)*
>
> *Over the past 2 weeks in my private practice office I have received 9 different mailings from Shire about Vyvanse, an average of about one every other day, but I expect the pace to pick up significantly. Today, my Vyvanse mailing invited me to a 'virtual roundtable series' to 'provide feedback on various support materials that Shire provides physicians to help them better understand… Vyvanse.' In other words, Shire has invited me and thousands of other physicians to be marketing consultants. No compensation was mentioned but I was provided the following number to register: 1-800-635-8730, program 2595. Readers are invited to do their own research on this opportunity.*
>
> *I'll keep you updated on future promotionals as they flood into my office. This should be interesting, as Shire is the most aggressive pharmaceutical marketer I've ever seen, and they are not shy about using CME programs to promote their products."*

On July 26, Shire announced second quarter results with CEO Emmens commenting, *"Revenues were up 31% led by Adderall XR and Daytrana in a growing ADHD market….importantly, we have just launched Vyvanse, our next generation ADHD product. We believe this product is best in class and early results are promising with positive feedback from both physicians and patients. In addition, we have received two FDA approvable letters in the ADHD category – for INTUNIV, a non-stimulant for ADHD, and SPD465, a longer acting version of Adderall XR for the treatment of adult ADHD." (p. 2).* The Shire statement indicates *"Adderall XR is the leading brand in the US ADHD market with an average market share of 26% during Q2 2007 (2006:26%),"* with $255 million in sales in Q2 2007, and *"Vyvanse was launched in the US in June 2007 following receipt of required regulatory approvals." (pp. 2-3).*

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Q2 Shire Press Release

On August 1, 2007, in view of evolving events in the ADHD treatment landscape and his own clinical use of LDX in the treatment of patients, Dr. Sanfilippo writes a GLG post entitled *"Some Clinical Observations on Shire's Vyvanse"* in specific connection to a news report entitled, "*Shire's New ADHD medication, Vyvanse, Now Available in U.S. Pharmacies Nationwide."* Among his observations,

> *"My previous commentaries on Vyvanse, the pro-drug amphetamine that recently entered the US market for the treatment of ADHD, was based on readings as well as discussions with colleagues; however, now that I have a small pool of patients taking it I am noticing a clinical profile that does separate it from Adderall XR and Concerta, the other long-acting stimulants in the market." (GLG, p. 20)*

In the GLG analysis, Dr. Sanfilippo outlines four key observations related to LDX, specifically: 1) its duration of action, 2) its slower time to efficacy, 3) ADHD/SUD comorbidity, and 4) dosing issues, and concludes,

> *"Is this the optimal kind of ADHD treatment? No, as what may be clinically advantageous to some many not be for others. I still have patients who like the fact that their Adderall XR or Concerta wears off just as they end their work day when they go for a run; or that they don't feel any effect in the evening. Some patients just like the flexibility of the short acting stimulants. And others who are content with their current medication will see no need to change over. But clearly, I think there is lots of room clinically for this drug and my initial impressions are more positive than my pre-marketing expectations." (GLG, p. 20).*

On August 23, Reuters reported that investment analysts said *"the overall level of demand had been subdued, with Vyvanse's market share at 2.4% total prescriptions after eight weeks on the market rather less than hoped,"* adding, *"While it was encouraging that Vyvanse was taking share from products like Johnson and Johnson's Concerta and Eli Lilly and Co's Strattera, feedback from pharmacies suggested demand so far had been underwhelming. An Anian survey of 14 urban and suburban U.S. pharmacies found only two had dispensed Vyvanse, while five stocked the drug. Dealers reported Credit Suisse analysts said in a note earlier this week that the penetration and ramp-up rate to date was 'somewhat disappointing,' although the market share from rivals were promising, indicated a mixed launch*

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8.23. 07 Reuters report

overall." On August 31, 2007, LDX carried 2.9% of the ADHD marketshare with a substantial percentage of patients taking the drug by virtue of "coupons," as featured in a presentation by Shire President, Specialty Pharmaceuticals, Michael Cola (UBS Global Life Sciences Conference; Slides 10, 12, September 24, 2007). This, as any reasonable person would appreciate in view of events from this period of time, strongly would suggest LDX was being largely prescribed by the kinds of POSAs who treat children for ADHD (ie, pediatricians, child and adolescent psychiatrists) since Vyvanse was FDA-approved for ADHD in school-age children and Shire's marketing of LDX coupons would have certainly been only to those POSAs who would have prescribed the Schedule II stimulant drug "on-label" (i.e., for its FDA indication). This information provides a composite behavioral profile of the kind of M.D./psychiatrist who would have been motivated to even prescribe LDX to a patient at the time of the invention.

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Reference 37

9.24.07 UBS Presentation, President Shire Specialty Pharmaceuticals, Michael Cola

On September 13, 2007, '813 is filed.

The following day after '813 was filed, on September 14, First World Pharma writes that shares in Shire fell *"as much as 7.5% after some analysts expressed disappointment with sales of recently-launched attention-deficit hyperactivity treatment Vyvanse."* FirstWorld added, "*However, Shire's chief financial officer, Angus Russell, responded that 'we're quite comfortable that things are going extremely well."* Quoting JPMorgan analysts Alistair Campbell and Craig Maxwell, First World Pharma writes, *" 'If Vyvanse share stalls in coming months, we will have serious doubts over our forecasts. The Vyvanse share of the combined Adderall XR/Vyvanse volume has been disappointing at just over 10 percent after 12 weeks.'"* Thus, two of JPMorgan's investment analysts point that LDX may be running into some unwelcome competition with its ***"block-buster long-acting mixed amphetamine-salt OLDER sister stimulant"*** Adderall XR.

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9.14. 2007. First World Pharma on Shire share fall

For a more thorough characterization of LDX in the ADHD marketplace during the quarter '813 was filed, Shire's 2007 "third quarter results" (as presented by slides on November 1, 2007, by CEO Emmens, CFO Angus Russell, and VP of Investor Relations Clea Rosenfeld) is referenced, as is the November 1 Earnings call transcript from "Seeking Alpha" (*http://seekingalpha.com/article/52666-shire-plc-q3-2007-earnings-call-transcript?page=1*). Notably, Q3 sales of Vyvanse were **$10.6 million** vs. $249 million for Adderall XR and 9.4 million for the transdermal methylphenidate patch Daytrana (slide 11). At this point in time, LDX's "popularity" among POSA's, as measured by the hard numbers of commercial sales, was "financially even" with its rather "unpopular MPH-based little sister long-acting skin-patch stimulant" Daytrana and, not surprisingly, overshadowed by its "popular AMPH-based big sister long-acting oral stimulat" Adderall XR by 23x its own barely 8-figure sales. Which gives "any reasonable person" a sense of where LDX was in the consciousness even among those POSAs who, at the time of the invention, would have been most motivated to prescribe it, namely, POSAs who treat ADHD, particularly in school-age children. With respect to the Q3 Conference Call that included 10 investment analysts from prominent firms like Goldman Sachs, Deutsche Bank, UBS Warburg, among others, Shire indicated that 84% patients who started on Vyvanse and completed baseline surveys reported having used a prescription for ADHD treatment prior to Vyvanse (Slide 26). CEO Emmens reported 40% of these had come from Adderall XR (p. 15 of Seeking

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REFERENCE 40: Q3 2007 transcript Seeking Alpha

Alpha Transcript). So again, there is yet more evidence that LDX is seen in view of other stimulants for the treatment of ADHD, especially Adderall XR – and particularly in children, as CEO Emmens makes it a point to say that Vyvanse couldn't be promoted in adults but expected to have that indication in April 2008, though acknowledges physicians do use *"these drugs in all kind of patients." (Slide 20).*

According to the Seeking-Alpha Q3 2007 Earnings Call transcript, CEO Emmens says, "*I think it's just a matter of physicians trying it [Vyvanse]. It's a new chemical entity, they want to see what it does and I think they want to get feedback from their patients and that's starting to happen*." Of course, this is what any POSA at the time of the invention would have recognized. Vyvanse was a new drug and its place in ***specifically ADHD treatment*** had yet to be understood because its differentiation from other long-acting stimulants, in particular, had yet to be recognized by POSAs for its therapeutic implications. So just at the time that Dr. Biederman was addressing the therapeutic implications of ***"stimulants generally"*** in patients with comorbid ADHD and BN, there were a very small group of people with a ***highly sophisticated understanding*** of LDX that were addressing the drug's therapeutic implications in for patients with ADHD. And regarding LDX's ***overall clinical profile***, as a POSA (familiar with stimulants in the treatment of ADHD) would have appreciated (generally) at the time of the invention, CEO Emmens says in the transcript, *"you got to remember that, from a physician standpoint, when New River was touting this drug, basically, their primary thing was about safety and abusability and all that stuff. That didn't play well with physicians. As we got out there later, as we bought the product and started doing our soft…the softer research, we…basically, it came…the most important thing that bothered them is the duration of activity, particularly as it relates to inattention. And the second is the smoothness, this onset, offset, causes…can cause personality differences in kids, especially they tend to get a flat affect when they come off the drug or else they might get a little buzz when they go into it. And this drug does not do that, and that is important to them. The third attribute was the whole absuability thing, they just…its kind of like, not my patients. So it's nice to have, but the other two are the ones that are going to drive business. So again, as I said, I wouldn't hang me hat on it because I think its going to be difficult to change the C2 [Schedule 2] to C3 [Schedule 3] thing. I just…we always thought that [abusability thing] was a challenge because* ***its basically an interpretation*** *and* ***it's a big statement when you say it****. But I think the perception of the physician that this gets better would be helfpful,* ***but, again, remember it's the third attribute****." (pp. 37-38).*

A publicly available slide set on "the state of the art of ADHD treatment," presented in Chicago in January 2008 to a group of investment analysts, speaks to the ADHD market and the prospective differentiating features of LDX in view of other stimulants. At that point in time, over four months after '813's filing, the investment world (as the medical community) was still trying to understand how LDX dimesylate was different than other long-acting stimulants in the treatment of ADHD. Any POSA at that time who would accurately represent the art would know that, as would any investment analyst familiar with the space at that time, as would "any reasonable person" provided basic information about events in the general

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Chicago GLG Presentation on ADHD, January 2008, L Sanfilippo MD

vicinity of the '813's filing. The presentation was given by Dr. Sanfilippo, through the Gerson Lehrman Group, with a second presentation on the same topic in NYC.

So here is the lesson, as "any reasonable person" would see it at the time of the invention and in view of the truth. As Dr. Sanfilippo taught on the therapeutic distinctions of LDX dimesylate that might separate it from the many other stimulant drugs available for the specific treatment of ADHD, he also taught on the therapeutic distinctions of LDX dimesylate that might separate it from the countless commercially available drugs that "increase NTs" as well from the very few commercially available drugs that had been proven successful for the treatment of BED. But it would be some time before the second aspect of his teachings would be disclosed for all its remarkable detail. But that time has come, and it has come on account of something called truth.

Binge Eating Disorder: Its Further Validation in a Multisite Study

Robert L. Spitzer
Susan Yanovski
Thomas Wadden
Rena Wing
Marsha D. Marcus
Albert Stunkard
Michael Devlin
James Mitchell
Deborah Hasin
R. Lynn Horne

(Accepted 14 October 1992)

Binge eating disorder (BED) is a new eating disorder that describes the eating disturbance of a large number of individuals who suffer from recurrent binge eating but who do not regularly engage in the compensatory behaviors to avoid weight gain seen in bulimia nervosa. This multisite study of BED involved 1,785 subjects drawn from 18 weight control programs, 942 subjects from five nonpatient community samples, and 75 patients with bulimia nervosa. Approximately 29% of subjects in weight control programs met the criteria for BED. In the nonpatient community samples BED was more common than purging bulimia nervosa. The validity of BED was supported by its strong association with (1) impairment in work and social functioning, (2) overconcern with body/shape and weight, (3) general psychopathology, (4) significant amount of time in adult life on diets, (5) a history of depression, alcohol/drug abuse, and treatment for emotional problems. © *1993 by John Wiley & Sons, Inc.*

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Binge eating disorder (BED) is a newly conceptualized eating disorder that describes the eating disturbance of a large number of individuals who suffer from recurrent binge eating but who do not regularly engage in the inappropriate compensatory behaviors to avoid weight gain that are seen in bulimia nervosa. Although the proposal for BED as a new eating disorder is recent (Spitzer et al., 1991), it is the logical extension of Stunkard's original description of binge eating (Stunkard, 1959) and the many studies in the 1980s, before the availability of the BED diagnostic criteria, that demonstrated the usefulness of binge eating as a clinical feature in the obese because of its association with a variety of important clinical features (Gormally, Black, Daston, & Rardin, 1982; Loro & Orleans, 1981; Marcus et al., 1985, 1988, 1990; Marcus, Wing, & Lamparski, 1985; Marcus, Wing, & Hopkins, 1988; Kolotkin, Revis, Kirkley, & Janick, 1987; Telch, Agras, & Rossiter, 1988; Telch, Agras, Rossiter, Wilfley, & Kenardy, 1990).

A multisite field trial of the diagnostic criteria for BED involving nearly 2,000 participants suggested the potential utility of the diagnosis for clinical and research purposes (Spitzer et al., 1992). The diagnosis was found to be common among participants in weight control programs, with 30% meeting the criteria for the disorder. The disorder was relatively rare in the community (2%). In both the weight control and community samples BED was strongly associated with severe obesity and a history of unstable weight, and was somewhat more common in females (ratio of proportion in females:males approximately 3:2).

In this paper we provide additional data about the diagnosis of BED, by answering the following questions in a second large multisite study:

1. Among individuals seeking help for weight control, how do individuals with and without BED differ on such clinical features as weight and diet history, reports of functional impairment associated with eating disturbance, history of various disorders and psychiatric treatment, and general measures of psychopathology?
2. How do individuals with BED differ from individuals with purging bulimia nervosa and from samples of nonpatients in the community on these same variables?
3. Because female college students are at risk for purging bulimia nervosa (Striegel-Moore, Silverstein, & Rodin, 1986), are they also at risk for BED? What is the range of the prevalence of BED and purging bulimia nervosa in samples of female college students?
4. In overnight subjects, is BED associated with an earlier onset of overweight and of dieting? Because some investigators have suggested that dieting may contribute to the onset of binge eating (Polivy & Herman, 1985; Tuschl, 1990; Herman & Polivy, 1990; Treasure, 1990; Wardle, 1990), does the occurrence of binge eating typically follow, rather than precede, a history of significant dieting in subjects with BED?

By providing information about the distinctive clinical features of BED that are external to its definition, we thereby provide data in support of the validity of BED as a diagnosis.

THE DIAGNOSTIC CRITERIA FOR BED

The diagnostic criteria currently recommended for BED are presented in Table 1. Criteria A through D are identical to those used in both multisite studies of BED (with the

Table 1. Diagnostic criteria for binge eating disorder

A. Recurrent episodes of binge eating, an episode being characterized by both of the following:
   (1) Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time in similar circumstances.
   (2) A sense of lack of control during the episodes, for example, a feeling that one can't stop eating or control what or how much one is eating.
B. During most binge episodes, at least three of the following:
   (1) Eating much more rapidly than usual.
   (2) Eating until feeling uncomfortably full.
   (3) Eating large amounts of food when not feeling physically hungry.
   (4) Eating alone because of being embarrassed by how much one is eating.
   (5) Feeling disgusted with oneself, depressed, or feeling very guilty after overeating.
C. Marked distress regarding binge eating.
D. The binge eating occurs, on average, at least two days a week for a 6-month period.
E. Does not occur only during the course of bulimia nervosa or anorexia nervosa.

exception of the omission from the initial criteria of a B item, "eating large amounts of food throughout the day with no planned mealtimes," which has a neglible effect on caseness). Criterion E, which excludes cases that currently meet the criteria for either anorexia nervosa or bulimia nervosa, was initially defined to anticipate a DSM-IV proposal (American Psychiatric Association, 1991) that would have limited bulimia nervosa to cases that involved purging behavior: vomiting, diuretics, or use of laxatives. Therefore, only cases of purging bulimia nervosa were excluded. Criterion E is now defined so as to recognize a nonpurging bulimia nervosa that will be included in DSM-IV (T.B. Walsh, personal communication, 1992). Later we show that excluding such cases from the diagnosis of BED has no appreciable effect on the magnitude of the association of BED with the validity variables examined in this study.

QUESTIONNAIRE ON EATING AND WEIGHT PATTERNS

The three-page questionnaire used in the first multisite study was expanded to seven pages by adding questions that operationalized the variables noted in item 1 above. All questions about current functioning and eating behavior focused on the past 6 months. Examples of some of the items are as follows: Impairment in social relations was evaluated by responses to the question: "During the past six months, how much has your relationship with people been affected by any of the following: overeating or thinking about eating, being upset about your eating, or being upset about your weight?" Subjects responded using a 5-point scale anchored by "Not at all" and "To an extreme degree." Overconcern with body/weight shape was evaluated by the following question: "Over the past six months, how important has your weight or shape been in how you feel about or evaluate yourself as a person—as compared to other aspects of your life, such as how you do at work, as a parent, or how you get along with other people?" Possible responses ranged from 1 ("Weight and shape were not very important") to 5 ("Weight and shape were the most important things that affected how you felt about yourself"). Amount of time on a diet was evaluated by the question: "Since you have been an adult—18 years old—how much of the time have you been on a diet, been trying to follow a diet, or in some way been limiting how much you were eating in order to lose weight or keep from regaining weight you had lost?" Possible responses ranged from 1 ("None or hardly any of the time") to 6 ("Nearly all of the time").

A history of depression was evaluated by a response to the question: "Have you ever had a time lasting at least two weeks when you were so depressed that it interfered with your ability to work or get along with people?" A history of alcohol abuse (and a comparable question for drug abuse) was evaluated by the question: "Have you ever had a time lasting at least a month when you or someone else thought you were having a problem with drinking too much alcohol?" A history of sexual abuse was evaluated by the question: "Were you ever the victim of incest, sexual abuse or rape?"

For data analysis all of the scaled questionnaire responses were dichotomized. For example, impaired relations with people because of "overeating or thinking about eating, being upset about your eating, or being upset about your weight" was dichotomized into "greatly" or "extremely" and "none" to "moderately." The item about the importance of weight/shape in self-evaluation was dichotomized into "was the most important thing" or "among the main things" and "not very important" or "played a part."

Subjects who entered later in the study also completed Derogatis's Brief Symptom Index (Derogatis & Melisaratos, 1983), a 53-item general measure of current psychopathology. For each item (e.g., "Nervousness or shakiness inside"), subjects note how much that problem has bothered or distressed them during the past week. Possible responses range from 0 ("Not at all") to 4 ("Extremely"). For data analysis, the 53 items are summarized into a global severity index and nine symptom scales.

Several questions about compensatory behaviors associated with nonpurging bulimia nervosa (fasting, excessive exercise, abuse of medication) were also added to the questionnaire that was given to some of the sample studied at the end of the study. (The complete questionnaire is available from the senior author upon request. Questions and computer analysis decision rules for diagnosing BED and bulimia nervosa according to DSM-IV criteria are included in the Appendix).

A clinician-administered version of the questionnaire was developed to test the agreement between a clinician evaluation of BED and the self-report evaluation from the questionnaire. A kappa of .60 was obtained for the agreement between clinician and questionnaire on the diagnosis of BED in 44 subjects in the United Weight Control sample. This modest agreement is comparable to the test-retest agreement commonly found for the major psychiatric disorders (Williams et al., 1992).

STUDY SAMPLES

Weight Control Samples

The weight control sample consisted of individuals currently enrolled in 18 different programs (see Acknowledgments for directors and names of programs). The programs employed a range of therapies used in the treatment of obesity, which included traditional nutritional counselling (within moderately restrictive diets), very-low-calorie diets, cognitive-behavioral approaches, and medication.

Six of these programs were affiliated with hospital or university eating disorders programs. Two of the samples consisted of private patients of two physicians who specialized in the treatment of eating disorders. Six of the programs involved random assignment of the subjects to a weight control treatment protocol, the efficacy of which was being evaluated.

In most of the programs, all of the subjects were tested at the same time, regardless

of how long they had been in treatment. Some programs, however, assessed new subjects as they entered the program until a sufficient number had been tested. Few subjects declined to participate in the study.

A small number of questionnaires with missing data on BED diagnostic criteria variables were eliminated, as were cases with frequent vomiting or use of diuretics or laxatives suggesting purging bulimia nervosa. The final weight control sample had 1,785 subjects.

Nonpatient Community Sample

This sample consisted of 214 new employees (professional and nonprofessional) of Presbyterian Medical Center enrolled over a 6-month period, who completed the questionnaire during their pre-employment physical examination. Few employees refused. Although not a random sample from the community, this group provides a useful contrast to the weight control samples.

College Student Samples

Questionnaires were completed by 728 students at three colleges in the United States and one in Canada: Wesleyan University, CT; Clemson University, SC; University of Nevada, NV; and the University of Toronto, Ontario, Canada (where about 25% of the students are of Asian background and the remaining primarily Caucasian). Most of the students were recruited in introductory psychology courses; some were part of the graduating class of 1992.

Bulimia Nervosa Samples

A sample of 75 normal weight women was drawn from two clinics in New York City which offered outpatient psychotherapy and medication for the treatment of bulimia nervosa. On the questionnaire all of the subjects met the criteria for purging bulimia nervosa by reporting at least two episodes a week for the past 6 months of binge eating and compensatory vomiting or use of laxatives.

RESULTS

All results for a given variable exclude cases with missing information on that variable. For that reason, the *N* for a specific item may be smaller than that for the total sample. Unless otherwise noted, statistical tests are two tailed.

Description of Study Samples

Table 2 describes the study samples. Subjects in the weight control samples had a mean age in the forties, community nonpatients in the thirties, and college students and bulimia nervosa samples in the twenties. As would be expected, most of the participants at weight control sites were female. Almost 80% of the student sample was female.

A height normalized measure of adiposity, the body mass index (BMI) (Garrow & Webster, 1985), was calculated for each subject's current and highest weight ever. Not

Table 2. Description of study samples

Samples	N	Mean Age (Range)	Female N (%)	White N (%)	College Graduate N (%)	BMI Mean Current	BMI Mean Highest	BED N (%)
Weight control (18 sites)	1,785	42.9 (15–80)	1588 (89.0)	1647 (92.3)	779 (43.6)	31.0	35.2	514 (28.8)
Community nonpatients (1 sample)	216	34.0 (18–70)	152 (70.4)	103 (47.7)	126 (59.2)	24.8	26.2	10 (4.6)
College students (4 samples)	728	22.3 (16–67)	573 (78.7)	357 (74.4)	77 (16.0)	22.1	23.6	18 (2.6)
Bulimia nervosa (2 samples)	75	25.8 (17–48)	85 (100)	65 (85.5)	32 (42.1)	22.8	25.7	

Note. BMI = body mass index; BED = binge eating disorder.

surprisingly, mean BMI values of subjects in the weight control programs were in the high range, while those in the other samples fell in the normal range (below 27.5).

Prevalence of BED

The overall prevalence of BED in the weight control samples was 28.8% (95% confidence interval from 27.9% to 29.7%), almost identical to that found in the weight control samples studied in the first multisite study (30.1%). There were interesting differences in the prevalence of BED based on the type of weight control program. The prevalence was lowest in the 491 subjects enrolled in the Jenny Craig Inc., program (15.9%). These subjects, on average, had the lowest "current" and "highest-ever" BMIs (27.8 and 32.0, respectively.) The highest prevalences of BED (52.2%, $N = 23$ and 56.6%, $N = 63$) were of the weight control samples from the two physicians who specialized in the treatment of patients with eating disorders. These subjects also had the highest current and highest-ever BMIs among the weight control samples (35.4 and 37.1, and 37.1 and 39.8, respectively).

As in the first multisite study, BED was somewhat more common in females than males (29.7% vs. 21.8%, $p = .02$). BED was not significantly more common in white subjects than nonwhite (primarily African-American) subjects (29.4% vs. 22.2%).

In the nonpatient community sample the prevalence of BED was 4.6% (95% confidence interval from 4.2% to 5.2%), similar to the 3.3% for the sample drawn from the same facility in the first phase of the field trial. BED was not significantly more common in females than males (5.3% vs. 3.1%). (For comparison purposes, the prevalence of purging bulimia nervosa was .5% [95% confidence interval from .36% to .64%]).

The prevalence of BED in the combined college student samples was 2.6% (95% confidence interval from 2.9% to 2.3%). BED was not significantly more common in females than males (2.8% vs. 1.9%). Of interest, the overall prevalence of BED in the females in the three U.S. student samples was 3.7% ($N = 15$) as compared with only .6% ($N = 1$) in the female sample from the University of Toronto (two-tail Fisher exact test = .048), suggesting the possible role of cultural factors in the development of BED.

The overall prevalence of bulimia nervosa in the female students was 1.2% ($N = 7$) (95% confidence interval from 1.0% to 1.4%), less than half that of BED.

Distinctive Clinical Features of BED

Table 3 presents the frequency of potentially distinctive clinical features of BED in four samples. The first and second columns are the weight control samples divided into those with the diagnosis of BED (BED+) and those without the diagnosis (BED−). The third and fourth columns are for the bulimia nervosa and nonpatient community samples, respectively. For each variable, the first row is the number of subjects, and the second row the percent of subjects in the sample with the variable. Thus, the second row of Table 3 indicates that in the weight control sample, 65.1% of the patients with BED (BED+) had impaired relations with people because of being upset by eating/weight as compared with 28.8% in the sample who did not have BED (BED−). The same variable was present in 57.3% of the bulimia nervosa sample and in only 7.4% of the nonpatient community sample.

The third row for each variable presents the odds ratio, which indicates how much larger the odds for this variable are for the BED+ subjects than for the other sample. All odds ratios have been adjusted by logistic regression to control for current BMI.

As can be seen, patients who meet criteria for the diagnosis of BED have significantly greater odds of having all of the potentially distinctive clinical features than subjects who are BED− or than nonpatient community subjects. In contrast, examination of the third column indicates that on some clinical variables BED+ subjects are different from bulimia nervosa subjects, whereas on other variables they are not distinguishable. As can be seen, a history of severe obesity and having gained and lost 20 lb five times or more, is far more common in BED than in bulimia nervosa. On the other hand, reports of impaired work, evaluating self primarily by weight/shape and a history of depression, alcohol abuse, drug abuse, and sexual abuse are more common in the subjects with bulimia nervosa. The two diagnostic groups do not differ on the other variables: reports of impaired relations, weight/shape interfering with feeling good, having seen a mental health professional, and being on diets more than half of adult life.

BED, Severe Obesity, and Onset of Overweight and of Dieting

As in the first multisite study, within the weight control sample the prevalence of BED was significantly associated with a history of severe obesity (defined as having had a BMI of 35 or greater, a value associated with high risk for obesity-related mortality [Lew & Garfinkel, 1979]). Forty-three percent of the subjects with BED, as compared with 27% of the subjects without BED, had a history of severe obesity. At their highest weight, subjects with BED were 11 lb heavier than subjects without BED.

Within the weight control sample, subjects with BED had an earlier onset of being overweight (at least 10 lb as a child, or 15 lb as an adult) than subjects without BED. The average age of onset of overweight for the subjects with BED (N = 502) was 15.9 (SD = 9.3) as compared with 19.5 (SD = 11.4) for those without BED (N = 1,151) ($p \leq .001$). The diagnosis of BED was associated with an earlier onset of significant dieting (losing at least 10 lb by dieting). The average age at onset of significant dieting for the weight control subjects with BED (N = 440) was 20.0 (SD = 8.1) as compared with 24.0 (SD = 10.8) for those without BED (N = 1,074) ($p \leq .001$).

The relationship between onset of dieting and onset of binge eating was examined by dividing the weight control subjects into three categories: those who binged before significant dieting, those who binged after significant dieting, and those who reported

Table 3. Frequency of the distinctive clinical features of BED in four groups: weight control BED+ and BED−, Nonpatient community, and bulimia nervosa samples, and odds ratios contrasting weight control BED+ with other samples

Clinical Feature	Weight Control BED+ N = 467–514 N (%)	Weight Control BED− N = 1,189–1,266 N (%) Odds Ratio BED+/BED−	Bulimia Nervosa N = 63–75 N (%) Odds Ratio BED+/BN−	Nonpatient Community N = 201–215 N (%) Odds Ratio BED+/NPC
Functional impairment				
Impaired relations with people because upset by eating/weight	334 (65.1)	364 (28.8) 4.5***	43 (57.3) 1.1	16 (7.4) 17.0***
Impaired work because upset by eating/ weight	228 (44.5)	219 (17.3) 4.7***	48 (64.0) .31***	10 (4.7) 3.8***
Evaluate self by weight/shape	412 (80.3)	722 (57.5) 3.1***	66 (89.2) .38*	63 (30.4) 8.8***
Weight/shape interferes with feeling good	428 (83.1)	586 (46.6) 5.8***	60 (80.0) .72	25 (11.9) 25.3***
Historical factors				
History of depression	217 (46.4)	326 (27.2) 2.3***	55 (73.3) .29***	34 (16.7) 4.1***
History of alcohol abuse	72 (15.4)	117 (9.7) 1.7***	22 (29.3) .47*	15 (7.4) 2.3**

History of drug abuse	59	43	16	11
	(12.6)	(3.6)	(21.3)	(5.5)
		3.8***	.41*	2.1*
Saw mental health	244	456	39	60
professional	(52.0)	(38.3)	(52.0)	(29.9)
		1.7***	1.1	2.6***
History of sexual abuse	92	166	17	29
	(19.6)	(14.0)	(27.0)	(14.4)
		1.5**	.45*	1.1
Weight and diet history				
History of severe	219	348	5	14
obesity	(2.6)	(27.4)	(6.7)	(6.5)
		1.9***	2.9*	3.8***
Gained and lost 20 lb	264	343	14	6
five times or more	(51.4)	(27.0)	(18.7)	(2.9)
		2.8***	2.8***	24.0***
On diets more than	380	627	61	45
half of adult life	(74.8)	(50.0)	(82.4)	(22.1)
		3.0***	.53	9.3***

Note. Odds ratios have been adjusted by logistic regression for current body mass index (BMI). BEDT = diagnosis of binge eating disorder; BED− = without diagnosis of binge eating disorder; BN = bulimia nervosa NPC = nonpatient community.

*$p \leq .05$.

**$p \leq .01$.

***$p \leq .001$.

that the age of onset of binge eating was the same as the age of onset of dieting. The onset of binge eating more commonly preceded than followed the onset of significant dieting. For subjects with BED (N = 387), 48.6% binged before dieting, 37.0% after dieting, and 14.5% the same age.

BED and General Measures of Psychopathology

Table 4 presents the means and standard deviations on Derogatis's Brief Symptom Index scale in four groups of subjects: the college sample, weight control subjects without BED, weight control subjects with BED, and the bulimia nervosa samples. On all scales, BED+ subjects had significantly higher values than BED− subjects ($p \leq .001$). On all scales but one, Interpersonal Sensitivity, the bulimia nervosa sample had significantly higher values than the BED+ subjects ($p \leq .001$). On all of the scales, the BED− sample has values that are closer to the values of the college sample than to the BED− sample.

BED and Nonpurging Bulimia Nervosa

A possible confounding of the association of BED with the variables reported so far is the inclusion in the diagnosis of BED of cases of nonpurging bulimia nervosa (i.e., excessive exercise, fasting, or abuse of medication in order to avoid weight gain from binge eating). In order to determine if this potential confounding is appreciable, further analyses were conducted on 724 subjects in the weight control samples who completed questionnaires that included inquiries about nonpurging bulimic behaviors.

In this sample, when subjects completed the questionnaire item on the abuse of medication, many subjects referred to use of diet pills which, unlike diuretics or thyroid hormone, are specifically designed to control appetite and therefore may not constitute an abuse of medication. Therefore the following analyses do not include this item. (A suggested revision of the wording of this item is included in the Appendix.)

Table 4. Means (and standard deviations) for the Brief Symptom Index scales in four groups: college sample, BED− and BED+ weight control, and bulimia nervosa sample

Brief Symptom Index Scales	College Sample N = 720	Weight Control BED− N = 833	Weight Control BED+ N = 296	Bulimia Nervosa N = 67
Global Severity Index	.68 (.51)	.49 (.46)	.89 (.67)	1.56 (.60)
Somatization	.42 (.51)	.34 (.46)	.64 (.78)	1.31 (.68)
Obsessive Compulsive	.97 (.72)	.71 (.66)	1.13 (1.02)	1.78 (.72)
Interpersonal Sensitivity	1.01 (.82)	.74 (.80)	1.40 (1.02)	1.60 (.80)
Depression	.78 (.76)	.56 (.71)	1.13 (1.01)	1.65 (.69)
Anxiety	.71 (.63)	.52 (.58)	.86 (.82)	1.59 (.72)
Hostility	.69 (.69)	.49 (.56)	.89 (.80)	1.83 (.78)
Phobic Anxiety	.34 (.47)	.23 (.44)	.55 (.72)	1.27 (.69)
Paranoid Ideation	.70 (.68)	.51 (.60)	.87 (.80)	1.59 (.70)
Psychoticism	.55 (.62)	.36 (.54)	.76 (.77)	1.72 (.77)

Note. BED− = without diagnosis of binge eating disorder; BED+ = diagnosis of binge eating disorder.

If the diagnosis of BED excludes all cases with nonpurging bulimia, the prevalence of BED is reduced by 12% (21.9% to 19.1%) but there was no appreciable effect on the adjusted odds ratios reported in Table 3. Thus, excluding cases of nonpurging bulimia nervosa from the diagnosis of BED, as in the diagnostic criteria now proposed, has no appreciable effect on the magnitude of the association of BED with the validity variables examined in this study.

DISCUSSION

This second multisite study of BED confirmed the findings reported in the first study: approximately 29% of individuals in a wide variety of weight control programs were distressed by recurrent binge eating and satisfied the initial diagnostic criteria for BED. Unlike purging bulimia nervosa which is much more common in females (Striegel-Moore et al., 1986), BED was only slightly more common in females than males in the weight control samples and was equally common in males and females in the community nonpatient and college samples. BED was as common in nonwhite subjects as in white subjects in both the weight control samples and the nonpatient community sample. As in the first multisite study, BED was associated with a lifetime history of severe obesity and frequent significant weight fluctuations.

The diagnosis of BED was strongly associated with variables that are external to the defining features of the disorder: reports of impairment in work and social functioning, overconcern with body/shape and weight, amount of time in adult life on diets, a history of depression or alcohol/drug abuse, and a history of treatment for emotional problems. Of note, this pattern of associations was independent of the severity of obesity and distinguishable from patients with purging bulimia nervosa. Subjects with purging bulimia nervosa, as compared with patients with BED, were more likely to report impaired work, evaluate themselves unduly by weight/shape, and to report a history of depression, and alcohol, drug, and sexual abuse. When BED was defined more stringently to exclude cases of nonpurging bulimia nervosa, the prevalence of the disorder dropped slightly but the magnitude of the association with external validity variables was unchanged.

Additional support for the validity of BED was provided by the consistent association of the diagnosis with general measures of current psychopathology. Subjects with BED obtained mean scores on the Brief Symptom Index scales that were significantly higher than those without BED. Other investigators have recently studied BED and have confirmed its association with general measures of psychopathology (Yanovski, Nelson, Dubbert, & Spitzer, 1992 manuscript; de Zwaan et al., in press). A submitted manuscript, Yanovski et al. (1992) has also demonstrated that within a sample of moderately and severely obese individuals, BED was associated with a lifetime prevalence of major depression, panic disorder, borderline personality disorder, and avoidant personality disorder. On general measures of current psychopathology, subjects with BED had lower values than those with purging bulimia nervosa, again providing support for the validity of the diagnosis of BED.

The prevalence of BED in the combined college student samples was 2.6%, similar to that obtained in the one college sample in the first phase of the field trial (2.7%), and higher than that of purging bulimia nervosa (1.2%). Thus, in both the community nonpatient sample and in the college samples, the prevalence of BED was higher than that of purging bulimia nervosa.

The number of subjects with BED in the nonpatient community sample and in the college sample was only 48 and may not be representative of untreated individuals in the community. However, it is of interest that only 20 of these individuals currently had BMIs in the overweight range (27.5 or greater) and only 25 had ever had BMIs in the overweight range. (A similar finding was obtained in the first phase of the field trial in a smaller sample of 19 community cases.) Thus, although in clinical settings the great majority of persons with BED will be overweight, a large portion of untreated individuals with BED in the community may be able to maintain a normal weight, perhaps because they repeatedly take off weight gained during periods of binge eating or markedly restrict caloric intake between binge episodes. Future studies with clinical interviews of normal weight individuals with BED are necessary to determine how appropriate weight is maintained.

Future studies are also needed of the cases of nonpurging bulimia that are now excluded from the diagnosis of BED. In the weight control sample, these cases did not differ in current BMI from the subjects with BED (32.8 and 32.3, respectively) nor in age (39.0 and 40.8, respectively) nor in odds ratio for being female (1.2 and 1.0, respectively). In these subjects the nonpurging behavior that was designed to compensate for the binge eating was not effective in maintaining a normal weight and may often have not been medically hazardous. Thus, future studies are needed to determine if the diagnosis of BED should only exclude those cases in which the compensatory behavior actually prevents significant weight gain or is medically hazardous, as is usually the case with purging bulimia nervosa.

The hypothesis that in patients with BED the onset of binge eating would more commonly follow than precede dieting (and significant weight loss) was not supported. These results are consistent with the results of a study of obese adolescents in whom binging more frequently preceded dieting than the converse (Berkowitz, Stunkard, & Stallings, 1992).

The criteria for BED have been deliberately set at a high threshold. The data from the first multisite study, as well as the results of a study by de Zwaan et al. (in press) indicate that the underlying disturbance represents a continuum of severity rather than a dichotomy. This lack of a sharp boundary for the diagnosis of BED is, however, also present for bulimia nervosa and such established psychiatric disorders as major depression and the various substance use disorders.

The results of the two multisite studies of BED, as well as the results of other studies of BED that have recently been completed (Yanovski et al., 1992, in press-a, in press-b de Zwaan, in press; LaChaussee, Kissileff, Devlin, Goldfein, & Walsh, in press) support the utility of the diagnosis for a variety of clinical and research purposes. BED appears to be a common eating disorder, distinct from bulimia nervosa, which affects a significant segment of the obese population, as well as some individuals of normal weight. Ongoing studies will help to better understand its etiology, pathogenesis, and most effective treatment.

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cisco, CA; Nina L. Dominy, M.S., Risk Factor Clinic, Portland, OR; Emily Fox Kales, Ph.D., Eating Disorders Program, McLean Hospital, Belmont, MA; Timothy D. Brewerton, M.D., Eating Disorders Program, Medical University of South Carolina, Charleston, S.C.; Ronna Saunders, LCSW, Center for Behavioral Change, Richmond, VA; Cathy Nonas, R.D., United Weight Control Corporation, New York, NY; Donald Pugatch, M.D., North Andover, MA; R. Lynn Horne, M.D., University of Nevada School of Medicine, Las Vegas, NV (private patients) and Eating Disorders Program, Lake Mead Hospital, Las Vegas, NV; Michael G. Perri, Ph.D., Weight Loss Program, Department of Clinical and Health Psychology, Health Science Center, University of Florida, Gainesville, FL; Jenny Craig, Inc., (14 sites in Portland, OR, Dallas, TX, and Las Vegas, NV.

Nonpatient community sample: John L. Roglieri, M.D., Director, Employee Health Service, Presbyterian Hospital, New York, NY.

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APPENDIX A

Questions and Decision Rules for Diagnosing Binge Eating Disorder, and Bulimia Nervosa

Questions

1. During the past *six* months, did you often eat within any two hour period what most people would regard as an unusually large amount of food?
   1 Yes 2 No (IF NO: GO TO 5)
2. When you ate this way, did you often feel you couldn't stop eating or control what or how much you were eating?
   1 Yes 2 No (IF NO: GO TO 5)
3. During the past *six* months, on average, how often did you have times when you ate this way—that is, large amounts of food with the feeling that your eating was out of control?

IF HAVING TROUBLE AVERAGING: There may have been some weeks when it was not present. Just average them in.

1 Less than 1 day a week
2 One day a week
3 Two or three days a week
4 Four or five days a week
5 Nearly every day

4. Did you *usually* have any of the following experiences during these occasions?
   a) Eating much more rapidly than usual — Yes — No
   b) Eating until you felt uncomfortably full — Yes — No
   c) Eating large amounts of food when you didn't feel physically hungry — Yes — No
   d) Eating alone because you were embarrassed by how much you were eating — Yes — No
   e) Feeling disgusted with yourself, depressed, or feeling very guilty after overeating — Yes — No
5. In general, during the past *six* months, how upset were you by overeating (eating more than you think is best for you)?
   1 Not at all
   2 Slightly
   3 Moderately
   4 Greatly
   5 Extremely
6. In general, during the past *six* months, how upset were you by the feeling that you couldn't stop eating or control what or how much you were eating?
   1 Not at all
   2 Slightly
   3 Moderately
   4 Greatly
   5 Extremely
7. During the past *six* months, how important has your weight or shape been in how you feel about or evaluate yourself as a person—as compared to other aspects of your life, such as how you do at work, as a parent, or how you get along with other people?
   1 Weight and shape were *not very important*
   2 Weight and shape *played a part* in how you felt about youself
   3 Weight and shape were *among the main things* that affected how you felt about yourself
   4 Weight and shape *was the most important thing* that affected how you felt about yourself
8. During the past *three* months, did you ever make youself vomit in order to avoid gaining weight after binge eating?
   1 Yes 2 No
   IF YES: How often—on average—was that?
   1 Less than once a week
   2 Once a week
   3 Two or three times a week
   4 Four or five times a week
   5 More than five times a week
9. During the past *three* months, did you ever take more than twice the recommended dose of laxatives in order to avoid gaining weight after binge eating?
   1 Yes 2 No
   IF YES: How often—on average—was that?
   1 Less than once a week
   2 Once a week
   3 Two or three times a week

4 Four or five times a week
5 More than five times a week

10. During the past *three* months, did you ever take more than twice the recommended dose of diuretics or water pills to avoid gaining weight after binge eating?
    1 Yes 2 No
    IF YES: How often—on average—was that?
    1 Less than once a week
    2 Once a week
    3 Two or three times a week
    4 Four or five times a week
    5 More than five times a week
11. During the past *three* months, did you ever fast—not eat anything at all for 24 hours—in order to avoid gaining weight after binge eating?
    1 Yes 2 No
    IF YES: How often—on average—was that?
    1 Less than 1 day a week
    2 Once day a week
    3 Two or three days a week
    4 Four or five days a week
    5 Nearly every day
12. During the past three months, did you ever exercise for more than an hour specifically in order to avoid gaining any weight after binge eating?
    1 Yes 2 No
    IF YES: How often—on average—was that?
    1 Less than once a week
    2 Once a week
    3 Two or three times a week
    4 Four or five times a week
    5 More than five times a week
13. During the past *three* months, did you ever take more than twice the recommended dose of a diet pill in order to avoid gaining weight after binge eating?
    1 Yes 2 No
    IF YES: How often—on average—was that?
    1 Less than once a week
    2 Once a week
    3 Two or three times a week
    4 Four or five times a week
    5 More than five times a week

Decision rules for diagnosing BED

Question	Response
#1 and 2	1 (binging)
#3	At least 3 (at least 2 days/week for six months)
#4 a) through e)	At least 3 items marked "Yes" (associated symptoms during binge eating episodes)
#5 or 6	Either item 4 or 5 (marked distress regarding binge eating)
No current Bulimia Nervosa (see below)	

Decision rules for diagnosing Purging Bulimia Nervosa

#1, 2	Same as BED (binging)
#3	At least 3 (at least 2 days/week for six months). Note: This is an approximation of the DSM-IV criterion of 2 episodes/week for three months.
#7	3 or 4 (overevaluation of weight/shape)
#8, 9 or 10	Either item at least 3, 4, or 5 (purging at least 2 episodes/week for three months).

Decision rules for diagnosing Nonpurging Bulimia Nervosa

#1, 2, 3, 7	Same as Purging Bulimia Nervosa
#8, 9, 10	Neither item 3 or more
#11, 12, or 13	Either item at least 3 (nonpurging compensatory behavior at least 2 episodes/week for three months)

REVIEW

Binge Eating Disorder: Current Knowledge and Future Directions

Susan ZelitchYanovski

Abstract

Binge eating disorder (BED) is a newly characterized eating disorder that encompasses individuals who have severe distress and dysfunction due to binge eating, but who do not regularly engage in inappropriate compensatory behaviors. While relatively uncommon in the general community, BED becomes more prevalent with increasing severity of obesity. BED is associated with early onset of obesity, frequent weight cycling, body shape disparagement, and psychiatric disorders. These associations occur independent of the degree of obesity. Although many individuals with BED have good short-term weight loss regardless of treatment modality, as a group they may be prone to greater attrition during weight-loss treatment and more rapid regain of lost weight. Current treatments geared toward binge eating behaviors include antidepressant medications, cognitive behavioral psychotherapy, and interpersonal psychotherapy; however, these treatments have little efficacy in promoting weight loss, and only modest success in long-term reduction of binge eating. As a significant proportion of obese individuals entering weight-loss treatment and research programs are likely to meet criteria for BED, those conducting clinical research should be aware of this distinct subgroup and determine the contribution of BED to outcome measures.
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Introduction

Binge eating disorder (BED) is a newly characterized eating disorder that encompasses individuals who have severe distress due to binge eating, but who do not regularly engage in inappropriate compensatory behaviors, such as purging or fasting. As approximately 30% of patients presented for specialized weight-loss treatment meet criteria for BED, affected individuals are likely to constitute a large proportion of subjects participating in clinical research studies. This review presents currently available data on the diagnosis, epidemiology, clinical characteristics, and treatment of BED, and suggests areas for future research.

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Background

Binge eating is common in the obese. While binge eating was first described by Stunkard (64) as a distinct pattern among the obese in 1959, few studies were devoted to further characterize obese binge eaters for the next two decades. Several reports in the 1980s, using varying definitions of binge eating and its severity, estimated that from 20%-50% of obese individuals seeking treatment had moderate to severe difficulties with binge eating (26,38,46). These individuals were found to have greater levels of psychopathology (43), to be more likely to drop out of weight-loss treatment (45), and to regain lost weight more rapidly (45) than similarly obese non-binge eaters. Some, but not all, studies also found lesser weight losses during behavioral treatment among those with identified difficulties with binge eating (27,34,74). Most evidence from these early studies indicated that there was a distinct subgroup among the obese who had serious difficulties with binge eating. However, the American Psychiatric Association's Diagnostic and Statistical Manual, the DSM-III-R, recognizes only one eating disorder involving binge eating: bulimia nervosa (4). Most individuals with bulimia nervosa are young women of normal weight who purge through the use of vomiting or laxatives. In order to encourage scientific inquiry and develop effective treatments for individuals with severe distress and impair-

ment due to binge eating who do not engage in inappropriate compensatory behaviors, Spitzer and his colleagues spearheaded an effort to characterize a new eating disorder, binge eating disorder (BED) (60,61). BED will be listed in an appendix for further study in the new version of the Diagnostic and Statistical Manual, 4th edition (DSM-IV).

Criteria for Diagnosis of BED

The preliminary criteria for binge eating disorder are listed in Table 1. These criteria were developed in consultation with the American Psychiatric Association's Work Group on Eating Disorders for the DSM-IV. Interviews were conducted with individuals seeking help because of distress about their eating. The primary feature described by these individuals was recurrent, uncontrolled overeating (62).

A self-administered questionnaire, the Questionnaire on Eating and Weight patterns (QEWP), was developed for determining the diagnosis as well as construct validity, and versions of this questionnaire have been used in multisite field trials of BED (59,62). The current version of the questionnaire (QEWP-R), along with decision rules for diagnosing BED, is included in Appendix A.

Table 1: Diagnostic Criteria for Binge Eating Disorder*

A. Recurrent episodes of binge eating. An episode of binge eating is characterized by both of the following:
(1) eating, in a discrete period of time (e.g., within any two hour period), an amount of food that is definitely larger than most people would eat during a similar period of time in similar circumstances
(2) a sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)

B. During most binge episodes, at least three of the following behavioral indicators of loss of control are present:
(1) eating much more rapidly than usual
(2) eating until feeling uncomfortably full
(3) eating large amounts of food when not feeling physically hungry
(4) eating alone because of being embarrassed by how much one is eating
(5) feeling disgusted with oneself, depressed, or feeling very guilty after overeating.

C. The binge eating causes marked distress

D. The binge eating occurs, on average, at least two days a week for a six-month period

E. Does not currently meet the criteria for anorexia nervosa or bulimia nervosa, purging or non-purging type.

*From Spitzer et al. (62)

The definition of binge eating in BED is identical to that which will be used in the diagnosis of bulimia nervosa in the DSM-IV and includes the requirements of both an unusually large amount of food as well as an accompanying feeling of loss of control. The frequency criterion, while arbitrary, was designed to insure a high threshold for labeling individuals with a psychiatric diagnosis. Preliminary studies show that subjects with BED have an average binge frequency of 3-5 days weekly (41). There is some evidence that individuals who binge eat less frequently than twice weekly may have similar characteristics (16,73). Therefore, researchers are encouraged to study varying frequencies of binge eating and how this might impact on outcome measures (61).

Further research is also necessary to better quantify the nature of binges or overeating episodes, both in terms of actual energy intake and in measures of loss of control. In addition, quantifying the number and duration of binge episodes may be difficult when individual episodes are not punctuated by purging. Marcus et al. found that almost 25% of binge episodes in obese binge eaters lasted an entire day (42). The Eating Disorders Examination (EDE) (12) differentiates eating episodes into subjective and objective bulimic episodes. In both types of episodes, the individual perceives loss of control over their eating and believes that he or she has consumed an unusually large amount of food. In an objective episode, the examiner concurs that the amount is definitely more than most people would eat, given the same context (i.e., time of day, hours since last meal), while if this judgment cannot be made with certainty, the episode is labeled as subjective. Additionally, individuals may have overeating episodes, in which there may be large food intake without loss of control. Use of sophisticated instruments may be helpful in more precisely determining the nature and degree of abnormal eating behaviors in this population .

Differentiating BED from bulimia nervosa is also problematic in that some individuals with BED engage in occasional (although not regular) compensatory behaviors (62). Furthermore, some compensatory behaviors such as exercise, caloric restriction, or use of appetite suppressants are not necessarily inappropriate in the obese. Since a diagnosis of bulimia nervosa is an exclusionary criterion for diagnosing BED, this distinction is not trivial. Further refinement of the diagnostic criteria, as well as research into compensatory mechanisms used by obese binge eaters, will help to clarify this issue.

A major disadvantage of developing diagnostic criteria for BED is that such criteria arbitrarily convert a continuous measure (severity of binge eating) into a categorical one (presence or absence of BED). Thus, important information about differing binge frequencies, severity of associated eating-related behaviors and cognitions, and response to treatment may be lost by prematurely rigid categorization. In addition to studying subjects with differing frequencies of binge eating, use of other well-validated methodologies to evaluate binge eating severity and differing patterns of eating behaviors may be very useful in better defining the phenomenology and response to treatment of these individuals.

One instrument which has been in use for a number of years is Gormally's Binge Eating Scale (BES) (26). The BES is a 16-item scale that was designed to determine severity of binge eating using behavioral manifestations as well as affective and cognitive factors related to binge eating. It has been shown to correlate well with clinical determinations of binge eating severity (26). Scores on the BES have also been shown to be correlated with increased energy intake in a laboratory setting (79), and have been successfully used to categorize severity of binge eating in many studies of obese binge eaters (1,39,43,45,76). Another well-validated instrument for assessing eating-related behaviors is the Three Factor Eating Questionnaire (63). This questionnaire measures three factors thought to be related to human eating behaviors: cognitive restraint of eating, which includes behaviors such as calorie counting and consciously limiting food consumption to avoid weight gain; disinhibition, which determines the degree of diminution of self-control caused by affective, cognitive, or pharmacologic factors; and hunger, which measures the extent to which the subject frequently experiences feelings of hunger. Its criterion validity in the measurement of populations with differing eating patterns, including obese binge eaters (39,45), subjects with bulimia nervosa (49,54), and normal-weight restrained eaters (54), has been well-established.

Epidemiology

Most information about the epidemiology of BED comes from two large, multisite field trials (59,62). The QEWP was the instrument used in these studies to determine the prevalence of BED, as well as associated demographic variables and clinical characteristics. Subjects included 1,795 individuals in weight-loss treatment programs, 1,124 individuals in a non-patient community sample (464 adults residing on Staten Island who were contacted via random digit dialing, 660 new employees of a medical center), 849 college students, 230 members of Overeaters Anonymous, and 75 normal-weight women receiving treatment for bulimia nervosa. Both in the first and second phases of the field trial, BED was found to be slightly more common in women than men (3:2) among patients attending weight-loss treatment programs. Similar female to male ratios were found both in the community and college samples, although this difference was not statistically significant due to the small number of subjects with BED. Its prevalence in non-Caucasians (primarily African-Americans) was similar to the prevalence in Caucasians in both the patient and community samples.

BED seems to be relatively uncommon in the community. The field trials found a prevalence of approximately 2.5% in non-patient community samples, with a similar prevalence among college students. Among subjects in the community sample meeting criteria for BED, only about half were obese (BMI >27.5 kg/m^2), indicating that other methods of weight control, such as intermittent caloric restriction, are being used to maintain a normal body weight. In the non-patient community sample, only about 5% of those who were obese met criteria for BED, indicating a low prevalence in obese individuals not seeking weight-loss treatment. Of 491 subjects enrolled in a commercial weight-loss program (Jenny Craig), most of whom were mildly obese (mean BMI 27.8 kg/m^2), 16% met criteria for BED. Most obese individuals in the field trial weight-control samples were enrolled in intensive treatment programs, such as university-affiliated behavioral treatment or very low calorie diet programs. The prevalence of BED in this sample was approximately 30%, remarkably similar to the prevalence reported in the early studies of binge eating. In members of Overeater's Anonymous, a self-help group for "compulsive overeaters," approximately 70% meet criteria for BED. Thus BED, while relatively rare in the community, becomes increasingly prevalent as severity of obesity and complexity of treatment increase.

Obese individuals with BED have an earlier onset of their obesity than those without BED (15.9 vs 19.5 y in the multisite trials), and have a more unstable weight history (38,62). Episodes of weight cycling, defined as losing and regaining more than 10 kg, are significantly more frequent among those with BED (62). Several studies have shown an association between increased severity of obesity and increased prevalence of BED (59,62,68).

The age of onset of BED is not known. Most individuals who are studied are enrolled in weight-control programs and tend to be in their mid- to late 30s, older than those with bulimia nervosa. In the field studies, subjects with BED reported an average onset of dieting at 20.0 y, compared to 24.0 y for those without BED (62). Onset of binge eating was reported by subjects who met criteria for BED at an average age of 20.7 y.

Among those who did not meet criteria but reported some binge eating, average age of onset was 22.5 y (Robert Spitzer, personal communication, 1992). However, this information is retrospective. The course of the disorder, including when binge eating becomes frequent and severe enough to meet diagnostic criteria for BED, remains to be determined.

Etiology

Dietary Restraint

While there is a strong association between strict dieting and binge eating in normal-weight women with bulimia nervosa (56), the evidence is by no means as clear in obese individuals with BED. In the multisite field trials, 49% of all individuals with BED reported that their binge eating started prior to weight-loss dieting, while only 37% reported dieting before binge eating. The remainder believed that the two started at about the same time (62). Other studies confirm that binge eating more frequently precedes dieting than vice versa (73). The retrospective nature of these findings limits their validity, and prospective studies are needed to resolve the question. Of interest, binge eating without purging has also been described in obese adolescent girls, very few of whom reported previous dieting (8).

While dietary restraint has long been postulated to lead to binge eating (30) and is undoubtedly a contributing factor in some obese individuals with BED, the nature and extent of this contribution remains in question. Cognitive restraint (as measured by the restraint subscale of the Three-Factor Eating Questionnaire) (63) is actually the same or *lower* in obese binge eaters than in non-binge eaters, while the hunger and disinhibition scales are higher (39,45,81). This is in contrast to women with bulimia nervosa, who score high on all three subscales (54). Disinhibition, or loss of control following cognitive, emotional, or pharmacological stimuli, does appear to be prevalent in a significant proportion of obese binge eaters.

Among obese clinic attendees, severe binge eating has been found to be predictive of a significant counter-regulatory response to a preload (47), supporting the hypothesis that a history of dieting/overeating may create a vulnerability to a greater degree of disinhibited eating. However, dieting and restraint are not necessarily synonymous, and current dieters may respond differently from non-dieters, independent of degree of restraint (40). Current weight (40) and presentation for weight-loss treatment (47) may also impact on response to dietary preloads. Some aspects of dietary restraint (such as portion control and calorie counting) may be helpful in moderating food intake (39).

In addition, the independent role of weight loss (rather than restrained eating *per se*) in the etiology of binge eating has not been adequately evaluated. The further characterization of dietary restraint and dieting behaviors and their interaction with binge eating is a fruitful area for research. One study (81), evaluating the effects of weight loss dieting on binge eating severity in subjects with and without BED, found that both frequency and severity of binge eating actually improved after weight-loss treatment among subjects with BED, and were unchanged in subjects without BED, despite increases in dietary restraint among both groups. Thus, the common contention that weight loss dieting in the obese leads to increases in binge eating frequency and severity remains unproven.

Dysphoric moods

Affective disorders are much more prevalent in obese subjects with BED than in those not meeting criteria for this disorder (43,80). Again, prospective studies are not available, and it is unknown if depression represents a cause or a consequence of BED, or if it is an unrelated factor. Many individuals with BED note that dysphoric moods, such as sadness, anger, or boredom precede a binge episode (37), and such moods may trigger disinhibition in susceptible individuals. Negative moods may act as potent stimuli for binge eating, even in the absence of a restrictive eating pattern (5). Negative affect, particularly guilt, is almost universal following binge eating among non-purging obese binge eaters (5). In those with bulimia nervosa, the act of purging may relieve the guilt and negative mood resulting from the binge episode (11).

Obsessive-compulsive disorder

Many patients with BED view themselves as "compulsive overeaters," and obsessive-compulsive disorder (OCD) is associated with both anorexia nervosa and bulimia nervosa (55). Central arginine vasopressin, which in animal studies significantly delays extinction of behaviors learned during aversive conditioning (57), has been found to be elevated in patients with OCD (3), anorexia nervosa (23), and bulimia nervosa (13), but there are no data available in patients with BED. Thus far, neither those with BED (43,80) nor the obese in general (29) have been found to have an elevated prevalence of obsessive compulsive disorder or obsessive-compulsive personality disorder.

Addiction

Some researchers, clinicians, and patients, view binge eating as an addictive behavior, similar to drug or alcohol addiction. Foods, particularly carbohydrates, are seen in this view as acting as mood-altering drugs, via elevation of the central neurotransmitter serotonin (77). Unfortunately, many of these studies are con-

founded by the palatable nature of foods containing both carbohydrate and fat. Women, in particular, prefer fat/sweet combinations (as opposed to fat/protein combinations) (18). There is little scientific evidence for "carbohydrate craving" during binge eating, and indeed, fats as opposed to carbohydrates appear to be preferentially consumed during binge episodes (79).

Similarities to other addictions have been noted. Perceived abstinence violations represent a distinct pathway to binge eating (5). Borderline personality disorder, which is often associated with impulsivity and substance abuse, has been reported in one study to be much more prevalent in obese individuals with BED than in those without BED (14% vs 1%) (80). An increased prevalence of personal alcohol abuse (33,62) and drug abuse (62) has been reported in obese binge eaters. Additionally, obese binge eaters appear to have an increased prevalence of familial alcohol and drug abuse compared with non-binge eaters (33,80). However, Wilson, Nonas, & Rosenblum (73) recently assessed 31 obese binge eaters and 139 obese non-binge eaters using a self-report version of the Eating Disorders Examination. They found no evidence of a general addictive tendency among obese binge eaters, who did not report greater lack of control over use of alcohol, nicotine, or gambling than obese non-binge eaters.

Sexual abuse

Sexual abuse has been postulated as etiologic for severe obesity (9,19), with some researchers hypothesizing a particular association with "compulsive overeating" (24). Preliminary studies have not supported an association between BED and sexual abuse, with prevalence of sexual abuse in obese subjects with BED similar to that reported in the general population (62,80). One study did find a significantly increased prevalence of "victimization," defined as a positive response to screening questions regarding physical abuse, sexual abuse, or other upsetting sexual experience, in obese binge eaters (33). It may be that certain types of sexual abuse, such as childhood incest, are causal in a minority of patients (71). Pope (51) has recently reviewed the difficulties with many studies indicating a high prevalence of sexual abuse in patients with eating disorders, and it appears that only well-designed epidemiological studies will resolve the issue.

Pathophysiology and Psychopathology of BED

Physiologic Evaluation

There is no evidence that individuals with BED are predisposed any more or less to the medical consequences of obesity than those without the disorder (76). However, since the prevalence of BED is increased with more severe obesity, patients with BED represent a population at risk for the medical complications of obesity. Few studies investigating physiologic differences between obese individuals with and without BED have been done, and results must be viewed as preliminary. O'Neil et al. (50) found no differences between obese patients with and without BED in fasting blood glucose or lipid profile after adjustments were made for differences in BMI. Yanovski et al. (82) found no differences in cortisol suppression after a 1 mg overnight dexamethasone suppression test between obese patients with and without BED either before or after an average 17 kg weight loss, despite a greater prevalence of depression in those with BED before weight loss.

Gastric capacity, as measured by filling an intragastric balloon, has previously been found to be increased in normal-weight bulimic women as compared with normal-weight controls (22). Geliebter et al. postulated that binge eating might enlarge gastric capacity, diminishing satiety signals and leading, through positive feedback, to ever increasing binge size. Recently, Geliebter et al. (21) measured gastric capacity in a similar manner in 9 obese women and found values intermediate between normal-weight controls and normal-weight women with bulimia nervosa. However, when they subdivided the obese women into binge and non-binge eaters, the obese binge eaters had gastric capacities similar to normal-weight bulimics, while the obese non-binge eaters had gastric capacities similar to normal-weight controls (data presented at NAASO meeting, Atlanta, GA, September 4, 1992). This may lead to the increased levels of hunger reported by these individuals. It would be interesting to measure both gastric emptying (slower in normal-weight bulimics than in normal controls (22)) and cholecystokinin (CCK) in response to meals in obese individuals with BED both before and after weight loss in order to determine the contribution of altered satiety signals to continued binge eating.

Ingestive Behaviors, Energy Expenditure, and Nutrient Partitioning

Two studies have evaluated food intake in a laboratory setting in subjects with BED as compared with obese controls. Both studies found that individuals with BED consumed significantly more energy than obese controls when asked to binge on a variety of palatable foods (25,79). Subjects with BED also ate significantly more than obese controls even when asked to eat normally, consuming more than 16 740 kJ (> 4000 kcal) at one meal (79). During the meal at which subjects were instructed to binge eat, subjects with BED, but not obese controls, consumed a significantly greater percentage of energy as fat and less as protein than in the normal meal (79). In that study, energy intake was found to be significantly correlated with scores on the Beck Depression

Inventory (7), suggesting a relationship between dysphoria and increased food consumption.

In a study evaluating food consumption through 7-day diet diary and 24-hour recall in obese binge eaters, Rossiter et al. found an average binge frequency of 4-5 days weekly, with average binge-size of 2520 kJ (602 kcal), (range 100-25 300 kJ (25 to 6048 kcal) (53). Protein and fiber consumption were decreased on binge days, and energy intake was significantly greater on binge days (9860 vs 6360 kJ [2357 vs 1528 kcal]). While this study is valuable in pointing out the wide range of foods and energy intake in what subjects subjectively consider a "binge," it is limited by both lack of a control group of obese non-binge eaters and the known inaccuracy of food records in estimation of energy intake, particularly in the obese (6,52). The average caloric intake reported by their subjects (70 kJ/kg [16.5 kcal/kg] on non-binge days and 110 kJ/kg [26.8 kcal/kg] on binge days) is inconsistent with the maintenance of their obese state, suggesting an effect of record keeping on eating behaviors or reporting, if energy expenditure is assumed to be similar to obese non-binge eaters. While it is possible that alternation of binge eating and restriction could affect energy expenditure, as has been reported both in abstinent patients with bulimia nervosa using indirect calorimetry (2,20), and weight-stable normal-weight restrained eaters using doubly labeled water (69), a preliminary report has found no difference in resting metabolic rate, as measured by indirect calorimetry, between obese women with and without BED, when adjustments were made for differences in lean body mass (50). Further studies of energy expenditure, particularly through the use of a metabolic chamber or doubly-labeled water, would be helpful in determining whether differences exist in energy expenditure between obese binge and non-binge eaters.

Yanovski & Sebring (81) studied the recorded food intake of 17 obese women with and 16 obese women without BED for 7-day periods before and after an average 22 kg weight loss. In contrast to the findings of Rossiter et al. (53), they found no evidence of alternating binge eating and severe caloric restriction among subjects with BED. While subjects with BED reported an increased frequency of binge days and larger energy intake during individual binge episodes than those without the disorder, they also reported ingesting significantly more energy during non-binge days. In fact, prior to weight loss, subjects *with* BED reported consuming more energy on *non-binge* days (11 280 kJ, 110 kJ/kg [2695 kcal, 25.3 kcal/kg]) than was reported by subjects *without* BED on *binge* days (9570 kJ, 90 kJ/kg [2287 kcal, 22.1 kcal/kg]). When predicted energy expenditure was calculated, subjects with BED reported ingesting 95% of their predicted energy expenditure before weight loss, vs only 64% for non-binge eaters. After weight loss, there was no difference between groups in reported energy intake or in percent of predicted energy expenditure reported as intake. These findings suggest that, before weight loss, individuals with BED may be more accurate in reporting their food intake, or less restrained by keeping food records, than obese non-binge eaters.

Individuals with BED also report an increased frequency of weight cycling, and while the evidence thus far does not support adverse effects of weight cycling on body composition or body fat distribution (75), systematic prospective evaluation of body composition before and after weight loss in this population is warranted.

Psychopathology

Increased psychiatric comorbidity has consistently been associated with BED. Distress and dysfunction have been reported in areas directly related to eating and obesity, as well as more globally. Subjects with BED have been shown to have more concern about shape and weight (62), and have more body shape disparagement (10) than those without the disorder.

McCann et al. (49) compared levels of psychiatric comorbidity in "non-purging bulimics" (mean BMI 30.2 kg/m^2) vs normal-weight women with bulimia nervosa. Those with purging bulimia nervosa were found to have elevated prevalence of current major depression, panic disorder, compulsive and narcissistic personality disorders compared with obese non-purging binge eaters, while non-purging bulimics had an increased prevalence of past substance abuse. Spitzer et al. (62) found that psychiatric symptoms, as measured by the Derogatis Brief Symptom Inventory (14) were higher in those with BED than in obese non-binge eaters, but lower than in normal-weight women with bulimia nervosa. Kirkley et al. (35) found that obese binge eaters had elevated scores on the MMPI on 10/13 scales compared to obese non-binge eaters, but showed less psychopathology than normal-weight women with bulimia nervosa. Thus, obese individuals with BED appear to have a degree of psychopathology that is somewhat less than those with bulimia nervosa, but greater than obese non-binge eaters.

Marcus et al. (43) studied 25 obese binge eaters and found rates of depression that were higher than in obese non-binge eaters, while Spitzer et al. (62) found that self-reported histories of depression, alcohol abuse, drug abuse, and psychotherapy were significantly more prevalent in subjects with BED. Yanovski et al. (80) administered structured diagnostic interviews to 128 obese men and women (BMI >30 kg/m^2) who were not currently in weight-loss treatment. They found an increased lifetime prevalence of major depression, dys-

thymia, panic disorder, bulimia nervosa, borderline personality disorder, and avoidant personality disorder in subjects with BED compared with those without the disorder. Among obese subjects without BED, the prevalence of both Axis I (major mental disorders) and Axis II (personality disorders) diagnoses was similar to that in the general population, even among the severely obese (mean BMI 45.1 kg/m^2). Spitzer et al. also found an association between BED and psychiatric symptoms that is independent of degree of obesity (62). Thus, the determination of the presence of BED has important implications for both design and analysis of studies evaluating psychopathology in the obese.

Treatment

Response to Weight-Loss Treatment

Table 2 shows results of clinical studies comparing weight-loss treatment results of obese binge and non-binge eaters conducted over the previous 10 years. The majority of these studies were prospective; however, they used differing definitions of binge eating as well as differing treatment modalities, making direct comparisons difficult.

Behavioral treatment of obesity

While there have been many reports of poor response to conventional behavioral therapy in those with severe binge eating (17,38,74), few studies have directly compared treatment outcomes between obese binge and non-binge eaters. Keefe et al. (34) retrospectively studied 38 females and 6 males who had completed a behavioral weight-loss treatment program. Twenty-three of the subjects met most or all DSM-III criteria for bulimia (which did not require compensatory purging). They found that identified binge eaters had poorer weight loss both at the end of treatment and at the six-month follow-up (although both groups lost additional weight in the six-months following treatment).

Marcus et al. (45) adapted standard behavioral weight-loss treatment to incorporate cognitive behavioral techniques that addressed eating and weight-related behaviors thought to be associated with binge eating. Binge and non-binge eaters were then randomly assigned to either standard or modified behavioral treatment. They found a group effect, in that binge eaters had significantly higher drop-out rates than non-binge eaters and regained their lost weight significantly faster. However, there was no differential treatment effect, suggesting that the modified behavioral treatment did not significantly impact on weight loss.

Very Low Calorie Diet Programs

The response of obese binge and non-binge eaters to very low calorie diet programs has also been evaluated in several studies. Yanovski et al. (78) studied 38 obese women, 21 of whom met preliminary DSM-IV criteria for BED, and 17 of whom clearly did not meet those criteria. Subjects underwent a 3350 kJ/day (800 kcal/day) diet for 12 weeks, followed by refeeding and caloric stabilization. While there was no overall difference in mean weight loss at the end of treatment, women with BED lost significantly less weight than women without BED during the middle third of treatment, encompassing the latter half of the modified fast and first half of refeeding, suggesting that this may be a time of particular vulnerability for individuals with BED. Similar percentages of women with and without BED were able to adhere absolutely to both the modified fast and prescribed food and formula regimen during refeeding. Among those who lapsed during the fast, however, BED (+) subjects consumed significantly more energy than BED (-) subjects. BED (+) subjects also reported more days with large (>4180 kJ [>1000 kcal) excess energy intakes during refeeding. Mean weight regain did not differ significantly between groups during the 12-month follow-up; however, subjects with BED were at increased risk for early major regain. Five of twenty binge eaters (vs 0/17 non-binge eaters) had regained over half of their lost weight by the 3-month follow up. Differential attrition was also observed during post treatment follow up. By 12 months post treatment, 76% of subjects with BED were available for follow-up, while 100% of non-binge eaters returned for follow-up evaluation. Poor outcome one year after treatment, defined as attrition from treatment, refusal to follow-up for reasons related to treatment failure, or regain of all lost weight was observed in 35% of subjects with BED, and in none of the subjects without BED (p=0.02). Thus, while mean weight loss and regain did not differ between groups, a significant number of subjects with BED had lesser weight loss, larger lapses in adherence, and faster regain of lost weight than similarly obese non-binge eaters. Binge eaters were also more likely to be lost to follow-up, which further decreases the probability of detecting differences between groups.

Wadden et al. (70) divided 235 obese women participating in a VLCD program into three groups: Binge eaters (12%), who met DSM-III-R criteria for bulimia nervosa with the exception of purging; episodic overeaters (11%), who reported binge eating episodes at least twice per week but without loss of control; and non-binge eaters, who did not meet the above criteria. They then followed their subjects through a 26-week very low calorie diet program similar to that described in the above study. They found no significant difference in either weight loss during the program or follow-up weight at one year, although the small number of

subjects available at follow-up may have not provided adequate power to detect differences. Episodic overeaters were significantly more likely to drop out of treatment during weeks 20-26, the time immediately following refeeding. This study emphasizes the need to investigate individuals who may eat objectively large amounts of food without associated loss of control, as they may also be at risk for attrition from treatment.

La Porte (36) examined the responses of obese binge and non-binge eaters (based on scores on the binge eating scale) to 10 weeks on a very low calorie diet program. He noted no significant differences in weight loss, adherence to diet, or drop-out rate, although there was a trend towards higher drop-out rate among binge eaters (32% vs. 17%). He also noted higher pre-treatment and within treatment levels of anxiety and depression among binge eaters. No follow-up of this group was reported.

Preliminary results from one study found no difference in 3-year follow up weight regain between 14 binge and 9 non-binge eaters who participated in a very low calorie diet program, with both groups maintaining approximately 43% of their initial weight loss (11.0 *S.D.* 10.3 kg, binge eaters; 12.9 *S.D.* 9.7 kg, non-binge eaters) (32) . However, interim weights and additional weight-loss treatment were not reported, and the large standard deviation for regain in both groups suggests that the extent to which individuals may have regained weight was quite variable.

Pharmacotherapy

Marcus et al. (44) conducted a double-blind placebo controlled study of fluoxetine combined with behavioral treatment. They found that fluoxetine caused more weight loss than placebo alone, but that there were no significant differences in weight loss or other outcome measures between binge and non-binge eaters. There was a non-significant trend, however, toward lesser weight losses among binge eaters in the fluoxetine group as compared to non-binge eaters by the end of treatment (3.9 vs 11.5 kg, p= 0.11, M. Marcus, personal communication, 1992).

Response to Eating Disorders Treatment

Because of the concerns that obese binge eaters may respond less well than non-binge eaters to standard weight-loss treatments, several studies have focused on therapies geared toward the eating disorder, rather than toward weight loss per se. Most of the techniques employed have been developed for use in patients with bulimia nervosa. The most common modalities used include cognitive-behavioral psychotherapy, interpersonal psychotherapy, and pharmacotherapy, usually with antidepressant medications.

Preliminary studies have indicated antidepressant medications may be more effective than placebo in reducing binge eating frequency among obese binge eaters, although not all studies have observed a significant difference (1,48). Both cognitive-behavioral psychotherapy (58,67,72) and interpersonal psychotherapy (72) have been shown to have some efficacy in reducing the frequency of binge eating in obese patients. A comparison of the two treatments found similar decreases in binge eating with either treatment, with the average number of binge eating episodes significantly lower than at baseline for up to one year post-treatment (72). Unfortunately, relapse is common after treatment is discontinued, and long-term follow-up is limited. Less than half of patients in that study were entirely abstinent from binge eating by 16 weeks post treatment (72). Additionally, significant weight losses have not been observed with either cognitive behavioral or interpersonal therapies geared toward binge eating in the obese, in the absence of specific strategies for weight loss (72). Ongoing studies are addressing the effectiveness of combined therapies and more intensive and protracted treatment. However, these early results indicate that currently available treatments for BED have only modest success in resolving binge eating behaviors, and minimal success in achieving significant weight loss.

Response to combined eating disorders and weight loss treatment

One published study has evaluated combined weight loss and eating disorders treatment in obese binge eaters. De Zwaan et al. (16) studied 64 women, 35% of whom reported recurrent binge eating of moderate to severe intensity. They conducted a double-blind placebo controlled study of cognitive behavioral psychotherapy vs dietary management and the antidepressant medication fluvoxamine vs placebo. No effect of treatment type on any outcome variable was found, with the exception of decreased post-treatment depression rating in binge eaters on fluvoxamine. While there were no significant differences between groups (binge vs non-binge eaters) in weight loss, there was a slightly higher drop-out rate among binge eaters, and a nonsignificant trend toward greater regains of lost weight at one year follow-up (4.63 vs 1.55 kg, p=0.1).

Implications for Obesity Research

The majority of studies support the contention that individuals with BED represent a distinct subgroup of the obese. Such individuals tend to have earlier onset of their obesity, spend more of their time on weight-loss diets, are more concerned with their shape and weight, and have more psychopathology than non-binge eaters, regardless of severity of obesity. Because severely

Table 2: Response of Obese Binge and Non-Binge Eaters to Weight Loss Treatment

Author	Treatment, weeks (diet/program)	Type of Criteria	Pre-Rx Wt (kg)		Number (F/M)		Drop outs during program		Weight loss kg (% total body weight)		Follow-up kg regained, (% of lost wt regained)		Number in follow-up/number started	
			BE	NBE	BE	NBE	BE	NBE	BE	NBE	BE	NBE	BE	NBE
Yanovski et al. 1993 (78)	VLCD + BT 12/26	BED [1], BES[2]	114.3	104.5	21F	17F	2 (10%)	0 (0)	19.6 (18%)	21.3 (21%)	3 months[3] 3.7(19%) 12 months[3] 8.5 (42%)	3 months 2.5 (13%) 12 months 10.4 (51%)	3 months 20/21; 12 months 16/21	3 months (17/17) 12 months 17/17
LaPorte, 1992 (36)	VLCD + BT 10/10	BES	108.1	109.0	19F 6M	15F 9M	5F 3M (32%)	1F 3M (17%)	18.7 (17%)	20.2 (19%)	N/A	N/A	N/A	N/A
Wadden et al., 1992 (70)	VLCD + BT 12/26	Binge eaters (BE) episodic overeaters (EO)[4]	BE: 97.8 EO: 99.0	101.6	BE: 29F EO: 26F	180F	BE: 14 (47%) EO[5] 15 (58%)	68 (37%)	BE: 21.5 (22%) EO: 19.4 (20%)	21.7 (21%)	Not Reported[6]	Not Reported	12 months 7/29 BE 6/26 EO	12 months 73/180
de Zwaan et al., 1992 (16)	CBT vs. DM ± fluvoxamine [7]	Self-report + clinical interview [8]	35.8[9] kg/m2	36.7 kg/m2	22F	44F	7 (32%)	9 (21%)	6.1	5.6	12 months 4.6 kg (76%)	12 months 1.6kg (28%)	N/A	N/A
Marcus et al., 1990[10] (44)	BT ± fluoxetine 52/52	DSM-III[11]	110.1	94.8	20F 2M	22F 2M	13 (59%)	11 (48%)	Fluox.3.9 (4%) Placebo +0.25 kg (0%)	Fluox: 11.5 (12%); Placebo +0.27 (0%)	3-6 months Fluox[12] +6.6 (>100%) Placebo +0.73 (>100%)	3-6 months Fluox[12] +4.4 (38%) Placebo -1.4 (>100% addnl. loss)	3-6 months 7/22	3-6 months 8/23
Marcus et al., 1988 (45)	BT[13] 10/10	DSM-III	84.2	81.2	35F	33F	9[14] (26%)	3 (9%)	4.7 (5%)	5.2 (6%)	6 months 2.8kg (60%),[15] 12 mo. 3 kg (65%)	6 months 0.5kg (10%) 12 mo 2.6 kg (50%)	6 month 26/35 12 month 26/35	6 month 30/33; 12 month 30/33
Keefe et al., 1984 (34)	BT 9/9	DSM-III	94.4	86	23 ?M/F	21 ?M/F	16		1.9[17] (2%)	4.4 (5%)	6 months -1.1kg (60% addnl loss)	6 months -1.1kg (30% addnl loss)	N/A	N/A

BE=binge eater, NBE=non-binge eater, VLCD=very low calorie diet, BT=behavioral therapy, CBT=cognitive behavioral therapy, DM=dietary management. [1]BED=preliminary DSM-IV criteria for binge eating disorder (Table 1) as assessed by the QEWP (Appendix A) [2]BES=binge eating scale (26) [3]Regain calculated for the 16/21 BED (+) subjects completing all follow-up visits. [4]BE defined by DSM-III-R criteria for bulimia nervosa with omission of purging, episodic overeaters defined by frequent episodes of overeating without subjective loss of control [5]EO were significantly more likely to drop out of treatment following refeeding than BE and NBE, $p<0.003$. [6]Overall weight regain was 8.8 kg at one year; however, separate figures were not reported for BE, EO, and NBE. [7]This was a double-blind placebo controlled study evaluating effectiveness of cognitive-behavioral therapy (CBT) vs. standard dietary management without behavior therapy (DM) and fluvoxamine vs placebo. No differences in wt-loss outcome measures were found as a function of treatment type [8]Self-report of moderate to severe binge eating on questionnaire +/- criteria for bulimia nervosa without fulfilling purging or frequency criteria. [9]Weight in kg not reported. BMI given [10]Some of these data are previously unpublished (M. Marcus, personal communication, December, 1992). [11]DSM III criteria for bulimia do not require compensatory purging. [12]Refers to group which was on active drug during the study. All medications were stopped at study endpoint. [13]BT was modified or standard. No differences on outcome measured were seen as a results of treatment type (modified vs standard therapy.) [14]Binge eaters vs non-binge eaters, $p<0.07$ [15]Binge eaters vs non-binge eaters, $p=0.02$ [16]Study was retrospective. Only completers interviewed, therefore drop-out and follow-up rate cannot be calculated. [17]$p<0.05$, binge eaters vs non-binge eaters.

obese individuals are more likely to have BED, and because their distress is likely to lead them to seek treatment, patients with BED most likely make up a disproportionate number of those in specialized obesity treatment programs. Unrecognized differences between subjects with and without BED in physiologic or psychological parameters, response to treatment, or long-term outcome could confound results, making valid interpretation difficult. For example, the great variability in prevalence of psychopathology among the obese reported in numerous studies can be explained, in large part, by the high prevalence of psychopathology in subjects with BED (65,80).

While the acute response to weight-loss treatment has not been significantly different in all studies, many have shown a trend toward lesser weight losses and faster regain among binge eaters. Formal metaanalysis of the published data could not be done due to significant differences in case definitions, type and length of treatment, and absence of standard deviations or standard errors in all studies. However, in every case, the trend is toward higher drop-out rate in subjects with BED or episodic overeating (Table 2). In addition, subjects with BED may be less likely to return for follow-up, further skewing treatment results.

Many obese individuals with BED appear to do well over the short term regardless of treatment. However, subsets (e.g., those with concomitant depression) may be particularly at risk for poor outcomes. Thus, even among subjects with BED, attempts should be made to determine which characteristics differentiate "responders" from "non-responders" in those undergoing various treatments. Further studies evaluating not only mean weight losses, but also non-parametric measures (such as failing to meet predetermined criteria for successful outcome), would be valuable in further characterizing individual differences in response to treatment.

Unlike anorexia nervosa (31) and bulimia nervosa (28), BED appears to be prevalent among the obese in both men and racial minorities. Racial and ethnic as well as sex differences may have an impact on response to treatment, even among patients with BED. Few studies of BED have included men and racial minorities, despite the serious medical complications of obesity in these groups, and special efforts should be made to study these groups in the future.

Weight maintenance, while a problem for obese individuals as a group, may be particularly problematic for individuals with BED. Longer-term follow up (which may need to be aggressive in this population) is urgently needed. Given the history of weight cycling in this population, frequent follow-up contacts (i.e., every three months) to track weight changes and involvement in treatment programs may be particularly desirable and give a more accurate picture than less frequent follow-up measurements.

As patients with BED seem to be particularly vulnerable to psychological impairment, studies of these individuals should also monitor long-term effects of weight loss and/or regain on psychological functioning. In particular, the long-term results of treatment on depression, body shape disparagement, and dietary restraint should be determined.

Individuals with severe obesity are a group of particular interest. Those undergoing surgical treatment for obesity may be quite likely to have BED, but this is currently unknown. Sugarman describes "sweet addicts" (66) who can outwit their gastric stapling procedures and may respond preferentially to gastric bypass. Evaluation of such patients for BED might be helpful in determining which surgical candidates might benefit from a given procedure.

Finally, obesity researchers should work in concert with their colleagues who treat eating disorders in designing clinical trials that will address both the patients' eating disorder as well as their obesity. Treatments that focus solely on one aspect of this complex problem at the expense of others are unlikely to be satisfying to either patient or clinician. The ultimate goal of matching treatments to the individual requires that we better characterize our obese patients into clinically useful subgroups. The recognition of BED offers one such opportunity to advance obesity research.

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Appendix A
QUESTIONNAIRE ON EATING AND WEIGHT PATTERNS—REVISED (QEWP-R)[1,2,3]

Last name_____ **First name**_____ **M.I.**____

Date_____ **I.D. Number** _____

Thank you for completing this questionnaire. Please circle the appropriate number or response, or write in information where asked. You may skip any question you do not understand or do not wish to answer.

1. Age ___ ___ years

2. Sex: 1 Male 2 Female

3. What is you ethnic/racial background?

1 Black (not Hispanic)
2 Hispanic
3 White (not Hispanic)
4 Asian
5 Other (please specify)
_____

4. How far did you get in school?

1 Grammar school, junior high school or less
2 Some high school
3 High school graduate or equivalency (GED)
4 Some college or associate degree
5 Completed college

5. How tall are you?

____ feet ___ ___ in

6. How much do you weigh now?

_____ lbs

7. What has been your highest weight ever (when not pregnant)?

_____ lbs

8. Have you ever been overweight by at least 10 lbs as a child or 15 lbs as an adult (when not pregnant)?

1 Yes 2 No or not sure

IF YES: How old were you when you were first overweight (at least 10 lbs as a child or 15 lbs as an adult?) If you are not sure, what is your best guess?

____ ___ years

9. How many times (approximately) have you lost 20 lbs or more — when you weren't sick — and then gained it back?

1 Never
2 Once or twice
3 Three or four times
4 Five times or more

10. During the past **six** months, did you often eat within any two-hour period what most people would regard as an unusually large amount of food?

1 Yes 2 No

IF NO: SKIP TO QUESTION 15

11. During the times when you ate this way, did you often feel you couldn't stop eating or control what or how much you were eating?

1 Yes 2 No

IF NO: SKIP TO QUESTION 15

12. During the past **six** months, how often, on average, did you have times when you ate this way — that is, large amounts of food **plus** the feeling that your eating was out of control? (There may have been some weeks when it was not present — just average those in).

1 Less than one day a week
2 One day a week
3 Two or three days a week
4 Four or five days a week
5 Nearly every day

13. Did you **usually** have any of the following experiences during these occasions?

a Eating much more rapidly than usual? Yes No

b Eating until you felt uncomfortably full? Yes No

c Eating large amounts of food when you didn't feel physically hungry? Yes No

d Eating alone because you were embarrassed by how much you were eating? Yes No

e Feeling disgusted with yourself, depressed, or feeling very guilty after overeating? Yes No

14. Think about a typical time when you ate this way —that is, large amounts of food **plus** the feeling that your eating was out of control.

a What time of day did the episode start?

1 Morning (8 AM to 12 Noon)
2 Early afternoon (12 Noon to 4 PM)
3 Late afternoon (4 PM to 7 PM)
4 Evening (7 PM-10 PM)
5 Night (After 10 PM)

b Approximately how long did this episode of eating last, from the time you started to eat to when you stopped and didn't eat again for at least two hours

____ hours ____ minutes

c As best you can remember, please list everything you might have eaten or drunk during that episode. If you ate for more than two hours, describe the foods eaten and liquids drunk during the two hours that you ate the most. Be specific—include brand names where possible and amounts as best you can estimate. (For example: 7 ounces Ruffles potato chips; 1 cup Breyer's chocolate ice cream with 2 teaspoons hot fudge; 2 8-ounce glasses of Coca-cola, 1 1/2 ham and cheese sandwiches with mustard).

d At the time this episode started, how long had it been since you had previously finished eating a meal or snack?

____ hours ____ minutes

15. In general, during the past **six** months, how upset were you by overeating (eating more than you think is best for you)?

1 Not at all
2 Slightly
3 Moderately
4 Greatly
5 Extremely

16. In general, during the past **six** months, how upset were you by the feeling that you couldn't stop eating or control what or how much you were eating?

1 Not at all
2 Slightly
3 Moderately
4 Greatly
5 Extremely

17. During the past **six** months, how important has your weight or shape been in how you feel about or evaluate yourself as a person— as compared to other aspects of your life, such as how you do at work, as a parent, or how you get along with other people?

1 Weight and shape were **not very important**
2 Weight and shape **played a part** in how you felt about yourself
3 Weight and shape **were among the main things** that affected how you felt about yourself
4 Weight and shape **were the most important things** that affected how you felt about yourself.

18. During the past **three** months, did you ever make yourself vomit in order to avoid gaining weight after binge eating?

1 Yes 2 No

IF YES: How often, **on average**, was that?

1 Less than once a week
2 Once a week
3 Two or three times a week
4 Four or five times a week
5 More than five times a week

19. During the past **three** months, did you ever take more than twice the recommended dose of laxatives in order to avoid gaining weight after binge eating?

1 Yes 2 No

IF YES: How often, **on average**, was that?

1 Less than once a week
2 Once a week
3 Two or three times a week
4 Four or five times a week
5 More than five times a week

20. During the past **three** months, did you ever take more than twice the recommended dose of diuretics (water pills) in order to avoid gaining weight after binge eating?

1 Yes 2 No

IF YES: How often, **on average**, was that?

1 Less than once a week
2 Once a week
3 Two or three times a week
4 Four or five times a week
5 More than five times a week

21. During the past **three** months, did you ever fast — not eat anything at all for at least 24 hours — in order to avoid gaining weight after binge eating?

1 Yes 2 No

IF YES: How often, **on average**, was that?

1 Less than one day a week
2 One day a week
3 Two or three days a week
4 Four or five days a week
5 Nearly every day

22. During the past **three** months, did you ever exercise for more than an hour **specifically** in order to avoid gaining weight after binge eating?

1 Yes 2 No

IF YES: How often **on average**, was that?

1 Less than once a week
2 Once a week
3 Two or three times a week
4 Four or five times a week
5 More than five times a week

23. During the past **three** months, did you even-take more than twice the recommended dose of a diet pill in order to avoid gaining weight after binge eating?

1 Yes 2 No

IF YES: How often **on average**, was that?

1 Less than once a week
2 Once a week
3 Two or three times a week
4 Four or five times a week
5 More than five times a week

24. During the past **six** months, did you go to any meetings of an organized weight control program? (e.g.Weight Watchers, Optifast, Nutrisystem) or a self-help group (e.g., TOPS, Overeaters Anonymous)?

1 Yes 2 No

IF YES: Name of program_____

25. Since you have been an adult—18 years old—how much of the time have you been on a diet, been trying to follow a diet, or in some way been limiting how much you were eating in order to lose weight or keep from regaining weight you had lost? Would you say...?

1 None or hardly any of the time
2 About a quarter of the time
3 About half of the time
4 About three-quarters of the time
5 Nearly all of the time

26. SKIP THIS QUESTION IF YOU NEVER LOST AT LEAST 10 LBS BY DIETING:
How old were you the first time you lost at least 10 lbs by dieting, or in some way limiting how much you ate? If you are not sure, what is your best guess?

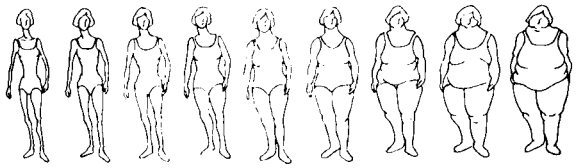
___ ___ years

27. SKIP THIS QUESTION IF YOU'VE NEVER HAD EPISODES OF EATING UNUSUALLY LARGE AMOUNTS OF FOOD ALONG WITH THE SENSE OF LOSS OF CONTROL: How old were you when you first had times when you ate large amounts of food and felt that your eating was out of control? If you are not sure, what is your best guess?

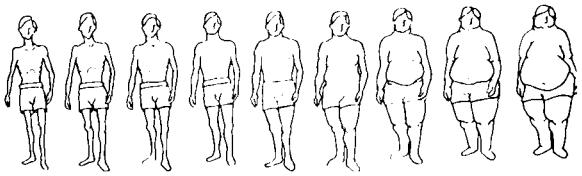
___ ___ years

28. Please take a look at these silhouettes. Put a circle around the silhouettes that most resemble the body build of your natural father and mother **at their heaviest.** If you have no knowledge of your biological father and/or mother, don't circle anything for that parent.

YOUR MOTHER



YOUR FATHER



DECISION RULES FOR DIAGNOSING BINGE EATING DISORDER USING THE QUESTIONNAIRE ON EATING AND WEIGHT PATTERNS, Revised[1,2,3]

(FOR EXAMINER'S USE ONLY)

DIAGNOSIS OF BED

QUESTION NUMBER	RESPONSE
10 **AND** 11	1 (BINGE EATING)
12	3, 4, OR 5 (AT LEAST 2 DAYS PER WEEK FOR SIX MONTHS)
13 a through e	3 OR MORE ITEMS MARKED "YES" (AT LEAST 3 ASSOCIATED SYMPTOMS DURING BINGE EATING EPISODES)
15 **OR** 16	4 0R 5 (MARKED DISTRESS REGARDING BINGE EATING)

DIAGNOSIS OF BED REQUIRES ALL OF THE ABOVE ALONG WITH THE ABSENCE OF PURGING OR NON-PURGING BULIMIA NERVOSA, AS DEFINED BELOW.

DIAGNOSIS OF PURGING BULIMIA NERVOSA

10 **AND** 11	1 (SAME AS BED)
12	3,4, OR 5 (AT LEAST 2 DAYS PER WEEK FOR SIX MONTHS) Note: This is an approximation of the DSM-IV criterion of at least 2 episodes/week for three months).
17	3 OR 4 (OVEREVALUATION OF WEIGHT/SHAPE)
18, 19, **OR** 20	**ANY** RESPONSE 3,4, OR 5 (PURGING AT LEAST 2 TIMES PER WEEK FOR THREE MONTHS)

DIAGNOSIS OF NON-PURGING BULIMIA NERVOSA	
10,11,12,17	SAME AS PURGING BULIMIA NERVOSA
18, 19, **AND** 20	**NO** RESPONSE 3, 4, OR 5 (NO FREQUENT COMPENSATORY PURGING)
21,22, **OR** 23	**ANY** RESPONSE 3, 4, OR 5 (COMPENSATORY NON-PURGING BEHAVIOR AT LEAST TWO TIMES PER WEEK FOR 3 MONTHS)

QUESTION FOR RESEARCH PURPOSES ONLY (NOT TO BE USED FOR DIAGNOSIS OF BED OR BULIMIA NERVOSA, PURGING OR NON-PURGING TYPE)	
14 a through d	EXAMINER'S JUDGMENT THAT AMOUNT OF FOOD DESCRIBED IS UNUSUALLY LARGE GIVEN CIRCUMSTANCES (I.E., TIME OF DAY, HOURS SINCE PREVIOUS MEAL) YES___ NO____ UNSURE_____

[1]Robert L. Spitzer, Susan Z. Yanovski, Marsha D. Marcus.

[2]The following individuals contributed to the development of previous versions of the QEWP:Stewart Agras, Michael Devlin, Deborah Hasin, James Mitchell, Cathy Nonas, Albert Stunkard, Thomas Wadden, B. Timothy Walsh, Rena Wing.

[3]Silhouettes from: Stunkard AJ, Sorensen T, Schulsinger F. Use of the Danish Adoption Register for the Study of Obesity and Thinness. In: Kety SS, Roland LP, Sidman RL, Matthysse S.W., eds. The Genetics of Neurological and Psychiatric Disorders. New York: Raven Press; 1983:119. Used by permission.

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Binge Eating Disorder: Recognition, Diagnosis, and Treatment

Timothy D. Brewerton, MD

A new diagnostic classification within the eating disorders group called "binge eating disorder" (BED) has been proposed in the DSM-IV. BED identifies a group of patients who regularly engage in binge eating without the regular use of compensatory purging. These patients appear to manifest a primary disturbance in eating behavior, although in some cases the binge eating may be a secondary symptom of depression and/or anxiety. The recurrent and chronic binge eating associated with BED clearly predisposes patients to the morbidity and mortality associated with obesity. Like bulimia nervosa, BED is associated with significant but generally less severe psychiatric comorbidity, including affective, anxiety, and personality disorders. The diagnosis, history, epidemiology, psychiatric comorbidity, and treatment of this proposed disorder are reviewed in this article.

Binge eating disorder (BED) has been proposed as a diagnostic entity and is now listed in the appendix of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).[1-6] BED is defined by recurrent episodes of binge eating at least 2 days a week for at least 6 months. In addition, there is a subjective sense of a loss of control over binge eating, which is indicated by the presence of 3 of 5 specific criteria. These include eating rapidly, eating when not physically hungry, eating when alone, eating until uncomfortably full, and feeling self-disgust about bingeing.

Albert Stunkard[7,8] first described binge eating in a subset of obese patients and coined the term "night eating syndrome" (NES), which is similar to but distinct from BED. The newer, evolved concept of BED does not have the nocturnal component as a requirement. In NES, binge eating occurs nocturnally and is followed by morning anorexia and food restriction, which is thought to contribute to the next cycle of overeating. Other unofficial but related terms have appeared in the literature to describe individuals with binge eating not complicated by purging, such as "obese binge eaters" or "compulsive overeaters."[9-11] Kornhaber[12] described the "stuffing syndrome" in 1970. Since the publication of the DSM-III in 1980, these individuals have been officially, yet nonspecifically, classified as having an "eating disorder not otherwise specified (EDNOS).[13]

The first acknowledgment of binge eating in American psychiatry's diagnostic classification system occurred in the DSM-III; designated "bulimia," it encompassed not only bingeing but purging and preoccupation with body shape and weight as well. The revised edition of the DSM-III (DSM-III-R), published in 1987, adopted the term "bulimia nervosa,"[14] which was coined by Gerald Russell in 1979. Russell conceptualized this syndrome as "an ominous variant of anorexia nervosa."[15] Binge eating per se, without counteractive weight-reducing behaviors, was not identified as a major psychiatric disorder or problem until the recent inclusion of BED in the DSM-IV appendix.[1]

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As our knowledge base about psychiatric disorders in general has increased over the years, our diagnostic classification system has evolved to describe them more accurately. Within this overall process, the eating disorders have only recently received serious research interest. The inclusion of nonpurging binge eating as an illness is a natural extension of this evolving process. Like bulimia first, and then bulimia nervosa, the diagnostic classification of BED will allow this group of patients to be further studied from a clinical research perspective and also to receive more accessible and appropriate treatment. In my view, BED depicts a serious psychologic problem that has been heretofore underrecognized and undertreated. However, the exact boundaries of BED remain to be further clarified, and it is likely that the criteria will continue to evolve as our knowledge base increases.

One of the major controversies regarding the diagnosis of BED includes its differentiation from nonpurging bulimia nervosa as currently defined in DSM-IV.[16] Nonpurging bulimia nervosa involves fasting and excessive exercise as compensatory behaviors, as well as preoccupation with body shape and weight.[1] However, the similarities between these 2 conditions appear to outweigh their relatively minor behavioral differences. In clinical practice, these disorders tend not to be distinct entities but exist on a continuum. Patients also go in and out of the criteria over time. It is very difficult clinically to distinguish between what are appropriate weight loss measures to combat obesity versus the excessive amount of counteractive exercise that characterizes nonpurging bulimia nervosa. In addition, both obese bingers[17,18] and BED patients have been reported to have similar attitudes about body weight and shape, as compared with both nonpurging[19] and purging bulimia nervosa patients.[20] Regardless of the appellation, it is clear from epidemiologic studies that a meaningful number of patients have clinically significant binge eating and related psychopathology, not complicated by purging, that warrants treatment.

In the laboratory, BED patients have been shown to eat significantly more calories during a binge meal than non-BED obese patients.[21,22] (Simple obesity is defined as a BMI>=30). Dietary restraint and/or disinhibition appear to play major roles in triggering binge episodes.[23-25]

As discussed above, the occurrence of binge eating in a subset of obese individuals has been noted by clinical investigators for some time. As a logical outgrowth of this work, the prevalence rate of BED was first reported in cohorts of obese patients attending weight loss clinics or programs.[3-5] In these samples, 20% to 46% of subjects were reported to meet BED criteria using self-report measures.[3,5,10,11] However, it is important to observe that patients tend to overestimate the presence of binge eating on self-report questionnaires, as opposed to the prevalence rates gained from structured interviews using standardized criteria, such as the Questionnaire of Eating and Weight Patterns.[8,26,27] Spitzer and colleagues[3] reported that the prevalence of BED in weight control samples as assessed by questionnaire was approximately 30%, with the rate being slightly higher in females than males. In 2 field studies of nonpatient community samples,[3] these authors reported BED prevalences of 3.3% and 4.6%, with the rates being comparable in females and males (5.3% vs 3.1%). In a college student sample,[3]

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the rate was 2.6%, and there was no significant difference in the rates between females and males, a striking difference between BED and bulimia nervosa patients. The validity of BED was supported by associations with impaired work and social functioning, overconcern with body shape and weight, general psychopathology, and amount of time on diets. No significant racial differences were found in BED prevalence rates in these studies.

A study of a representative sample of 3006 adult women in the US was carried out by our group using a structured telephone interview based on DSM-III-R and proposed DSM-IV criteria.[28-30] Target households were identified by random digit dialing and were taken from four stratified regions of the US. We found that 1.0% of adult women met lifetime BED criteria, with about two thirds of these women meeting current criteria (6- and 12-month prevalence). BED respondents were distinct from another 2.4% of women who met lifetime criteria for bulimia nervosa. Surprisingly, there were no significant differences in age, weight, or race between respondents with BED and respondents with bulimia nervosa, although both groups were significantly younger and heavier than non-eating-disordered respondents. Because these results were obtained from a carefully, controlled representative sample of US women, they confirm that a substantial number of American adult women have clinically significant problems with binge eating not complicated by purging. When the binge duration criteria were relaxed from 6 to 3 months, the rate of BED increased from 1.0% to 1.6%.[28]

In a community study from California using a structured telephone interview, 1.8% of 455 adult women met DSM-IV BED criteria.[31] Another 3.8% of women met all but the frequency criteria for BED.

In a questionnaire-based community study from Norway involving 1849 adult women, the lifetime prevalence of BED was 3.2%.[32] And a similar study from France[33] based on a self-report questionnaire found a 9% to 15% BED rate in weight control samples and a 0.7% rate in a community sample of 447 women who were not patients. Although these studies have major methodologic differences, the results suggest that the prevalence of BED, like that of bulimia nervosa, may vary by culture and country.

The medical comorbidity associated with BED is essentially the same as that associated with obesity, including increased morbidity and mortality from cardiovascular disease, hyperlipidemia, adult-onset diabetes mellitus, and certain cancers, such as endometrial and breast cancers. This risk increases linearly as weight or body mass index (BMI; weight divided by height squared, or kg/m^2) increases. Because of the increasingly recognized overlap between obesity and psychiatric disorders,[34] and society's continued stigmatization of both the obese and the mentally ill, psychiatric input is going to be increasingly required for the optimal treatment of these patients. This relationship is further complicated by the fact that many psychotropic medications, as well as some nonpsychotropic drugs, are associated with weight gain and other possible medical complications. Obese patients with BED have been reported to have greater degrees of eating and weight-related pathology, as well as body image distortion and preoccupation, when compared with non-BED obese patients.[11,35,36]

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Obese patients with BED who attend weight loss clinics have been reported to have a harder time remaining in weight loss programs and losing weight.[10,37] However, in one controlled study comparing BED obese and non-BED obese patients, the presence of BED did not affect weight-loss outcome or dropout rate.[38] In a community study, Ferguson and Spitzer[39] reported that unsuccessful dieters were more likely to meet BED criteria than successful dieters. No differences in resting metabolic rate, thyroid hormone levels, or serum lipid levels between obese bingers and obese nonbingers has been reported.[40,41] Obese bingers were reported to have a higher degree of weight cycling in one study,[42] but not in another.[41]

The relationship between BED and other psychiatric comorbidity has been of major clinical and research interest. A number of investigators have reported that a subset of obese patients engage in overeating or bingeing in response to emotional stress, so-called "emotional eating."[43,44] BED patients have a greater tendency to overeat in response to negative mood states than other patients.[19] Systematic studies of obese patients meeting BED criteria indicate higher-than-expected rates of affective, anxiety, and personality disorders, in addition to emotional problems in general.[40,42,44-49] In one study of 107 obese women with BED, a significant positive relationship was found between severity of binge eating and degree of psychiatric symptomatology, as measured by several psychometric instruments (Binge Eating Scale [BES] SCL-90, Beck Depression Inventory, Inventory of Interpersonal Problems, Rosenberg Self-Esteem Scale).[44] DeZwaan and colleagues[42] also found an association between binge eating and a number of measures of psychopathology (HAM-A, HAM-D, Three-Factor Questionnaire, Binge Eating Scale, Eating Disorder Inventory, Beck Depression Inventory, New York State Self-Esteem Scale.)

In the National Women's Study, Dansky and colleagues[28] found that the lifetime prevalence of major depression was 31% in BED respondents and 36% in bulimia nervosa respondents. Both of these rates were significantly higher than the 15% rate of major depression in the nonbingeing comparative group. It is notable that major depression was not present in the majority of respondents, given that some BED opponents argue that binge eating is merely a symptom, albeit atypical, of depression, but these results do not support this assertion in most people with BED. A recent study of 30 BED patients vs. 30 non-BED patients confirms the finding that dysphoric emotional states often trigger binge eating episodes and a sense of loss of control.[50] However, these patients are not necessarily clinically depressed at the time of bingeing. In one study of the chronological relationship between the times of onset of bingeing, dieting, and depression, it was found that BED subjects tended to begin bingeing during adolescence and prior to the onset of depression, dieting, or obesity.[51] Nevertheless, the higher rates of depression and anxiety associated with BED support an affect-regulation hypothesis for binge eating.

Dansky and associates[28] also found that the lifetime prevalence of posttraumatic stress disorder (PTSD) was 21% in BED respondents compared with 9% in nonbingeing respondents. Unlike bulimia nervosa, rates of criminal-victimization experiences (including rape, molestation, attempted sexual assault, and aggravated assault) were

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comparable to the non-BED/non-bulimia nervosa group. However, given the higher rate of lifetime PTSD, the subjects with BED may have been exposed more often to other types of traumatic experiences or stressors than were subjects without BED. In a clinical sample, Yanovski and coworkers[47] also failed to find a difference in reported rates of sexual abuse in BED versus non-BED obese subjects. However, BED patients did have significantly higher rates of panic disorder and personality disorder in this study.

Clinical experience dictates that BED patients often report histories of significant family dysfunction, if not overt childhood physical and emotional abuse and/or neglect. Hodges and colleagues[52] studied the perceived family environments of 131 eating disorder patients presenting for evaluation and treatment, including 43 patients with BED.[52] Scores on the Family Environment Scale (FES) indicated less cohesion in the families of BED patients compared with the families of anorexia nervosa, but not bulimia nervosa, patients. In addition, lower scores were found on the activity-recreation subscales for the BED group compared with all other eating disorder subtypes (anorexia nervosa, bulimia nervosa, and anorexia nervosa plus bulimia nervosa). The BED group also had higher conflict and control subscale scores and lower cohesiveness, expressiveness, independence, intellectual-cultural, and activity-recreation subscale scores compared with 2 normal control samples.

Higher rates of impulsive behaviors, such as kleptomania and compulsive buying, have been reported in patients with BED.[53] Likewise, higher rates of cluster B and C personality disorders have been reported in patients with BED.[46,34] Although rates of substance abuse disorders were not significantly higher in obese BED patients compared with obese non-BED patients, the rate of alcoholism in family members of BED patients was significantly higher.[47] Given these relationships, patients with BED have been hypothesized to fall within the continuum of compulsive-impulsive disorders[53] and affective spectrum disorders.[54]

Behavioral treatments for obesity have been shown to work repeatedly, but only in the short term for the vast majority of patients.[37] Patients with BED appear to be more resistant to these commonly employed strategies and are more likely to relapse in the long-term, even if initially successful. In fact, it may be that dietary restraint (ie, dieting) has a disinhibiting effect on "binge eating," thereby contributing to the marked weight fluctuations that these patients often manifest. In addition, emotional issues and psychiatric comorbidity are not typically addressed in purely behavioral forms of treatment. These patients may have a variety of needs that are best approached from the standpoint of a biopsychosocial model. Therefore, a multidisciplinary approach is often required, including working with the patient's internist or family practitioner, dietitian, psychotherapist, and physical therapist. A common philosophy of treatment is to put the goal of weight loss on the "back-burner" initially. Decreasing binge eating by normalizing eating behavior and addressing associated emotional symptoms and/or psychiatric disorders must take precedence for successful treatment to occur.

Guided by the successes in the treatment of bulimia nervosa,[55,56] depression, and anxiety disorders, recent studies using sophisticated, manual-driven, cognitive-behavioral therapy

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(CBT) have shown promise in the treatment of BED. This form of psychotherapy pays particular attention to the patient's behavior and thinking rather than the underlying feelings or psychodynamics. There have been only a few controlled trials of CBT in BED so far. In a 10-week study of CBT versus waiting-list controls in 44 women with nonpurging bulimia, Telch and colleagues[57] found a 94% decrease in the frequency of binge eating episodes, while the waiting-list controls showed a decrease of only 9%. Seventy-nine percent of the CBT group became completely abstinent from bingeing.

In a similar study comparing 10 weeks of group CBT versus group interpersonal psychotherapy (IPP) versus waiting-list controls in 46 nonpurging bulimic patients, Wilfrey and associates[58] found that the number of binge days per week decreased by 48% during group CBT, 71% during group IPP, and 10% during the wait-list period. However, Agras and coworkers[59] reported that IPP offered no added benefit to BED patients unresponsive to CBT. In a study of obese binge eaters, Smith and others[60] reported an 81% decrease in the frequency of binge eating episodes following 16 weeks of CBT, but there was no control group in this study.

Given the available data, treatment should initially focus on the reduction of binge eating per se as well as on eating regular meals with little or no snacking, particularly before bedtime. In addition, treatment should identify and challenge cognitive distortions. If binge eating and the associated lack of restraint and disinhibition are successfully controlled, then some degree of weight loss may become an automatic secondary effect. Patients may have more energy to embark on a mild-to-moderate exercise regimen and may also be generally less depressed and anxious. However, in patients unresponsive to behavioral and/or psychotherapeutic treatments, psychopharmacologic approaches should be considered.

Because of its strong links to affective illness and other disorders linked to serotonin dysregulation,[61] clinical investigators have hypothesized that the selective serotonin reuptake inhibitors (SSRIs) would be a good treatment for both obesity and BED (Table I). A double-blind placebo-controlled study (N=45) of fluoxetine in the treatment of obesity showed an early weight loss response, but this effect completely disappeared by the end of 1 year on the drug.[62] In another study of fluoxetine in 45 obese patients (with and without binge eating), Marcus and colleagues[63] reported that patients who received fluoxetine plus behavior modification therapy lost significantly more weight than those on placebo and behavior modification.[63] This difference between fluoxetine and placebo persisted regardless of the presence of binge eating; however, the sample sizes of these subsets were too small for definitive conclusions regarding the similarities and differences between bingeing and nonbingeing obese patients.

Preliminary open-label studies of fluvoxamine and paroxetine in BED patients have indicated significant reductions in binge frequency.[54] More controlled studies of BED with new-generation antidepressants are clearly needed, but this class of drugs holds promise. In particular, sertraline, venlafaxine, and nefazodone are also likely to significantly impact binge eating favorably given their serotonin reuptake inhibition.

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Tricyclic antidepressants. Some data exist regarding the possible role of tricyclic antidepressants (TCAs) in the treatment of BED. In a 12-week study of 23 women with nonpurging bulimia, McCann and Agras[64] reported that desipramine reduced binge eating by 63% compared with a 6% increase reported with placebo. In another study of 33 bingeing obese patients and 22 patients with bulimia nervosa, Alger and associates[65] reported no significant difference in binge frequency following treatment with imipramine or naltrexone versus placebo. However, imipramine significantly reduced binge duration in bingeing obese patients. Tricyclic antidepressants, especially desipramine, may therefore play a role in the treatment of BED, as they do in bulimia nervosa. However, in clinical practice, it is generally recommended that the first-line psychopharmacologic treatment strategy involve an SSRI.[54]

TCAs are often associated with weight gain, probably resulting from a combination of hyperphagia induction via stimulation of noradrenergic pathways in the hypothalamus and a decrease in metabolic rate. The use of MAOIs is of questionable value in a population that loses control over eating and thus would have difficulty maintaining the necessary food restrictions. However, MAOIs could be a consideration in clear-cut cases of atypical depression that are unresponsive to SSRIs, venlafaxine, nefazodone, desipramine, and/or dexfenfluramine.

There has been more recent interest in dexfenfluramine (dextrorotatory fenfluramine) since its US release in 1996 for the treatment of obesity. In a large double-blind placebo-controlled study in 4 European countries, dexfenfluramine has been shown to significantly reduce weight loss by an average of 10% over the course of 1 year.[66] This amount of weight loss, although modest, is known to significantly reduce medical comorbidity in obese patients (eg, improving hypertension, hyperlipidemia, and glycemic control). Notably, depression, headache, asthenia, and diarrhea were the major reasons given by subjects for study discontinuation. Dexfenfluramine appears to have little or no potential for abuse, given that animal studies indicate no hedonic-reinforcing properties (similar to saline).

Studies of d,l-fenfluramine (racemic fenfluramine) have shown that acute administration significantly reduces binge eating in bulimic subjects.[67] Drug trials in patients with bulimia nervosa have been equivocal, but suggest a possible beneficial effect of fenfluramine in certain cases.[68,69] Its use must be weighed carefully against the rare life-threatening adverse effect of primary pulmonary hypertension, which is estimated to occur in 23 to 46 cases per million annually, compared with 1 to 2 cases per million annually in the general population.[70] The use of dexfenfluramine is also limited by the manufacturer's relative contraindication for concomitant SSRI use. Concomitant use of SSRIs and dexfenfluramine runs the risk of inducing the serotonin syndrome, which is characterized by mental status change (delirium, hypomania), hypertonus, myoclonus, restlessness, tremor, diaphoresis, shivering, and hyperreflexia. But even more importantly, an SSRI or TCA is likely to inhibit the uptake of dexfenfluramine into the presynaptic neuron, which is required for its therapeutic action, thereby negating its effect on serotonin release. There have been reports of adverse effect from racemic fenfluramine withdrawal (eg, depression), so this agent and dexfenfluramine should be

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tapered slowly, never abruptly, when discontinued.[71,72]

Results from a recently published double-blind controlled study of dexfenfluramine in BED patients indicates a significant 3 times reduction in binge eating as compared with that for placebo.[73] After controlling for the effects of baseline weight and depression scores, the magnitude of dexfenfluramine's effect over placebo was increased. However, it is important to note that binge eating frequency returned to pretreatment levels after the drug was discontinued, much like the weight gain that usually occurs upon discontinuation of all anorexiants. Although related, it may be that the pharmacologic mechanisms underlying reduction in binge eating are significantly different from those underlying weight reduction.

There are no published reports on the use of psychostimulants in the treatment of BED. Even though acutely administered stimulants suppress binge eating,[74] the risks of addiction and the possible induction of affective and psychotic symptomatology make this agent class undesirable as a therapeutic tool.

The opiate antagonists show some possible therapeutic potential in the pharmacologic treatment of BED. In an acute challenge study, Marrazzi and colleagues[75] studied naltrexone in double-blind placebo-controlled fashion in 1 BED subject and found that naltrexone significantly reduced binge frequency and urges to binge. However, this finding contrasts with the study by Alger and associates[65] in which naltrexone was no different from placebo in obese bingers (but naltrexone did reduce bingeing in bulimic subjects). The opiate antagonist naloxone has also been reported to significantly reduce binge eating in BED patients.[76] Naloxone significantly suppressed energy intake relative to saline in binge eaters but not in nonbinge eaters, and butorphanol had no significant effect on food intake.[76] These studies may be relevant to the finding that obese BED subjects have significantly higher pain detection thresholds compared with non-BED obese patients and normal controls.[77]

In the only study so far that assessed the combination of psychotherapy with medication, the addition of desipramine did not increase the anti-binge eating effect of CBT. However, weight loss was facilitated by the combination.

BED is a well-validated diagnostic entity proposed in DSM-IV that is characterized by recurrent binge eating without purging of any kind. It is distinguished from bulimia nervosa, nonpurging type, by the absence of fasting or excessive exercise as a way of "undoing" the weight-promoting effects of bingeing. However, in the clinical setting, these conditions overlap considerably, and it is difficult to distinguish them from each other. BED occurs in approximately 1% of women in the US and in a sizable proportion of those seeking weight loss in bariatric programs. It is important that the diagnosis is not based on self-report alone but also on clinical interview. BED carries specific comorbidities, especially obesity, major depression, and anxiety disorders (particularly panic disorder and PTSD). Treatment approaches show promise in both the psychotherapeutic and psychopharmacologic realms. It is prudent to start with CBT and to aggressively treat associated psychiatric comorbidity, perhaps with an SSRI initially. If

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this fails, a trial of desipramine, dexfenfluramine, nefazodone, venlafaxine, naltrexone or naloxone is a consideration. As in other psychiatric and medical disorders, the benefits versus the risks (of both treatment and nontreatment) must be weighed carefully.

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Anorectics on Trial: A Half Century of Federal Regulation of Prescription Appetite Suppressants

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Beginning with the passage of the Federal Food, Drug, and Cosmetic Act in 1938 and escalating with the 1962 Kefauver-Harris amendments, increasing pressure has been placed on pharmaceutical manufacturers to demonstrate that a drug's benefits outweigh its risks. Nowhere has the question of risk versus benefit come under greater scrutiny than with anorectics. After the approval in the 1940s and 1950s of a number of amphetamine and amphetamine-like compounds for the treatment of obesity, the U.S. Food and Drug Administration struggled to define the efficacy and safety of these agents. Labeling restrictions on duration of use and warnings about abuse and addiction ultimately contributed to the reduced use of anorectics. That trend continued until the mid-1990s, when the off-label use of fenfluramine plus phentermine (fen-phen) and the approval of dexfenfluramine gave rise to widespread, long-term use of anorectics to treat obesity. The adverse effects that came to be associated with fenfluramine and dexfenfluramine, leading to their eventual withdrawal from the market, gave pause to regulators, physicians, patients, and drug companies alike. Sibutramine, the latest anorectic to enter the market, is now the focus of a landmark trial that is examining, for the first time, whether drug-induced weight loss reduces the risk for fatal and nonfatal cardiovascular disease.

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The regulation of drugs in the United States began in earnest in 1938 when Congress passed the Federal Food, Drug, and Cosmetic Act (1). Under this law, manufacturers had to provide the Food and Drug Administration (FDA) with evidence of a drug's safety before it was allowed on the market. In 1962, Congress amended the 1938 act to give the FDA the authority to require that drug companies provide evidence of a drug's efficacy in addition to its safety (2). From these events evolved the linchpin question of drug regulation: Do the drug's benefits outweigh the risks?

Nowhere has the question of risk versus benefit come under greater scrutiny than with drugs used to treat obesity. To understand why this is so, this article examines, from a regulatory perspective, the first 50 years of interactions among the FDA, the drug industry, and academic researchers as they began to negotiate the balance of safety and efficacy of appetite-suppressing drugs used to treat obesity.

The First FDA-Approved Obesity Drugs

In November 1943, Abbott Laboratories of Abbott Park, Illinois, submitted a New Drug Application (NDA) for desoxyephedrine (Desoxyn) to the FDA's Drug Division. The company was seeking approval of their amphetamine for the treatment of narcolepsy, mild depression, postencephalitic Parkinson syndrome, chronic alcoholism, cerebral arteriosclerosis, and hay fever (3). The data submitted to support the drug's approval included review articles from academia, case reports from clinicians, and a 3-page testimonial from a patient with narcolepsy. Desoxyn was approved for all the proposed indications in December 1943 (4).

One year later, the director of the FDA's Drug Division authorized the approval of Hydrin (Endo Products, Garden City, New York), another desoxyephedrine compound. The indications for use of Hydrin were similar to those for Desoxyn, with 1 notable exception: Hydrin was approved as an adjunct in the treatment of obesity. No sooner, however, had the FDA approved Hydrin for obesity than those involved questioned the wisdom of their action. "The use of desoxyephedrine in [obesity] is wholly irrational and exposes the patient unnecessarily to a potent drug," read a January 1946 letter from the new acting medical director of the FDA's Drug Division to the manufacturer of Hydrin (5).

What caused the FDA's abrupt turn of opinion regarding the use of Hydrin to treat obesity is unclear. The most likely explanation is that the FDA's acting medical director also served as a consultant to the American Medical Association's (AMA) Council on Pharmacy and Chemistry—a highly influential group whose opinions on the therapeutic value of drugs shaped clinical practice. In its 1946 edition of *New and Nonofficial Remedies*, the Council "went on record as disapproving general recognition of claims for the use of amphetamine in the treatment of obesity" (6).

The FDA clearly mandated that companies seeking to secure an obesity indication for a desoxyephedrine compound would have to submit evidence of the drug's safety when specifically used to treat obesity under the direction of a physician. Good fortune for the companies soon came in the form of an article titled "The Obese Patient," which reported that 110 obese patients treated with 2 mg of desoxyephedrine 3 times daily lost up to 24.5 kg without apparent elevations in blood pressure or evidence of addic-

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tion (7). These data, along with the AMA Council's tepid endorsement of amphetamines for the management of obesity, led the FDA to approve Desoxyn and Hydrin "as adjuncts to the dietary management of obesity" in 1947 (8, 9).

In an attempt to develop drugs that would retain the anorectic effect of amphetamines without their stimulatory properties or the potential for addiction, industry chemists tinkered with the parent amphetamine molecule and synthesized 5 compounds known as the amphetamine *congeners* (**Table**). Applications for all of these drugs were submitted to the FDA soon after desoxyephedrine's approval, and all sought a single indication: the treatment of obesity. Reviewers from the FDA found no evidence that the amphetamine congeners were unsafe (particularly in comparison with the amphetamines), and by 1960 all 5 drugs were approved as adjuncts in the management of obesity.

Table. **U.S. Food and Drug Administration–Approved Anorectics, 1947–1997**

Generic Name	Trade Name	Year Approved
Desoxyephedrine*	Hydrin,† Desoxyn‡	1947
Phenmetrazine*	Preludin§	1956
Diethylpropion*	Tenuate‖	1959
Phentermine*	Ionamin¶	1959
Phendimetrazine*	Bontril,** Plegine††	1959
Benzphetamine*	Didrex‡‡	1960
Fenfluramine	Pondimin§§	1973
Mazindol	Sanorex‖‖	1973
Chlorphentermine	Presate¶¶	1973
Dexfenfluramine	Redux***	1996
Sibutramine	Meridia‡	1997

* Approved before passage of Kefauver-Harris amendments.
† Endo Products, Garden City, New York.
‡ Abbott Laboratories, Abbott Park, Illinois.
§ Ciba-Geigy Corp., Ardsley, New York.
‖ Merrell National Drug, Cincinnati, Ohio.
¶ Strasenburgh Laboratories, Rochester, New York.
** Carnick Laboratories, Summit, New Jersey.
†† Ayerst Laboratories, Rouses Point, New York.
‡‡ Upjohn, Kalamazoo, Michigan.
§§ Robins Co., Richmond, Virginia.
‖‖ Sandoz Pharmaceuticals, East Hanover, New Jersey.
¶¶ Warner Chilcott, Morris Plains, New Jersey.
*** Wyeth Ayerst, Philadelphia, Pennsylvania.

The Kefauver-Harris Amendments and the Drug Efficacy Study

In 1962, Congress passed the Kefauver-Harris amendments to the Food, Drug, and Cosmetic Act (2). This legislation mandated, among other things, that new drug applications contain substantial evidence of a drug's efficacy from "adequate and well-controlled investigations." While this law had immediate implications for new drugs, compounds approved between 1938 and 1962 were not covered by this legislation. The commissioner of the FDA therefore made the decision to retroactively apply the standard of "substantial evidence of effectiveness" to drugs approved before 1962. To assist in this ambitious endeavor, which became known as the Drug Efficacy Study, the FDA called on the National Research Council of the National Academy of Sciences (10). In 1966, 27 panels of academics began their reviews of the available data on the efficacy of nearly 3000 drug preparations. To account for the evolving definition of substantial evidence of efficacy and for the variation in the quantity and quality of the available data, the advisory panels categorized drugs as "effective," "effective but" (drugs for which there was evidence of efficacy but more efficacious or safer drugs were available), "probably effective," "possibly effective," "ineffective," or "ineffective as a fixed combination" (11).

The task of assessing the weight-loss efficacy of the amphetamines and the amphetamine congeners fell to the Psychiatric Drug Panel. After 3 years of review, the Panel concluded that as treatments for obesity, the amphetamines were "possibly effective" and the amphetamine congeners were "effective but" (12, 13). Reasons given for considering these drugs less than effective included the short duration of the studies and the lack of evidence showing that the drugs altered the natural history of obesity.

The FDA considered the Psychiatric Drug Panel's findings and ultimately agreed that the available data did not support an "effective" classification for the amphetamines or the amphetamine congeners. Thus, in 1970, all manufacturers of the anorectics were given 6 months (later extended to 12 months) to obtain and submit substantial evidence of their drug's effectiveness from adequate and well-controlled clinical studies. Absent definitive efficacy data, the FDA threatened to revoke the obesity indications or to remove the drugs from the market (14).

As the companies began studies to demonstrate their drugs' efficacy, the FDA began its search for criteria to define this yet-to-be-demonstrated efficacy.

The FDA's Struggle To Define the Efficacy of Weight-Loss Drugs

For guidance on how to define the efficacy of the anorectics, the FDA turned first to Thaddeus E. Prout, an endocrinologist and associate professor of medicine at Johns Hopkins University (15). Regulators met with Prout, 8 other academics, and the medical director from Abbott Laboratories to discuss the development of the anorectics in general and the definition of their efficacy in particular (16). Prout's working group reached many conclusions, the most influential of which was a recommendation that the efficacy of the anorectics be defined as statistical superiority of drug versus placebo. In other words, as long as the average weight lost by patients taking the drug was greater than the average amount lost by those taking placebo and the difference was statistically significant (that is, $P < 0.05$), the drug should be considered effective. Prout's group declined (or was unable) to define clinically significant weight loss.

Still seeking to determine how much weight must be lost to reap clinical benefit, the FDA next turned to one of

its advisory committees for help. Instead of offering an answer to this question, however, the committee dodged the issue by referring to Prout's recommendation that efficacy be defined as statistical superiority of drug to placebo (17).

Why would no one define clinically significant weight loss? Perhaps the prevailing mindset and available evidence didn't lend themselves to the task. By the early 1970s, much data existed to link obesity with excess mortality (18), type 2 diabetes (19), elevated serum cholesterol levels (20), and hypertension (21). Many years would still need to pass, however, before large end point trials (such as the Lipid Research Clinics) would provide the medical community with evidence that drugs, through their effects on biomarkers such as serum cholesterol or blood pressure, could substantially alter the clinical course of a chronic disease (22). Without the availability of such data, how would one even begin to define clinically significant weight loss? Nonetheless, concluding that an obesity drug was effective if it caused statistically significantly more weight loss than placebo would have been attractive to drug regulators for 2 reasons: It was objective, and it left no room for argument.

The Amphetamine Anorectic Drug Project and the Balance of Benefits versus Risks

In June of 1972, the FDA publicly discussed the results of their Amphetamine Anorectic Drug Project—a crude meta-analysis of weight-loss data from more than 10 000 patients who had participated in 200 weight-loss studies involving all of the major amphetamine and amphetamine congeners. Among these drugs was fenfluramine, which had been under regulatory review since 1967 (23). The studies, which had been conducted in response to the FDA's 1970 request for "substantial evidence" of the anorectics' efficacy, ranged in duration from 3 weeks to 6 months, although few patients were exposed to a drug for more than 12 weeks.

The meta-analysis indicated that obese patients treated with active drug lost "a fraction of a pound more a week" than those treated with placebo, a "trivial" yet statistically significant difference (24). The results from the Amphetamine Anorectic Drug Project led the FDA to officially declare that the amphetamines and the amphetamine congeners were effective for the treatment of obesity (25, 26).

Yet efficacy was only half of the story. After passage of the Kefauver-Harris amendments in 1962, drug regulation was governed by evaluations of benefit versus risk. For more than a decade, the major perceived risk for the anorectics, as emphasized in a series of high-profile congressional hearings, was addiction (27). Although the amphetamines clearly posed a risk for addiction, the addictive potential of the amphetamine congeners was not as well studied and remained open to debate. Nevertheless, on the basis of structural similarities and some anecdotal evidence, many believed that the amphetamine congeners also posed a risk for abuse and addiction.

The FDA discussed many options to deal with its concerns regarding the balance of benefits and risks for the anorectics, including removing the obesity indication, removing the drugs from the market, requiring additional studies of efficacy and safety, or imposing greater restrictions on production and distribution. In the end, a compromise was reached. All of the amphetamine and amphetamine congeners would remain on the market and keep their obesity indication, but all would be restricted to short-term use (a few weeks), and all would be prominently labeled to warn against the risk for addiction (26). Although use of the anorectics for only a few weeks theoretically reduced the risk for addiction, this restriction also eliminated the potential for clinical benefit vis-à-vis sustained weight loss with extended use of the drugs. Regardless of whether the new labeling restrictions were right or wrong, they marginalized the anorectics and contributed to the eventual decline in their use.

A Transition to Long-Term Treatment of Obesity

The decrease in the use of anorectics during the 1970s and 1980s came to an abrupt end when prescription rates for phentermine and fenfluramine skyrocketed in the mid-1990s (28). This revival was stimulated by the juxtaposition of a dramatic increase in the prevalence of obesity with publication of a single study in which 121 obese individuals received treatment with placebo or phentermine plus fenfluramine for up to 4 years (29, 30). Although less than one third of the patients completed this study (and most regained weight during its latter stages), the findings, published in 1992, were cast in a very favorable light by the lay press, fueling the phen-fen craze (31).

In addition to popularizing off-label use of 2 aging anorectics, the phen-fen studies presaged a transition from short-term to long-term drug treatment of obesity. The first drug to garner FDA approval for the long-term treatment of obesity was dexfenfluramine, an isomer of fenfluramine.

When an FDA advisory committee met in September 1995 to discuss the dexfenfluramine application, the agency finally had working guidelines for the development of obesity drugs. Recommendations stipulated that at least 1500 obese patients be studied for 1 year under placebo-controlled conditions and that 200 to 500 of these patients continue drug treatment for a second year in an open-label manner. The 2 criteria used to define an obesity drug as effective were that a mean difference in weight loss of at least 5% between the drug- and placebo-treated patients after 1 year was noted or a greater proportion of patients lost at least 5% of their weight after 1 year of treatment with the drug than with the placebo.

These efficacy criteria were based on 2 tiers of evidence

linked by speculation. First, data indicated that as little as a 5% reduction in weight improved blood pressure, serum cholesterol levels, and blood glucose control (32). Second, evidence from clinical trials of some medications demonstrated that modest drug-induced decreases in biomarkers, such as blood pressure and cholesterol, substantially reduced cardiovascular events and, in some cases, death (33–36). Thus, one only needed to take a small leap of faith, argued some researchers, to expect that modest drug-associated reductions in weight would reduce the risk for irreversible morbidity and mortality.

At face value, the clinical evidence from the dexfenfluramine application supported the drug's efficacy. In a 1-year trial involving 822 obese patients, 64% of patients treated with dexfenfluramine lost at least 5% of their baseline weight, compared with 43% of placebo-treated patients (37). The most common treatment-emergent adverse events in this trial were drowsiness, dry mouth, and diarrhea, problems certainly not worthy of serious concern.

What did concern some regulators and members of the advisory committee were animal data linking dexfenfluramine to neurotoxicity and epidemiologic data linking dexfenfluramine (particularly when used for more than 3 months) to an increased risk for primary pulmonary hypertension, an invariably fatal disease (38). Proponents of dexfenfluramine argued that the finding of neurotoxicity in preclinical models was not clinically relevant because the animals received extremely high doses of the drug. In support of this position, dexfenfluramine had been widely used in Europe for years, and no evidence of serious neurologic damage had come to light.

To put the primary pulmonary hypertension risk into perspective, an academic consultant remarked that the risk for fatal anaphylaxis from penicillin was much higher. Furthermore, echoing the rationale supporting the FDA's efficacy criteria for obesity drugs, dexfenfluramine had been shown to induce a 5% weight reduction and subsequent improvement in cardiovascular risk factors in a significant proportion of patients treated for up to 1 year. By extrapolating from available evidence, clinicians could have expected these changes to reduce the risk for serious morbidity and even death. As a professor of pulmonary medicine later argued, "the risk of developing PPH [primary pulmonary hypertension] [from dexfenfluramine] is about 1000-fold less than the risk of dying from the complications of obesity" (39).

Similar arguments convinced 6 advisory committee members to vote in favor of approving dexfenfluramine. Five members, however, did not believe that the available data supported a favorable balance of benefit to risk and voted against approval. As the advisory committee's split vote made clear, the availability of long-term data on body weight did little to illuminate whether the benefits of dexfenfluramine outweighed its risk—no more than when regulators, on the basis of short-term data, had to address this question for the amphetamines and amphetamine congeners in the early 1970s. In both cases, the FDA ultimately concluded that the drugs' benefit–risk profiles were favorable when, and only when, the drugs were used in accordance with the approved labeling.

When dexfenfluramine was approved in 1996 for the long-term treatment of obesity, it was labeled only for patients who were at substantially increased risk for illness because of their weight. This risk was defined as either a body mass index greater than 30 kg/m^2 or a body mass index of at least 27 kg/m^2 in the presence of comorbid conditions, such as hypertension, diabetes, and hypercholesterolemia (40). To reduce needless long-term exposure (and therefore the risk for primary pulmonary hypertension), the labeling recommended that patients who did not lose at least 4 pounds during the first month of treatment should stop taking the drug because they were unlikely to achieve a 5% reduction in weight with continued treatment. Furthermore, the increased risk for primary pulmonary hypertension, particularly when the drug was taken for more than 3 months, was highlighted in the labeling in a large, boldface font—1 step removed from the most restrictive labeling, a black box warning.

Within a year of its approval, dexfenfluramine was being dispensed at a rate of 85 000 prescriptions per week (41). Within a year and a half of its approval, the drug was off the market, as was fenfluramine. Reports implicated the 2 drugs in a wave of unusual cases of left-sided valvular degeneration—a risk that no one saw coming, and to this day, one that eludes a biomechanistic explanation (42).

The void created by the withdrawal of dexfenfluramine in September 1997 was quickly filled with sibutramine. Like dexfenfluramine, sibutramine's regulatory path to approval involved intense debates over the balance of its benefits and risks. One of these debates played out in a 1996 advisory committee meeting in which regulators, their academic advisors, and sibutramine's manufacturer and its consultants discussed the drug's approvability (43).

Few disputed that sibutramine was an effective drug, at least as defined by the FDA's efficacy criteria. Following a year of treatment, approximately 60% of 320 obese patients treated with the drug lost at least 5% of their baseline weight; in comparison, about 30% of 160 placebo-treated patients achieved that goal. The point of contention, as regulators repeatedly emphasized, was what to make of the drug's tendency to increase blood pressure and pulse rate. In the preapproval trials, treatment with sibutramine was associated with mean increases in systolic and diastolic blood pressure of approximately 1 mm Hg to 3 mm Hg, respectively, and an average increase in heart rate of about 5 beats/min (44).

The company openly conceded that sibutramine, as a sympathomimetic, did have pressor effects. However, they claimed that the small average increase in blood pressure would be offset by the favorable changes in lipid levels that accompanied sibutramine-induced weight loss.

This concept of negating risk factors found a quanti-

tative voice in a professor of epidemiology who spoke on behalf of the company (45). Using mathematical models of Framingham data, the speaker showed the advisory committee calculations of risk for coronary heart disease for various hypothetical clinical scenarios of sibutramine use. In a population of 40-year-old nondiabetic, nonsmoking women, for example, the increase in coronary heart disease risk associated with a 2–mm Hg increase in blood pressure caused by sibutramine would be offset by the reduction in risk associated with the reduction of 0.26 mmol/L (10 mg/dL) in total serum cholesterol level. An increase in serum high-density lipoprotein cholesterol level of 0.05 mmol/L (2 mg/dL) would also accompany a 5-kg sibutramine-induced reduction in body weight. Therefore, the overall 8-year risk for coronary heart disease in this population of patients would actually decrease by 11.0%.

Response to this line of reasoning was generally favorable, although several people thought the use of 0.26 mmol/L (10 mg/dL) as the standard decrease in total cholesterol level was generous given the inconsistent lipid changes observed in the sibutramine preapproval trials. Nevertheless, when the members of the advisory committee were asked whether they believed the benefits of sibutramine outweighed its risks, 4 voted yes and 5 voted no.

Lacking a clear mandate, regulators left the advisory committee meeting once again faced with the difficult task of making a regulatory decision based on a rough estimation of the long-term risk–benefit profile of an obesity drug. As long as sibutramine met accepted standards of efficacy and safety and the labeling accurately described the drug's potential benefits and risks (in particular, the need to monitor blood pressure and pulse), some regulators held that physicians, as learned intermediaries, were the appropriate final arbiters of whether the balance of benefits and risks for sibutramine was favorable for a given patient. Sibutramine was approved for the long-term treatment of obesity in November 1997, just weeks shy of the 50th anniversary of desoxyephedrine's approval for the treatment of obesity in 1947.

Emblematic of the polarization over anorectics, a consumer advocacy group derided the news of sibutramine's approval as a prelude to "another diet drug disaster," whereas a seasoned academic hailed FDA's decision as "great news for dieters" (45, 46).

CONCLUSION

To be sure, polarization remains the legacy of the first half-century of the FDA's regulation of anorectics. Yet, 8 years since the approval of sibutramine, use of the drug remains steady at about 50 000 prescriptions a month, suggesting that the drug has found favor with some dieters; meanwhile, no evidence has surfaced to suggest that sibutramine has become "another diet drug disaster" (47).

This is not to say that some did not try to make that case. Following the deaths of 2 young women taking sibutramine in Italy in 2002, that country temporarily suspended the drug's marketing license (48). This news then triggered some of the drug's opponents to question whether sibutramine should remain on the U.S. market (49).

European drug regulators were quick to conclude, on the basis of an assessment of the 2 deaths in Italy as well as other safety data, that sibutramine's risk–benefit profile was still favorable and that the drug should remain on the European market (50). This exoneration, however, was accompanied by a proviso with worldwide regulatory ramifications: Abbott Laboratories, the manufacturer of sibutramine, would have to conduct a large trial to definitively examine the drug's risk–benefit profile in obese patients at risk for cardiovascular disease (51). The Sibutramine in Cardiovascular Outcomes (SCOUT) trial is underway and aims to study 9000 patients for up to 5 years. This will be the first trial to verify or refute the long-held assumption that drug-induced weight loss—in this case, with sibutramine—reduces the risk for fatal and nonfatal cardiovascular disease.

Not only is SCOUT a landmark study, it reminds us that there is no substitute for data from large, long-term controlled trials for making the most accurate assessment of a drug's risks and benefits. This fact will weigh heavily on the minds of FDA regulators as they, amid calls to reduce the size and scope of obesity drug registration trials, begin the process of updating the agency's *Guidance for the Clinical Evaluation of Weight-Control Drugs* (52).

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America's First Amphetamine Epidemic 1929–1971

A Quantitative and Qualitative Retrospective With Implications for the Present

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Using historical research that draws on new primary sources, I review the causes and course of the first, mainly iatrogenic amphetamine epidemic in the United States from the 1940s through the 1960s. Retrospective epidemiology indicates that the absolute prevalence of both nonmedical stimulant use and stimulant dependence or abuse have reached nearly the same levels today as at the epidemic's peak around 1969. Further parallels between epidemics past and present, including evidence that consumption of prescribed amphetamines has also reached the same absolute levels today as at the original epidemic's peak, suggest that stricter limits on pharmaceutical stimulants must be considered in any efforts to reduce amphetamine abuse today. (*Am J Public Health.* 2008;98:974–985. doi: 10.2105/AJPH.2007.110593)

THE UNITED STATES IS experiencing an outbreak of amphetamine abuse. The latest national surveys show that about 3 million Americans used amphetamine-type stimulants nonmedically in the past year, 600 000 in the past week, and that 250 000 to 350 000 are addicted.[1] Although survey data indicate that the number of nonmedical users of amphetamine-type stimulants may have stabilized, the number of heavy users with addiction problems doubled between 2002 and 2004.[2] Thus, the public health problem presented by amphetamines may still be increasing in severity; in many ways it surpasses that of heroin.[3] Although all of this is widely appreciated, the history of an even larger amphetamine epidemic 4 decades ago is less well-known.

ORIGINS OF THE EPIDEMIC, 1929–1945

The original amphetamine epidemic was generated by the pharmaceutical industry and medical profession as a byproduct of routine commercial drug development and competition. Searching for a decongestant and bronchodilator to substitute for ephedrine, in 1929, biochemist Gordon Alles discovered the physiological activity of beta-phenylisopropylamine (soon to be known as amphetamine). Alles published his first clinical results with the compound in 1929,[4] began amphetamine's clinical development in collaboration with pharmacologists and clinicians at the University of California, and received a patent on its orally active salts in 1932.[5] Meanwhile, possibly inspired by Alles's work, the Philadelphia firm Smith, Kline and French (SKF) investigated the base form of amphetamine and patented it in 1933. SKF marketed it as the Benzedrine Inhaler, a capped tube containing 325 mg of oily amphetamine base and little else. For congestion, one was meant to inhale amphetamine vapor every hour as needed.[6] Although no legal category of prescription-only drugs existed in the 1930s,[7] the Benzedrine Inhaler was advertised for over-the-counter sale upon its introduction in 1933 and 1934 and for the next 15 years.[8]

At the end of 1934, Alles transferred his patent on amphetamine salts to SKF, and the firm sponsored the drug's further clinical development.[9] In 1937, the American Medical Association (AMA) approved advertising of SKF's "Benzedrine Sulfate" racemic amphetamine tablets for narcolepsy, postencephalitic Parkinsonism, and minor depression.[10] (The voluntary AMA "Seal of Approval" system, in which mainly academic medical experts evaluated data submitted by manufacturers before

allowing advertising in cooperating journals, was the only drug efficacy regulation at the time.[11]) Amphetamine therapy for minor ("neurotic") depression quickly found acceptance among psychiatrists and neurologists in the late 1930s. SKF-funded Harvard psychiatrist Abraham Myerson played a particularly influential role, theorizing that amphetamine adjusted hormonal balance in the central nervous system by creating or amplifying adrenergic stimulation so as to promote activity and extraversion. Because Meyerson understood minor depression as anhedonia caused by suppression of natural drives to action, amphetamine represented an ideal depression therapy to him.[12]

Fueled by advertising and marketing urging general practitioners to prescribe the drug for depression, and at the same time promoting Myerson's rationale for that use, annual sales of Benzedrine tablets (mainly 10 mg) grew steadily to about $500 000 in 1941, over 4% of SKF's total sales.[13] Thus, by World War II, amphetamine in tablet form was finding commercial success and gaining credibility as a prescription psychiatric medication (the first "antidepressant"), despite sporadic reports of misuse.[14] The war years did nothing to diminish the drug's growth in popularity; by 1945, SKF's civilian amphetamine tablet sales had quadrupled to $2 million, including $650 000 in sales of the firm's new "Dexedrine" dextroamphetamine tablets.[15]

The US military also supplied Benzedrine to servicemen during the war, mainly as 5-mg tablets, for routine use in aviation, as a general medical supply, and in emergency kits.[16] The British military also supplied Benzedrine tablets during the war, and the German and Japanese military supplied methamphetamine.[17] Of course, not all amphetamine supplied by the military was ingested by servicemen, nor did users ingest it ad libitum; there were rules limiting the drug's use.[18] However, these were not well observed. For instance, in a 1945 army survey of fighter pilots, of the 15% (13 of 85) who regularly used amphetamine in combat, the majority "made their own rules" and took Benzedrine whenever they "felt like it" rather than as directed.[19]

Along with growth in amphetamine use for psychiatric indications, the war years also saw an explosion of amphetamine consumption for weight loss, although this medical usage was not yet approved by AMA and not advertised by SKF. Off-brand pills manufactured by smaller companies dominated this market. In 1943, SKF filed suit for patent infringement against one of these manufacturers, a New Jersey concern named Clark & Clark, producer of both 10-mg Benzedrine look-alike tablets and colorful diet pills containing metabolism-boosting thyroid hormone and 5 mg of amphetamine. The company's output was a matter of dispute, but on the basis of sworn testimony from both sides, combined amphetamine production for civilian use by SKF and Clark & Clark in late 1945 must have stood between 13 million and 55 million tablets monthly and may be conservatively estimated at about 30 million tablets monthly, each containing 5 to 10 mg of amphetamine salts.[20] This national (civilian) consumption rate for the United States in 1945 was sufficient to supply half a million Americans with 2 tablets daily, the standard dosage schedule for depression and weight loss. Past-year use in 1946 would have almost certainly been higher, because many were only occasional users.

Unsurprisingly, given such widespread availability of so inherently attractive a drug, significant abuse of amphetamine quickly developed. One noteworthy 1947 publication hinted at its dimensions. Psychiatrists Russell Monroe and Hyman Drell, stationed at a military prison in 1945, encountered large numbers of agitated, hallucinating patients. A survey revealed that one quarter of the imprisoned personnel were eating the contents of Benzedrine Inhalers, which then contained 250 mg of amphetamine base. Almost one third of the

"...if the individual is depressed..."

"... if the individual is depressed or anhedonic ... you can change his attitude ... by physical means just as surely as you can change his digestion by distressing thought ... *In other words, drugs and physical therapeutics are just as much psychic agents as good advice and analysis* and must be used together with these latter agents of cure."

Myerson, A.—*Anhedonia*—Am. J. Psychiat., July, 1922.

When this was written—in 1922—the only stimulant drugs employed in the treatment of simple depression were of limited effectiveness.

Only in the last decade has there been available—in Benzedrine Sulfate—a therapeutic weapon capable of alleviating depression, overcoming "chronic fatigue" and breaking the vicious circle of anhedonia.

BENZEDRINE SULFATE TABLETS

(racemic amphetamine sulfate)

SMITH, KLINE & FRENCH LABORATORIES, PHILADELPHIA, PA.

XIII

Amphetamine was successfully marketed as the first antidepressant in the late 1930s and 1940s, together with a particular understanding of depression as anhedonia.

Source. ***California Western Medicine*** **62 (April 1945): 33 (advertising section) and** ***American Journal of Psychiatry*** **101 (March 1945): xiii (advertising section).**

In the 1950s, competition among pharmaceutical firms boosted amphetamine consumption dramatically, after expiration of the Alles and Smith, Kline and French patent in 1949.

Source. ***Journal of the American Medical Association*** **147 (1951): 19 (advertising section).**

abusers (8% of the prison population) had begun this practice in the military before imprisonment. Only 11% of the inhaler abusers (3% of the prison population) had used some form of amphetamine nonmedically before the war. Twenty-seven percent of abusers had been given amphetamine during military service, mainly by an officer and in tablet form, compared with 5% of nonabusers—an odds ratio of 7.0. There is thus strong evidence that Benzedrine abuse, although an existing practice, was multiplied many times by military exposure, at least among vulnerable subpopulations. And although these prisoners were not typical of military personnel, neither, in the judgment of the psychiatrists, were most of them particularly abnormal young men.[21]

To sum up, by the end of World War II in 1945, less than a decade after amphetamine tablets were introduced to medicine, over half a million civilians were using the drug psychiatrically or for weight loss, and the consumption rate in the United States was greater than 2 tablets per person per year on a total-population (all ages) basis.[22] Up to 16 million young Americans had been exposed to Benzedrine Sulfate during military service, in which the drug was not treated as dangerous nor was its use effectively controlled, helping normalize and disseminate nonmedical amphetamine use. Misuse and abuse, especially of the cheap nonprescription Benzedrine Inhaler but also of tablets, were not uncommon. However, as often occurs in the first flush of enthusiasm for new pharmaceuticals, abuse, adverse effects, and other drawbacks had not yet attracted much notice.

"By the end of World War II in 1945, less than a decade after amphetamine tablets were introduced to medicine, over half a million civilians were using the drug psychiatrically or for weight loss, and the consumption rate in the United States was greater than 2 tablets per person per year on a total-population (all ages) basis."

GROWTH OF THE EPIDEMIC, 1945–1960

In 1945 and 1946, the courts upheld Alles's patent on amphetamine salts, affirming SKF's monopoly control of oral amphetamine until late 1949.[23] With recouped business from infringing firms, SKF's annual sales of amphetamine tablets (Benzedrine and Dexedrine Sulfate) doubled, from $2.9 million in 1946 to $5.7 million in 1947.[24] With AMA approval to advertise amphetamine for weight loss that year, sales climbed further to $7.3 million in 1949, despite competition from methamphetamine-based weight loss and antidepressant products such as Abbot's Desoxyn and Wellcome's Methedrine.[25] Following expiration of Alles's patent in late 1949, consumption of pharmaceutical amphetamines in the United States surged. On the basis of voluntary manufacturer surveys, the Food and Drug Administration (FDA) placed 1952 production of amphetamine and methamphetamine salts at nearly quadruple the agency's 1949 estimate by similar methods.[26] Given that SKF amphetamine sales in the period did not grow significantly, virtually all this expansion in amphetamine supply was driven by the marketing efforts of competitors.[27]

During the 1950s, fierce commercial competition helped drive amphetamine consumption higher still. In a particularly innovative effort to expand medical usages for the drug, in late 1950, SKF introduced a product called Dexamyl, a blend of dextroamphetamine and the barbiturate sedative amobarbital.[28] Intended to overcome the unpleasant agitation that many users experienced with amphetamine and to quell anxiety without drowsiness, Dexamyl was marketed with great success for everyday "mental and emotional distress" in general practice and also as a weight-loss remedy striking at the emotional causes of overeating.[29] Competing firms answered with their own sedative–amphetamine combinations, such as Abbot's Desbutal and Robins's Ambar, blends of methamphetamine and pentobarbital or phenobarbital, respectively.[30] Creative amphetamine combination products from both SKF and its competitors proliferated throughout the 1950s.[31]

According to FDA manufacturer surveys, by 1962, US production reached an estimated 80 000 kg of amphetamine salts, corresponding to consumption of 43 standard 10-mg doses per person per year on a total-population basis.[32] Thus, in amphetamine alone, the United States in the early 1960s was using nearly as much psychotropic medication as the 65 doses per person per year in the present decade that social critics today find so extraordinary.[33] And the 1960s are rightly remembered for excessive minor tranquilizer consumption, around 14 standard doses per person per year on the basis of retail prescription sales.[34] It is rarely appreciated that in the early 1960s, amphetamines were actually consumed at a higher rate than tranquilizers. This oversight may be caused by excessive reliance on retail prescription audits (inappropriate for amphetamines when billions were dispensed directly; see the next section) and neglect of the fact that amphetamine obesity medications were just as psychotropic as amphetamine-based antidepressants. Through the rest of the 1960s, FDA estimates of amphetamine production would grow little beyond 8 billion 10-mg doses, implying that consumption of the drug had already reached saturation levels in 1962. This conclusion, based on voluntary FDA production surveys, draws independent support from flat retail prescription sales from 1964 to 1970.[35]

The best published evidence of the nature and prevalence of medical amphetamine consumption around 1960 comes from studies in the United Kingdom, thanks to the National Health System, which facilitates comprehensive prescription monitoring and correlation of physicians with base populations. A study of retail prescriptions filled in the Newcastle area during 1960 found that about 3% were for amphetamines, consistent both with UK national prescribing figures and with contemporary prescribing in the United States according to commercial audits.[36] Given similarities in culture and medical practices, the British findings therefore shed light on amphetamine use in America around 1960, at least for drugs dispensed at pharmacies.[37]

In the Newcastle study, quantities dispensed were sufficient to supply more than 1% of the total population with 60 tablets per month; two 5-mg doses of dextroamphetamine daily was the most common prescription, according to a 1961 companion study that audited family practitioners in the same area.[38] Dexamyl—in Britain called Drinamyl—was the most commonly prescribed amphetamine product. About one third of amphetamine prescriptions were for weight loss, one third for clear-cut psychiatric disorders (depression, anxiety), and the remaining third for ambiguous, mostly psychiatric and psychosomatic complaints (tiredness, nonspecific pain). The largest age group among the medical users were those aged 36 to 45 years, and 85% of all amphetamine patients were women.[39] Even making the simplifying assumption that weight loss prescriptions were entirely for women and taking into account that women seek medical attention more often than men, these figures indicate that per doctor visit around 1960, a woman was twice as likely as a man to receive an amphetamine prescription to adjust her mental state—much like minor tranquilizers in the same period.[40]

By about 1960, widespread consumption had begun to make amphetamine's negative health consequences more evident. Amphetamine psychosis had already been observed in the 1930s among long-term narcoleptic users of the drug, and individual case reports mounted during the 1940s and early 1950s.[41] Initially, psychotic episodes were attributed to latent schizophrenia "unmasked" by the drug or to some other preexisting psychiatric pathology in the user.[42] In Philip Connell's definitive 1958 study of 40 cases, however, the British psychiatrist persuasively showed that amphetamine psychosis could happen to anyone, and eventually would, given enough of the drug.[43] The highly uniform set of paranoid symptoms—sinister voices emanating from toilet bowls, spies following one's every move—in a wide variety of personality types argued against any shared constitutional feature of the patients' mentality or neurology. Also, the psychosis generally took time to develop, suggesting a dosage-dependent cumulative effect. And although almost all of Connell's patients had engaged in nonmedical use before their crises, a large proportion had first taken amphetamines by prescription, so they could not be dismissed as deviant thrill-seekers. Finally, patients recovered fully a week or two after they ceased amphetamine use, essentially proving they had not been schizophrenic.[44]

Evidence was also emerging around 1960 that amphetamine is truly addictive, instead of merely "habituating" like caffeine, as leading pharmacologists had asserted when the drug was first introduced.[45] Postwar changes in thinking about addiction, promoted particularly by the World Health Organization, facilitated this new perspective on amphetamine by moving the concept away from an

opiate model, defined by acute physiological withdrawal, toward a psychosocial model of "drug dependency" defined by compulsive behavior and erosion of function.[46] Indeed, the previously mentioned British research uncovered evidence of significant dependency on prescribed amphetamines. In Newcastle in 1961, 0.8% of a very large study population received amphetamine prescriptions during a 3-month audit period; according to their physicians, between one fifth and one quarter of these amphetamine patients were "habituated or addicted" or dependent to some extent.[47] Taking the sample in these studies as representative (as the investigators intended), between 2% and 3% of the total population must have received amphetamines by prescription in the course of a year.[48] This, together with the 0.2% of the general population identified as "habituated or addicted," implies a dependency rate among past-year medical amphetamine users of 6.7% to 10%.[49]

To distinguish between the habituation and addiction reported by Newcastle physicians, another northern British study of the early 1960s enrolled family practitioners to dispense Dexamyl tablets, identical-looking placebos, or plain white tablets containing Dexamyl's active ingredients to their apparently amphetamine-dependent patients on a double-blind basis. The study found that about one third of "habituated or addicted" medical Dexamyl users were in fact physically dependent.[50] Taken together with the prevalence estimates in the previous paragraph, this outcome implies extensive iatrogenic amphetamine addiction in the early 1960s—that is, 2.2% to 3.3% of all patients receiving amphetamine prescriptions in a given year.[51]

At the end of the 1950s, the monoamine oxidase inhibitor and tricyclic antidepressants were introduced and quickly acclaimed by psychiatrists as superior to amphetamines for depression. In the United States, however, prescribing rates for amphetamines did not decline significantly in the 1960s,[52] despite the availability of alternatives and increasing awareness of amphetamine's defects. At that time, the vast majority of psychiatric medications were prescribed in primary care, much more so than today.[53] Why, then, did family practitioners continue to prescribe mental health drugs that psychiatric specialists judged inferior?

The answer lies in the type of patient for whom amphetamine-based prescriptions had become typical in the 1950s and the trends and exigencies of primary care. At least one third of primary care office visits are motivated by complaints for which the physician can find no organic explanation, a longstanding fact of life for general practitioners that received official recognition in the 1950s.[54] "Psychosomatic medicine" enjoyed a postwar vogue, and as a substitute for the archaic bromides and nerve tonics then still commonly prescribed, primary care authorities in the 1950s began advocating barbiturates, amphetamine, and amphetamine–barbiturate combinations for the mild depressions and other emotional disturbances presumed to be driving such mysterious complaints.[55] Psychiatric specialists writing on general practice also endorsed these prescribing approaches, although they understood sympathy, reassurance, and time as the main therapeutic agents for all neurotic ailments.[56] Assisted by such trends in medical thought, along with pharmaceutical marketing that reinforced them, amphetamines became first-line treatments for emotional distress and psychosomatic complaints in the 1950s.

In the 1960s, the continuing preference of family doctors for amphetamines caused psychiatrists some consternation. Evidently, the newer drugs did not work as well for the typical distressed amphetamine patient, even though they worked better on bona fide depressives in controlled clinical trials. As one specialist lamented in 1965, general practitioners had tried newer antidepressants, but they prescribed them in subtherapeutic doses to avoid toxicity (in the case of monoamine oxidase inhibitors) and unpleasant side effects (in the case of tricyclics). Used as placebos to tide patients over their difficulties, amphetamines were superior because they were more agreeable and improved compliance. After a brief experiment, many primary care physicians therefore went "back to the old standbys, amphetamine and amphetamine-barbiturate combinations."[57] As one general practitioner explained in 1970, only amphetamine kept certain patients "capable of performing or even enjoying their duties"[58]—that is, of managing their problems of living. In the United States, medical amphetamine use declined only after 1970, when new laws restricted prescribing. In Britain, however, there was a clamor for physicians to show restraint with such dangerous and addictive medicines by the mid-1960s,[59] leading to voluntary moratoriums around 1968 that apparently succeeded in reducing national amphetamine prescribing rates.[60] This difference might be explained by a public health insurance framework in the United Kingdom that reduced

incentives to overprescribe drugs popular with patients.

THE EPIDEMIC'S CRISIS IN THE 1960s

In the early 1960s, amphetamines were still widely accepted as innocuous medications. Apart from vast numbers of middle-aged, middle-class patients receiving low-dose prescriptions from family doctors to help them cope with their daily "duties," in much the same way that their doctors prescribed minor tranquilizers,[61] a significant quasi-medical gray market in amphetamines had developed. For instance, for his painful war injuries and also to help maintain his image of youthful vigor, President John F. Kennedy received regular injections containing around 15 mg of methamphetamine, together with vitamins and hormones, from a German-trained physician named Max Jacobson.[62] Known as a doctor to the stars and nicknamed "Dr Feelgood," Jacobson also treated Cecil B. DeMille, Alan Jay Lerner, Truman Capote, Tennessee Williams, the Rolling Stones, and ironically, Congressman Claude Pepper of Florida, a noted antidrug campaigner.[63] Jacobson's concoctions were peculiar, but he was far from unique in his readiness to prescribe or dispense amphetamines for the price of a consultation.[64]

Large quantities of amphetamines were also dispensed in the 1960s directly by diet doctors and weight loss clinics, many of which were essentially subsidiaries of off-brand diet pill manufacturers. Huge profits could be made when the pharmacist was cut out in this fashion; one dispensing diet doctor paid $71 for 100 000 amphetamine-containing tablets and sold them for $12 000.[65] One widely cited estimate placed the number of amphetamine tablets consumed annually via this channel at 2 billion.[66] Finally, according to the FDA, of the roughly 8 billion to 10 billion 10-mg amphetamine tablets manufactured by drug firms annually in the United States by the late 1960s, up to one half were "diverted" from medical channels altogether.[67] As CBS television revealed in 1964, with a few hundred dollars and a fake company letterhead, anyone could purchase millions of tablets direct from manufacturers by mail, notwithstanding pharmaceutical industry pretensions to self-regulation.[68] When tighter regulation made this tactic more difficult in the later 1960s, wholesale quantities were shipped from manufacturers to Mexico (even to addresses like the Tijuana Golf Course's 11th hole) and immediately reimported.[69]

The FDA's crude population-level amphetamine consumption estimates based on manufacturing surveys (80 000–100 000 kg of amphetamine salts produced for a total population of around 200 million in 1969, or up to 50 10-mg doses per person) were supplemented with prevalence estimates from the first modern drug use surveys. A national survey conducted in late 1970 and early 1971 found past-year usage of amphetamine-type drugs by 5% of American adults. This study was designed exclusively to measure medical, prescribed drug use.[70] A more thorough, roughly simultaneous survey in New York State explored both nonmedical and medical amphetamine use. It found that 6.5% of the state's 13.8 million residents older than 14 years had used amphetamines in the past 6 months. If one counts only those using oral amphetamines made by pharmaceutical firms (the great majority) in the past 6 months, 39% sometimes used them nonmedically and 22% "abused" the drugs, defined as both obtaining drugs without prescription and using them on social occasions.[71]

Because the New York survey's past-6-month medical amphetamine usage rates were lower than, and consistent with, the national survey's past-year prevalence figures, we might reasonably (indeed, with conservative bias) extrapolate the New York study's combined medical and nonmedical usage rates to all 149.4 million Americans older than 14 years. By this extrapolation, at least 9.7 million Americans were past-year users of amphetamines in 1970. If we may also extrapolate the New York misuse rates, 3.8 million took amphetamines nonmedically and 2.1 million abused the drugs by the New York criteria.[72]

To the extent that amphetamine addiction is determined biologically by active compound, dosage form, and dosage schedule or availability, we may safely (again, with conservative bias) apply dependency rates derived from the early-1960s British studies of medical users to the United States of the late 1960s, because the same pills were being distributed on the same prescriptions. If we apply the higher range of the British medical amphetamine dependency rate (reflecting freer supply, predictably higher dependency rates among recreational than medical users, and the more plausible past-year Newcastle prescription rate of 2%) to the inferred national population of past-year medical and nonmedical amphetamine users combined, the United States in 1970 had 970 000 amphetamine users meeting some criteria of dependence and about 320 000 addicts.[73] These should be regarded as minimal figures given the

multiple sources of conservative bias in our national past-year amphetamine usage estimates for 1970 and 1971. Furthermore, 1970 to 1971 prevalence presumably underestimates amphetamine use at the epidemic's peak around 1969, because consumption in the United States was already declining when the surveys were conducted.[74]

As noted, in the United States, large-scale diversion from medical channels was widely acknowledged early in the 1960s, and amphetamine control measures were discussed in Congress throughout the decade. The legislation that in 1965 became the Drug Abuse Control Amendments was originally intended to restrict the manufacture of amphetamines, along with barbiturates. However, the version passed into law stressed penalties for the unauthorized *distribution* of these drugs and the "counterfeiting" of *any* name-brand pharmaceuticals, no matter how safe.[75] The manufacture of such potentially dangerous pharmaceuticals remained "an area where guidance has to be provided without enforcement," as the drug industry's spokesmen urged.[76] National consumption of amphetamines showed no sign of decline following the legislation's implementation.

Drug abuse in general became an increasingly exigent political topic during the later 1960s, as popular concern mounted about widespread amphetamine abuse everywhere from leafy suburbs to Vietnam to hippie enclaves like Haight-Ashbury.[77] In 1969, another congressional hearing was devoted to the theme "Crime in America—Why 8 Billion Amphetamines?"[78] The legislation that emerged, the 1970 Comprehensive Drug Abuse Prevention and Control Act, established the modern set of controlled substance "schedules" in harmony with new international agreements and enabled federal narcotics authorities to establish and enforce production quotas on drugs in the most strictly controlled Schedules I and II. However, reflecting industry interests, only a handful of rarely prescribed injectable methamphetamine products were placed in Schedule II, while some 6000 oral amphetamine products on the US drug market were classed in Schedule III, meaning they were subject to no manufacturing quotas and to looser recordkeeping and their prescriptions could be refilled 5 times.[79] The impact on amphetamine consumption was not dramatic, with reported legal production dropping only 17% between 1969 and 1970.[80]

Although congressional focus on a comparatively small but frightening population of methamphetamine-injecting "speed freaks" spared industry any major inconvenience in 1970,[81] law enforcement authorities had not forgotten that 80% or 90% of amphetamines seized on the street were pills manufactured by US pharmaceutical firms.[82] Civil servants now stepped forward where elected representatives feared to tread. In mid-1971, the Bureau of Narcotics and Dangerous Drugs (BNDD; forerunner to today's Drug Enforcement Administration [DEA]) exercised administrative authority gained under the 1970 act by shifting all amphetamine products to Schedule II, including methylphenidate (Ritalin) and the diet drug phenmetrazine (Preludin), both of which had proved attractive to high-dose injection abusers. Drugs in Schedule II required a fresh prescription each time they were filled, and doctors and pharmacists had to keep strict records or face prosecution. Prescription sales of amphetamines and related drugs shot up when the new restrictions were announced and then plummeted 60% below their original level when they came into effect.[83] Large numbers of doctors and patients obviously realized that their "medical" usage was difficult to justify.

The move to Schedule II empowered federal narcotics authorities, in consultation with the FDA, to set quotas limiting the production of amphetamines to quantities required by medicine. Meanwhile, the FDA was narrowing legitimate uses of the amphetamines, retroactively declaring the drugs to be of unproven efficacy in obesity and depression. Manufacturers were invited to submit applications demonstrating efficacy, but in general these submissions were based on older trials and were found wanting by modern standards of clinical research. Only narcolepsy and "hyperkinetic disorder of childhood" (today's attention deficit disorder, then rare) remained approved usages.[84]

While the FDA pursued its reevaluation of amphetamine efficacy, in 1971, the BNDD took applications from firms wishing to manufacture Schedule II drugs, a procedure that required reporting of past production. According to this reporting, US firms applying for 1971 quotas manufactured 17 000 kg of amphetamine base and 8000 kg of methamphetamine base in 1969. (In terms of the units used in prior voluntary FDA surveys, this figure equals about 3 billion 10-mg amphetamine sulfate tablets and 1 billion 10-mg methamphetamine hydrochloride tablets—altogether, 4 billion doses, a fair estimate of actual medical consumption in 1969 given the context of reporting).[85]

The BNDD originally set 1971 quotas to allow the manufacture of about 15 000 kg of amphetamine and methamphetamine base combined, 40% less than reported 1969 levels. Another 40% cut in the quantity of amphetamines manufactured in the United States was slated for 1972. Given the prescribing slump that followed Schedule II listing, however, the BNDD, with FDA agreement, instead set production levels for 1972 at one fifth of 1971 levels and at one tenth of reported medical production (or about one twentieth of actual production) in 1969.[86] Under the supply controls imposed by the 2 agencies, amphetamines became relatively minor drugs of abuse by the late 1970s, while illicit cocaine use exploded.[87]

Table 1—Estimated Prevalence of Amphetamine Misuse and Dependency in the United States at Peak of First and in Current Epidemics, Expressed as Numbers of Individuals and Percentage of Total Population

Year	Past Year Nonmedical Amphetamine Use, Millions (%)	Physical Dependency or Addiction, Thousands (%)	Total US Population, Millions
1970	3.8[a] (1.9)	320[b] (0.16)	203[c]
2002	3.2[d] (1.1)	303[d] (0.10)	291[c]

Source. For references to footnotes, see endnote 91.
[a]Derived by taking past-6-month New York State usage prevalence figures as indicators of national past-year usage.
[b]Derived by applying upper-range medical dependency and addiction rates from early 1960s in northern Britain to total US medical and nonmedical amphetamine-using population in 1970. Note that the informal but relatively stringent "physical addiction" of the 1960s is not identical to "dependence" as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.
[c]From the Bureau of the Census.
[d]Data for 2002 are consistent with more recent household drug use survey data.

RECENT TRENDS IN THE LIGHT OF HISTORY

The first amphetamine epidemic was iatrogenic, created by the pharmaceutical industry and (mostly) well-meaning prescribers. The current amphetamine resurgence began through a combination of recreational drug fashion cycles and increased illicit supply since the late 1980s.[88] On the basis of treatment admissions data, methamphetamine abuse doubled in the United States from 1983 to 1988, doubled again between 1988 and 1992, and then quintupled from 1992 to 2002.[89] According to usage surveys, during 2004, some 3 million Americans consumed amphetamine-type stimulants of all kinds nonmedically, twice the number of a decade earlier. As noted, 250 000 to 350 000 of them were addicted.[90] Thus, in terms of absolute numbers, the current epidemic has now reached approximately the same extent and severity as that of the original epidemic at its peak in 1970, when there were roughly 3.8 million past-year nonmedical amphetamine users, about 320 000 of whom were addicted (Table 1). (Of course, the national population then was about 200 million compared with 300 million today, meaning that in relative terms today's epidemic is only two thirds as extensive.)

Another striking similarity between present and past epidemics relates to the role of pharmaceutical amphetamines. Although illicitly manufactured methamphetamine launched the current epidemic, in step with rising amphetamine abuse in recent years, the United States has seen a surge in the legal supply and use of amphetamine-type attention deficit medications, such as Ritalin (methylphenidate) and Adderall (amphetamine). American physicians, much more than those in other countries, apparently are again finding it difficult to resist prescribing stimulants that patients and parents consider necessary, or at least helpful, in their struggle with everyday duties.[91] According to DEA production data, since 1995, medical consumption of these drugs has more than quintupled, and in 2005, for the first time exceeded amphetamine consumption for medical use at the epidemic's original peak: 2.5 billion 10-mg amphetamine base units in 1969 vs 2.6 billion comparable units in 2005.[92] Thus, just as the absolute prevalence of amphetamine abuse and dependency have now reached levels matching the original epidemic's peak, so has the supply of medical amphetamines (Figure 1).

Might the recent increases in both medical and nonmedical amphetamine use be related, and if so, how? Childhood stimulant treatment for attention deficit disorder as a cause of later nonmedical amphetamine consumption is one possible connection that has received considerable attention. Although controversy remains, the weight of evidence suggests that medication prescribed for attention deficit disorder does not predispose individuals to stimulant abuse or dependence.[93] Moreover, if there is a statistical association, it may link stimulant misuse to attention deficit disorder per se (rather than to medication),[94] as one would expect if some nonmedical amphetamine use is in fact self-medication. Nevertheless, this line of inquiry does not eliminate any possible relationship between prescribing for attention deficit disorder and rates of stimulant abuse. Even if there is no connection at the

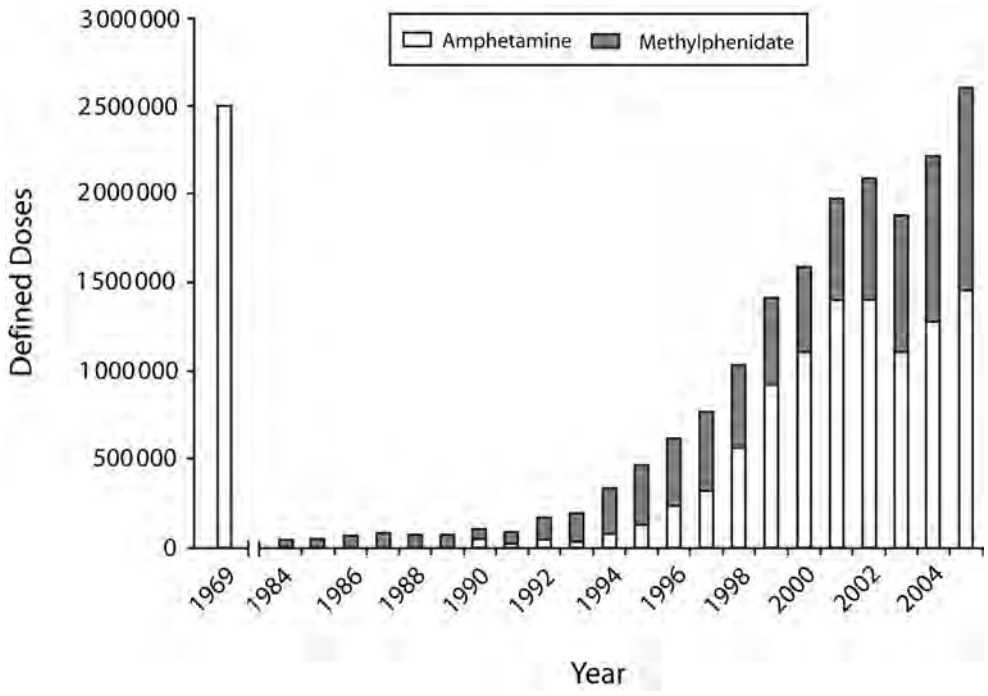

FIGURE 1—US medical consumption of amphetamine and methylphenidate, expressed as common dosage units (10-mg amphetamine and 30-mg methylphenidate, anhydrous base), based on Drug Enforcement Administration production quota figures.[92]

individual level, there may be one at the population level.

Other than converting attention deficit disorder patients into abusers, prescribed amphetamines can contribute to the national stimulant epidemic in at least 2 other ways. For one, the mere distribution of so many stimulant tablets in the population creates a hazard. Diversion from students with attention deficit prescriptions to those without is known to occur in high schools, and at American universities, both diversion and nonmedical use by those with prescriptions are commonplace.[95] In 2005, some 600 000 Americans used psychiatric stimulants other than methamphetamine nonmedically in the past month.[96] Thus, legally manufactured attention deficit medications like Adderall and Ritalin appear to be supplying frequent, and not just casual, misusers. A detailed analysis of stimulant abuse in recent national household drug surveys found not only that 1.6 million of the 3.2 million past-year nonmedical users of stimulants in the United States used strictly nonmethamphetamine psychiatric stimulants in the past year, but that over 750 000 of them had never used any stimulants except attention deficit pharmaceuticals *in their entire lives*. In that study, those who abused only nonmethamphetamine (i.e., pharmaceutical) stimulants in the past year accounted for one third of the approximately 300 000 Americans estimated to be amphetamine addicted (reflecting the fact that nonmethamphetamine users have a somewhat lower rate of frank addiction than methamphetamine users.[97] On this evidence alone, one can fairly describe the high production and prescription rates of these medications as a public health menace of great significance.

Besides iatrogenic dependence and diversion to nonmedical users, there is another way that widespread prescription of amphetamine-type stimulants can contribute to an amphetamine epidemic. When a drug is treated not only as a legal medicine but as a virtually harmless one, it is difficult to make a convincing case that the same drug is terribly harmful if used nonmedically. This is what happened in the 1960s and is presumably happening today. Thus, to end their rampant abuse, amphetamines had to be made strictly controlled substances and their prescription sharply curtailed. Today, amphetamines are widely accepted as safe even for small children, and this return of medical normalization inevitably undermines public health efforts to limit amphetamine abuse. We have not yet reached the point where up to 90% of the amphetamines sold on the street are products of US pharmaceutical firms, as the federal narcotics chief reluctantly admitted before Congress in 1970.[98] But with half the nation's nonmedical users evidently consuming pharmaceutical amphetamines only, the comments made by Senator Thomas Dodd in those hearings echo strongly today. America's drug problems were no accidental development, Dodd observed; the pharmaceutical industry's "multihundred million dollar advertising budgets, frequently the most costly ingredient in the price of a pill, have pill by pill, led, coaxed and seduced post–World War II generations into the 'freaked out' drug culture" plaguing the nation.[99] Any effort to deal harshly with methamphetamine users today in the name of epidemic control, without touching medical stimulant production and prescription, is as impossible practically as in 1970—and given historical experience, even more hypocritical. ■

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FDA Regulation of Obesity Drugs: 1938 - 1999

Eric Colman, MD
Division of Metabolic and Endocrine Drugs
September 8, 2004

Food and Drug Laws

- 1906 – President T. Roosevelt signs the original Food and Drugs Act
- 1938 - President F. Roosevelt signs Food, Drug, and Cosmetic Act
  - Labeling provisions
  - Advertising provisions
  - Drug manufacturers must submit evidence of a drug's safety prior to marketing (sulfanilamide)
  - New Drug Applications (NDA)

REFERENCE 6

The Amphetamines

- Lesses, M.F. and Myerson A. Benzedrine sulfate as an aid in the treatment of obesity. 1938 *New Engl J Med;* 218:119-124
- Benzedrine (amphetamine sulfate) approved by the FDA in 1939
- Desoxyephedrine approved in 1943
- Obesity indication for desoxyephedrine approved in 1947
  - "The sympathomimetic amines have been found of value, when administered under the supervision of a physician, as an adjunct to the dietary management of obesity"
  - warned against its use in persons with cardiovascular disease, hypertension, or insomnia and in those who were "neurotic or hyperexcitable."
- Amphetamines: amphetamine sulfate, desoxyephedrine (methamphetamine), dextroamphetamine, amphetamine + barbiturate

The Amphetamine-Like Drugs 1956-1960

- Phenmetrazine
- Phendimetrazine
- Phentermine
- Benzphetamine
- Diethylpropion
  - "any [obese] patient, including the adolescent, geriatric, and gravid, as well as the special-high risk situations of the cardiac, hypertensive, and diabetic [patient]."
  - "tolerance, habituation, or addiction [did] not develop," … ideal for "long-term use"

An Epidemic

- Widespread illicit use and abuse of amphetamines
  - 1958 – 3.5 billion tablets
  - 1967 – 8 billion tablets
  - 1967 – 23 million prescriptions (80% female)
- Most commonly prescribed for obesity
- Drug Abuse Control Amendments of 1965
  - Increased record keeping throughout the system of manufacture, distribution, prescription, and sale
- Controlled Substances Act of 1970
  - Schedules 1-5

1962 Kefauver-Harris Amendments

- Legislation mandated that new drug applications contain substantial evidence of a drug's effectiveness
  - "adequate and well-controlled investigations"
- What should be done regarding efficacy assessments for drugs approved between 1938 and 1962?
- National Research Council of the National Academy of Sciences
- Drug Efficacy Study (DESI)

The Drug Efficacy Study 1966-1969

- Psychiatric Drug Panel reviewed the available data on the efficacy of the amphetamines and the amphetamine-like drugs
- Categories of efficacy:
  - Effective
  - Effective, but……
  - Probably effective
  - Possibly effective
  - Ineffective

The Drug Efficacy Study Results

- Amphetamines "Possibly effective"
- Amphetamine-like drugs "Effective but……."
- Reasons for Psychiatric Drug Panel's conclusions:
  - Studies were of short duration;
  - There was no available evidence that the drugs altered the natural history of obesity;
  - There was some evidence that the anorectic effects may have been strongly influenced by the suggestibility of the patient;
  - There were concerns about the adequacy of the controls in some of the clinical studies.

Regulatory Consequences of DESI

- 1970 - FDA concluded that the amphetamines were Possibly effective…. as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction
- Industry directed to submit evidence of weight-loss efficacy from adequate and well-controlled trials of more than a few weeks duration
- No formal FDA position regarding the efficacy of the amphetamine-like drugs

Formation of FDA's Obesity Drug Policy in the Early 1970s

- The Prout Consultant Group
- Neuropharmacology Drugs Advisory Committee
- The Amphetamine-Anorectic Drug Project

The Prout Consultant Group

- Eight external consultants headed by Thaddeus Prout, an endocrinologist from Johns Hopkins
- April 1971 meeting:
  - Weight-loss drugs are potentially of value
  - Efficacy trials should be at least 12 weeks in duration
  - Long-term follow up of patients was not the responsibility of drug companies
  - Efficacy of the weight-loss drugs should be defined as statistical superiority of drug to placebo

The Neuropharmacology Drugs Advisory Committee

- September 1971
- What criteria should be used to define clinically significant weight loss?
- Reference made to Prout's recommendation that efficacy be defined as statistical superiority of drug to placebo
- Still no answer on what defines clinically significant weight loss

The Amphetamine-Anorectic Drug Project

- A meta-analysis of clinical data submitted to FDA
- All amphetamine and amphetamine-like compounds (including fenfluramine and sanorex)
- 200 clinical studies
- 10,000 patients
  - Patients treated with active medication lost "some fraction of a pound a week more than those on placebo"
  - Data did not suggest that one drug was superior to another nor that the amphetamines as a class were more effective than the amphetamine-like drugs.

REFERENCE 6

Consequences of the Amphetamine –Anorectic Drug Project

- 1973 Agency declared the amphetamine and amphetamine-like drugs *effective* for the treatment of obesity
- Class labeling - concern about abuse led FDA to impose a short-term (a few weeks) indication for obesity on all amphetamine and amphetamine-like drugs

FDA's Continued Action Against The Amphetamines

- 1979 Federal Register notice calling for removal of the obesity indication for the amphetamines
  - Continued evidence of abuse from DAWN
  - No evidence that the amphetamine were more effective for obesity than the amphetamine-like drugs
- Industry response
  - Analyses of data from DAWN were incorrect
  - Problems with illicit production and use were the purview of state medical boards and the DOJ, not FDA
  - Abuse required use beyond a few weeks, so this was off-label use of the drug; again not an issue for FDA
  - More favorable risk-to-benefit profiles for the amphetamine-like drugs not a legitimate reason to take action against the amphetamines

Phentermine + Fenfluramine

- Phentermine – stimulant
- Fenfluramine – sedative
- Long-term studies in the 1980s by Weintraub et al.
- The rise of Phen-Fen

Prescriptions for Phentermine and Fenfluramine#		
	1992	1996
Phentermine	2,000,000	11,000,000
Fenfluramine	69,000	7,000,000

Regulatory Shift

- 1992 regulatory responsibility for obesity drugs transferred from the Division of Neuropharmacology Drugs to the Division of Metabolic and Endocrine Drugs
- Effective drug treatment requires long-term or indefinite use
- Pre-approval studies should therefore be long-term
- Jan. 1995 Advisory Committee discusses the Obesity Guidance document

Obesity Guidance - 1996

- Efficacy criteria:
  - Mean weight loss in drug group is at least 5% greater than mean weight loss in placebo group
  - Proportion of patients who lose at least 5% of baseline weight is greater in drug vs. placebo group
- Size and duration of phase 3 trials
  - 1500 patients studied for one-year under placebo-controlled conditions
  - 200-500 patients for an additional year of open-label study

Long-Term Treatment of Obesity

- Dexfenfluramine approved in 1996
  - Removed from market in 1997
- Sibutramine approved in 1997
  - MERIDIA is indicated for the management of obesity, including weight loss and maintenance of weight loss, and should be used in conjunction with a reduced calorie diet.
- Orlistat approved in 1999
  - XENICAL is indicated for obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet. XENICAL is also indicated to reduce the risk for weight regain after prior weight loss.

Summary

- Benefits: defining or quantitating the efficacy of weight-loss drugs has been problematic
  - 1940s-1960s: ????
  - 1960s: statistically significantly more weight loss
  - 1990s: clinically significant weight loss is 5%
- Risks: safety issues have dominated the regulatory history of the weight-loss drugs
  - Illicit use and abuse
  - Primary pulmonary hypertension
  - Cardiac valvulopathy
  - Blood pressure and pulse

Conclusion

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Food and Drug Administration's Obesity Drug Guidance Document: A Short History

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Food and Drug Administration's Obesity Drug Guidance Document

A Short History

Eric Colman, MD

An estimated 70% of adult men and 60% of adult women in the United States are overweight or obese.[1] Excess body fat increases the likelihood of developing hypertension, dyslipidemia, and type 2 diabetes mellitus and is an independent risk factor for cardiovascular disease.[2–4] Obesity is linked to an increased risk for certain cancers, osteoarthritis, and sleep apnea.[5–8] Obese people are stigmatized.[9] Medical costs attributable to obesity are enormous.[10] The healthcare community and patients would thus welcome the development and approval of new obesity drugs with favorable benefit-risk profiles.

To facilitate drug development, the US Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research issues guidance documents for the pharmaceutical industry. These documents provide the agency's current thinking on therapeutic indications, target populations, clinical trial designs, and data analyses. This article examines the origins and evolution of the FDA's guidance document for the development of drugs to treat obesity.

Background

In 1947, the FDA approved the first prescription obesity drug, desoxyephedrine or methamphetamine.[11] Approval of amphetamine congeners (eg, phentermine), fenfluramine, and other appetite suppressants followed over the next 2½ decades. Then, in 1973, with the country struggling with a long-running epidemic of amphetamine abuse, the FDA, concerned about the abuse potential of the amphetamine congeners and their transient efficacy, limited the indication of all obesity drugs to short-term use (ie, a few weeks).[11,12] This restriction did little to counter opinions that vanity was the only reason to lose weight and that obesity drugs had no role in long-term weight loss.

This mindset began to change in subsequent years. "[While] most public attention and economic activity related to obesity has been devoted to cosmetic and esthetic concerns about body weight, it has become increasingly obvious that obesity is a serious public health concern, with adverse effects on health and longevity," declared members of a 1985 National Institutes of Health (NIH) Consensus Conference on obesity.[13] Long-term studies (eg, >6 months) of approved and investigational obesity drugs were also initiated during this time period.

The discovery in the early 1990s of leptin, an adipocyte-derived hormone integral to the regulation of body weight, coincided with the transfer of regulatory oversight of obesity drugs from the FDA's Division of Neuropharmacologic Drugs to the Division of Metabolism and Endocrinology Products (the Division).[14]

1995 FDA Advisory Committee Meeting

In 1995, the Division convened a public meeting with its advisory committee and a number of obesity experts to facilitate the development of a guidance document for the development of obesity drugs.

The overriding message from the first day of presentations by experts in the field was that obesity is a chronic disease.[15] And as with any chronic disease, pharmacotherapy is effective only when taken long term. There was no reason to believe, it was pointed out by an academic bariatrician, that a patient with hypertension would benefit long term from a short course of an antihypertensive. Why, then, did some people persist in believing that long-term pharmacotherapy had no place in the treatment of obesity? First, he remarked, "obesity is a stigmatized condition" (G. Bray, Endocrinologic and Metabolic Drugs Advisory Committee Meeting).[16] If obese individuals would simply push themselves from the dining room table, the refrain went, they would have no need for an obesity drug. Second, he noted that obesity drugs suffered under the "negative amphetamine halo."[16] The approved weight-loss drugs had structural similarities to amphetamine. Thus, many believed that they were addictive and should be avoided. Third, he indicated that in past studies, by and large, pharmacologically induced weight loss was not maintained long term.[17]

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Yet, this bariatrician displayed optimism as he presented data to the committee demonstrating that dexfenfluramine-associated weight loss was sustained for 1 year.[18] Furthermore, combining fenfluramine, a serotonergic compound, with phentermine, an adrenergic compound (fen-phen), he observed, was a very effective way to lose weight and sustain it long term.[19] Some obese individuals treated with this combination, he informed the committee, were able to reach and maintain ideal body weight for as long as 4 years.

"Did any of these studies really address the issue of morbidity and mortality?" asked an advisory committee member (J. Cara, Endocrinologic and Metabolic Drugs Advisory Committee Meeting).[20] "The numbers are too small for mortality," responded the bariatrician.[16] "I mean, what is the mortality of a 30-year-old population? You need tens of thousands. You really can't address that question … so the answer is no."[16] Regarding morbidity, he stressed that the fen-phen studies demonstrated "improved high density lipoprotein cholesterol levels and decreased triglyceride [levels]."[16] Furthermore, "… you can get a reduction in blood pressure with modest reductions in body weight," he continued.[16] "How would you design a trial to be able to provide data about long-term morbidity and mortality if all you looked at was simply weight loss?" inquired another committee member (E. Siris, Endocrinologic and Metabolic Drugs Advisory Committee Meeting).[21] That, according to the bariatrician, was an issue best handled by the National Institutes of Health, not drug companies. The first studies to demonstrate that lowering cholesterol or blood pressure with drugs reduced cardiovascular morbidity and mortality, he indicated, were government-sponsored trials. Drug development would be stifled, he believed, if companies were required to evaluate morbidity or mortality end points before drug approval.

On the second day of the meeting, a senior FDA official reminded the committee that the obesity drug guidance was not intended to be an obstacle to drug development. Rather, it was viewed as a means to advance the field of obesity pharmacotherapy by ensuring that new drugs were approved on the basis of "sound scientific data showing benefits to health and well-being" (G. Troendle, Endocrinologic and Metabolic Drugs Advisory Committee Meeting).[22] "If the old policies are continued," she cautioned, "and drugs are approved on the basis of a few kilograms of weight loss for 3- to 6-month intervals following which there is a clear tendency for excess weight to return, medical experts will continue to believe that in the long-run patients would be better off if left untreated."[22]

Nearing the meeting's end, the Division asked the advisory committee a number of questions: Is weight loss alone an appropriate end point on which to base approval of a new drug? What degree of weight loss should be considered clinically significant? And what duration of preapproval study is appropriate to assess the efficacy and safety of a new drug?

The majority of the committee believed that weight loss alone would be sufficient for approval, provided that it was clinically significant, which was variously referred to as a 5%, a 5% to 10%, or a 10% to 15% reduction in body weight. Most members supported 1-year trials to assess efficacy, with some recommending a second year for efficacy and safety.

The 1996 Draft Obesity Drug Guidance

After the 1995 advisory committee meeting, a draft guidance for obesity drugs was published in 1996.[23] The goal of this guidance was to facilitate the development of drugs to improve health and self-esteem by reducing body fat.

The target population included individuals with a body mass index (BMI) $\geq$30 kg/m^2 or $\geq$27 kg/m^2 if accompanied by weight-related comorbidities such as hypertension, dyslipidemia, and type 2 diabetes mellitus. These BMI thresholds reflected a recommendation that individuals be treated when their body weight was at least 20% above "desirable weight" based on Metropolitan Life Insurance data from 1983.[24] A BMI of $\approx$27 kg/m^2 for men and women corresponded to being 20% above desirable weight and was associated with increased risks for hypertension, hypercholesterolemia, and diabetes mellitus, as well as premature death.

The guidance recommended that the pivotal studies be randomized, double blind, and placebo controlled for 1 year, with open-label drug exposure during a second year. Only subjects whose weight loss plateaued and remained above ideal body weight after at least 6 weeks of lifestyle modification were to be randomized to active drug or placebo. Approximately 1500 subjects were to complete 1 year of double-blind, placebo-controlled treatment, with 200 to 500 completing a second year of open-label drug exposure. These sample sizes mirrored those historically used for the development of lipid-altering drugs and were aimed at assessing safety rather than efficacy because far fewer subjects would generally be necessary to demonstrate statistically significant weight loss. Because diet-induced reductions in body weight of 5% to 10% reduced blood pressure, indexes of glycemia, and levels of triglycerides and increased levels of high-density lipoprotein cholesterol, the guidance used 5% as an efficacy benchmark.[25] In addition to assessing efficacy by comparing the mean changes in body weight between treatment groups, it was also considered informative to compare the frequency of 5% weight-loss responders between treatment groups.

Hence, demonstration of weight-loss efficacy was possible if the drug effect is significantly greater than the placebo effect and the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5% or the proportion of subjects who lose at least 5% of their initial body weight is significantly greater in subjects on drug than placebo.

Efficacy was to be assessed after 1 year of treatment. Companies were encouraged to measure biomarkers of cardiovascular and metabolic risk because they may have a place in determining the balance of benefit versus risk for the drug.

Approval of Drugs for the Long-Term Treatment of Obesity

Although the development programs for dexfenfluramine (Redux), sibutramine (Meridia), and orlistat (Xenical) were initiated before publication of the 1996 draft obesity guidance, they were all aimed at gaining regulatory approval for the treatment of obesity without restriction on the duration of

use. The mean placebo-subtracted weight loss associated with these drugs after 1 year of treatment was <5%, but a greater proportion of drug-treated compared with placebo-treated subjects lost at least 5% of baseline body weight.[26–28] In general, biomarkers of cardiovascular risk moved in the appropriate direction with dexfenfluramine and orlistat.[29,30] However, the stimulation of the sympathetic nervous system by sibutramine led to small to modest increases in blood pressure and pulse relative to placebo.[31]

Some scientists were convinced, on the basis of primate data, that dexfenfluramine was a neurotoxin.[32] Others pointed to epidemiological data indicating that dexfenfluramine increased the risk for primary pulmonary hypertension, a rare but fatal disease.[33] Because this risk did not manifest until at least 3 months of exposure to the drug, it was argued that the benefit-risk profile could be enhanced by limiting the use of dexfenfluramine to overweight and obese individuals who lost at least 4 pounds during the initial month of treatment because they were more likely to lose at least 10% of their initial body weight by the end of 1 year of treatment.[34] The chief safety issue with orlistat was the possibility of developing a fat-soluble vitamin deficiency.[35,36] Vitamin supplementation, it was assumed, would negate this potential harm. The sympathomimetic effects of sibutramine were concerning but deemed manageable through monitoring of blood pressure and pulse.

All things considered, the FDA believed that the benefits of these drugs outweighed their risks, and each was approved for the long-term treatment of obesity: dexfenfluramine in 1996, sibutramine in 1997, and orlistat in 1999.

Postapproval data linking dexfenfluramine and fenfluramine (approved in 1973 for short-term use) to cardiac valve damage—requiring valve replacement in some cases—rendered the benefit-risk profiles of these drugs unfavorable.[37,38] Both were removed from the market in 1997.

The 2004 FDA Advisory Committee Meeting

In 1998, the National Institutes of Health issued *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults*.[39] In these guidelines, normal weight was defined as a BMI of 18.5 to 24.9 kg/m^2; overweight, as a BMI of 25 to 29.9 kg/^{2}; obesity, as a BMI ≥30 kg/m^2; and extreme obesity, as a BMI ≥40 kg/m^2. The classifications were based largely on cross-sectional data relating BMI to mortality in which the risk for death in some, but not all, analyses begins to increase at a BMI of ≈25 kg/m^2.[40–42] Given the new weight classifications and other developments in the field of obesity since issuance of the 1996 obesity guidance, the Division again convened its external advisory committee and a group of obesity experts in 2004 to discuss updating the guidance document.

Because the recommended target population for drug therapy in the 1996 obesity drug guidance included individuals with BMIs of ≥27 kg/m^2 and overweight was defined in the 1998 National Institutes of Health guidelines as a BMI of 25 to 29.9 kg/m^2, a researcher from the Centers for Disease Control and Prevention was asked by the Division to provide the advisory committee with an overview of the epidemiology of overweight, with a focus on data related to individuals with BMIs in the range of 25 to <27 kg/m^2.

As recent data from the National Health and Nutrition Examination Surveys indicated, the Centers for Disease Control and Prevention researcher pointed out to the committee that ≈30 million American adults had a BMI in the range of 25 to <27 kg/m^2.[43] About 12 million, half of whom were ≥60 years of age, had hypertension, hypercholesterolemia, or diabetes mellitus. She highlighted that, in general, the prevalence of diabetes mellitus, hypertension, and hypercholesterolemia increased as BMI increased but without clear inflection points.

There was little information on the health benefits of weight loss in this BMI range of 25 to <27 kg/m^2, the Centers for Disease Control and Prevention researcher observed, because these individuals had not, for the most part, been included in weight-loss studies. Nonetheless, she remarked, "short-term weight loss has beneficial effects on risk factors such as blood pressure and cholesterol" (K. Flegal, Endocrinologic and Metabolic Drugs Advisory Committee Meeting), and most studies suggest that the relationship between weight loss and risk factor improvement is monotonic.[44] "You would infer from this," she continued, "that weight loss is very likely to improve blood pressure and other risk factors, certainly in the range of BMI of 25 to 27 [kg/m^2], as well as perhaps at any weight level."[44] This researcher cautioned, however, that "there are [some] observational studies that suggest some association of weight loss with increased rather than decreased mortality."[44]

As an FDA drug use specialist next informed the committee, white women accounted for ≈80% of obesity drug prescriptions in the United States, with ≈60% of the prescriptions being written for individuals between 18 and 44 years of age and 33% for people 45 to 64 years of age.[43] Although the majority of obesity drugs were paid for by cash, the committee learned, third-party payment had increased from ≈20% to 30% during the years 1999 to 2003.[43]

The morning session of the meeting concluded with a presentation by a bariatrician and then president of the American Obesity Association. "I have looked into the eyes of [obese] people and seen the pain and heard the pain as they talk, and I have failed them and I think we have all failed them" (R. Atkinson, Endocrinologic and Metabolic Drugs Advisory Committee Meeting), he opined to the committee.[45] Discussing barriers to the use of drugs to treat obesity, he stated that "obesity is the last bastion of socially acceptable bigotry."[45] Physician ignorance was another barrier. Economics played a part. Drugs approved for the long-term treatment of obesity are expensive and "insurance companies and employers are worried about breaking the bank."[45] Additional barriers to obesity drugs were "limited choices and poor efficacy."[45]

During the afternoon session, the committee responded to a number of questions posed by the Division, including 3 fundamental ones: Should the target population for drug treatment be expanded to include individuals with BMIs of 25 to <27 kg/m^2 with an obesity-related comorbidity? Should obesity drug efficacy continue to be judged by the 5% weight-loss benchmark? And should preapproval trials of

Table 1. Key Features of the Food and Drug Administration's 2007 Draft Obesity Drug Guidance

Target population
BMI ≥27 kg/m^2 plus a weight-related comorbidity or a BMI ≥30 kg/m^2
Size and duration of the phase 3 clinical trials
≥4500 Overweight and obese subjects studied for at least 1 y
Efficacy criteria
Mean placebo-subtracted weight loss ≥5% or proportion of drug-treated subjects who lose ≥5% of baseline body weight is ≥35% and approximately double the proportion who lose ≥5% in the placebo group
Secondary end points of interest
Blood pressure and pulse
Lipoprotein lipids
Fasting glucose and insulin
Hemoglobin A_{1c} (in diabetics)
Waist circumference
Quality of life
Primary analysis population
Intention to treat

BMI indicates body mass index.

investigational obesity drugs include a second year of open-label drug exposure?

Some panelists recommended lowering the target population to include individuals with BMIs of 25 to <27 kg/m^2 with at least 1 obesity-related comorbidity; however, the majority favored keeping the BMI cutoff at ≥27 kg/m^2 when accompanied by a comorbidity. As 1 panelist commented, "… because we don't have outcomes data related to mortality or morbidity [with drug-induced weight loss], I personally would not lower the BMI cut point …." (M. Wierman, Endocrinologic and Metabolic Drugs Advisory Committee Meeting).[46]

There was uniform agreement by the committee that weight-loss efficacy should continue to be defined by the 5% benchmark. Some panelists favored a second year of open-label drug exposure, although more believed that 1-year trials would provide sufficient data to assess the preapproval efficacy and safety of a new obesity drug.

The 2007 Draft Obesity Drug Guidance

After this latest advisory committee meeting, an updated draft guidance was issued in 2007 for the purpose of facilitating development of obesity drugs for medical weight loss, defined as a long-term reduction in fat mass with a goal of reduced morbidity and mortality through quantifiable improvements in biomarkers such as blood pressure, lipids, and hemoglobin A_{1c} (Table 1).[47]

The target population for inclusion in studies of investigational obesity drugs remains individuals with a BMI ≥30 kg/m^2 or ≥27 kg/m^2 when accompanied by weight-related comorbidities. The 2007 draft guidance recommends that subjects with extreme obesity (ie, BMI >40 kg/m^2) be included in development programs. To define efficacy and to provide a reasonable estimate of safety, the guidance recommends that ≈3000 subjects be randomized to active doses of the investigational drug and no fewer than 1500 subjects be randomized to placebo for 1 year. This sample size provides 80% power to rule out with 95% confidence an ≈50% increase in the incidence of an adverse event that occurs at a rate of 3% in the placebo group (ie, 4.5% versus 3%).

To simulate the real-world setting, a lifestyle modification program that strikes an appropriate balance between effectiveness and simplicity was recommended as standard of care for all study subjects.

Efficacy continues to be assessed with the 5% mean and categorical criteria: The difference in mean weight loss between active-treated and placebo-treated groups is at least 5% and the difference is statistically significant, and the proportion of subjects who lose ≥5% of baseline body weight in the active-treated group is at least 35%, approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

The standard that the proportion of active-treated group who lose ≥5% of baseline body weight be at least 35% and approximately double the proportion in the placebo group was based on clinical trial data from previously approved obesity drugs. In long-term studies of sibutramine and orlistat, the proportion of subjects treated with active drug plus lifestyle modification who lost at least 5% of baseline body weight was generally double the proportion of subjects treated with placebo plus lifestyle modification.[27,28] Moreover, because the absolute proportion of subjects losing at least 5% of baseline body weight is directly related to the intensity of the lifestyle modification program, data from a clinical trial of orlistat conducted in the primary care setting that used a realistic real-world lifestyle modification program provided the basis for the requirement that at least 35% of subjects treated with active drug lose at least 5% of baseline body weight.[48]

In general, an obesity drug will be considered effective if after 1 year of treatment either of the above efficacy criteria was satisfied. Moreover, improvements in blood pressure, lipids, glycemia, and other weight-related comorbidities commensurate with the degree of weight loss are expected and will be factored into the benefit-risk assessment of the drug.

The dropout rates in long-term obesity drug trials have historically been high (eg, ≈40%–50%). Although the guidance does not stipulate a maximally tolerated dropout rate, in addition to encouraging companies to do all they can to increase subject retention, the guidance recommends that body weight measurements in all subjects who prematurely withdraw from long-term clinical trials be obtained near the calendar date at which they were scheduled to complete the trial. This will allow the primary efficacy analyses to be conducted with a modified intention-to-treat population, defined as subjects who received at least 1 dose of study drug and have at least 1 postbaseline assessment of body weight. To assess the effect of dropouts on the weight-loss results, companies are encouraged to conduct sensitivity analyses using imputation strategies.

New to the 2007 draft guidance are sections on the study of overweight and obese individuals with type 2 diabetes, combination drug therapy, the treatment of medication-induced weight gain, and the development of obesity drugs for the pediatric population.

Study in Overweight and Obese Type 2 Diabetics

Compared with nondiabetic subjects, overweight and obese subjects with type 2 diabetes mellitus often lose less weight on obesity drugs and may face unique safety issues such as risk for sulfonylurea-induced hypoglycemia after weight loss (if the dose of sulfonylurea is not appropriately lowered or the drug discontinued). Therefore, the 2007 draft guidance recommends that the efficacy and safety of obesity drugs be examined in a trial dedicated to overweight and obese subjects with type 2 diabetes mellitus. Successful completion of a single trial may lead to inclusion of glycemia-related data in the clinical studies section of the labeling of the drug but is not considered sufficient to support approval of a standalone indication for the treatment of type 2 diabetes mellitus.

Companies interested in obtaining a standalone indication for the treatment of type 2 diabetes mellitus for their obesity drug are required to study their drug comprehensively as an antidiabetic agent and are referred to the FDA guidance documents *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*[49] and *Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*.[50]

Of note, the 2007 draft obesity drug guidance states that for an obesity drug to obtain a standalone indication for the treatment of type 2 diabetes mellitus, it should be shown that the drug effectively treats type 2 diabetes mellitus through a mechanism that is independent of weight loss. However, the agency has reconsidered this requirement since issuance of the draft guidance. Thus, a drug with a principal mechanism of action of weight loss may gain approval and a standalone indication for the treatment of type 2 diabetes mellitus by showing clinically and statistically significant improvement in glycemia within the context of a full development program aligned with the 2 antidiabetic drug guidance documents.

Parenthetically, a weight-loss–inducing antidiabetic drug could be approved for the treatment of obesity if the weight loss satisfied the mean or categorical obesity drug efficacy criterion and the development program was, in general, aligned with the key features of the obesity drug guidance, including study in overweight and obese nondiabetic subjects.

Fixed-Dose Combination Products

Two or more drugs may be combined into a single fixed-dose combination when each component makes a contribution to the claimed effects and the dosage of each component is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug.[51] Special cases of this general rule include the addition of a component to enhance the safety or effectiveness of the principal component or to minimize the potential for abuse of the principal active component.

The draft guidance recommends that the efficacy and safety of fixed-dose combination obesity drugs be compared with the individual components and placebo in phase 2 trials of sufficient duration to capture the maximal or near-maximal weight-loss effects of the drugs. Although the guidance does not define a minimum difference in weight loss between a fixed-dose combination and its individual components, a combination drug that is associated with at least twice the weight loss observed with each of the individual components will be viewed more favorably than a combination that does not achieve this degree of relative weight loss. If a fixed-dose combination drug is shown to be more effective than its individual components in a phase 2 study, the phase 3 trials may be limited to examining the efficacy and safety of the combination compared with placebo over the course of 1 year. The efficacy of the combination will be assessed with the standard 5% mean and categorical weight-loss criteria.

Treatment of Medication-Induced Weight Gain

A number of drugs, notably psychotropics, are associated with moderate to marked weight gain and new-onset type 2 diabetes mellitus.[52–54] The 2007 draft guidance recommends that subjects eligible for participation in trials examining the efficacy and safety of obesity drugs for the treatment of medication-induced weight gain have a documented increase in body weight of at least 5% within 6 months of starting a drug known to cause weight gain. Furthermore, subjects should have BMIs $\geq$30 kg/m^2 or $\geq$27 kg/m^2 with comorbidities at the time of study screening. Because many, if not most, obesity drugs act within the central nervous system, as do many drugs that cause weight gain, the guidance stresses the need to demonstrate that the efficacy and safety of the medication causing weight gain are not adversely affected by a centrally acting obesity drug. For example, it would be important to document that the efficacy of an antipsychotic used to treat schizophrenia was not diminished when coadministered with a centrally acting obesity drug. Efficacy of a drug used to treat medication-induced weight gain will be assessed with the standard 5% mean and categorical weight-loss criteria.

Obesity Drug Development in the Pediatric Population

In terms of obesity drug therapy for children and adolescents, the 2007 draft guidance recommends that the efficacy and safety of an investigational obesity drug first be examined in adults before studies are initiated in pediatric subjects. Additionally, to ensure that the most appropriate dose or doses are studied, an assessment of the pharmacokinetics of an obesity drug in pediatric subjects may be necessary before embarking on long-term studies. Trials examining the efficacy and safety of obesity drugs in pediatric subjects should be randomized, double blind, and placebo controlled and should be 1 year in duration.

Initial studies should be limited to adolescents (ie, 12–16 year olds) with age- and sex-matched BMIs >95th percentile and $\geq$1 weight-related comorbidities. Once a satisfactory benefit-risk profile has been established in this high-risk group, studies of lower-risk adolescents or children will be considered. Linear growth needs to be taken into account in assessments of changes in body weight of pediatric subjects. Hence, the primary efficacy parameter of obesity drugs in pediatric subjects should be a function of the change in BMI. The 2007 draft guidance does not provide a sample size for the phase 3 trials of pediatric subjects. Rather, the size of the pediatric development program will be determined on the

basis of the mechanism of action of the drug and its safety profile in adults.

The efficacy assessment of an obesity drug in pediatric subjects will take into account the effectiveness of the product in adults and the magnitude of the difference in the mean and categorical changes in BMI in active- versus placebo-treated subjects.

With respect to the overall safety assessment of investigational obesity drugs, in addition to standard biochemical and clinical monitoring of patients, on the basis of research implicating activation of the $5HT2_b$ receptor as the mechanism responsible for dexfenfluramine- and fenfluramine-associated valvular heart disease, the 2007 draft guidance recommends that serotonergic compounds that interact directly with the 5HT2 receptor system be evaluated with serial echocardiography to rule out cardiac valve injury.[55,56] Moreover, the draft guidance notes that as new scientific data emerge, the need for specific safety assessments for investigational obesity drugs may change accordingly. As detailed below, recent experience with rimonabant and sibutramine is illustrative in this regard.

Rimonabant

The endocannabinoid system is involved in a vast array of physiological functions, including energy homeostasis. Activation of cannabinoid type 1 receptors in the central nervous system influences appetite and feeding behavior, whereas activation in the periphery affects substrate metabolism in fat, skeletal, and liver cells.[57] Rimonabant was the first-in-class cannabinoid type 1 receptor antagonist developed for the treatment of obesity.

Data submitted to the FDA in a new drug application in 2005 indicated that, over the course of 1 year, rimonabant 20 mg once daily was associated with an ≈5% mean reduction in body weight compared with placebo in overweight and obese nondiabetics.[58] Approximately 50% of rimonabant-treated subjects lost at least 5% of initial body weight compared with ≈20% of placebo-treated subjects. Changes in biomarkers of cardiovascular and metabolic risk were favorable with rimonabant treatment. Thus, rimonabant was an effective obesity drug when gauged by the standards of the draft obesity drug guidance.

However, the doubling of reports of anxiety and depression, a signal for suicidal ideation as identified by a retrospective analysis of adverse event data, and an ill-defined constellation of neurological signs and symptoms in rimonabant-treated subjects led an FDA advisory committee to unanimously conclude that, on the basis of the available data, the potential benefits of rimonabant did not outweigh the potential risks.[59] The rimonabant application was voluntarily withdrawn from the FDA by the sponsor shortly after the advisory committee meeting. On the basis of this experience, the draft obesity guidance recommends that the development programs for centrally acting obesity drugs prospectively assess neuropsychiatric function, including suicidality, with validated instruments.

Meanwhile, the European Medicines Agency had approved rimonabant for the treatment of obesity in 2006. And the favorable changes in biomarkers of cardiometabolic risk associated with rimonabant led the sponsor of the drug to initiate the Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial in 2005. This study of ≈9000 subjects randomized to rimonabant and ≈9000 to placebo was powered to demonstrate a 15% reduction in the relative risk of major cardiovascular events in rimonabant-treated subjects. Demonstration that long-term treatment with rimonabant reduced the incidence of cardiovascular death, myocardial infarction, or stroke would have greatly enhanced the benefit-risk profile of the drug.

But, in January 2009, the European Medicines Agency suspended the marketing authorization for rimonabant.[60] This action followed an updated assessment of available data indicating that the risk for serious psychiatric disorders, including suicide, appeared to be higher than observed in the preapproval clinical trials. Together with evidence that many real-world patients were taking rimonabant for short periods of time and therefore were unable to reap the benefits of sustained weight loss, European regulators concluded that the benefits of rimonabant no longer outweighed its risks. At the time the marketing and worldwide study of rimonabant came to an end, participants in the CRESCENDO trial had been treated for an average of 13.8 months (planned duration was at least 33 months). The interim hazard ratio for major cardiovascular events was 0.97 (95% confidence interval, 0.84–1.12; $P=0.68$).[61] Psychiatric disorders were reported by 32% of the subjects in the rimonabant group compared with 21% of the subjects in the placebo group. Four individuals randomized to rimonabant committed suicide compared with 1 randomized to placebo.

Sibutramine and the Sibutramine Cardiovascular Outcomes Trial

From 2002 to 2009, the Sibutramine Cardiovascular Outcomes (SCOUT) trial was conducted in Europe, Australia, and Latin America. SCOUT was a randomized, double-blind, placebo-controlled study designed to test the hypothesis that long-term treatment with sibutramine reduces the risk for major cardiovascular events.[62] Approximately 10 000 overweight and obese subjects between 51 and 88 years of age with or at risk for cardiovascular disease received lifestyle modification plus once-daily placebo or lifestyle modification plus 10 or 15 mg once-daily sibutramine. Three cardiovascular risk subgroups were defined at baseline: (1) subjects with type 2 diabetes mellitus with no history of cardiovascular disease, (2) those with a history of cardiovascular disease without type 2 diabetes mellitus, and (3) subjects with a history of cardiovascular disease with type 2 diabetes mellitus.

After an average of 3.4 years of treatment, the mean reduction in body weight was 3.8% in the sibutramine group and 1.8% in the placebo group. Throughout the trial, mean systolic and diastolic blood pressures and heart rate were slightly and statistically significantly higher in the sibutramine compared with the placebo group. The incidence of major cardiovascular events, defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or resuscitated cardiac arrest, was 11.4% in the sibutramine group compared with 10% in the placebo group (hazard ratio, 1.16;

Table 2. Incidence of Major Adverse Cardiac Events in Subgroups of Cardiovascular Risk From the SCOUT Trial

	MACE				
Subgroup	Sibutramine	Placebo	HR	95% CI	Interaction *P**
DM only					
N	1151	1141			0.56
n (%)	69 (6.0)	70 (6.1)	1.0	0.72–1.40	
CVD only					
N	722	745			
n (%)	73 (10.1)	61 (8.2)	1.3	0.91–1.80	
CVD+DM					
N	3016	2998			
n (%)	418 (13.9)	359 (12.0)	1.2	1.0–1.40	

SCOUT indicates Sibutramine Cardiovascular Outcomes trial; MACE, major adverse cardiac events; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; and CV, cardiovascular disease.

*Log-rank test interaction *P* value.

95% confidence interval, 1.03–1.31; $P=0.02$). This risk corresponds to ≈4 excess major cardiovascular events per 1000 patient-years. Interestingly, post hoc exploratory analyses suggested that sibutramine-associated increases in blood pressure did not predict increased risk for major cardiovascular events.[63]

Although the results of SCOUT indicated that sibutramine increased rather than decreased the risk for cardiovascular events, Abbott Laboratories, the sponsor of the drug, questioned the relevance of the data to the real-world setting. The labeling for sibutramine recommended against use in individuals with a history of cardiovascular disease because of its sympathomimetic properties, whereas roughly 75% of subjects enrolled in SCOUT had a history of coronary artery, cerebrovascular, and/or peripheral artery disease. This enrichment, however, was necessary to ensure a sufficient number of clinical events to examine the effect of sibutramine on the atherothrombotic process. Nonetheless, it was argued that because ≈60% of individuals prescribed sibutramine in the United States were <50 years of age, many without a history of cardiovascular disease, the results of SCOUT were less than informative.[64] Support for this was to be found in the cardiovascular risk subgroup analysis from SCOUT. The hazard ratio for major cardiovascular events in the subgroup of subjects without a history of cardiovascular disease was 1.0 (95% confidence interval, 0.72–1.40; Table 2). Yet, there was no statistical evidence of treatment heterogeneity among the 3 cardiovascular risk subgroups (log-rank interaction, $P=0.56$). Furthermore, the results in the subgroup without documented cardiovascular disease were consistent with as much as a 40% increase in the relative risk for major cardiovascular events. Additionally, prescription-use data indicated that people >50 years of age, some with congestive heart failure, ischemic heart disease, or cardiac arrhythmias, were being prescribed sibutramine.[64]

Absent convincing evidence that sibutramine offered noncardiovascular benefits to offset the cardiovascular risk observed in the SCOUT trial, the FDA concluded that, at the population level, the benefit-risk profile of the drug was unfavorable.[65–68] Moreover, the FDA determined that risk-mitigation strategies aimed at enhancing the benefit-risk profile of sibutramine at the individual-patient level, by, for example, ruling out subclinical cardiovascular disease before sibutramine was started or using on-drug increases in blood pressure as a predictor of cardiovascular risk, were impractical and not supported by clinical trial data, respectively.[69] On October 8, 2010, sibutramine was voluntary withdrawn from the US market.[70]

Given the experience with sibutramine, the Division plans to hold an advisory committee meeting in 2012 to discuss what role cardiovascular risk assessment should play in the overall benefit-risk evaluation of obesity drugs, in particular those with pressor effects.

New Obesity Drugs

In 2010, the Division held public advisory committee meetings to discuss 3 new obesity drug applications: (1) a fixed-dose combination of phentermine and topiramate, (2) lorcaserin, and (3) a fixed-dose combination of naltrexone and bupropion. At the time of this writing, these 3 applications remain under FDA review. Because a federal regulation precludes the FDA from publicly discussing information about unapproved applications except under certain situations such as a public advisory committee meeting, interested readers are referred to the proceedings from the 2010 advisory committee meetings for details on the efficacy and safety profiles of phentermine plus topiramate, lorcaserin, and naltrexone plus bupropion.[71–74]

Conclusions

As several academic bariatricians recently wrote, "many factors have mitigated against active drug development, including the poor safety and efficacy of previous[ly approved] antiobesity drugs."[75] Nevertheless, despite this unfortunate history, obesity drug research remains very active.[76] Moreover, the adverse physical, emotional, and economic effects of obesity ensure that the goals of developing and approving obesity drugs with favorable benefit-risk profiles will endure.

Disclosures

None.

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KEY WORDS: cholesterol ■ diabetes mellitus, type 2 ■ hypertension ■ lipids ■ obesity

Obesity Pharmacotherapy from a Regulatory Perspective: Overview and Key Challenges

NI Hutchinson[1] and SW Ryder[1]

Obesity is an epidemic with tremendous impact on both patients and health-care systems globally. This paper explores some of the questions related to the clinical development of new pharmacotherapies in the context of an evolving regulatory perspective. These include patient entry criteria, clinical database size, study designs, weight loss end points (including those for maintenance of weight loss and prevention of weight regain), clinically important patient-reported outcomes, comorbidity/risk factor end points, and challenges in establishing safety and efficacy in adolescent/pediatric patients, and approaches to the development of combination pharmacotherapies. Ultimately, patients, physicians, academia, industry, payers, and governments must continue to partner with regulators to help establish the appropriate balance between the known adverse consequences associated with inadequate treatment of the growing obesity epidemic and the concern for potential unknown risks that may be associated with the long-term use of new pharmacotherapies.

OBESITY EPIDEMIC

Significant medical need

Obesity has been recognized by the World Health Organization as a chronic disease of significant health concern globally.[1] In the United States, it is estimated that 127 million (MM) (64.5%) adults are overweight (body mass index (BMI) $>25\,kg/m^2$), 60 MM (30.5%) are obese (BMI $>30\,kg/m^2$), and nine MM (4.7%) are severely obese (BMI $>40\,kg/m^2$).[2,3] The rapidly increasing incidence of overweight and obese children and adolescents is an even more disturbing trend.[4,5] Obesity is associated with numerous serious comorbidities, and increased mortality,[6–10] and is thought to be a key driver in the increased incidence of type II diabetes, which is also reaching epidemic proportions.[1] The critical need to stop, and ultimately to reverse, these trends has motivated governments, health organizations, health-care professionals, researchers, and patient groups globally to seek improved approaches to both prevent and treat obesity. However, because of the limitations of the existing therapeutic options, including current pharmacotherapies (**Table 1**), there continues to be significant unmet medical need, which in turn drives the search for new, safe, and effective, approved pharmacotherapies.

EVOLUTION OF THE REGULATORY PERSPECTIVE

A detailed review of the history of the regulatory approval of appetite suppressants in the United States was recently published by Colman.[11] It provides an overview of the key drivers that influenced the evolution of the FDA perspectives regarding the efficacy and safety of weight loss drugs and the key challenges to balancing the risks and benefits in this therapeutic area. As the understanding of the causes of obesity, its associated risk factors, and long-term consequences has grown, and experience with existing therapies has increased, the regulatory perspective has evolved. Although safety has always been a key regulatory concern, the perspective on efficacy, and its definition, has also evolved.

1996 FDA DRAFT GUIDANCE FOR THE CLINICAL EVALUATION OF WEIGHT-CONTROL DRUGS

FDA's Endocrine and Metabolic Drugs Advisory Committee (EMDAC) was convened in 1995 to make recommendations for a draft FDA guidance document on clinical evaluation of weight-loss drugs.[12] The guidance was published in 1996[13] and incorporated many of the NIH recommendations for management of obesity.[14] The FDA guidance recommends that the target patient population for obesity drug therapy be those patients moderately to markedly obese with a BMI of $\geqslant 30\,kg/m^2$ that are without obesity-related comorbidities, or those patients with a BMI of $\geqslant 27\,kg/m^2$ that have obesity-related comorbidities. For the first time, the FDA offered a definition of clinically relevant weight loss to set the standard for drug efficacy. That definition was, and still is, a mean

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Table 1 FDA approved weight-loss drugs

Pharmacotherapy	Year	Treatment duration	Mechanism and status
Desoxyephedrine	1947	Short term	Amphetamine
Phenmetrazine	1956	Short term	Amphetamine congener
Phentermine	1959	Short term	Amphetamine congener Currently most prescribed weight-loss therapy in US; withdrawn in EU 2000
Diethylproprion	1959	Short term	Amphetamine congener
Phendimetrazine	1959	Short term	Amphetamine congener
Benzphetamine	1960	Short term	Amphetamine congener
Mazindol	1973	Short term	Amphetamine congener
Fenfluramine	1973	Short term	Serotonin agonist, withdrawn 1997, associated with pulmonary hypertension and valvulopathy
Dexfenfluramine	1996	Long term	Serotonin agonist, withdrawn 1997, associated with pulmonary hypertension and valvulopathy
Sibutramine	1997	Long term. Indicated for weight loss and maintenance of weight loss	Serotonin and noradrenaline reuptake inhibitor. Label contains warning for substantial increases in blood pressure and pulse rate in some patients and requirement for regular monitoring.
Orlistat	1999	Long term. Indicated for weight loss and weight maintenance, and reducing risk of weight regain	Pancreatic lipase inhibitor for blocking fat absorption. Label contains clinical data demonstrating delay in onset of type II diabetes in patients with impaired glucose tolerance and data on use in obese adolescents. Recently approved for OTC.
Rimonabant[a]	-	-	CB-1 antagonist:

OCT, over the counter. [a]FDA "approvable" letter February 2006. Approved in EU June 2006.

weight loss $\geqslant$5% in drug- versus placebo-treated patients or a statistically significant increase in the proportion of patients losing $\geqslant$5% body weight in the drug-treated versus placebo-treated group at 1 year. Measurement of other effects was encouraged, such as obesity-associated cardiovascular risk factors (lipids, blood pressure, and glucose tolerance) to permit an assessment of the overall benefit versus risk of therapy with a drug. Additionally, with the transition of the treatment approach from short- to long-term pharmacotherapy, the guidance stipulated that long-term exposure data would be required to establish safety: a minimum of 1 year of placebo-controlled exposure in 1,500 patients treated with drug, followed by a second year of drug exposure (potentially open-label) in 200–500 patients. The guidance also recommended including into the clinical weight loss studies a run-in phase with a weight loss program without drug for $\sim$6 weeks, or until weight loss has plateaued, and then to enroll only those patients who remain above their weight goal after the run-in phase to avoid treating patients unnecessarily with drug. Other data that were noted as being relevant, but for which the guidance provided no specific recommendations, included maintenance of weight loss, changes in obesity-related risk factors (*e.g.*, the distribution of body fat) and development of comorbidities (*e.g.*, diabetes or osteoarthritis).

ON-GOING EFFORTS TO UPDATE FDA DRAFT GUIDANCE

Since the publication of the United States guidance in 1996, knowledge and experience with anti-obesity therapy has continued to grow along with the medical need. In 2003, the Commissioner of Food and Drugs established the FDA's Obesity Working Group. In their 2004 report,[15] the Obesity Working Group recommended greater support for prevention, including improvements in nutritional labeling and education, and revising and reissuing FDA's 1996 draft Guidance for the Clinical Evaluation of Weight-Control Drugs. The FDA's EMDAC met in September 2004[16] to discuss proposed changes to the guidance. Topics discussed included the potential role of drugs in treatment and prevention of obesity, target populations at risk for obesity and its sequelae, evidentiary standards for proof of meaningful efficacy; and evidentiary standards for demonstration of acceptable safety. The EMDAC continued to support the existing recommendations for study size and duration and recommended continued support for the 5% placebo-corrected weight-loss criterion. Support was also provided for retaining the definition for the target adult population for drug therapy: BMI $\geqslant$30 or $\geqslant$27 kg/m^2 with comorbidities. The majority of the Committee did not support lowering the BMI from 27 to 25 kg/m^2 with or without comorbidities. It was felt that patients with a lower BMI should not be included without a much greater assurance of drug safety. An updated United States draft guidance document has not yet been issued.

DRUG DEVELOPMENT AND REGULATORY CHALLENGES – SELECTED KEY ISSUES

There are a number of key development and regulatory challenges that remain to be addressed to support and

improve the investigation and establishment of efficacy and safety of new obesity pharmacotherapies.[17]

Patient entry criteria

As knowledge of the natural history of obesity and the impact of weight loss or maintenance in various patient groups continues to accrue, clinical trial entry criteria and the patient population for which drug therapy may be appropriate should be regularly re-evaluated. Furthermore, as the safety and tolerability of long-term drug therapy becomes better established, and the benefits of drug therapy better defined, a reduction in the BMI criteria for treatment in defined subsets of patients at significantly higher risk for comorbidities may be considered, for example, younger to middle-aged patients with a strong family history of type II diabetes.

Clinical database size

Enhancements in the planning and the acquisition and analysis of clinical trial information are key priorities for improved drug development. These enhancements include improvements in study design, the issuance of risk management plans for each development candidate and a commitment to "continuous development" from preapproval, through introduction and growing use in medical practice. As these enhancements are implemented, the size of the clinical database required to support progression of a candidate to the next stage of development, approval, and postapproval should be revisited.

Updated study designs

Study design review and improvement are critical to enhancing the development of novel anti-obesity pharmacotherapies. For example, the need for a 4 to 8-week weight-loss run-in period before administration of study medication in a weight-loss clinical trial should be reevaluated based on the knowledge that lifestyle modification alone is generally ineffective in achieving and maintaining clinically relevant weight loss, and also based on the demonstrated benefit of combining lifestyle modification with pharmacotherapy.[18] A key intent of the weight-loss run-in period before initiation of study drug was to identify those patients who are able to achieve adequate weight loss by lifestyle modification alone and who, therefore, do not require supplemental pharmacotherapy. However, given the limitations of lifestyle modification alone, this rationale becomes less compelling, particularly in weight-loss studies of longer duration (1–2 years). Of note, many, if not most, obese patients enrolling in weight loss clinical trials have a history of unsuccessful efforts at sustained weight loss using lifestyle modifications alone. Importantly, the inclusion of a weight-loss run-in period before the initiation of drug therapy alters relevant baseline measurements, thereby obscuring a true understanding of drug effect on changes in weight and obesity-related risk factors.

Another topic to be addressed related to study design is the appropriate level of background lifestyle intervention administered to all clinical study participants in conjunction with placebo or drug treatment. Although the NIH Clinical Guidelines recommend that weight-loss drugs only be used as part of a comprehensive weight-loss program, including concomitant lifestyle modifications,[19,20] the extent of lifestyle intervention in clinical studies can vary widely. Clinical studies designed to support registration and labeling of new pharmacotherapies should lead the way to showing the most effective use of current weight-loss therapies, with the caveat that lifestyle interventions in the trial context should balance both the need to be reasonably "translatable" to the real world setting and the need to enhance retention of patients in studies. Performing drug studies in patients in the absence of a meaningful lifestyle-modification program would be inconsistent with treatment guidelines and would exacerbate the rate of patient dropout from such weight-loss studies. The high proportion of study dropouts remains a key issue in the conduct of anti-obesity trials and continues to be an issue in planned statistical analyses. A review, discussion, and guidance on the preferred statistical method to address dropouts would also assist in establishing consistency across drug development programs.

Weight-loss study end points

Maintaining weight loss is one of the most difficult aspects of obesity management.[19,20] Therefore, the development of therapies that can either enhance sustained weight loss or help to prevent regain of weight lost via lifestyle modification, would both help to motivate patients and address a key unmet medical need. In this light, criteria that support indications for "the maintenance of weight loss" and "the prevention of weight regain" would be useful. For example, what is the definition of "weight maintenance" and how does this differ from a demonstration of a durable drug effect? What difference from placebo, at what time point, would be acceptable to support an indication for maintenance of weight loss? For example, would maintaining a 5% mean weight-loss difference versus placebo at 1 year be adequate, or would a specific comparison relative to baseline, or to weight nadir on treatment, also be required? With respect to the prevention (or delay) of regain of previous weight loss, is weight loss induced by a low calorie diet[21] the most appropriate for assessing a drug effect on weight regain and what level of initial weight loss should be used for inclusion into a study examining a drug effect on weight regain? A definition of weight maintenance ($\pm$ 3% of body weight) has been proposed.[22] Would demonstration of statistically greater proportion of drug-treated patients compared with placebo with weight increases of 3% or less at a specified time point (*e.g.*, 3 or 6 months) after initial weight loss be acceptable or would a measure of patients who retained a clinically relevant weight loss ($>5\%$) 6–12 months after initiation of drug therapy following initial weight loss be required? The definition of clinically important changes in patient report outcomes also needs to be established for weight-loss therapeutics.

Co-morbidity/risk factor end points

Guidance is needed on what improvements in obesity-related risk factors and comorbidities would represent a benefit for the purpose of labeled claims. The current (1996) United States guidelines state that information related to changes in risk factors may be mentioned in the clinical-study section of the label. However, the new FDA labeling guidance[23] may reduce the information previously included in the clinical study section. Will demonstration of improvements in risk factors, improvements in comorbidities, or in specific clinical outcomes (*e.g,*. prevention of diabetes, reduction in cardiovascular morbidity/mortality) continue to be included in the clinical-study section of the label, or would data adequate to support an indication be required to incorporate this information into the label? If so, what are the specific evidentiary standards to be met? Would there be a requirement to demonstrate that the changes in risk factors or outcomes observed were beyond those anticipated from weight loss alone and how could that be demonstrated?

Adolescent/pediatric therapy

Guidance on how and when to evaluate efficacy and safety in adolescents and children is needed. Key questions include the extent of safety database in adults required before initiation of studies in adolescents or children (in addition to preclinical requirements), the entry criteria for adolescents and children into weight loss clinical studies, differences in study design/end points in a growing patient population compared with adults, and requirements and definitions for demonstrating long-term effects.

Combined therapy

Owing to the complex mechanisms that regulate body weight, it is unlikely that a single pharmacologic agent that alters one aspect of biological control will adequately address the unmet medical need associated with obesity.[24,25] However, treatment with a combination of pharmacotherapies targeting different mechanisms has the potential to achieve significantly greater weight loss than use of any single agent, as exemplified by fenfluramine–phentermine.[26] Unfortunately, in the case of fenfluramine–phentermine, one component of the combination (fenfluramine) was associated with unexpected serious adverse events.[27–29] As combination pharmacotherapies have the potential to provide additive (or synergistic) effects, both beneficial and adverse, it is important to outline that specific studies would be appropriate to support the safe and effective combined use of two weight-loss pharmacotherapies. For example, what should be the clinical basis for selecting the pharmacotherapies for combined use and for the development of fixed dose combinations? Additional points for consideration include the appropriate preclinical safety assessments, clinical safety parameters, and the required duration and size of studies based on the knowledge of each of the drug components. The use of combined weight-loss drugs may be critical to attaining adequate weight-loss efficacy to impact significantly the obesity epidemic, just as combined therapies are the mainstay of optimizing therapy for other cardiovascular risk factors, such as hypertension.

EU regulatory guidance

Soon after publication of the 1996 FDA weight-loss guidance, the EU weight-loss guidance was released for comment (1997) and implemented (1998).[30] An updated EU guidance on the development of drugs for the treatment of obesity was published in June 2006,[31] which touches on a number of the key issues mentioned above. One key aspect of the updated EU guidance that has not changed from the original is the primary efficacy end points required, at least a 10% reduction from baseline in body weight (not placebo-adjusted) that is also statistically greater than that associated with placebo and with a greater proportion of responders ($>10\%$ weight loss) after 1 year treatment. Another key aspect that has not changed is the continued recommendation for a weight-loss run-in before initiating study drug. With regard to safety, the EU guidance did not make a specific recommendation on the size and duration of patient exposure beyond the long-term studies required to demonstrate efficacy, but did recommend that special efforts be made to assess potential adverse effects associated with the specific drug class being evaluated.

SUMMARY

Addressing the growing obesity epidemic and developing new pharmacotherapies to support safe and effective treatment is an important unmet medical need. Obesity is a serious medical condition that significantly increases the risk for comorbidities, such as cardiovascular disease and type II diabetes. Additional treatment options, including new pharmacotherapies, have become increasingly important. As the clinical and regulatory perspectives on anti-obesity development continue to evolve, it will be important to balance the known long-term risks associated with inadequate treatment of the growing obesity epidemic, with the concern for potential unknown risks associated with the long-term use of new pharmacotherapies. Patients, physicians, academia, industry, payers, and governments must continue to partner with regulators to help establish the appropriate balance between the benefit and risk associated with the long-term use of new pharmacotherapies in specific patient populations.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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Review

Long-term Pharmacotherapy in the Management of Obesity

National Task Force on the Prevention and Treatment of Obesity

Objectives.—To examine the rationale for long-term use of medications in the management of obesity, to provide an overview of published scientific information on their safety and efficacy, and to provide guidance to patients and practitioners regarding risks and benefits of treatment.

Data Sources.—Original reports and reviews obtained through electronic database searches on anorexiant drugs supplemented by a manual search of bibliographies.

Study Selection.—English-language articles that discussed the role of medications in the treatment of human obesity, and studies that evaluated their safety and efficacy for a minimum of 24 weeks.

Data Extraction.—Studies were reviewed by experts in the fields of nutrition, obesity, and eating disorders to evaluate study design and the validity of authors' conclusions.

Data Synthesis.—The long-term use of medications in the management of obesity is consistent with the current consensus that obesity responds poorly to short-term interventions. Net weight loss attributable to medication is modest, ranging from 2 to 10 kg, but patients taking active drug are more likely to lose 10% or more of initial body weight. Weight loss tends to reach a plateau by 6 months. Weight remains below baseline throughout treatment, although some studies show partial weight regain despite continued drug therapy. Most adverse effects are mild and self-limited, but rare serious outcomes have been reported.

Conclusions.—Pharmacotherapy for obesity, when combined with appropriate behavioral approaches to change diet and physical activity, helps some obese patients lose weight and maintain weight loss for at least 1 year. There is little justification for the short-term use of anorexiant medications, but few studies have evaluated their safety and efficacy for more than 1 year. Until more data are available, pharmacotherapy cannot be recommended for routine use in obese individuals, although it may be helpful in carefully selected patients.

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THE PREVALENCE of obesity in the United States has increased substantially during the past decade. One of 3 US adults is now considered overweight.[1] Obesity contributes to many adverse health outcomes, including non–insulin-dependent diabetes mellitus and cardiovascular disease,[2] as well as to an increase in both cardiovascular and all-cause mortality.[3] Obesity-related conditions are estimated to contribute to 300 000 deaths yearly, ranking second only to smoking as a cause of preventable death.[4] The annual economic costs of obesity in the United States from excess medical expenses and loss of income are reported to exceed $68 billion,[5] a figure that does not include the more than $30 billion spent yearly on diet foods, products, and programs.[6]

The long-term outcome of nonsurgical obesity treatment is frequently unsatisfactory.[7] Although recent advances in the understanding of molecular mechanisms underlying obesity provide great hope for the development of treatments targeted to specific metabolic defects, such treatments are probably years away.

Many physicians and patients are confused about the appropriate role of medications in the management of obesity. The majority of weight-loss medications prescribed in the 1950s and 1960s were amphetamines. The use of these medications was widespread and often indiscriminate.[8] As behavioral treatments and dietary manipulations to achieve weight loss improved, medications were thought to provide little additional benefit to behavioral treatment.[9] During the ensuing 20 years, medication usage for the treatment of obesity decreased dramatically. Indeed, no new medication was approved by the Food and Drug Administration (FDA) for the treatment of obesity between 1973 and 1996.[10] The reports by Weintraub et al[11-19] showing sustained weight loss with the use of a combination of fenfluramine hydrochloride and phentermine resin have fueled the extraordinary interest of patients, professionals, and the media. The number of prescriptions written for fenfluramine has increased from about 60 000 in 1992 to a projected 1.1 million in 1995,[20] an almost 20-fold increase. The explosion of interest has led to such developments as the establishment of clinics devoted to the prescription of weight-loss medications (*Fortune.* December 11, 1995:164-173).

The purpose of this article is to examine the rationale for long-term use of medications in the treatment of obesity, to review the data currently available on the safety and efficacy of long-term pharmacotherapy for the management of obesity, and to provide guidance to patients and practitioners regarding risks and benefits of such therapy, on the basis of current scientific knowledge.

RATIONALE FOR LONG-TERM USE OF MEDICATIONS IN MANAGEMENT OF OBESITY

Comprehensive treatment programs that incorporate behavioral modalities to improve diet and increase physical activity induce weight loss sufficient to produce significant health benefits in many obese individuals.[21] Unfortunately, improvements in risk factors are not maintained if weight is regained,[22] and the vast majority of those who attempt weight loss eventually regain their lost weight.[7] Therefore, the major challenge facing obese patients and health care providers is to improve the ability to sustain, rather than to achieve, weight loss.

A complete list of members of the National Task Force on the Prevention and Treatment of Obesity and their financial disclosures appear at the end of this article.

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The realization that obesity is a chronic disease of multifactorial origin that responds poorly to currently available nonsurgical treatments has promoted a renewed interest in the use of medications. Recognition of the need for long-term (perhaps lifelong) treatment has led many to embrace the concept of long-term medical therapy, as is used in other chronic diseases.[23,24]

REGULATIONS GOVERNING PRESCRIPTION OF ANOREXIANT DRUGS

All currently available anorexiant agents, with the exception of dexfenfluramine, are approved by the FDA only for the short-term treatment of obesity. The FDA regulates the advertising and promotion of prescription drugs to ensure that such activities are not false or misleading, are fairly balanced, and are directed to approved uses.[25] However, these regulations do not restrict the physician's ability to prescribe those drugs in differing amounts, for differing durations, or for conditions other than those for which FDA approval has been granted. Such off-label use of prescription medications is common (*Wall Street Journal.* August 31, 1995:B1).

Although the decision to place drugs on prescription is within the jurisdiction of the FDA, classification of a drug as a controlled substance places further restrictions on its prescription. The Controlled Substances Act places all regulated substances into 1 of 5 schedules (I to V) on the basis of their medical use, potential for abuse or dependence, and safety.[26] All currently approved prescription anorexiant agents are controlled substances on schedules II to IV.

Individual state medical boards have the authority to restrict physicians' prescription of controlled substances to a greater extent than that required by the Controlled Substances Act, and regulations for the use of anorexiant agents vary widely from state to state. In a survey of state pharmacy boards, conducted by the Weight-Control Information Network, Bethesda, Md, in August 1995 (Joanne Gallivan, MS, RD, written communication, August 3, 1995), restrictions on the prescription of anorexiant agents exceeding the federal regulatory standards were not imposed by 40 states, while 10 others had restrictions ranging from outright ban (Tennessee) to restrictions on the length of treatment (Utah) to requirements for documentation of continuing weight loss (Ohio). These regulations are changing rapidly, as state regulatory agencies respond to the extraordinary interest in long-term use of these drugs.[27]

MECHANISMS OF ACTION AND CLASSIFICATION OF DRUGS USED TO TREAT OBESITY

Three basic mechanisms underlie the effects of drugs on weight loss or prevention of weight gain.

Reduction of Energy Intake

Food intake may be reduced by decreasing appetite or by increasing satiety. Drugs that affect appetite are commonly known as "anorectic" or "anorexiant" medications. The mechanism of action of so-called anorexiant agents may not be limited to decreased appetite. Some of these medications may also have acute effects on thermogenesis.[28,29] Some investigators also believe that anorexiant medications may alter the body weight "set point" (the level at which body weight is defended),[30] although it is difficult to test underlying mechanisms for this hypothesis.

Anorexiant agents affect neurotransmitter activity and are of 2 main classes: those that affect the catecholaminergic system (the amphetamines, benzphetamine, phendimetrazine, phentermine, mazindol, diethylpropion, and phenylpropanolamine) and those that affect the serotonergic system (fenfluramine, dexfenfluramine, fluoxetine, sertraline, and other antidepressant selective serotonin reuptake inhibitors [SSRIs]). Amphetamines and closely related compounds are not recommended for the treatment of obesity by most experts because of their high potential for abuse.[8] Of the nonamphetamine centrally acting anorexiant medications, only phendimetrazine, phentermine, mazindol, diethylpropion, phenylpropanolamine, fenfluramine, and dexfenfluramine are currently approved in the United States for weight control. Phenylpropanolamine and benzocaine (a local anesthetic) are the only drugs currently allowed to be marketed as over-the-counter weight-control products (Michael Weintraub, MD, FDA, oral communication, 1996). Dexfenfluramine is the dextro isomer of fenfluramine. It is the active form of the racemic mixture and has a greater potency than fenfluramine. In April 1996, the FDA approved dexfenfluramine for use up to 1 year in the treatment of obesity (according to manufacturer's prescribing information for Redux [Wyeth Laboratories, Philadelphia, Pa]). Fluoxetine, sertraline, and other antidepressant SSRIs, while available by prescription, are not approved for the treatment of obesity. A listing of centrally active medications currently approved for the treatment of obesity in the United States is shown in the Table. A mixed serotonergic and catecholaminergic reuptake inhibitor, sibutramine, is currently undergoing clinical trials in the United States.[31]

Reduction of Absorption of Nutrients

Drugs that block the action of digestive enzymes or that block absorption of nutrients (such as fat) from the gastrointestinal tract may reduce total energy available to the body. Orlistat, an inhibitor of gastric and pancreatic lipase,[32] is an example of this type of drug. Medications in this class are experimental in the United States. Clinical trials evaluating their safety and efficacy are ongoing.

Increase in Energy Expenditure

Energy expenditure may be increased by increasing physical activity or metabolic rate, for example, through changes in sympathetic nervous system tone or uncoupling of oxidative phosphorylation. Drugs that affect thermogenesis-metabolism include ephedrine (including its combination with caffeine and/or aspirin)[33,34] and experimental agents, such as BRL 26830A, a β-adrenoceptor agonist.[35] None of these medications is currently approved by the FDA for weight control.

LONG-TERM STUDIES OF DRUG TREATMENT FOR OBESITY

Relatively few human trials of pharmacotherapy for the treatment of obesity for periods of 6 months or more have been conducted. Many earlier studies were not placebo controlled, randomized, or blinded. Few involved more than 100 patients, and they often lacked sufficient detail about patient selection, trial performance, or data analysis. In particular, the way in which the data from dropouts were analyzed is often not well described, making interpretation of results difficult.[36] Although there have been several well-controlled studies of single-drug treatment for periods up to 1 year,[37-39] only 1 long-term controlled study documenting the safety and efficacy of the fenfluramine-phentermine combination has been published.[11] In addition, the total number of subjects in published studies who had been taking any anorexiant drug for more than 2 years is fewer than 200.[8,11,40]

Behavioral treatment of obesity without added medications results in an average weight loss of 8.5 kg after 21 weeks of treatment, with an average weight loss of 5.6 kg at a mean of 53 weeks of follow-up.[41] Therefore, studies of the efficacy of drug treatment must be judged against the efficacy of nondrug treatments currently available. Open-label studies without appropriate control groups provide little information on how much additional weight loss is attributable to the drug. Only studies in which medication was compared with placebo or concur-

Currently Approved Drugs for the Treatment of Obesity in the United States*

Generic Name	Trade Name(s)	Dosage	Drug Enforcement Administration Schedule
Amphetamine/dexamphetamine†	Biphetamine	12.5-20 mg/d	II
Methamphetamine hydrochloride†	Desoxyn	10-15 mg/d	II
Benzphetamine hydrochloride	Didrex	25-50 mg 1-3 times daily	III
Phendimetrazine tartrate	Bontril, Plegine, Prelu-2, X-Trozine	105 mg/d	III
Phentermine			IV
Hydrochloride	Adipex-P, Fastin, Oby-trim	18.75-37.5 mg/d	
Resin	Ionamin	15-30 mg/d	
Diethylpropion hydrochloride			IV
Immediate release	Tenuate	25 mg 3 times daily	
Controlled release	Tenuate Dospan	75 mg/d	
Mazindol	Sanorex, Mazanor	1-3 mg 1-3 times daily	IV
Dexfenfluramine hydrochloride	Redux	15 mg 2 times daily	IV‡
Fenfluramine hydrochloride	Pondimin	20-40 mg 1-3 times daily	IV‡
Phenylpropanolamine hydrochloride	Dexatrim, Acutrim	75 mg/d	Over the counter

*Data from *Physicians' Desk Reference* and *Physicians' Desk Reference for Nonprescription Drugs* (Montvale, NJ: Medical Economics Co; 1996 and 1995, respectively). Only dexfenfluramine is currently approved for more than short-term ("a few weeks") use for the treatment of obesity.

†Amphetamines are not recommended by most experts for the treatment of obesity, because of their high potential for abuse or dependence.

‡The Food and Drug Administration Drug Abuse and Endocrinologic and Metabolic Drugs Advisory Panels recommended removing fenfluramine and its isomers (including dexfenfluramine) from the controlled dangerous substances list in 1995, but as of this writing this drug is still on schedule IV.

rent nondrug control with both groups undergoing comparable adjunctive treatment (ie, behavioral therapy, diet, and physical activity) for a minimum of 24 weeks were reviewed. Original reports were obtained through a MEDLINE search of articles from 1966 through 1996 for the terms *anorectics, pharmacological therapy, clinical trials, obesity, fenfluramine, dexfenfluramine, phentermine, mazindol, diethylpropion,* and *serotonin reuptake inhibitors,* supplemented by a manual search of bibliographies. Studies published only in abstract form or in languages other than English are not included. In the instances in which sites participating in a multisite study published their data separately, only the overall results of the multisite study are reported, to avoid duplicate reporting of patient data. Twenty studies reviewed met these criteria.*

SINGLE-DRUG TREATMENT

Medications Currently Approved for Treatment of Obesity in the United States

Two small placebo-controlled trials of diethylpropion lasting longer than 24 weeks have been conducted.[42,43] Both were limited by high attrition rates, with fewer than 10 subjects completing the study in each group. In 1 of these studies, treatment was intermittent, rather than continuous, limiting interpretation of the results.[42] The only long-term studies investigating the efficacy of mazindol have been open label and uncontrolled.[44,45] A double-blind, placebo-controlled trial of continuous or intermittent therapy with phentermine found that both intermittent and continuous phentermine were equally effective, leading to increased weight loss compared with placebo.[46] Another study[47] that alternated fenfluramine and phentermine, given continuously or intermittently, found no significant advantage to alternating the 2 drugs compared with using either alone. In addition, intermittent use of fenfluramine was less effective than continuous dosing and was more likely to produce adverse effects. That study lacked a placebo or diet control group.

Of the 5 long-term studies that used fenfluramine alone, 2 were open label, with diet-only control groups.[48,49] One of these found greater weight loss with active drug (significance not reported),[48] while the other found no significant difference compared with placebo.[49] An open-label study with concurrent behavioral treatment and wait-list controls[50,51] found that fenfluramine, with or without behavioral therapy, increased weight loss relative to the groups receiving behavioral therapy alone. During a 1-year follow-up, however, patients who had received fenfluramine treatment, with or without behavior therapy, regained significantly more weight than those who had received behavioral treatment alone. Only 10 of 42 enrolled patients completed a 1-year, double-blind, placebo-controlled trial of fenfluramine that required successful maintenance of weight loss for continuation.[52] In the only published placebo-controlled, long-term study of fenfluramine in obese children and adolescents, body mass index (BMI, weight in kilograms divided by the square of height in meters) and percentage overweight decreased significantly in the treatment group compared with the control group among study completers.[53] It is unclear how the children were selected for participation in this study and whether it was randomized or double-blind.

Dexfenfluramine, the dextrorotatory isomer of fenfluramine, both stimulates the release and inhibits reuptake of central serotonin, increasing brain serotonin levels.[54] Dexfenfluramine reduces daily energy intake by about 10% to 15%.[55]

The largest controlled trial to date of long-term (≥24 weeks) pharmacotherapy for obesity was that of Guy-Grand et al,[37] known as the INDEX Study. In that multinational study, 822 obese patients were treated for 12 months with either dexfenfluramine or placebo. Of those who continued in the study for 12 months, the dexfenfluramine group showed a modest, although statistically significantly larger (9.8 vs 7.2 kg), weight loss than the placebo group. Twice as many patients treated with active drug achieved a loss of more than 10% of total body weight compared with those who received placebo. The weight loss in this 1-year study was primarily seen in the first 6 months. Within 2 months of treatment discontinuation, both body weight and energy intake increased to a greater extent in the medication group than in the placebo group, and the significant difference in weight loss between groups disappeared.[56] Similar results have been reported in other, smaller studies.[57-59] Dexfenfluramine also appears to promote weight maintenance for 6 months after treatment with a very low-energy diet.[60,61]

Medications Not Currently Approved for the Treatment of Obesity in the United States

Sibutramine.—Sibutramine, an investigational new pharmacological agent, acts as a reuptake inhibitor for both norepinephrine and serotonin.[31] Results from 1 site of a multisite, 24-week,

*References 11-19, 37-39, 42, 43, 46, 48-53, 57-62, 64-66. A table summarizing these studies is available on the World Wide Web at http://www.niddk.nih.gov/NutritionDocs.html/LtStudy/table.htm.

double-blind study have been reported.[62] This study compared placebo and 6 dosages of sibutramine in conjunction with modest restriction of energy intake and an activity and lifestyle change program. Weight loss after 24 weeks was greater for active drug than for placebo for all treated groups except those at the lowest 2 dosages, and those who took active drug were more likely to lose more than 10% of initial body weight.

Antidepressant SSRIs.—Antidepressant SSRIs inhibit reuptake of serotonin in the central nervous system. They are currently approved for the treatment of depression (fluoxetine, sertraline, paroxetine) and obsessive-compulsive disorder (fluoxetine). Unlike the tricyclic antidepressants, which frequently promote weight gain, fluoxetine and other SSRIs have been shown to promote weight loss in some patients. Therefore, fluoxetine and sertraline have been evaluated for their potential as weight loss drugs.

Fluoxetine.—Fluoxetine appears to show dose-related efficacy for weight loss, with 60 mg daily showing greater efficacy for weight loss than lower dosages.[63] Several trials that used fluoxetine as a weight-loss drug for 24 weeks or more have been reported. In a 6-month study of fluoxetine in 30 obese elderly patients with non–insulin-dependent diabetes,[64] greater weight losses were seen in the active treatment group only during the first 2 months of treatment, with a plateau in weight loss during the remaining 4 months of treatment. A 1-year multicenter trial of fluoxetine vs placebo in 458 obese outpatients[38] found that the group that received active drug attained a small but statistically significant difference in weight loss compared with the placebo group at 20 weeks. After 20 weeks, however, slow regain continued despite the use of active drug, and by 1 year of treatment, average weight loss between groups did not differ. This same pattern of weight loss for 4 to 6 months followed by regain has been reported in other studies.[39,65]

Sertraline.—One 54-week, double-blind, placebo-controlled study of women who had completed a 26-week very-low-energy diet program found that at 6 weeks those taking sertraline showed a small weight loss, compared with a small gain in the placebo group.[66] However, sertraline-treated patients began to gain weight after this time, and by week 26, there was no difference in weight between the medication and placebo groups.

COMBINED DRUG TREATMENT FOR OBESITY

The rationale for the use of combination therapy to treat obesity is that drugs with different mechanisms of action might be used in smaller amounts, providing efficacy equivalent to or greater than that of the full dose of a single drug, with fewer adverse effects.[11] Although hundreds of studies have used single-drug treatment for obesity, few trials have used combination therapy. The only combination regimen that has been studied for 24 weeks or more with medications approved for the treatment of obesity in the United States is fenfluramine-phentermine.[67]

In 1984, Weintraub et al[68] demonstrated that combining low doses of phentermine with fenfluramine resulted in weight loss similar to that acheived with single-drug treatment with either drug. Patients taking combination therapy reported fewer adverse cardiovascular and central nervous system effects than were seen with phentermine alone. In 1992, Weintraub and colleagues[11-19] published results of a multiyear trial of obese patients with the use of this drug combination. Because of the complexity of the design and the frequent citation of this study as a justification for the routine use of these drugs in the treatment of obesity, the design and results are presented here in some detail.

After a 6-week run-in period of intensive behavior modification and individualized dietary and exercise instruction, 121 patients were randomly assigned to receive behavioral treatment along with either a combination of 60 mg of fenfluramine hydrochloride and 15 mg of phentermine resin or placebo. All adjunctive modalities (behavioral treatment, exercise, and dietary instruction) were continued throughout the entire study period. During the first double-blind portion of the trial, which lasted for 28 weeks, those taking combination therapy lost significantly more weight than those taking placebo (14.3 vs 4.6 kg). Weight loss reached a plateau after approximately 18 weeks of active treatment (24 weeks after the study began) but was maintained throughout the remaining 10 weeks of the double-blind trial. After the initial 34-week period, all patients who remained in the trial (including those initially taking placebo) were treated either continuously or intermittently from weeks 34 to 104 with the fenfluramine-phentermine combination. In 7 patients who failed to respond to the active treatment with weight loss, a higher dose was given ("augmentation"), but no additional benefit was noted by increasing the dose in these nonresponders. During weeks 104 to 156, the investigators attempted to optimize clinical response by means of an algorithm that aimed to achieve 120% of ideal body weight while minimizing adverse effects. At week 156, the 40% of the original cohort (n=51) who were still participating were studied in a second double-blind phase with the active drugs (n=27) vs placebo (n=24) until week 190. At this point, all subjects stopped taking medication and were followed up for an additional 20 weeks.

It should be noted that only 27 patients were taking active drug at the end of the 3½-year drug-study period, and 48 patients remained in the study through the 20-week follow-up period. In addition, a gradual regain was seen (approximately 3 kg between weeks 60 and 104 in the continuous therapy group and an additional 4 kg between weeks 165 and 190 in those who received drug during the second double-blind study). Weight regain was significantly less in the medication group than in the placebo group during the second double-blind phase. By week 190, the 27 patients still receiving active treatment had lost about 7 kg from baseline vs about 2 kg among those in the placebo group. When patients were followed up after discontinuation of anorexiant medications, weight was regained, with an average regain of 2.7 kg over 20 weeks.

In summary, this double-blind, placebo-controlled study showed that long-term combination pharmacotherapy for the treatment of obesity is feasible. The medications improved weight loss, relative to placebo, and some effects were sustained for more than 3½ years in the 27 patients who received active treatment through week 190. Weight tended to reach a plateau by 6 months, and some regain was seen between years 2 and 3, despite continued treatment. When medication was discontinued, weight returned toward baseline. Some patients did not respond to the combined treatment, and for most of these patients an increase in dosage did not appear to improve efficacy.

SUMMARY OF EFFICACY OF PHARMACOTHERAPY FOR WEIGHT LOSS

Studies of both single-drug and combination therapy carried out over 6 months or more showed modest efficacy, compared with placebo, in the reduction of body weight. Net weight loss attributable to drug generally ranged from 2 to 10 kg. Response to treatment was variable, and those who took active drug were more likely than those who took placebo to achieve a clinically significant weight loss (≥10% of initial body weight). Most of the weight loss occurred during the first 6 months of treatment. Weight then tended to be maintained or to increase slightly for the duration of

treatment. Because of the small number of patients who were treated for periods longer than 12 months, it is unknown whether weight would continue to increase despite active therapy for longer periods. Exceptions to the sustained effects of anorexiant medications were fluoxetine and sertraline, with which, on average, significant regain of weight occurred after the first 6 months of treatment despite continued drug treatment. Therefore, on the basis of currently available data, antidepressant SSRIs do not appear to be efficacious for long-term treatment of obesity and are not recommended for this indication alone.

Weight was regained when any weight loss medications were discontinued. Several months after discontinuation of medication, there was generally no difference in weight between the groups that previously received active drug and those that received placebo.

Currently, no single drug emerges as having superior efficacy in either promoting or sustaining weight loss. The 1 long-term, placebo-controlled study of the fenfluramine-phentermine combination suggests that combination therapy may allow greater weight losses than single-drug treatment, but no direct comparison was made. Larger studies are needed to determine whether long-term treatment with combination therapy is safer or more efficacious than single-drug therapy.

POTENTIAL BENEFITS OF LONG-TERM PHARMACOTHERAPY FOR MANAGEMENT OF OBESITY

Over the short term, weight loss in obese individuals results in reduction in a number of risk factors for disease. Although numerous studies have shown that weight loss improves cardiovascular risk factors and insulin sensitivity,[69] few studies have examined the long-term benefits of voluntary weight loss on morbidity and mortality. In large part, absence of such data reflects the likelihood of relapse among obese individuals who lose weight. Data from obese individuals who have achieved long-term weight loss through gastric surgery show improvement in cardiovascular risk,[70] insulin sensitivity,[71] and quality of life,[72] although reduction in mortality has yet to be demonstrated. One observational study has shown a decrease in mortality after intentional weight loss in never-smoking overweight women who had preexisting obesity-related health conditions,[73] and a dietary intervention study has shown a decrease in cardiovascular morbidity and mortality among patients who had myocardial infarctions and who lost weight with a high-fiber, low-fat diet.[74]

Some physicians may consider the modest weight losses attainable with anorexiant treatment to be insufficient rationale for their use. However, a 5% to 15% reduction in body weight, which should be achievable in many patients by means of pharmacotherapy in conjunction with behavioral treatment, can lead to significant improvements in obesity-related comorbidities.[75,76] Many,[57,59,77] but not all,[22,65] studies of pharmacotherapy for treatment of obesity show the expected reductions in such risk factors as dyslipidemias, insulin resistance, and blood pressure with weight loss. Whether medication has any independent effects on risk factors for obesity-related disease remains unknown.[78-80] Although reduction in health risks, improvement in quality of life, and amelioration of obesity-related diseases are important potential benefits of long-term pharmacotherapy for the management of obesity, studies are needed to demonstrate reductions in morbidity and mortality with drug treatment.

POTENTIAL ADVERSE EFFECTS OF LONG-TERM PHARMACOTHERAPY FOR TREATMENT OF OBESITY

There are several areas of concern when long-term obesity treatment with pharmacological agents is considered.

Potential for Abuse or Dependence

Although amphetamines frequently result in abuse or dependence, abuse is less frequent with schedule III medications and uncommon with schedule IV medications such as phentermine, mazindol, and fenfluramine.[81-83] Abuse of fenfluramine and its isomers appears to be rare, although a few case reports and case series have been published.[84,85] Anorexiant medications should be used with caution in patients with a history of substance abuse.

Development of Tolerance

Tolerance to weight-reducing effects of some anorexiant agents has been described.[86] It is often assumed that tolerance has developed if weight loss ceases before weight has normalized.[11] Most studies of anorexiant drugs show a plateau in weight loss after 4 to 6 months of treatment. This plateau probably represents the limits of efficacy of currently available agents (weight loss of 5-10 kg) rather than tolerance.[87] Similarly, weight regain after drugs are discontinued is not evidence that these drugs are ineffective; rather, it indicates efficacy. Drugs cannot be expected to exert their effects if they are no longer taken. There is some indication that regain may occur despite long-term drug treatment in some patients[36]; whether weight regain while taking medication represents tolerance remains to be determined.

Avoidance of Responsibility

There is concern that patients may not take responsibility for their condition or will rely on medication as a "magic bullet." The unjustified perception that obesity is a volitional state rather than a disease contributes to the reluctance of health professionals, patients, and regulators to accept the use of long-term pharmacotherapy for its treatment. Long-term drug treatment for control of chronic health-threatening conditions, such as abnormalities in blood glucose, blood pressure, and lipids, is well established, even though many of these conditions also respond to changes in lifestyle, such as diet and exercise. This realization should not prevent aggressive medical treatment of risk factors to prevent morbidity and mortality. Obesity, on the other hand, is frequently viewed as a consequence of weakness, lack of willpower, or a lifestyle "choice"—the choice to overeat and underexercise. It should be stressed that the use of medication in obesity treatment does not change the necessity of making changes in diet and exercise; rather, it may enable patients to sustain long-term changes despite considerable environmental and biologic pressures for weight regain.[88]

Adverse Effects

The potential for adverse effects of anorexiant medications is of more concern because they are used in a condition that affects millions of people, many of whom are basically healthy.

Minor Adverse Effects.—Adverse effects of serotonergic drugs, including fenfluramine and dexfenfluramine, include diarrhea, polyuria, dry mouth, sleep disturbance, and somnolence.[54,83] Fluoxetine and other SSRIs have a number of adverse effects, including asthenia, insomnia, nausea, diarrhea, sweating, nervousness, tremor, dyspepsia, and sexual dysfunction.[89] Catecholaminergic agents such as phentermine may cause symptoms of central nervous system stimulation, including insomnia, nervousness, and euphoria. Increased blood pressure and tachycardia may also occur.[83] Adverse effects of current anorexiant medications are usually mild to moderate and improve with continued treatment,[36,54] although some patients continue to be bothered by adverse effects.[15]

Depression.—Depression, during treatment or on withdrawal of active drug, has been reported with dexfenfluramine,[90,91] fenfluramine,[47] and the fenfluramine-phentermine combination,[67] although it is unclear whether the incidence is greater than that seen with placebo.[36,92] Exacer-

bations of manic episodes in patients with bipolar disorder have also been anecdotally reported with the fenfluramine-phentermine combination (Richard Atkinson, MD, oral communiation, October 6, 1996.) Many studies excluded patients with current or past depression or bipolar disorder from study entry, making estimates of fenfluramine-associated exacerbations difficult.

Neurotoxic Effects.—Concerns have also been raised about potential neurotoxic effects of serotonergic agents.[93] Administration of high doses of dexfenfluramine intraperitoneally or subcutaneously in rats causes a long-lasting depletion of serotonin.[94] Others argue that the depletion of brain serotonin, thought to be secondary to excessive stimulation of the presynaptic serotonin receptors, does not represent evidence of neurotoxic effect because levels can be restored by pretreatment with serotonin and recover spontaneously with time.[95] Nonhuman primates receiving subcutaneously administered dexfenfluramine develop changes in serotonergic neuronal function that may be long-lasting[96]; however, the dosage, route of administration, and animal model chosen have been criticized by some as inappropriate predictors of the effect of dexfenfluramine in humans.[54,97,98] Evidence of neurotoxic effects in humans has not been reported with fenfluramine or dexfenfluramine, but further studies evaluating the possibility of subtle neuropsychological changes, particularly with prolonged administration, are warranted.

A particular area of concern is the potential for adverse effects or potentiation of toxic effects with combination therapy.[99] Short-term memory loss, which appears reversible, has been reported in up to 13% of patients taking the fenfluramine-phentermine combination in open-label fashion.[67,100] Detailed neurocognitive testing for changes in memory before, during, and after combination drug treatment has not been reported.

Primary Pulmonary Hypertension.—Reversible and irreversible primary pulmonary hypertension (PPH) has been reported in patients undergoing therapy with anorexiant agents, including fenfluramine and dexfenfluramine.[101-103] Primary pulmonary hypertension is a rare but serious cardiopulmonary disorder that occurs at an annual rate of 1 to 2 cases per million per year in the general population.[104] The International Primary Pulmonary Hypertension Study was a case-control study carried out in 4 European countries that evaluated the association between the development of PPH and anorexiant use.[104-106] The study found that individuals with PPH were 6.3 times more likely than controls to report anorexiant drug use (95% confidence interval [CI], 3.0-13.2). For use of anorexiant drugs in the year before the onset of symptoms, the odds ratio was 10.1 (95% CI, 3.4-29.9). In addition, cases were 23.1 times more likely than controls to report having used anorexiant medications for more than 3 months (95% CI, 6.9-77.7). This translates to an estimate of between 23 and 46 cases per million per year,[107] or 1 in 22 000 to 44 000 patients per year. A maximum lifetime self-reported BMI of greater than 30 kg/m^2 was also associated with an increased risk of PPH, after adjustment for anorexiant use (odds ratio, 1.9; 95% CI, 1.0-3.6). The majority of exposures were to dexfenfluramine or fenfluramine, which were used by 23% of patients and 6% of controls. The results suggest that the use of anorexiant agents for more than 3 months is associated with an increased risk of the development of PPH. Although the absolute risk of pulmonary hypertension attributable to the use of anorexiant agents is likely to be extremely small, physicians and patients should be aware of this association in determining the risk-benefit ratio of long-term drug treatment. These findings reinforce the recommendation that these drugs not be taken for "cosmetic" weight loss.[107] However, concern regarding the increased risk of this rare condition must be viewed in the context of the major excess in morbidity and mortality attributable to obesity.

IDENTIFICATION OF APPROPRIATE PATIENTS FOR DRUG TREATMENT OF OBESITY AND SELECTION OF TREATMENT GOALS

If physicians choose to treat obesity with medications, they and their patients must compare the known adverse effects and limited long-term safety data with the potential benefits of long-term sustained weight loss.

The North American Association for the Study of Obesity[87] has recommend that a BMI greater than 27 kg/m^2 be considered the minimum indication for treatment with anorexiant agents for patients without existing obesity-related comorbidities.The new anorectic usage guidelines of the American Society of Bariatric Physicians also recommend a BMI 27 kg/m^2 or more or a percentage of body fat of 30 or more for women and 25 or more for men as minimum indications for anorexiant treatment in patients without existing comorbidities (James Merker, written communication, October 1996). The Committee on Nutrition of the Massachusetts Medical Society has recommended drug therapy only in patients with medically significant obesity, in which group they include adults who have gained 13.5 kg or more since 18 years of age.[108] Labeling information for dexfenfluramine recommends a minimum BMI of 30 kg/m^2 for treatment, or 27 kg/m^2 in the presence of obesity-related risk factors. Even in patients with a BMI above the minimum levels recommended for drug treatment, the decision to use medications should be based on such factors as previous unsuccessful attempts to lose weight and maintain weight loss with conventional therapies, the number and severity of associated comorbidities, family history of obesity-related disease, and the presence or absence of other medical conditions (such as depression or ischemic heart disease) that might impact on drug choice or risk. For example, an obese patient with a BMI of 28 kg/m^2 but with a gynoid obesity pattern and no evidence of insulin resistance, blood pressure elevation, or dyslipidemia would likely be an inappropriate candidate for drug treatment. In a severely obese patient with android obesity, insulin resistance, and hypertension who has failed to lose weight or maintain weight loss with conventional treatments, physician and patient might decide that the known risks of the patient's medical condition outweigh the risks of treatment.

When the goals of treatment and the efficacy of a particular drug or combination of drugs are determined, improvement in health and reduction in risk of disease should be primary goals. Attainment of "ideal body weight" in most severely obese individuals is both unrealistic and unnecessary for improvement in health.[109] Both patient and physician should be aware that reduction to an average body weight should not be expected in most treated patients with currently available medications. Even modest weight loss, such as 5% to 10% of initial body weight, has been shown to have positive benefits on risk factors for disease,[110] and weight loss of this magnitude may be realistic for many patients.

Physicians who use medications for the treatment of obesity should have a thorough understanding of their mechanisms of action, indications and contraindications for use, adverse effects, and interactions with other medications. Continuing medical education courses that focus on obesity and its management may be helpful in enabling physicians to care appropriately for these challenging patients, who often have numerous comorbid conditions and are taking multiple medications. Careful ongoing monitoring, including assessment for adverse effects, the need to adjust or eliminate concurrent medication, and evaluation of the drug's impact on the patient's physical and psychological health, is essential. Because of the rare, but serious, association between anorexiant use and PPH, physicians should be

alert to the onset of dyspnea, changes in exercise tolerance, angina, syncope, or lower-extremity edema that might signal the development of this disorder.[107] Anorexiant medications should be discontinued in these patients, and the symptoms should be evaluated.

Although not an exhaustive list, the following include some of the cautions and contraindications of which the prescribing physician should be aware: anorexiant agents should be used with caution in patients with cardiac arrhythmias, symptomatic cardiovascular disease, or severe systemic disease, such as hepatic or renal failure.[54,83] Anorexiant agents of all classes are contraindicated in patients taking monoamine oxidase inhibitors and should not be administered until a washout period of more than 14 days has elapsed. Glaucoma is a contraindication for many anorexiant drugs.[83] Administration of fenfluramine and dexfenfluramine may result in decreased blood glucose levels and blood pressure. Therefore, physicians must carefully monitor patients who are taking antihypertensive and hypoglycemic medications for the need to decrease dosage. Because the serotonergic anorexiant agents can cause drowsiness, caution should be used when these medications are combined with other central nervous system depressants. Anorexiant agents may also interact with general anesthetics and should be discontinued before surgery whenever possible.[83] Caution and careful monitoring are needed when fenfluramine or dexfenfluramine is used in patients with a history of depression, and caution is required when using anorexiant agents of all classes in patients with a history of major psychiatric illness, including bipolar disorder. The product labeling for dexfenfluramine states that this medication should not be used with other serotonergic agents. No data are available on use of antidepressant SSRIs with serotonergically active anorexiant agents, such as fenfluramine and dexfenfluramine; however, a "serotonin syndrome" has been described with the combination of SSRIs and other serotonergic medications, including sumatriptan and dihydroergotamine.[111] Given the similar mode of action of antidepressant SSRIs and serotonergic anorexiant medications, their concomitant use should be viewed with caution.

Although the abuse potential of schedule IV anorexiant medications is low, physicians should be alert to the potential for misuse of these agents by such populations as weight-conscious athletes, nonobese individuals, and persons with eating disorders.

Safe use in pregnancy and lactation has not been established for any anorexiant medication, and they should be discontinued in women who become pregnant unless the potential benefits outweigh the potential risk to the fetus (according to the manufacturers' prescribing information).

Childhood and adolescent obesity is increasing in this country and is of special concern. However, only 1 published study has evaluated the safety and efficacy of antiobesity agents in children or adolescents for periods of 6 months or more,[53] and that study had major limitations in design and reporting.[112] Pharmacotherapy in this group should be considered experimental and should be carried out only in specialized treatment programs, preferably in the context of a clinical trial, and with the approval of the appropriate institutional review board.

Although mean weight losses with pharmacotherapy are modest compared with those attributable to placebo, response to treatment is variable. Some patients show little response to pharmacological treatment, while others respond with large and clinically meaningful weight loss.[10] Appropriate use of pharmacotherapy in selected obese patients would improve if those who are most likely to respond could be identified. Unfortunately, preliminary studies have failed to identify which patients are likely to be responsive to a given medication or class of medications. Further research is needed to determine whether such factors as race or ethnicity, sex, degree of overweight, age at onset of overweight, or eating style (such as binge eating) can predict response to a given medication.[113] However, several studies have found that clinically significant weight loss within the first several weeks of treatment with a given drug predicts further responsiveness to that same drug.[91,114] Therefore, an initial trial period of several weeks with a given drug or combination of drugs may help determine their efficacy in a given patient. If a patient does not respond to a drug with reasonable weight loss (eg, 0.45 kg/wk) after a 4-week trial period, the physician should reassess the patient to determine adherence to the medication regimen and adjunctive therapies or the need for dosage adjustment. If the patient continues to be unresponsive to the medication, the physician should consider its discontinuation.

THE ROLE OF BEHAVIORAL TREATMENT

Many of the recent and better-designed studies that evaluated the efficacy of drug treatment for obesity combined medication with behavioral approaches to improve diet and increase physical activity. Early studies suggested that the use of anorexiant drugs might interfere with the efficacy of behavioral treatment.[50,51] However, subsequent studies have shown little evidence that anorexiant medications interfere with behavioral interventions.[15,115] Furthermore, there is some indication that combining medication with behavioral treatment may produce larger initial weight losses than administration of the same drug during routine medical care.[38,51] Although further research will determine the optimal content and timing of combined behavioral and drug treatments for obesity, some evidence suggests that combining behavioral treatment for obesity with other modalities, including drug therapy or bariatric surgery, can improve health-promoting behaviors independent of weight loss.[15,115,116] Finally, the efficacy of drug therapy depends on the patient's ability to adhere to the therapeutic regimen. Behavioral interventions may play an important role in keeping patients in treatment over the long term.[117] For these reasons, physicians who choose to administer anorexiant medications should do so only in the context of a comprehensive program that includes nutrition education and behavioral treatment.

CONCLUSIONS

Long-term pharmacotherapy, when combined with appropriate behavioral approaches to improve diet and increase physical activity, helps some obese patients lose weight and maintain weight loss for at least 1 year. The major promise of pharmacotherapy lies not in its ability to improve the amount of weight lost during the initial months of treatment, but in its potential to enhance longer-term maintenance of weight lost with conventional therapies.

Because obesity is a disorder that cannot be expected to remit without continued treatment, short-term (weeks or months) treatment of obesity with drugs is generally not warranted. Treatment with medications will likely need to be continued for years, and perhaps for the lifetime of the patient, to sustain weight loss and improve health. To date, there have been few published studies in which patients received anorexiant medications for more than 1 year. In particular, information on the safety and efficacy of drug combinations in the treatment of obesity is extremely limited.[67]

Until more data are available, pharmacotherapy cannot be recommended for routine use in obese individuals, although it may be helpful in carefully selected patients. If physicians choose to use medications in the long-term management of obesity, patients should be fully informed about the nonstandard use of some drugs, their potential adverse effects, and the scarcity of long-term studies available.

Physicians who prescribe anorexiant medications are encouraged to participate in ongoing clinical trials wherever feasible. Ultimately, physician and patient need to balance carefully the potential risks of therapy against the potential benefits of sustained reduction in body weight in the responsive patient.

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Prescription Medications for the Treatment of Obesity

U.S. Department of Health and Human Services

NATIONAL INSTITUTES OF HEALTH

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WIN *Weight-control Information Network*

Obesity is a chronic disease that affects many people. To lose weight and maintain weight loss over the long term, it is necessary to modify one's diet and engage in regular physical activity. Some people, however, may require additional treatment. As with other chronic conditions, such as diabetes or high blood pressure, the use of prescription medications may be appropriate for some people who are overweight or obese.

Prescription weight-loss medications should be used only by patients who are at increased medical risk because of their weight. They should not be used for "cosmetic" weight loss. In addition, patients should have previously tried to lose weight through diet and physical activity.

Prescription weight-loss drugs are approved only for those with:

- A body mass index (BMI) of 30 and above.
- A BMI of 27 and above with an obesity-related condition, such as high blood pressure, type 2 diabetes, or dyslipidemia (abnormal amounts of fat in the blood).

BMI is a measure of weight in relation to height that helps determine if your weight places your health at risk. A BMI of 18.5 to 24.9 is considered healthy. A BMI of 25 to 30 is considered overweight, and a BMI over 30 is considered obese. (See WIN's brochure *Weight and Waist Measurement: Tools for Adults* for more information.)

Although most side effects of prescription medications for obesity are mild, serious complications have been reported. Also, few studies have evaluated the long-term safety or effectiveness of weight-loss medications. Weight-loss medications should *always* be combined with a program of healthy eating and regular physical activity.

The information in this fact sheet may help you decide if and what kind of weight-loss medication may help you in your efforts to reach and stay at a healthy weight. It does not replace medical advice from your doctor.

Weight-loss medications should *always* be combined with a program of healthy eating and regular physical activity.

Medications That Promote Weight Loss

Table 1 provides an overview of medications that may be prescribed for weight loss.

Table1

Generic Name	Food and Drug Administration Approval for Weight Loss	Drug Type	Common Side Effects
Sibutramine	Yes; long term (up to 1 year) for adults	Appetite Suppressant	Increased blood pressure and heart rate
Phentermine	Yes; short term (up to 12 weeks) for adults	Appetite Suppressant	Increased blood pressure and heart rate, sleeplessness, nervousness
Diethylpropion	Yes; short term (up to 12 weeks) for adults	Appetite Suppressant	Dizziness, headache, sleeplessness, nervousness
Phendimetrazine	Yes; short term (up to 12 weeks) for adults	Appetite Suppressant	Sleeplessness, nervousness
Orlistat	Yes; long term (up to 1 year) for adults and children age 12 and older	Lipase Inhibitor	Gastrointestinal issues (cramping, diarrhea, oily spotting)
Bupropion	No	Depression Treatment	Dry mouth, insomnia
Topiramate	No	Seizure Treatment	Numbness of skin, change in taste
Zonisamide	No	Seizure Treatment	Drowsiness, dry mouth, dizziness, headache, nausea
Metformin	No	Diabetes Treatment	Weakness, dizziness, metallic taste, nausea

Food and Drug Administration-Approved Prescription Weight-loss Medications

Most of the Food and Drug Administration (FDA)-approved weight-loss medications are approved for short-term use, meaning a few weeks, but doctors may prescribe them for longer periods of time—a practice called "off-label" use. (See the box on the following page for more information about off-label use.) Sibutramine and orlistat are the only weight-loss medications approved for longer-term use in patients who are significantly obese. Their safety and effectiveness have not been established for use beyond 2 years, however.

Appetite Suppressants. Most available weight-loss medications approved by the FDA are appetite-suppressant medications. These include sibutramine, phentermine, phendimetrazine, and diethylpropion. Appetite-suppressant medications promote weight loss by decreasing appetite or increasing the feeling of being full. These medications make you feel less hungry by increasing one or more brain chemicals that affect mood and appetite. Phentermine and sibutramine are the most commonly prescribed appetite-suppressants in the United States.

NOTE: Amphetamines are a type of appetite suppressant. However, amphetamines are not recommended for use in the treatment of obesity due to their strong potential for abuse and dependence.

Lipase Inhibitors. The drug orlistat reduces the body's ability to absorb dietary fat by about one-third. It does this by blocking the enzyme lipase, which is responsible for breaking down dietary fat. When fat is not broken down, the body cannot absorb it, so it is eliminated and fewer calories are taken in.

In early 2007, orlistat was approved for over-the-counter (OTC) sale for adults age 18 and over. This means that the drug may be purchased without a prescription. The OTC version of orlistat is sold under the brand name alli. Alli is meant to be taken with a reduced-calorie, low-fat diet, exercise, and a daily multivitamin. Its side effects are similar to those for prescription orlistat. Anyone considering taking alli should read information about side effects, drug interactions, and usage recommendations on the drug's packaging or website, *http://www.myalli.com.*

Other Medications

The following types of medication(s) are not FDA-approved for the treatment of obesity. However, they have been shown to promote short-term weight loss in clinical studies and may be prescribed off-label.

Drugs to treat depression. Some antidepressant medications have been studied as appetite-suppressant medications. While these medications are FDA-approved for the treatment of depression, their use in weight loss is an off-label use (see the box below). Studies of these medications have generally found that patients lose modest amounts of weight for up to 6 months, but that patients tend to regain weight while they are still on the drug. One exception is bupropion. In one study, patients taking bupropion maintained weight loss for up to 1 year.

Drugs to treat seizures. Two medications used to treat seizures, topiramate and zonisamide, have been shown to cause weight loss. Whether these drugs will be useful in treating obesity is being studied.

What is "off-label" use?

Although the FDA regulates how a medication can be advertised or promoted by the manufacturer, these regulations do not restrict a doctor's ability to prescribe the medication for different conditions, in different doses, or for different lengths of time. The practice of prescribing medication for periods of time or for conditions not FDA-approved is known as off-label use. While such use often occurs in the treatment of many conditions, you should feel comfortable about asking your doctor if he or she is using a medication or combination of medications in a manner that is not approved by the FDA. The use of more than one weight-loss medication at a time (combined drug treatment) is an example of an off-label use. Using weight-loss medications other than sibutramine or orlistat for more than a short period of time (i.e., more than "a few weeks") is also considered off-label use.

Until more information on their safety or effectiveness is available, using combinations of medications for weight loss is not recommended.

Drugs to treat diabetes. The diabetes medication metformin may promote small amounts of weight loss in people with obesity and type 2 diabetes. How this medication promotes weight loss is not clear, although research has shown reduced hunger and food intake in people taking the drug.

Drug combinations. The combined drug treatment using fenfluramine and phentermine (known as "fen/phen") is no longer available due to the withdrawal of fenfluramine from the market after some patients experienced serious heart and lung disorders. (See the "Potential Risks and Concerns" section on the following page.) Little information is available about the safety or effectiveness of other drug combinations for weight loss, including fluoxetine/phentermine, phendimetrazine/phentermine, orlistat/sibutramine, herbal combinations, or others. *Until more information on their safety or effectiveness is available, using combinations of medications for weight loss is not recommended, except as part of a research study.*

Drugs in development. Many medications are being tested as potential treatments for obesity. The makers of one drug, rimonabant, applied for FDA approval in 2007 but withdrew the application after a scientific panel recommended against the drug's use. Although rimonabant is approved for use in some countries, it is *not* approved for use in the United States.

Potential Benefits of Medication Treatment

People respond differently to weight-loss medications, and some people experience more weight loss than others. Weight-loss medications lead to an average weight loss of about 10 pounds more than what you might lose with nondrug obesity treatments. Maximum weight loss usually occurs within 6 months of starting the medicine. Weight then tends to level off or increase during the remainder of treatment.

Over the short term, weight loss in individuals who are obese may reduce a number of health risks. Studies have found that weight loss with some medications improves blood pressure, blood cholesterol, triglycerides (fats), and insulin resistance (the body's inability to use blood sugar). New research suggests that long-term use of weight-loss drugs may help individuals keep off the weight they have lost. However, more studies are needed to determine the long-term effects of weight-loss drugs on weight and health.

Potential Risks and Concerns

Research has yet to determine the long-term health effects of weight-loss drugs. To date, the longest study is a 4-year investigation of orlistat. Most other studies have lasted 6 to 12 months or less. In addition, research has not examined rare side effects (those occurring in less than 1 per 1,000 patients), and the optimal duration of treatment is unknown.

When considering long-term weight-loss drugs to treat obesity, you should consider the following areas of concern and potential risks.

Potential for abuse or dependence. Currently, all prescription medications to treat obesity except orlistat are controlled substances, meaning doctors need to follow certain restrictions when prescribing them. Although abuse and dependence are not common with nonamphetamine appetite-suppressant medications, doctors should be cautious when they prescribe these medications for patients with a history of alcohol or other drug abuse.

Development of tolerance. Most studies of weight-loss drugs show that a patient's weight tends to level off after 6 months while still on the drug. Although some patients and doctors may be concerned that this shows tolerance to the medications, the leveling off may mean that the medication is no longer effective. Based on the currently available studies, it is not clear if weight gain with continuing treatment is due to drug tolerance. A recent study found that orlistat aids in weight maintenance over a 3-year period, but more research is needed to confirm these findings and investigate other drugs.

Reluctance to make behavioral changes while using prescription medications. Patients who are overweight or obese should be able to seek medical treatment to prevent health risks that can cause serious illness and death. Weight-loss drugs, however, are not "magic bullets" or a one-shot fix for this chronic disease. They should always be combined with a healthy eating plan and increased physical activity.

Side effects. Because weight-loss drugs are used to treat a condition that affects millions of people, many of whom are basically healthy, the possibility that side effects may outweigh benefits is of great concern. Most side effects of these drugs are mild and usually improve with continued use. Rarely, serious and even fatal outcomes have been reported. Some of the common side effects of the drugs are explained on the next page.

Because weight-loss medications are used to treat a condition that affects millions of people, the possibility that side effects may outweigh benefits is of great concern.

Because obesity is a chronic disease, any treatment, whether drug or nondrug, may need to be continued for years, and perhaps a lifetime, to improve health and maintain a healthy weight.

Orlistat. Some side effects of orlistat include cramping, intestinal discomfort, passing gas, diarrhea, and leakage of oily stool. These side effects are generally mild and temporary, but may be worsened by eating high-fat foods. Also, because orlistat reduces the absorption of some vitamins, patients should take a multivitamin at least 2 hours before or after taking orlistat.

Sibutramine. The main side effects of sibutramine are increases in blood pressure and heart rate, which are usually small but may be of concern in some patients. Other side effects include headache, dry mouth, constipation, and insomnia. People with poorly controlled high blood pressure, heart disease, irregular heartbeat, or history of stroke should not take sibutramine, and all patients taking the drug should have their blood pressure monitored on a regular basis.

Other appetite suppressants. Phentermine, phendimetrazine, and diethylpropion may cause symptoms of sleeplessness, nervousness, and euphoria (feeling of well-being). People with heart disease, high blood pressure, an overactive thyroid gland, or glaucoma should not use these drugs.

Two appetite-suppressant medications, fenfluramine and dexfenfluramine, were withdrawn from the market in 1997. These drugs, used alone and in combination with phentermine (fen/phen), were linked to the development of valvular heart disease and primary pulmonary hypertension (PPH), a rare but potentially fatal disorder that affects the blood vessels in the lungs. There have been only a few case reports of PPH in patients taking phentermine alone, but the possibility that phentermine use is associated with PPH cannot be ruled out.

Commonly Asked Questions About Weight-Loss Drugs

Q: Can drugs replace physical activity or changes in eating habits as a way to lose weight?

A: No. Studies show that weight-loss medications work best when combined with a weight-control program that helps you improve your eating and physical activity habits. Ask your doctor about ways you can improve your eating plan and become more physically active.

Q: How do I decide which drug is right for me?

A: Choosing a weight-loss drug is a decision between you and your health care provider. You will consider the drug's side effects, your

family's medical history, and your current medical conditions and medicines.

Q: What medical history, conditions, or medications might influence my decision to take a weight-loss drug?

A: Let your doctor know if any of the following applies to you, as these factors may affect which weight-loss drugs you can take, if any:

- History of drug or alcohol abuse.
- History of eating disorders.
- History of depression or manic depressive disorder.
- Pregnancy or breast-feeding.
- Migraine headaches requiring medication.
- Glaucoma.
- Diabetes.
- Heart disease or heart condition, such as an irregular heart beat.
- High blood pressure.
- Use of blood-thinning medication.
- Use of monoamine oxidase (or "MAO") inhibitors or antidepressant medications.
- Plan to have surgery that requires general anesthesia.

Q: How long will I need to take weight-loss medications to treat obesity?

A: The answer depends upon whether the medication helps you to lose and maintain weight and whether you have any side effects. Because obesity is a chronic disease, nondrug treatment including diet changes and regular physical activity may need to be continued for years, and perhaps a lifetime, to improve health and maintain a healthy weight. However, like many other types of drugs, there is still little information on how safe and effective weight-loss medications are for many years of use. At least one study has shown that intermittent use (1 month on medication and 1 month off medication) may help some people lose and maintain weight, but more research is needed.

Q: Will I regain some weight after I stop taking weight-loss medications?

A: Probably. Most studies show that the majority of patients who stop taking weight-loss medications regain the weight they lost. Maintaining healthy eating and physical activity habits may help you regain less weight or keep it off.

Q: Can children or teens use weight-loss medications?

A: Prescription orlistat is currently approved for use in teens age 12 or above. Other weight-loss drugs are not approved for use in children under age 16, although studies in children and teens are ongoing. Sibutramine and metformin are two drugs being studied in clinical trials. Early reports show them to be safe and effective, but more research is needed and they have not been FDA-approved for children or adolescents.

Q: Will insurance cover the cost of weight-loss medication?

A: Currently, many insurance companies will not pay for weight-loss drugs, but this is changing as insurers begin to recognize obesity as a chronic disease. Contact your insurance company to find out if prescription weight-loss medication is covered under your plan. A 1-month prescription can cost from 60 dollars to more than twice this amount. Ask a staff member at your pharmacy what a 1-month supply of the medication you are considering taking will cost.

Most patients should not expect to reach an "ideal" body weight using currently available medications. However, even a modest weight loss of 5 to 10 percent of your starting body weight can improve your health. Together, you and your doctor can make an informed choice as to whether medication can be a useful part of your weight-control program.

Additional Resources

Food and Drug Administration
Provides information about drug approvals, prescription drugs, OTC drugs, drug safety, clinical trials, public health alerts, and other topics.

5600 Fishers Lane
Rockville, MD 20857–0001
1–888–INFO–FDA (1–888–463–6332)
http://www.fda.gov

Mayo Clinic
Offers information about drugs and supplements.
http://www.mayoclinic.com/health/drug-information/DrugHerbIndex

National Center for Complementary and Alternative Medicine
Provides information on nonconventional therapies, such as herbal supplements and acupuncture.

9000 Rockville Pike
Bethesda, MD 20892
1–888–644–6226
TTY: 1–866–464–3615
http://www.nccam.nih.gov

National Library of Medicine
Offers information about drugs, supplements, and herbal products.

8600 Rockville Pike
Bethesda, MD 20894
1–888–FIND–NLM (1–888–346–3656)
http://www.nlm.nih.gov/medlineplus/druginformation.html

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Weight-control Information Network

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http://www.win.niddk.nih.gov

The Weight-control Information Network (WIN) is a service of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health, which is the Federal Government's lead agency responsible for biomedical research on nutrition and obesity. Authorized by Congress (Public Law 103–43), WIN provides the general public, health professionals, the media, and Congress with up-to-date, science-based health information on weight control, obesity, physical activity, and related nutritional issues.

Publications produced by WIN are reviewed by both NIDDK scientists and outside experts. This fact sheet was also reviewed by Myrlene Staten, Ph.D., Senior Advisor, Diabetes Translational Research; Division of Diabetes, Endocrinology, and Metabolic Diseases; NIDDK.

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Pharmacologic Agents in the Treatment of Obesity

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INTRODUCTION

The purpose of this chapter is to review the data supporting the safety and efficacy of appetite suppressants, lipase inhibitors, anticonvulsants, antidepressants, and other agents in the treatment of obesity. There are currently two approved medications for long-term obesity management, although it is not unusual in clinical practice for medications to be prescribed ''off label'' to achieve weight loss. Furthermore, an intensive effort is underway by many pharmaceutical companies to bring more agents to market against a growing epidemic of obesity and its comorbidities, particularly type 2 diabetes. The noradrenergic drugs phentermine, diethylpropion, benzphetamine, and phendimetrazine are approved only for short-term use. Sibutramine, a norepinephrine–serotonin reuptake inhibitor, is approved for long-term use. Also approved for long-term use is orlistat, which inhibits pancreatic lipase and can block hydrolysis of 30% of the dietary triglyceride in subjects eating a 30% fat diet. A growing trend is the use of antidepressants and anticonvulsants (bupropion, topiramate, and zonisamide) for weight management and the review will cover the evidence supporting their weight loss effects. Several newer drugs (rimonibant, axokine) in clinical trials investigation will also be discussed. Despite limitations in the number

and efficacy of current medications, the future prospects for obesity pharmacotherapy are optimistic.

Medicating for treatment of obesity can be a useful adjunct to diet and exercise and can help selected patients achieve and maintain meaningful weight loss. A report from the National Heart, Lung and Blood Institute of the NIH entitled Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adult—The Evidence Report emphasizes the need for physicians to address obesity in their patients (1). The Guidelines sanction the clinical use of weight loss drugs approved by the food and drug administration (FDA) for long-term use as part of a concomitant lifestyle modification program. Currently, this would include only sibutramine (trade-named Meridia or Reductil) or orlistat (Xenical). According to the Guidelines, medications are appropriate for those patients who have been unsuccessful in previous weight loss attempts and whose body mass index (BMI) exceeds 27 kg/m^2 who have associated conditions such as diabetes, hypertension, or dyslipidemia, or whose BMI exceeds 30 kg/m^2. Still, for many physicians, treatment of obesity is not a routine part of their clinical practices, and the majority of medications prescribed for weight loss are not those recommended as superior choices by the guidelines.

Drug treatment for obesity has been tarnished by a number of unfortunate problems (2). Since the introduction of thyroid hormone to treat obesity in 1893, almost every drug that has been tried in obese patients has led to undesirable outcomes that have resulted in their termination. Thus, caution must be used in accepting any new drugs for treatment of obesity, unless the safety profile would make it acceptable for almost everyone. The most recent medical disaster was the reports of valvular heart disease associated with the use of fenfluramine and dexfenfluramine (3–5). These drugs are potent releasers of serotonin and are associated with heart valve damage similar to that seen in carcinoid syndrome. Thankfully, the extent of the problem has not proven to be as great as first suspected (4,5). It is now recognized that risk for valvulopathy associated with fenfluramine is associated with duration of exposure to the medication and that the lesions are likely to remit off medication (4–7). The finding, however, will add caution when any future drugs are marketed to treat obesity and will provide support for those who believe drug treatment of obesity is inappropriate and risky.

Another issue to be considered is the way that all weight loss medications have been viewed as having the addictive properties of amphetamine (8). Abuse of either phentermine or diethylpropion is rare and sibutramine has evidence of abuse potential (2,9).

Another misconception about drug treatment of obesity is that the drugs are ineffective because weight regain occurs when drug treatment is stopped (10). Surgeries for obesity such as gastric bypass and gastric banding

have been demonstrated in one large registry study to produce >16% weight loss from baseline that is sustained for up to 10 years from baseline (11,12). As long as the treatment is enforced (the surgical band in place and the restrictive and malabsorptive modifications to gastrointestinal architecture unchanged) weight loss will be maintained. If the surgery is reversed, weight regain occurs. As clinicians, we do not expect to cure such diseases as hypertension or hypercholesterolemia with medications. Rather, we expect to palliate them. When the medications for any of these diseases are discontinued, we expect the disease to recur. This means that medications only work when used. Of the currently available medications used for weight management, a chronic approach to treatment is required.

Two final misconceptions must be addressed regarding pharmacotherapy for obesity. A weight loss of less than 15% is considered unsatisfactory by most obese patients (12). Yet the reality is that none of our current treatment approaches, except gastric bypass, produce a consistent weight loss of >15% for the average patient (13). When weight loss plateaus at a level above their desired cosmetic goal, patients usually stop medications. Patients seem to want to take medications to lose weight, but do not seem willing to take medications to maintain modest weight losses.

Last to consider is the lack of appreciation for the meaningful health benefits produced by sustained weight loss, even though only 5% to 10% from baseline. Loss of 5% to 10% in the obese can translate into improvement in glycemic control, [important, considering the epidemic of diabetes (14)] improvement in blood pressure and hypertension control, and improvements in lipid profile, in symptoms of sleep apnea, arthritis, and other comorbid conditions (1). Furthermore, modest weight loss can translate into reduction in morbidity. Weight loss of 7% from baseline produced a 58% reduction in risk for developing type 2 diabetes over two to five years in individuals with impaired glucose tolerance (15). Similar diabetes risk reduction with modest weight loss has been demonstrated in the Finnish Diabetes Prevention Program (16).

Physicians must be cognizant of these misconceptions; they are barriers to success. It is against these limitations that the review examines medications currently in use for obesity management in primary care practice settings. Table 1 describes the medications that will be discussed.

DRUGS APPROVED BY THE FDA WITH AN INDICATION FOR WEIGHT MANAGEMENT

There are only two agents currently available with FDA approval and an obesity indication for long term use—orlistat and sibutramine. Some older agents are still available in the United States and approved for short-term use, i.e., ''a few weeks.'' Those older agents include diethylpropion, phentermine, benzphetamine, and phendimetrizme.

Table 1 Drugs Approved by the FDA for Treatment of Obesity

Drug	Trade names	Dosage	DBA schedule
Pancreatic lipase inhibitor approved for long-term use			
Orlistat	Xenical	120 mg tid before meals	–
Norepinephrine serotonin reuptake inhibitor approved for long-term use			
Sibutramine	Meridia Reductil	5–15 mg/day	IV
Noradrenergic drugs approved for short-term use			
Diethylpropion	Tenuate	25 mg tid	IV
Phentermine	Adipex-P	15–37.5 mg/day	IV
	Ionamin slow release	15–30 mg/day	
Benzphetamine	Didrex	25–50 mg tid	III
Phendimetrazine	Bontril Prelu-2	17.5–70 mg tid	III
Medications used off-label for weight management			
Topiramate	Topamax	50–200 mg/day	–
Zonisamide	Zonegran	400–600 mg/day	–
Fluoxetine[a]	Prozac Sarafem	60 mg/day	–
Bupropion	Wellbutrin	400 mg/day	–
Venlafaxine	Effexor	75–225 mg/day	–

[a]Weight loss efficacy is only demonstrated for a few weeks and then weight regain occurs on fluoxetine.
Abbreviation: FDA, food and drug administration.

Phentermine, Diethylpropion, Benzphetamine, Phendimetrazine, and Mazindol

This group of agents have been available in the U.S. market for more than 30 years. The published clinical data supporting their safety and efficacy consists of a few studies, each enrolling a few patients and most studies are of short duration. Only a handful of clinical trials for this group equals or exceeds 24 weeks duration. By far, phentermine is the most popular drug in this group and the others are not widely available. Phentermine is the most frequently prescribed weight loss agent in the United States, probably because it is inexpensive, since it is no longer protected by patent.

The best and one of the longest of the clinical trials reporting phentermine's weight loss efficacy lasted 36 weeks and compared placebo treatment against continuous phentermine or intermittent phentermine (Fig. 1) (17). The intermittent regimen was four weeks of phentermine 15 mg/day followed by four weeks of placebo. This was compared to continuous phentermine at 15 mg/day or placebo. Both continuous and intermittent phentermine therapy produced more weight loss than did placebo. In the drug-free

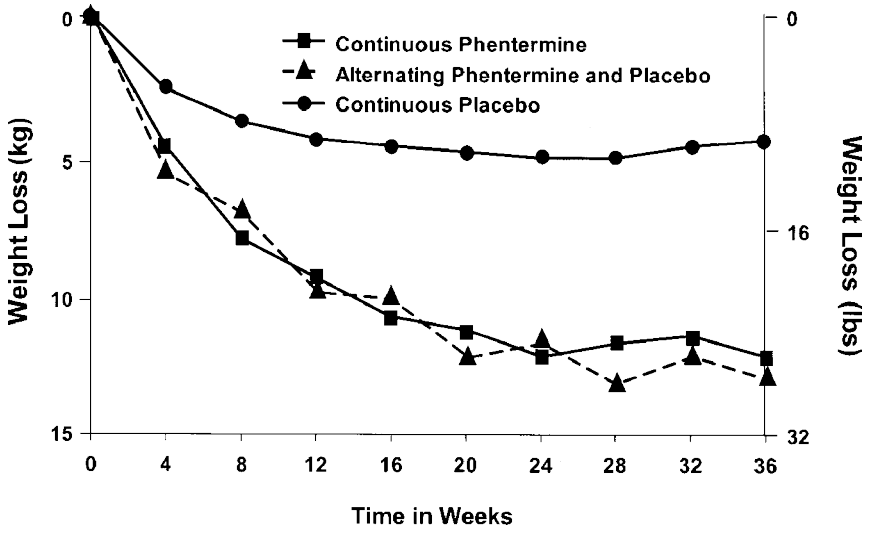


Figure 1 Comparison of weight loss with continuous and intermittent therapy using phentermine. Overweight patients were randomized to receive either placebo or one of two dosing-regimens with phentermine. One regimen provided 15 mg/day each morning for nine months and the other provided 15 mg/day for one month and then a month of no treatment. Source: From Ref. 17.

periods the patients treated intermittently slowed their weight loss only to lose more rapidly when the drug was reinstituted. As can be observed in Figure 1, intermittent phentermine produced comparable weight loss to continuous phentermine.

Phentermine and diethylpropion are classified by the U.S. Drug Enforcement Agency as schedule IV drugs, and benzphetamine and phendimetrazine as schedule III drugs, although states may schedule these agents differently. This regulatory classification indicates the government's belief that they have the potential for abuse, although this potential appears to be very low. Phentermine and diethylpropion are only approved for a ''few weeks'' use, which is usually interpreted as up to 12 weeks. Weight loss with phentermine and diethylpropion persists for the duration of treatment, suggesting that tolerance does not develop to these drugs. If tolerance were to develop, the drugs would be expected to lose their effectiveness or require increased amounts of drug for patients to maintain weight loss. This does not occur. Phentermine is not available in Europe. A review in a prestigious journal recommends obtaining written informed consent if phentermine is prescribed for longer than 12 weeks, because this is off-label usage and there are not sufficient published reports on the use of phentermine for long-term use (18).

The side effect profile for sympathomimetic drugs is similar (1). They produce insomnia, dry mouth, asthenia, and constipation. Sympathomimetic drugs can also increase blood pressure.

Sibutramine (Meridia[1], Reductil in Europe)

In contrast to the older sympathomimetic drugs in Table 1, sibutramine has been extensively evaluated in several large-scale multicenter trials lasting 6 to 24 months conducted in men and women of all ethnic groups with ages ranging from 18 to 65 years and with a BMI between 27 and 40 kg/m^2. Sibutramine's clinical research history has been recently reviewed (19).

There is a dose–response effect with sibutramine. In a six-month dose-ranging study of 1047 patients, 67% of sibutramine treated patients achieved a 5% weight loss and 35% lost 10% or more. Data from this multicenter trial are shown in Figure 2 (20,21). There is a clear dose–response in this 24-week trial, and regain of weight occurred when the drug was stopped, indicating that the drug remained effective when used.

In another interesting study by virtue of the magnitude of weight lost, patients who initially lost weight eating a very low calorie diet were

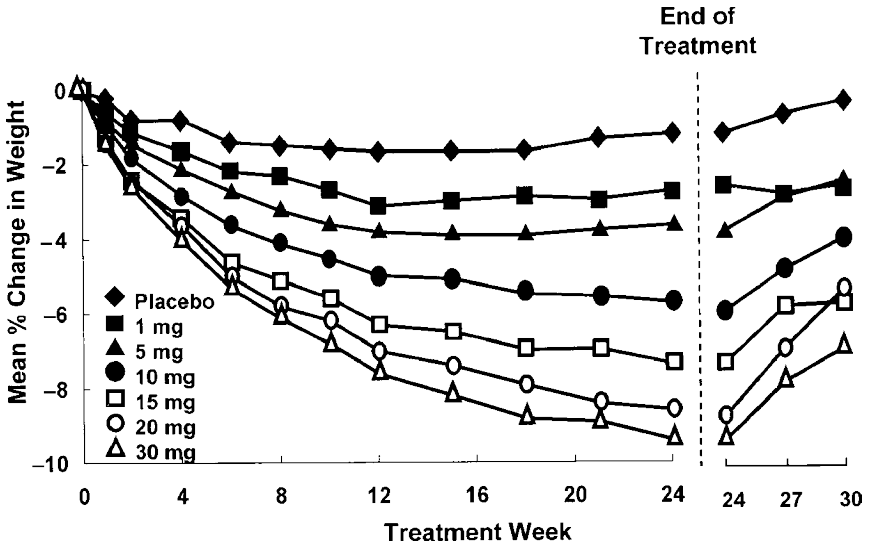


Figure 2 Dose-related weight loss with sibutramine. A total of 1047 patients were randomly assigned to receive placebo or one of six doses of sibutramine in a double-blind fashion for six months. By the end of the trial of sibutramine treated patients, weight loss had plateaued for most doses. When the drug was discontinued at six months, weight was regained, indicating that the drug remained effective during treatment. Source: From Ref. 35.

randomized to sibutramine 10 mg/day or placebo, and behavioral program. Sibutramine produced additional weight loss (−16% from baseline at 1 year), whereas the placebo-treated patients regained weight (22). These results indicate that the response to sibutramine is dependent on the intensity of the behavioral approaches that are used with sibutramine. By combining a very low calorie diet and intensive behavioral therapy along with sibutramine, the total weight loss at one year was quite impressive.

A number of observations about sibutramine can be drawn from the Sibutramine Trial of Obesity Reduction and Maintenance (STORM Trial), but the effects of sibutramine in aiding weight maintenance are the most persuasive aspect of the trial (23). Seven centers participated in this trial where 605 patients were initially enrolled in an open-label fashion and treated with 10 mg/day of sibutramine for six months (Fig. 3). Those patients who lost more than 5% (and 77% of enrolled patients met this goal) were then randomized, two-thirds to sibutramine and one-third to placebo. During the 18-month double-blind portion of the trial, the placebo-treated patients steadily regained weight, maintaining only 20% of their weight loss at the end of the trial. In contrast, the subjects treated with sibutramine maintained their weight for 12 months and then regained an average of only 2 kg, thus maintaining 80% of their initial weight loss after two years (24). In spite of the difference in weight at the end of the 18 months of controlled observation, the mean blood pressure of the sibutramine-treated patients

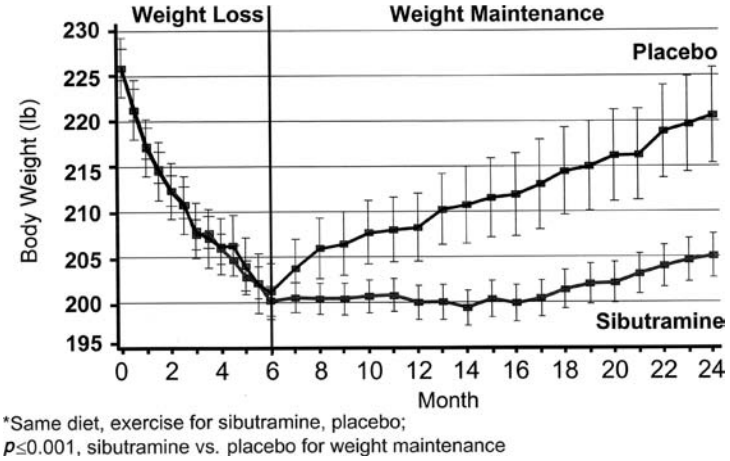


Figure 3 The Sibutramine Trial of Obesity Reduction and Maintenance (STORM). In the six-month weight loss period, 605 patients received sibutramine 10 mg/day. At six months, 352 patients were randomized to receive placebo. Both groups received the same diet and exercise counseling. There was a dose titration allowed to a maximum of 20 mg/day sibutramine. Source: From Ref. 38.

was still higher than in the patients treated with placebo, even though they had a weight difference of several kilograms.

Sibutramine given continuously for one year has been compared to placebo and sibutramine given intermittently (25). In this study (Fig. 4), patients who had lost −2% or –2 kg after four weeks of treatment with sibutramine 15 mg/day were randomized to placebo as continued sibutramine versus sibutramine prescribed intermittently (weeks 1–12, 19–30, and 37–48). Both sibutramine treatment regimens gave equivalent results and were significantly better than placebo. As illustrated in Figure 4, the effect of stopping sibutramine results in small increases in weight, which is then reversed when the medication is restarted.

Four clinical trials document sibutramine use in patients with diabetes. One was for 12 weeks and the other three studies were for 24 weeks (24,26–28). In the 12-week trial, diabetic patients treated with sibutramine 15 mg/day lost −2.4 kg (2.8%) compared to −0.1 kg (0.12%) in the placebo group (29). In this study, Hemoglobin A1c (HbA1c) fell −0.3% in the drug-treated group and remained stable in the placebo-treated group. In the study by Gockel et al. (27)

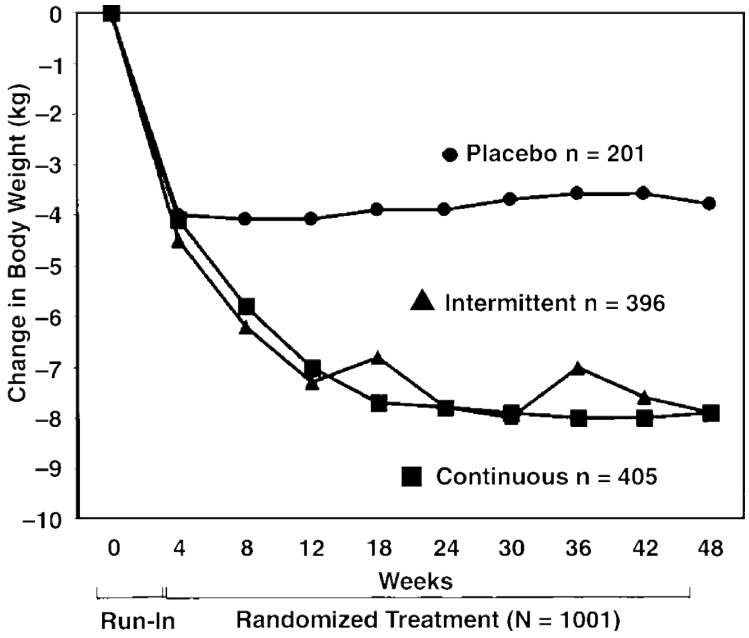


Figure 4 Sibutramine given intermittently or continuously compared to placebo. Mean (SE) change in body weight during the study period. Patients (n ¼ 1102) received sibutramine 15 mg/day. Those who lost 2% or 2 kg in four weeks were randomized to placebo (n ¼ 395) versus continued sibutramine (n ¼ 405) versus intermittent sibutramine (weeks 1–12,19–30, and 37–48) (n ¼ 395). Source: From Ref. 25.

60 female patients who had poorly controlled glucose levels (HbA1c > 8%) on maximal doses of sulfonylureas and metformin were randomly assigned to sibutramine 10 mg twice daily or placebo. The weight loss at 24 weeks was −9.6 kg in the sibutramine treated patients and −0.9 kg in those on placebo. The improvements in glycemic control were equally striking. In the sibutramine-treated patients, HbA1c fell −2.73% compared to −0.53% with the placebo. Insulin levels fell −5.66 U/mL compared to −0.68 U/mL for placebo and fasting glucose fell −124.88 mg/mL compared to −15.76 mg/mL for placebo. While the weight loss in most of the studies of patients with diabetes does not appear as great as in nondiabetic patients, in all of the studies the percentage of patients who achieved weight loss ≥5% from baseline was significantly greater than placebo. In all studies the degree of weight loss corresponds to the degree of improvement in glycemic control.

Two trials have been reported using sibutramine to treat hypertensive patients over one year, and two additional studies provide data on 12 weeks of treatment (21,30–32). In all instances, the weight loss pattern favors sibutramine. However, except for one study, mean weight loss, though favorable, was associated with small increases in mean blood pressure (31). In a three-month trial all patients were receiving b-blockers with or without thiazides for their hypertension (32). The sibutramine-treated patients lost −4.2 kg (4.5%) compared to a loss of −0.3 kg (0.3%) in the placebo-treated group. Mean supine and standing diastolic and systolic blood pressure were not significantly different between drug-treated and placebo-treated patients. Heart rate, however, increased þ5.6 ± 8.25 (M ± SD) bpm in the sibutramine-treated patients as compared to an increase in heart rate of þ2.2 ± 6.43 (M ± SD) bpm in the placebo group.

McMahon et al. (21) reported a 52-week trial in hypertensive patients whose blood pressure was controlled with calcium channel blockers with or without b-blockers or thiazides. Sibutramine doses were increased from 5 to 20 mg/day during the first six weeks. Weight loss was significantly greater in the sibutramine-treated patients, averaging −4.4 kg (4.7%) as compared to −0.5 kg (0.7%) in the placebo-treated group. Diastolic BP decreased −1.3 mmHg in the placebo-treated group and increased by þ2.0 mmHg in the sibutramine-treated group. The SBP increased þ1.5 mmHg in the placebo-treated group and by þ2.7 in the sibutramine-treated group. Heart rate was unchanged in the placebo-treated patients, and increased þ4.9 bpm in the sibutramine-treated patients (21). One small study in eight obese men demonstrated that an aerobic exercise program mitigated the adverse blood pressure effects of sibutramine (33).

Since the dose of sibutramine influences the amount of weight loss with the drug, the intensity of the behavioral component is also likely to have an effect (21,28). This is readily demonstrated in a study by Wadden (34). With minimal behavioral intervention, the weight loss in that study was about 5 kg over 12 months. When group counseling to produce behavior

modification was added to sibutramine the weight loss increased to 10 kg, and when a structured meal plan using meal replacements was added to the medication and behavior plan, the weight loss increased further to −15 kg (34). This indicates that the amount of weight loss observed during pharmacotherapy is due in part to the intensity of the behavioral approach.

Sibutramine is available in 5, 10, and 15 mg pills; 10 mg/day as a single daily dose is the recommended starting level with titration up or down based on response. Doses above 15 mg/day are not recommended by the FDA. The chance of achieving meaningful weight loss can be determined by the response to treatment in the first four weeks. In one large trial, of the patients who lost −2 kg (−4 lb) in the first four weeks of treatment, 60% achieved a weight loss of more than 5%, compared to less than 10% of those who did not lose −2 kg (−4 lb) in four weeks (21,35). Except for blood pressure, weight loss with sibutramine is associated with improvement in profiles of cardiovascular risk factors. Combining data from the total of 11 studies on sibutramine showed a weight-related reduction in triglyceride, total cholesterol, and LDL cholesterol and a weight loss related rise in HDL cholesterol that was related to the magnitude of the weight loss (36).

Sibutramine should not be used in patients with a history of coronary artery disease, congestive heart failure, cardiac arrhythmias, or stroke. There should be a two-week interval between termination of monoamine oxidase inhibitors (MAOIs) and beginning sibutramine. Sibutramine should be used only with caution with selective serotonin reuptake inhibitors (SSRIs). Because sibutramine is metabolized by the cytochrome P_{450} enzyme system (isozyme CYP3A4) when drugs like erythromycin and ketoconazole are taken, there may be competition for this enzymatic pathway and prolonged metabolism can result.

There are two issues to consider regarding blood pressure management and sibutramine use. The first is the development of clinically significant blood pressure elevations. Individual blood pressure responses to sibutramine are quite variable. From the studies reviewed, withdrawals for clinically significant blood pressure increase are usually 2% to 5% of participants in the trial. Higher doses tend to produce higher withdrawal rates, thus lower doses are preferred (35). The other issue with blood pressure increases is the small mean increase of 2 to 4 mmHg in systolic and diastolic blood pressure that occurs in sibutramine treated patients versus controls. Weight loss is usually associated with improvement in risk factors for cardiovascular disease (blood pressure, lipids, measures of glycemic control). If sibutramine has mixed effects on risk factors, with improvement in some (lipids, glycemic control) but slight worsening of others, then the prescribing physician must use judgment in the decision to continue sibutramine.

Managing potential increases in blood pressure should be a part of the sibutramine treatment plan. Evaluation of blood pressure two to four

weeks after starting sibutramine is recommended. The initial dose is usually 10 mg/day. About 5% of patients who take sibutramine will have unacceptable increases in blood pressure and for them, the medication should be stopped.

Orlistat (Xenical[1])

Orlistat is a potent selective inhibitor of pancreatic lipase that reduces intestinal digestion of fat. The drug has a dose-dependent effect on fecal fat loss, increasing it to about 30% of ingested fat on a diet that has 30% of energy as fat (37). Orlistat has little effect in subjects eating a low-fat diet, as might be anticipated from the mechanism by which this drug works (37).

A number of long-term clinical trials with orlistat lasting six months to four years have been published, and these have been reviewed recently (38).

The results of one two-year trial are shown in Figure 5 (9). The trial consisted of two parts. In the first year patients received a hypocaloric diet calculated to be 500 kcal/day below the patient's requirements. During the second year the diet was calculated to maintain weight. By the end of year one the placebo-treated patients lost −6.1% of their initial body weight and

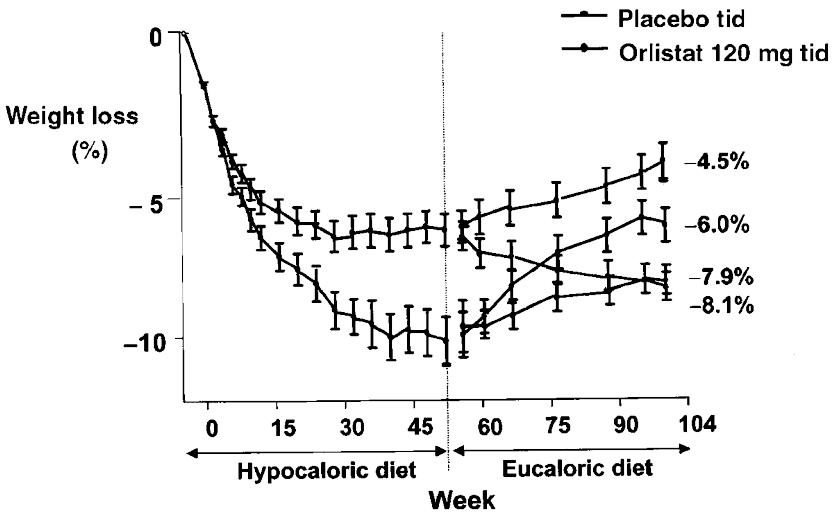


Figure 5 Orlistat and body weight change over two years of treatment. A total of 743 patients were randomized to receive either orlistat 120 mg three times daily or placebo for the first year and were then re-randomized to the same groups for a second year. Following the four-week single-blind (SB) run in, the first double-blind (DB) period utilized a diet that was calculated to be 600 kcal/day below maintenance, and the second DB period used a diet that was intended to maintain body weight. Source: From Ref. 39.

the drug-treated patients lost −10.2%. The patients were re-randomized at the end of year one. Those switched from orlistat to placebo gained weight from −10% to −6.0% below baseline. Those switched from placebo to orlistat lost from −6% to −8.1%, which was essentially identical to the −7.9% in the patients treated with orlistat for the full two years.

In a second two-year study, 892 patients were randomized (40). One group remained on placebo throughout the two years (n ¼ 97 completers) and a second group remained on orlistat 120 mg three times a day for two years (n ¼ 109 completers). At the end of one year, two-thirds of the group treated with orlistat for one year were changed to orlistat 60 mg three times a day (n ¼ 102 completers) and the others to placebo (n ¼ 95 completers) (40). After one year, the weight loss was −8.67 kg in the orlistat-treated group and −5.81 kg in the placebo group ($p < 0.001$). During the second year, those switched to placebo after one year reached the same weight as those treated with placebo for two years (−4.5% in those with placebo for two years and −4.2% in those switched from orlistat to placebo during year two).

In a third two-year study, 783 patients enrolled in a trial where, for two years, they remained in the placebo group or one of two orlistat-treated groups at 60 or 120 mg three times a day (40,41). After one year with a weight loss diet, the completers in the placebo group lost −7.0 kg, which was significantly less than the −9.6 kg in the completers treated with orlistat 60 mg thrice daily or −9.8 kg in the completers treated with orlistat 120 mg thrice daily. During the second year when the diet was liberalized to a ''weight maintenance'' diet, all three groups regained some weight. At the end of two years, the completers in the placebo group were −4.3 kg below baseline, the completers treated with orlistat 60 mg three times daily were −6.8 kg and the completers treated with orlistat 120 mg three times daily were −7.6 kg below baseline.

Another two-year trial that has been published was carried out on 796 subjects in a general practice setting (42). After one year of treatment with orlistat 120 mg/day, completers (n ¼ 117) had lost −8.8 kg compared to −4.3 kg in the placebo completers (n ¼ 91). During the second year when the diet was liberalized to ''maintain body weight,'' both groups regained some weight. At the end of two years, the orlistat group receiving 120 mg three times daily was 5.2 kg below their baseline weight compared to −1.5 kg for the group treated with placebo. The percent change in body weight over two years of orlistat at 60 and 120 mg is depicted in Figure 6 which represents pooled data from multiple studies extracted from the integrated database of volunteers treated in a general practice setting.

Weight maintenance with orlistat was evaluated in a one-year study (43). Patients were enrolled who lost more than 8% of their body weight over six months eating a 1000 kcal/day (4180 kJ/day) diet. The 729 patients were one of four groups randomized to receive either placebo or 30, 60, or 120 mg of orlistat three times a day for 12 months. At the end of this time

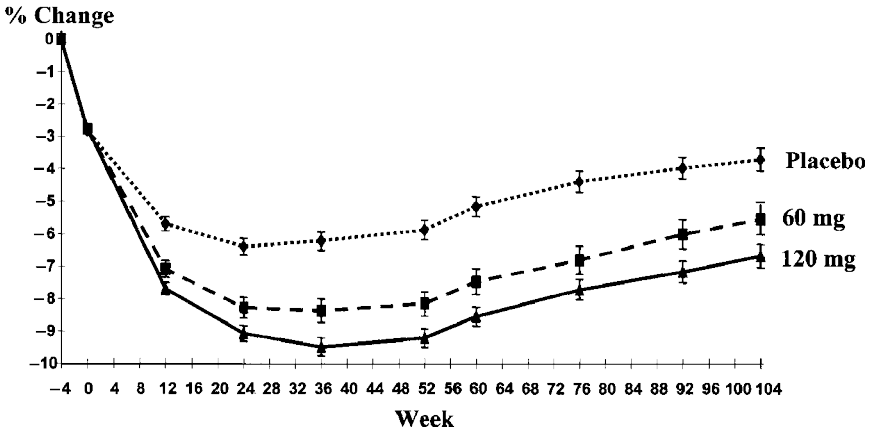


Figure 6 Orlistat in primary care practices. Percent change from initial body weight over two years of treatment. Data derived from an integrated data base. Source: From Ref. 37.

the placebo-treated patients had regained 56% of their body weight, compared to 32.4% in the group treated with orlistat, 120 mg three times a day. The other two doses of orlistat were not statistically different from placebo in preventing the regain of weight.

The modest weight reduction observed with orlistat treatment may have a beneficial effect on lipids and lipoproteins. Orlistat seems to have an independent effect on LDL cholesterol. From a meta-analysis of the data relating orlistat to lipids in five double-blind, randomized, placebo-controlled studies, orlistat-treated subjects had almost twice as much reduction in LDL cholesterol as their placebo-treated counterparts for the same weight loss category reached after one year (44).

One study is representative of the effects of orlistat on weight loss and on cardiovascular risk factors, particularly serum lipids, in obese patients with hypercholesterolemia (45). The main findings were that orlistat promoted clinically significant weight loss and reduced LDL-C in obese patients with elevated cholesterol levels more than could be attributed to weight loss alone. Another study, the ObelHyx study, demonstrates an additional 10% LDL-C lowering in obese subjects with baseline elevated LDL-C levels compared to placebo (46).

Orlistat's independent cholesterol-lowering effect probably reflects a reduction in intestinal absorption of cholesterol. Since lipase inhibition by orlistat prevents the absorption of approximately 30% of dietary fat, the prescribed diet of 30% of energy from fat would thus become in effect a 20% to 24% of available fat in the diet when associated with orlistat treatment. It has been hypothesized that inhibition of gastrointestinal lipase

activity may lead to retention of cholesterol in the gut through a reduction in the amount of fatty acids and monoglycerides absorbed from the gut, and/or may lead to sequestration of cholesterol within a more persistent oil-phase in the intestine. Partial inhibition of intestinal fat and cholesterol absorption probably leads to decreased hepatic cholesterol and saturated fatty acid concentration, upregulation of hepatic LDL receptors, and decreased LDL-C levels.

The orlistat-treated subjects in trials lasting for at least one year were analyzed by Heymsfield et al. (47), who found that orlistat reduced the conversion of impaired glucose tolerance (IGT) to diabetes and that the transition from normal to impaired glucose tolerance was also reduced in subjects treated with orlistat for one year. In orlistat-treated subjects the conversion from normal glucose tolerance to diabetes occurred in 6.6% of patients, whereas approximately 11% of placebo-treated patients had a similar worsening of glucose tolerance. Conversion from IGT to diabetes was less frequent in orlistat-treated patients than in placebo-treated obese subjects, by 3.0% and 7.6%, respectively (47). Although these data are based on a retrospective analysis of one-year trials in which data on glucose tolerance was available, it shows that modest weight reduction—with pharmacother- apy—may lead to an important risk reduction for the development of type II diabetes.

One study randomized 550 insulin-treated patients to receive either placebo or orlistat 120 mg three times a day for one year (48). Weight loss in the orlistat-treated group was $-3.9 \pm 0.3\%$ compared to $-1.3 \pm .0.3\%$ in the placebo-treated group. Hemoglobin Alc was reduced -0.62% in the orlistat-treated group, but only -0.27% in the placebo group. The required dose of insulin decreased more in the orlistat group, as did plasma cholesterol (48).

Orlistat, in a study in patients with diabetes, improved metabolic control with a reduction of up to -0.53% in hemoglobin Alc (HbA1c) and a decrease in the concomitant ongoing antidiabetic therapy, despite limited weight loss (29). Independent effects of orlistat on lipids were also shown in this study (29). Orlistat also has an acute effect on postprandial lipemia in overweight patients with type 2 diabetes. By lowering both remnant-like particle cholesterol and free fatty acids in the postprandial period, orlistat may contribute to a reduction in atherogenic risk (49).

The longest clinical trial with orlistat is the Xenical Diabetes Outcome Study (XENDOS) (50). In this four-year randomized, placebo-controlled clinical trial 1640 patients were assigned to received orlistat 120 mg three times daily plus lifestyle and 1637 patients to receive matching placebos plus lifestyle. The study enrolled Swedish patients with a BMI $\geq 30\,kg/m^2$ with normal or impaired glucose tolerance (21%). More than 52% of the orlistat and 34% of the placebo-treated patients continued to adhere to the clinical protocol. The patients receiving orlistat were -6.9 kg below their baseline

weight by the end of year 4 compared to −4.1 kg for the placebo-treated group ($p < 0.001$). Cumulative incidence of diabetes was 9.0% in the placebo group and 6.2% in the orlistat group, a 37% reduction in relative risk. Xendos provides evidence, not only of therapeutic benefit in terms of diabetes risk reduction, but also that long-term clinical trials of anti-obesity drugs can be successfully implemented.

Orlistat is not absorbed to any significant degree and its side effects are thus related to the blockade of triglyceride digestion in the intestine (37). Fecal fat loss and related GI symptoms are common initially, but subside as patients learn to use the drug (38,39). During treatment, small but significant decreases in fat-soluble vitamins can occur although these almost always remain within the normal range (51). However, a few patients may need supplementation with fat-soluble vitamins that can be lost in the stools. Since it is impossible to tell a priori which patients need vitamins, we routinely provide a multivitamin with instructions to take it before bedtime. Absorption of cyclosporin may also be significantly affected by orlistat.

Combining Orlistat and Sibutramine

Since orlistat works peripherally to reduce triglyceride digestion in the GI track and sibutramine works on noradrenergic and serotonergic reuptake mechanisms in the brain, their mechanisms do not overlap at all and combining them might provide additive weight loss. To test this possibility Wadden et al. (52) randomly assigned patients to orlistat or placebo in addition to sibutramine, following a year of treatment with sibutramine alone. During the additional four months of combination treatment there was no further weight loss. This result was a disappointment, but additional studies are obviously needed before firm conclusions can be made about combining therapies.

MEDICATIONS USED IN OBESITY MANAGEMENT, BUT WHICH DO NOT HAVE AN FDA-APPROVED INDICATION

Topiramate

Topiramate is a neuropsychiatric agent approved for treatment of certain forms of epilepsy, either as monotherapy and in combination with other antiepileptic drugs. Topiramate is a carbonic anhydrase inhibitor that also affects the $GABA_A$ receptor.

In a pooled analysis of a number of epilepsy trials, topiramate was shown to produce progressive weight loss over 18 months which was maintained for the 24 months of observation (53). Patients who had baseline weight exceeding 100 kg lost proportionally more weight compared to those with normal weight (53).

A prospective observational study of topiramate was performed in patients with epilepsy who were taking at least one antiepileptic medication, and provided an opportunity to observe weight effects of the drug (54). Of 49 patients who enrolled, 11 withdrew because of adverse events or because of subject choice (4,7). There were 38 who completed one year of topiramate exposure. The mean topiramate dose for completers was 129 mg/day. In those 38 subjects, there was −7.3% reduction in body weight at one year. The proportional weight loss was greater in the eight obese subjects (−11% from baseline). Patients lost more body fat than lean mass, as assessed by dual emission X-ray absorptiometry. In patients who lost weight, body fat mass was reduced −14.7% at one year, while lean body mass was only reduced −4.8%.

A number of clinical trials with topiramate were begun, but were stopped while in progress in order that the formulation of the drug could be reevaluated. To date, only one of these studies has been published (55). In that multicenter, placebo-controlled, dose-ranging study, topiramate was given for six months to 385 obese patients at doses of 64, 96, 192, or 384 mg daily. Figure 7 shows the weight loss results for completing subjects in this study. The mean percent weight loss in an intention to treat, last observation carried forward are more modest; at six months weight loss was −2.6% for placebo, −5.0%, −4.8%, −6.3%, and −6.3%, respectively, for

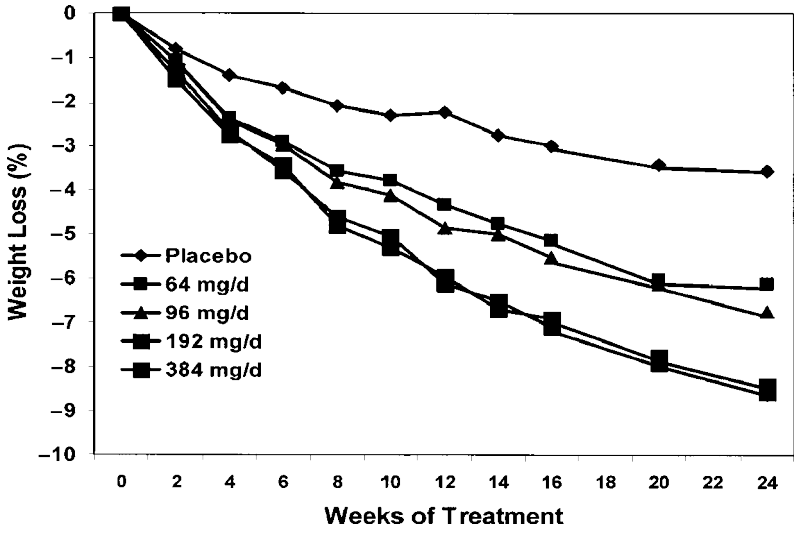


Figure 7 Topiramate dose-ranging study. Percent body weight change over time for subjects who completed the 24-week study. Topiramate produced significantly greater weight loss than placebo; the two higher doses were similar but significantly greater than the two lower doses. Source: From Ref. 55.

the 64, 96, 192, and 384 mg doses. While this weight loss pattern is relatively modest, the drug would be expected to show additional weight loss for up to 18 months, if the earlier clinical observation is correct (53).

While the clinical observations of weight loss with topiramate show promise, safety and tolerability are important. The chief safety issues with the medication are acute glaucoma, renal stones, and cognitive impairment (discussed below). Acute glaucoma is an extremely rare side-effect signaled by visual impairment and requires immediate cessation of the drug and opthalmalogical management for preservation of vision. Because topiramate is a carbonic anhydrous inhibitor, taste perversions (with carbonated drinks) are to be expected, as are paresthesias and increased risk for renal calculi.

Central nervous system symptoms are the most worrisome aspect of developing topiramate for an obesity indication. Cognitive impairment, described as mental slowing, somnolence or word-finding difficulty are reported with increased frequency on adverse event reporting forms. In the topiramate-treated patients in the published six month weight loss study, the adverse event (AE) reporting prevalence of difficulty with memory was 20% compared to 8% in placebo-treated patients (55). The AE prevalence of difficulty with concentration was 10% in those treated with topiramate compared to 5% of those treated with placebo. Overall in that study, 21% of topiramate-treated patients withdrew for adverse events compared to 11% of those on placebo. To improve tolerance, the manufacturers recommend slow dose titration. In the published weight loss six month trial, topiramate was started at 16 mg/day for one week, raised to 16 mg twice a day for week 2, and titrated upward in weekly increments of 32 mg/day until the target dose was reached (55).

Topiramate has been investigated and shown efficacy in migraine prevention, in bipolar disorder and in binge eating disorders (56–59). Its future development as an anti-obesity agent is uncertain, as additional longer term clinical trials have not been initiated.

Despite tolerability issues, interest in topiramate remains strong among obesity researchers, in part because of the prolonged weight loss effect of the drug, in part because of its uncertain mechanism of action, and in part because of its potential independent effect on glycemic control, which remains an unresolved issue.

Zonisamide

Zonisamide is marketed as an antiepileptic drug, is a sulfonamate derivative, and is a weak carbonic anhydrase inhibitor, all characteristics similar to topiramate. In clinical trials in epilepsy patients who took zonisamide in addition to other epilepsy medications, weight loss was observed as a side effect (60).

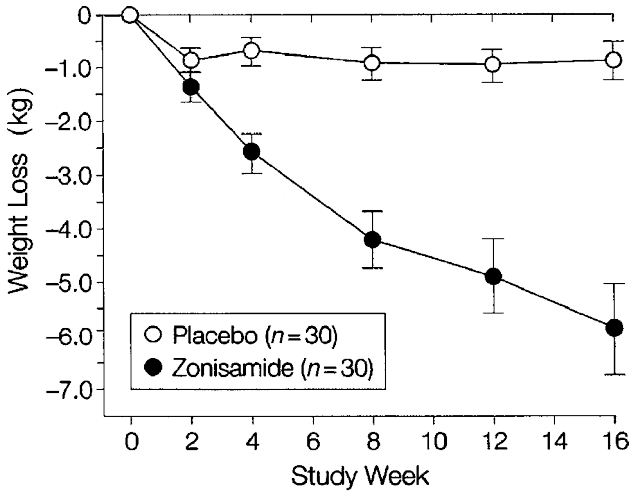


Figure 8 Zonisamide trial in 60 obese patients. Percent body weight changes from baseline to week 16 is depicted for obese patients randomized to either zonisamide or placebo. Data is from a last observation carried forward, intent-to-treat analysis shows statistically significant weight loss for the zonisamide group. Error bars indicate SE. Source: From Ref. 61.

In a 16-week double-blind randomized clinical trial, Gadde et al. (61) randomized 60 obese subjects to placebo or 600 mg/day of zonisamide. All patients were instructed in a 500 kcal/day deficit diet. Figure 8 demonstrates the weight loss pattern in this study of zonisamide and placebo-treated patients. During the 16-week double-blind period the zonisamide-treated patients lost −5.98%, compared to −1.09% in the placebo group. During the first 16 weeks of treatment, six zonisamide and three placebo subjects withdrew. Of the zonisamide-treated patients, 19 entered a 16-week single-blind extension and their mean weight loss was −9.4% at 32 weeks. In terms of safety, the chief issue was the adverse event reporting of fatigue by 10 in the zonisamide group and only one in the placebo group. There was also slight elevation of serum creatinine associated with zonisamide use, from 0.78 to 0.92 mg/dL. Zonisamide has been shown in epilepsy trials to be frequently associated with dizziness, cognitive impairment and somnolence and, rarely, with kidney stones and hematologic disease.

Antidepressants—Fluoxetine, Bupropion, and Venlafaxine

Most antidepressants are associated with weight gain (62). However, fluoxetine and bupropion have been evaluated in clinical trials for weight loss and venlafaxine has weight loss reported as a side effect in its prescribing information.

There was initial enthusiasm for fluoxetine as a weight loss agent when it was shown to produce dose-related weight loss in a small eight-week study of fluoxetine 10, 20, 40, and 60 mg and placebo (63). However, the weight loss efficacy was not replicated in a large (458 subject), 52-week, double-blind, 10-site trial (64). In that study, as shown in Figure 9, fluoxetine, 60 mg daily, was compared to placebo and did not produce a treatment difference at week 52. There was statistically significant greater mean weight loss compared to placebo early in the study, but after week 28 there is progressive weight regain despite continued treatment. While fluoxetine may play a role in management of depression in obese patients, it is an ineffective agent for long-term weight management.

Bupropion is a norepinephrine and dopamine reuptake inhibitor with FDA-approved indications for major depression and smoking cessation. Sustained-release bupropion has been shown to be associated with weight loss in overweight and obese subjects treated with the drug for depression (65).

Sustained-release bupropion was evaluated in a multi-center, double-blind, placebo-controlled randomized trial (66). In that study, there were 327 subjects randomized to placebo, or either 300 or 400 mg of daily bupropion SR. The results are shown in Figure 10. All subjects were randomly allocated to receive either placebo or active treatments (bupropion SR 300 mg/day or bupropion SR 400 mg/day) in a double-blind manner for 24 weeks. Then placebo-treated patients were randomized to either 300 or 400 mg of daily bupropion SR for 24 additional weeks. There was a dose–response relationship evident with mean weight loss of −7.2% and −10.1% for bupropion SR 300 and 400 mg, respectively, at 24 weeks. These were net

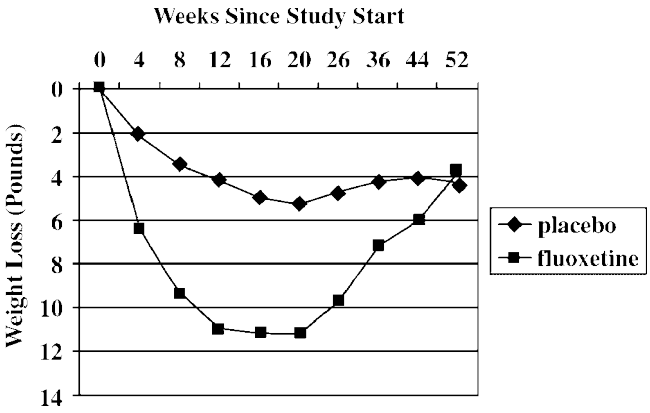


Figure 9 Fluoxetine trial for overweight and obesity. Percent body weight change over time for obese subjects randomized to daily fluoxetine 60 mg or placebo. After week 26, there are no statistically significant differences between the treatment groups. Source: From Ref. 64.

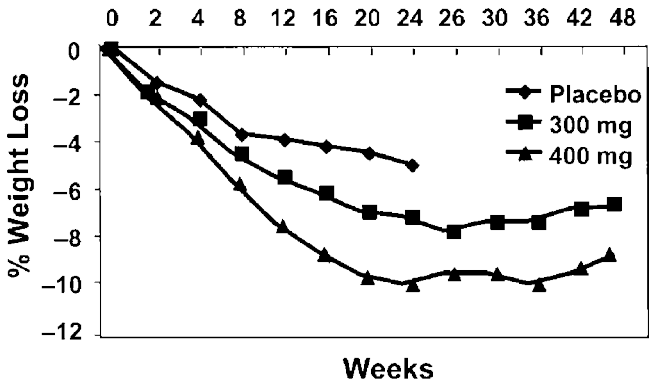


Figure 10 Bupropion SR and weight loss over 48 weeks. Percent weight loss from baseline over time is displayed as mean values with SEM. Bupropion SR 400 mg (—) produced significantly greater weight loss than bupropion SR 300 mg (&) at weeks 24, 26, 30, 36, and 40 and greater weight loss than placebo () at weeks 12, 16, 20, and 24. Source: From Ref. 66.

−2.2% and −5.1% more than placebo. At 48 weeks, mean weight loss was −7.5% and −8.6% for bupropion SR 300 mg and 400 mg, respectively. The medication was well tolerated in this study with no significant difference in adverse events across treatment groups. Anxiety or insomnia led to withdrawal more often with bupropion SR treatment than with placebo, but these differences were not statistically significant.

Bupropion SR 300 mg/day has been evaluated in 422 obese patients with depression symptoms (Beck Depression Inventory Score of 10–30) in a randomized, double-blind, placebo-controlled study (67). Those patients on bupropion lost more weight at six months (−4.6% mean weight lost from baseline compared to −1.8% for the placebo group). However, there was no statistically significant difference between groups in prevalence of patients reporting ≥ 50% decrease in depressive symptoms. Improvement in depressive symptoms was related to weight loss ≥5%, regardless of treatment ($p < 0.0001$).

In summary, bupropion would seem a good choice for therapeutic trial in the depressed obese patient, since it has a favorable weight profile. For obese patients with depressive symptoms, bupropion might also be beneficial, provided there is a weight loss effect. The chief obstacle to recommending bupropion for the management of obesity in a general population would be the lack of an FDA-approved indication for weight management. Considering the large body of evidence documenting the safe use of the drug for depression, it is reasonable for clinicians to add it to the therapeutic tool-box for obesity. Bupropion seems to aid lifestyle approaches to produce weight loss roughly equivalent to sibutramine

and orlistat. Clinicians should be familiar with its side effect profile and prescribe with care. Bupropion should not be given to patients with a history of epilepsy. Its side effect profile shows increased incidence of agitation, anxiety, and insomnia.

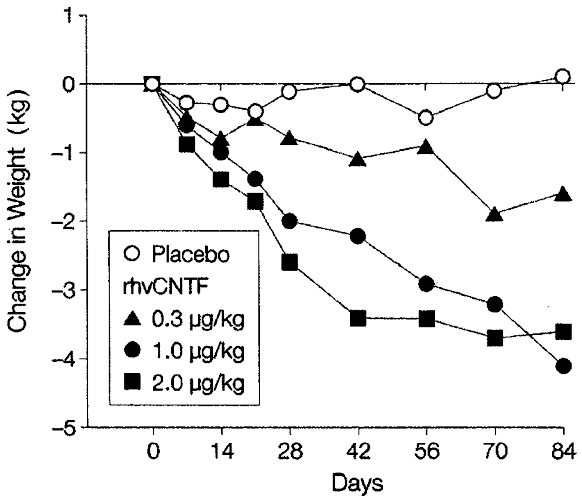
Venlafaxine (marketed as Effexor) is a reuptake inhibitor of serotonin and norepinephine, like sibutramine, and has a chemical structure similar to sibutramine. Venlafaxine is used for treatment of depression. Although there are no studies of this medication as a weight loss agent, the prescribing information documents treatment emergent anorexia reported in 11% of patients treated with venlafaxine and only 2% of those on placebo. A loss of 5% or more of body weight occurred in 6% of patients treated with venlafaxine and 1% on placebo. Venlafaxine has a side effect profile similar to sibutramine (68). Thus, venlafaxine would be among preferred choices for managing depression in obese patients.

FUTURE DIRECTIONS

Based on an explosion of knowledge regarding the biology of food intake and energy balance regulation, many pharmaceutical companies are searching for novel obesity drugs. The first of this new paradigm to developing obesity medications based on biologic advances—leptin—has thus far failed to produce meaningful weight loss in the healthy obese population. Leptin would seem to be a promising agent for obesity management. It is a peptide produced in adipose tissue. Leptin mutations result in obesity in animals and humans and treatment with recombinant leptin reverses obesity in these individuals (69,70). Leptin levels in the blood are highly correlated with the amount of body fat. A dose-ranging clinical trial of subcutaneously administered recombinant human leptin in obese individuals demonstrated only modest weight loss at 24 weeks and problems with reactions at the local injection site (71). The issue in human obesity may be resistance to leptin's action, suggesting that this may have limited usefulness in the general population of obese individuals.

Axokine is the trade name for a modified form of ciliary neurotrophic factor (CNTF). It acts through the same janus-kinase-signal for transduction and translation (JAK-STAT) system that leptin acts through. CNTF will reduce food intake in animals that lack leptin or the leptin receptors (72). In a clinical trial for amyotrophic lateral sclerosis, the drug was noted to reduce weight.

CNTF has been evaluated in a 12-week, double-blind, randomized, dose-ranging study at seven sites (73). There were 173 patients who received daily subcutaneous injections of placebo or one of three doses of CNTF (0.3, 1.0, or 2.0 mg/kg). All patients received instruction in a diet to reduce daily consumption by 500 kcal. Figure 11 depicts weight loss results. The mean weight loss over 12 weeks is modest, though statistically significant.



No. of Patients						
Placebo	31	30	27	25	22	23
rhvCNTF						
0.3 µg/kg	31	28	26	26	24	24
1.0 µg/kg	37	33	33	30	27	27
2.0 µg/kg	33	24	20	20	19	19

Figure 11 CNTF treatment for obesity. Data shown are available data as observed at each time point. Beginning at week 2, the 1.0 mg/kg dosage group was statistically significantly different from placebo ($p = 0.02$). At day 84, all treatment groups show a statistically significant difference in weight compared with the placebo group ($p < 0.05$). Abbreviation: CNTF, ciliary neurotrophic factor. Source: From Ref. 73.

The chief issues with CNTF as a weight loss agent are that the parenteral medication invokes antibody formation (in 45–87% of patients in the cited study). Injection site reactions, nausea and cough, coupled with modest weight loss, limit the drug's usefulness in clinical practice.

The next medication expected to make it to market based on the ''new biology'' of food intake and energy balance regulations is rimonibant. Endocannabinoids may be involved in the regulation of food intake. Early results of two clinical trials of rimonibant have been posted on a website (74). Rimonibant is the first of a new class; CB1 blockers. This agent selectively blocks the CB1 receptor and is proposed to normalize the endocannabinoid system. The drug is being evaluated as an aid to both weight loss and smoking cessation.

The ''new biology'' of obesity has resulted in interest in other therapeutic targets. Several pharmaceutical companies are seeking to identify antagonists to the neuropeptide Y (NPY) receptor and agonists of cholecystokinin

(CCK). Peripheral peptides such as ghrelin and peptide yy (PPY) are other promising targets.

SUMMARY

At present only two drugs are approved for long-term treatment of obesity. Sibutramine inhibits the reuptake of serotonin and norepinephrine. In clinical trials it produces a dose-dependent 5% to 10% decrease in body weight. Its side effects include dry mouth, insomnia, asthenia, and constipation. In addition, in clinical trials, sibutramine produces a small mean increase in blood pressure and pulse that mandates attention to blood pressure monitoring on follow-up visits. Sibutramine is contraindicated in some individuals with heart disease. Orlistat is the other drug approved for long-term use in the treatment of obesity. It works by blocking pancreatic lipase and thus increasing the fecal loss of triglyceride. One valuable consequence of this mechanism of action is the reduction of serum cholesterol that averages about 5% more than can be accounted for by weight loss alone. In clinical trials, it too produces a 5% to 10% loss of weight. Its side effects are entirely due to undigested fat in the intestine (steatorrhea) that can lead to increased frequency and change in the character of stools. It can also lower fat-soluble vitamins. The ingestion of a vitamin supplement before bedtime is a reasonable treatment strategy when orlistat is prescribed.

Among the medications that have been on the market for more than 30 years, phentermine is still widely prescribed for obesity management, despite a lack of extensive clinical trial evidence supporting its use.

Several medications that are available and approved by the FDA for indications other than weight loss are also used in the clinic. Bupropion has been used widely for management of depression and smoking cessation when used with a lifestyle approach. It produces weight loss similar to that of orlistat and sibutramine. Its safety profile is relatively good with chief concern being its contraindication in seizure disorders.

Topiramate generates interest among clinicians who manage obesity because of the duration and amount of weight loss, although tolerability and safety profile limit its usefulness. Cognitive dysfunction, renal calculi, paresthesias, and acute glaucoma make this medication difficult to employ in the otherwise healthy obese population.

Other medications may play a role in managing the obese patient; zonisamide, fiuoxetine, and venlafaxine, were also discussed in this review.

Finally, the future of obesity pharmacotherapy holds promise—and disappointments, too. While recombinant leptin has not shown efficacy in the general obese population, and recombinant ciliary neurotrophic factor shows efficacy only in a subgroup, early results with rimonibant are promising. Similar successes and failures are almost certainly in store in the development of additional drugs to treat obesity.

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Review

Current and Investigational Antiobesity Agents and Obesity Therapeutic Treatment Targets

Harold E. Bays

Abstract

BAYS, HAROLD E. Current and investigational antiobesity agents and obesity therapeutic treatment targets. *Obes Res.* 2004;12:1197–1211.

Public health efforts and current antiobesity agents have not controlled the increasing epidemic of obesity. Investigational antiobesity agents consist of 1) central nervous system agents that affect neurotransmitters or neural ion channels, including antidepressants (bupropion), selective serotonin 2c receptor agonists, antiseizure agents (topiramate, zonisamide), some dopamine antagonists, and cannabinoid-1 receptor antagonists (rimonabant); 2) leptin/insulin/central nervous system pathway agents, including leptin analogues, leptin transport and/or leptin receptor promoters, ciliary neurotrophic factor (Axokine), neuropeptide Y and agouti-related peptide antagonists, proopiomelanocortin and cocaine and amphetamine regulated transcript promoters, α-melanocyte-stimulating hormone analogues, melanocortin-4 receptor agonists, and agents that affect insulin metabolism/activity, which include protein-tyrosine phosphatase-1B inhibitors, peroxisome proliferator activated receptor-γ receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin; 3) gastrointestinal-neural pathway agents, including those that increase cholecystokinin activity, increase glucagon-like peptide-1 activity (extendin 4, liraglutide, dipeptidyl peptidase IV inhibitors), and increase protein YY3-36 activity and those that decrease ghrelin activity, as well as amylin analogues (pramlintide); 4) agents that may increase resting metabolic rate ("selective" β-3 stimulators/agonist, uncoupling protein homologues, and thyroid receptor agonists); and 5) other more diverse agents, including melanin concentrating hormone antagonists, phytostanol analogues, functional oils, P57, amylase inhibitors, growth hormone fragments, synthetic analogues of dehydroepiandrosterone sulfate, antagonists of adipocyte 11B-hydroxysteroid dehydrogenase type 1 activity, corticotropin-releasing hormone agonists, inhibitors of fatty acid synthesis, carboxypeptidase inhibitors, indanones/indanols, aminosterols, and other gastrointestinal lipase inhibitors (ATL962). Finally, an emerging concept is that the development of antiobesity agents must not only reduce fat mass (adiposity) but must also correct fat dysfunction (adiposopathy).

Key words: adiposopathy, insulin, leptin, treatment target

Introduction

Obesity is the most common metabolic disease in developed nations. Despite public health education and initiatives, its prevalence continues to increase, with >30% of adults in the United States being obese and >60% of adults being overweight or obese (1). The World Health Organization has estimated that worldwide, over one billion adults are overweight, with at least 300 million of them being obese (2). The increasing prevalence of obesity among children and adolescents is also of great concern (3) and suggests a likelihood of worsening obesity trends in future adults. Obesity leads to, or significantly increases the risk of, comorbidities involving various body systems including 1) cardiovascular [hypertension, congestive cardiomyopathy, varicosities, pulmonary embolism, coronary heart disease (CHD)[1]], 2) neurological (stroke, idiopathic intracranial hypertension, meralgia parethetica), 3) respiratory (dyspnea, obstructive sleep apnea, hypoventilation syndrome, Pickwickian syndrome, asthma), 4) musculoskeletal (immobility, degenerative osteoarthritis, low back pain), 5) skin (striae distensae or "stretch marks," venous stasis of the

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[1] Nonstandard abbreviations: CHD, coronary heart disease; GI, gastrointestinal; 5-HT, 5-hydroxytryptamine (serotonin); CNS, central nervous system; GABA, γ-aminobutyric acid; CB, cannabinoid; BBB, blood-brain barrier; JAK/STAT, janus kinase/signal transducer and activator of transcription; CNTF, ciliary neurotrophic factor; NYP, neuropeptide Y; AgRP, agouti-related peptide; POMC, proopiomelanocortin; CART, cocaine and amphetamine regulated transcript; PYY, protein YY3-36; MC, melanocortin; αMSH, α-melanocyte-stimulating hormone; CRH, corticotropin-releasing hormone; PI3K, phosphatidylinositol 3 kinase; IRS-1, insulin receptor substrate; PTP, protein-tyrosine phosphatase; PPAR, peroxisome proliferator activated receptor; CCK, cholecystokinin; GLP-1, glucagon-like peptide-1; DPP IV, dipeptidyl peptidase IV; RMR, resting metabolic rate; UCP, uncoupling protein; BAT, brown adipose tissue; MCH, melanin-concentrating hormone; DHEAS, dehydroepiandrosterone sulfate.

lower extremities, lymphedema, cellulitis, intertrigo, carbuncles, acanthosis nigricans, skin tags), 6) gastrointestinal (GI; gastro-esophageal reflux disorder, nonalcoholic fatty liver/steatohepatitis, cholelithiasis, hernias, colon cancer), 7) genitourinary (stress incontinence, obesity-related glomerulopathy, breast and uterine cancer), 8) psychological (depression and low self-esteem, impaired quality of life), and 9) endocrine (metabolic syndrome, type 2 diabetes, dyslipidemia, hyperandrogenemia in women, polycystic ovarian syndrome, dysmenorrhea, infertility, pregnancy complications, male hypogonadism) (4).

Therefore, it has been a therapeutic and research goal to develop strategies to reduce the worldwide obesity epidemic (5,6) and a research goal to develop safe and effective antiobesity drugs, analogous to what has occurred with hypertension, dyslipidemia, and diabetes (7).

Current Therapies

Amphetamines (dextroamphetamine) have been used as antiobesity drugs, but can cause unacceptable tachycardia and hypertension. They also have a high rate of abuse potential and do not have a U.S. Food and Drug Administration indication for the treatment of obesity. Other sympathomimetic adrenergic agents, including phentermine, benzphetamine, phendimetrazine, mazindol, and diethylpropion, have less abuse potential than amphetamines; but these agents may have adverse cardiovascular side effects, and their indicated use is only short term (~12 weeks) (8) for the treatment of what is commonly a chronic metabolic disease. In 2000, the appetite suppressant phenylpropanolamine was removed from the over-the-counter market in the United States because of unacceptable risks of stroke, especially in adult women.

Sibutramine is a noradrenaline and serotonin (5-HT) reuptake inhibitor drug that has an indication for treatment of obesity by primarily increasing satiety (although some thermogenic effects may exist as well) (9). Sibutramine-associated weight loss occurs within the first 6 months of treatment, may be maintained for at least 2 years (10,11), and may have favorable effects on CHD risk factors, such as increasing high-density lipoprotein-cholesterol and decreasing triglyceride blood levels (12), as well as improving glucose control in patients with diabetes (13,14). However, because patients administered sibutramine may experience increases in blood pressure and heart rate, sibutramine's use is contraindicated in patients with uncontrolled hypertension, CHD, cardiac dysrhythmias, congestive heart failure, or stroke (15).

Orlistat, a gastrointestinal lipase inhibitor that impairs the absorption of dietary fat, has been shown to result in significant and sustained weight reduction for at least 2 years (16) and to favorably affect CHD risk factors. Orlistat may improve lipid blood levels (17,18), improve glucose metabolism in obese patients with and without diabetes (19–21), and reduce high blood pressure (22). Orlistat use frequently results in adverse events including flatus, oily stools, fecal urgency or fecal incontinence, and abdominal pain, particularly among patients who do not follow the recommended low-fat diet. Daily multivitamin supplementation is recommended to prevent the potential of impaired absorption of fat-soluble vitamins (A, D, E, and K) that may theoretically occur with long-term use.

Antiobesity Agents that Affect Neurotransmitters and/or Neural Ion Channels (Table 1)

From a public health standpoint, diet, exercise, lifestyle, and behavior modifications (23,24) should be the first steps in obesity management. Avoidance of drugs known to potentially contribute to obesity is another step.

Various drugs and drug classes are known to affect body weight. Steroid hormones (glucocorticoids, estrogens, progestins), diabetes therapies (insulin, sulfonylureas, thiazolidinediones), highly active antiretroviral protease inhibitors, β-adrenergic blockers (most commonly described with nonselective β-blockers such as propranolol), some α-adrenergic blockers, and certain antihistamines (diphenhydramine) may increase body weight. Agents that affect the central nervous system (CNS) may either increase or decrease body weight. CNS drugs associated with increased body weight include some antidepressants [tricyclic antidepressants, irreversible monoamine oxides (MAO) inhibitors, mirtazapine, and some selective serotonin reuptake inhibitors (such as paroxetine)], antiserotonin agents (pizotifen), some antiseizure drugs (valproate, gabapentin, and carbamazepine), some psychotropic drugs (clozapine, olanzapine, risperidone, quetiapine, thioridazine, divalproex, and chlorpormazine) (25), and lithium. CNS drugs that may decrease body weight are described later.

The weight gain and metabolic effects associated with some of these CNS drugs may be of potential clinical significance, and monitoring for significant weight gain, dyslipidemia, and diabetes has been recommended (25). For example, while it has been suggested that caloric intake may be decreased with dopamine antagonists such as risperidone in some patients with Prader-Willi syndrome (26), most studies have suggested that certain psychotropic drugs (including risperidone) are not only associated with weight gain, but also may be a particular concern in adolescents, perhaps increasing the risk of type 2 diabetes (27,28).

Thus, it is clinically useful to know the potential for weight gain or loss when using CNS drugs in the obese patient (Figure 2). Bupropion is an aminoketone unrelated to tricyclic antidepressants or selective serotonin reuptake inhibitors that seems to be a weak inhibitor of the neuronal uptake of norepinephrine, serotonin, and dopamine and is currently indicated for the treatment of depression and smoking ces-

sation. It also has been shown to be effective in promoting weight loss in clinical trials in patients with or without depression (29,30). However, the antiobesity effects have been variable among individual patients, and bupropion does not currently have a specific indication for weight loss.

Other noradrenaline reuptake inhibitors are also sometimes used as antidepressant agents. GW320659 is a noradrenaline reuptake inhibitor that has undergone evaluation as both an antiobesity agent and a potential treatment for attention deficit hyperactivity disorder (31,32).

Dexfenfluramine and fenfluramine were dual 5-HT reuptake inhibitors and serotonin-releasing agents that were not indicated for treatment of depression, but had previously been used for suppression of appetite as antiobesity drugs. They were subsequently withdrawn from the market because of the onset of heart valve abnormalities thought to be related to the stimulation of peripheral (heart) 5-hydroxytryptamine (5-HT) 2b receptors (7,33,34). Investigational "selective" 5-HT 2c receptor agonists under development may induce satiety by selective effects on the hypothalamus while avoid toxicities to the heart.

Topiramate is a derivative of the naturally occurring sugar monosaccharide D-fructose and was originally developed as a diabetes treatment. Studies have suggested some potentially favorable effects on glucose tolerance and insulin sensitivity in animals administered topiramate and some glucose lowering in obese type 2 diabetic patients. However, direct antihyperglycemic effects of topiramate (independent of weight loss) have not been proven clinically, and topiramate's indicated use has been as an antiseizure drug. Topiramate modulates neuronal sodium and calcium channels, enhances γ-aminobutyric acid (GABA)-coupled ion channel flux, and blocks glutamate receptors. Topiramate has been shown to be efficacious in treating binge-eating disorder (35) and may increase energy expenditure in rats (36), but the potential for increased energy expenditure in humans has yet to be proven. A 6-month clinical trial of topiramate showed weight loss compared with placebo, but 21% of topiramate subjects withdrew because of adverse events (compared with 11% of placebo-administered patients) (37). In another trial, after >1 year (60 weeks) of treatment, topiramate continuously and significantly reduced mean body weight and significantly reduced mean visceral abdominal fat (38). The most common adverse effects of topiramate include cognitive dysfunction and (mostly transient) paresthesias, which may be related to the fact that topiramate is a weak inhibitor of carbonic anhydrase (types 2 and 4). A controlled-release formulation is currently in development that may maintain weight loss benefits with reduced risk of adverse side effects.

Zonisamide is also an antiseizure drug being evaluated for potential benefits in treatment of obesity. Zonisamide has serotonergic and dopaminergic activity and may also block neuronal sodium and calcium channels. In a small 16-week trial of 60 subjects (92% women) administered a hypocaloric diet, Zonisamide was shown to result in greater weight loss compared with placebo, with few adverse effects (39).

As noted before, antipsychotic drugs functioning as dopamine antagonists may be associated with weight gain and potentially increase the risk of abnormalities in glucose metabolism. However, not all antipsychotic drugs that have dopamine antagonist activity are necessarily associated with weight gain (e.g., ziprasidone and aripiprazole) (25). Ecopipam is a dopamine antagonist that was being evaluated as a weight loss agent in obese subjects, including patients with diabetes (31). It is no longer in development as an antiobesity agent.

Finally, cannabinoid (CB) receptors may control neurotransmitters, including 1) glutamate and possibly other excitatory amino acids, 2) GABA and glycine and possibly other inhibitory amino acids, and 3) noradrenaline, 5-HT, dopamine, acetylcholine, neuropeptides, and possibly other monoamines (40). Rimonabant is an example of a CB antagonist that blocks the CB-1 receptor that may be involved with appetite. It was developed through the observation that cannabis smokers may experience increased appetite ("munchies") (41). Rimonabant may increase satiety and cause weight reduction. It is currently under development as an antiobesity agent and is being studied in phase III clinical trials of over 6000 patients, including patients with type 2 diabetes (42). Early results suggest favorable effects on lipids such as triglyceride, high-density lipoprotein-cholesterol levels, and small dense low-density lipoprotein particles, and a reduction in the number of patients meeting the criteria for the metabolic syndrome (43).

Investigational Antiobesity Agents that Affect the Leptin/Insulin/CNS Pathways

Leptin (derived from Greek *leptos*, meaning thin) is a hormone produced predominantly by fat cells that normally circulates and crosses the blood-brain barrier (BBB) (Table 2). In obese humans, leptin blood levels generally correlate with the amount of fat stored in the body. Leptin stimulates cytokine or cytokine-like receptors and is sometimes characterized as a cytokine. An important effect of leptin receptor stimulation is the promotion of the janus kinase/signal transducer and activator of transcription (JAK/STAT) cascade, which is one of the major mechanisms by which cytokine receptors transduce intracellular signals and is a pathway that mediates important leptin-induced CNS effects.

The CNS (especially the hypothalamus) may influence caloric balance due to actions on 1) feeding through effects on the CNS neuroendocrine system involved with appetite and behavior, 2) autonomic nervous system activity through effects on energy expenditure, and 3) hormone secretion

Table 1. Examples of antiobesity agents in development

CNS agents that affect neurotransmitters or neural ion channels
Antidepressants (bupropion)
Noradrenaline reuptake inhibitors (GW320659)
Selective 5HT 2c receptor agonists
Antiseizure agents (topiramate, zonisamide)
Some dopamine antagonists
CB-1 receptor antagonists (rimonabant)
Leptin/insulin/CNS pathway agents
Leptin analogues
Leptin transport and/or receptor promoters
CNTF (Axokine)
NPY antagonists
AgRP antagonists
POMC promoters
CART promoters
αMSH analogues
MC4 receptor agonists
Agents that affect insulin metabolism/activity [PTP-1B inhibitors, PPAR γ receptor antagonists, short-acting bromocriptine (ergoset), somatostatin agonists (octreotide), and adiponectin/Acrp30 (Famoxin or *F*atty *A*cid *M*etabolic *OX*idation *IN*ducer)]
Gastrointestinal-neural pathway agents
Agents that increase CCK and PYY activity
Agents that increase GLP-1 activity (extendin 4, liraglutide, DPP IV inhibitor)
Agents that decrease ghrelin activity
Amylin (pramlinitide)
Agents that may increase RMR
"Selective" β-3 stimulators/agonist
UCP homologues
Thyroid receptor agonists
Other agents
MCH antagonists
Phytostanol analogues
Functional oils
P57
Amylase inhibitors
Growth hormone fragments
Synthetic analogues of DHEAS (fluasterone)
Antagonists of adipocyte 11B-hydroxysteroid dehydrogenase type 1 activity
CRH agonists
Carboxypeptidase inhibitors
Inhibitors of fatty acid synthesis (cerulenin and C75)
Indanones/indanols
Aminosterols (Trodusquemine/trodulamine)
Other gastrointestinal lipase inhibitors (ATL962)

CNS, central nervous system; 5HT 2c, 5-hydroxytryptamine 2c; CB, cannabinoid; CNTF, ciliary neurotrophic factor; NPY, neuropeptide Y; AgRP, agouti-related peptide; POMC, proopiomelanocortin; CART, cocaine and amphetamine regulated transcript; alpha-MSH, alpha melanocyte-stimulating hormone; MC4R, melanocortin-4 receptor; PTP, protein-tyrosine phosphatase; PPAR, peroxisome proliferator activated receptors; Acrp30, adipocyte complement-related protein of 30kDa; CCK-A, Cholecystokinin-A; GLP-1, glucagon-like peptide-1; PYY, Protein YY3-36; DPP, dipeptidyl peptidase; RMR, resting metabolic rate; UCP, uncoupling protein; MCH, melanin concentrating hormone; DHEAS, dehydroepiandrosterone sulfate; CRH, corticotropin releasing hormone.

Table 2. Examples of select endocrine and metabolic factors released from fat cells

Examples of hormones released from fat cells*
Leptin
Adiponectin (adipoQ, adipocyte complement-related protein of 30 kDa)
Resistin
Examples of cytokines released from fat cells*
Tumor necrosis factor-α
Interleukin-6
Examples of other enzymes, molecules, or factors described as being released from fat cells
Acylation-stimulating protein (ASP)
Adipophilin
Adipsin
Agouti protein
Angiotensinogen
Apolipoprotein E
Endothelin-1
Fasting-induced adipose factor (FIAF)
Cholesteryl ester transfer protein (CETP)
Estrogen
Free fatty acids
Galectin-12
Insulin-like growth factor (IGF-1)
Lactate
Lipoprotein lipase
Macrophage inhibitory factor (MIF)
Metallotionein
Monobutyrin
Nitric oxide synthase
Phospholipid transfer protein
Plasminogen activator inhibitor (PAI-1)
Prostaglandins I_2 & F_2 prostacyclins
Retinol-binding protein
Tissue factor
Transforming growth factor β (TGF_β)

* Cytokines are proteins that are secreted by one cell for the purpose of autocrine effect or paracrine effects, and are often involved in the inflammatory and immune processes. Adipocyte hormones are sometimes referred to as cytokines, as they may have potential autocrine or paracrine effects or, at least, may result in subsequent actions that result in autocrine or paracrine effects.

through effects on secretion of growth hormone, thyroid-related hormones, cortisol, insulin, sex steroids, etc. (44). Thus, decreased leptin/insulin activity in the CNS may promote obesity through increased caloric balance as a result of effects on 1) the CNS neuroendocrine system, 2) decreased energy expenditure through targeted sympathetic nervous system effects on fat, muscle, and liver, and 3) effects on secretion of hormones, all resulting in positive caloric balance and weight (fat) gain (Figure 1).

Leptin, in some respects, may be considered a counter-regulatory hormone that acts in a similar way to that of a thermostat by signaling the hypothalamus when the body has too little, sufficient, or too much fat. In fact, direct administration of leptin into the CNS reduces caloric balance, with subsequent weight loss that may be caused entirely by loss of fat (45). Thus, with excessive fat, leptin's signaling to the hypothalamus should theoretically result in decreased food intake through effects on the brain and increased energy expenditure through effects on the sympathetic nervous system. This may, in fact, occur in lean individuals, particularly if they engage in routine physical exercise. However, this counterregulatory effect clearly fails to prevent excessive fat accumulation in obese patients, presumably because obese patients with elevated leptin blood levels have leptin insensitivity or other circumstances that overcome or overwhelm leptin's antiobesity signaling effects. Administration of more leptin may seem like a reasonable solution. Unfortunately, while some clinical trials have suggested modest benefit with peripheral leptin or leptin analogue administration, other studies have been disappointing (46,47).

Nonetheless, other leptin analogues or agonists are undergoing development that may prove to be more effective than previous preparations or native leptin (48). Leptin promoters are also in development that may increase peripheral leptin levels through increased gene expression. However, simply increasing leptin blood levels might not be expected to overcome significant "resistance" to leptin as might occur through 1) impaired leptin transport across the BBB, 2) impaired leptin receptor-stimulated functions, or 3) impaired response to leptin-induced hormones/factors. Instead, agents that target leptin resistance may prove to be promising targets in improving leptin's CNS activity.

Reducing leptin resistance may theoretically be achieved through improving leptin's transport across the BBB. Although obese patients frequently have elevated leptin blood levels, they may not necessarily have elevated leptin cerebral spinal fluid levels, likely because of 1) decreased transport capacity, 2) partial saturation of the transport mechanism, and/or 3) inability of the leptin transporter to be up-regulated, all resulting in a limitation of how much circulating leptin crosses the BBB. Currently, it is not entirely clear exactly how leptin crosses the BBB. Some evidence supports an uncharacterized leptin transporter in the brain capillary endothelium. Leptin BBB transport may also be augmented through leptin receptor variants or through leptin receptors themselves. Either way, increasing

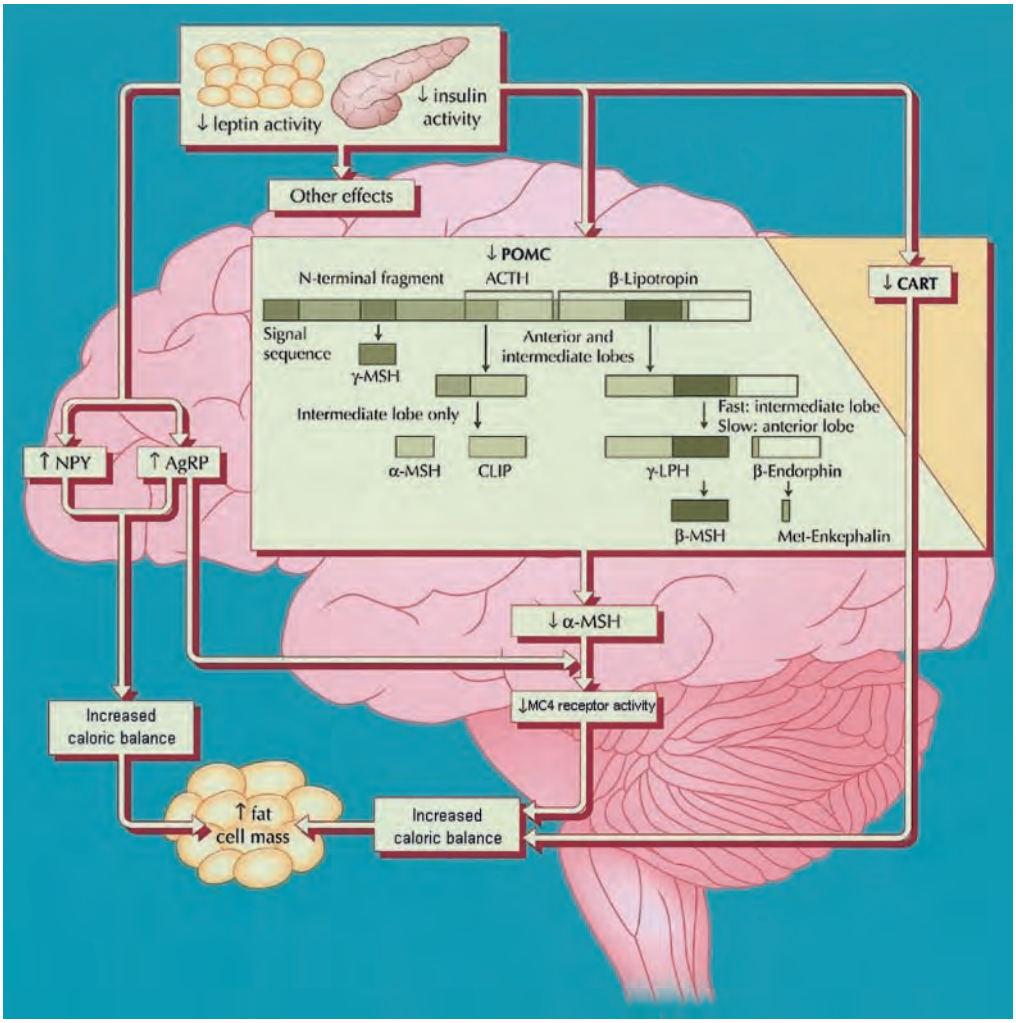

Figure 1: Simplified and illustrative select antiobesity drug targets of the leptin/insulin/CNS pathways. Although circulating levels may be increased, CNS leptin and insulin activity may be decreased in obese patients. Decreased CNS leptin and insulin activity may increase NPY/AgRP, decrease POMC and CART, and have other effects (such as decreased αMSH and decreased MC4 receptor activity), leading to positive caloric balance (fat weight gain). Targets of antiobesity agents include the following: (1) Leptin analogues, leptin gene promoters, leptin-like agonists (Axokine), leptin BBB transport enhancers, and leptin receptor facilitators; (2) NPY and AgRP antagonists; (3) POMC and CART promoters (CART peptides); (4) αMSH analogues; (5) MC4 receptor agonists; and (6) agents that favorably affect insulin metabolism/activity. Through these pathways and other effects, CNS leptin and insulin activity may affect feeding, targeted sympathetic nervous system activity (and thus, influence energy expenditure), and secretion of various neuroendocrine factors/hormones. *NYP, AgRP, POMC, and CART are found in the arcuate nucleus of the hypothalamus.

leptin BBB transport, or otherwise increasing CNS leptin receptor activity, may prove to be an important antiobesity target.

Leptin-like effects may also be increased through ciliary neurotrophic factor (CNTF). CNTF was first characterized as a trophic factor for motor neurons in the ciliary ganglion and spinal cord. During its evaluation for potential treatment of amyotropic lateral sclerosis, CNTF was serendipitously found to result in weight loss. Axokine (Regeneron Pharmaceuticals, Tarrytown, NY) is a second-generation variant of CNTF that seems to activate leptin-like postreceptor mechanisms in leptin-resistant animals through CNTF receptors in the hypothalamus and is under development as an antiobesity agent. Axokine has been shown to promote weight reduction in early clinical trials (49). A much larger phase III study showed that Axokine was generally well tolerated, with the main adverse events being mild injection site reactions, nausea, and cough. The weight loss achieved by Axokine was limited by the development of Axokine antibodies. Nonetheless, in the >30% of the 1467 subjects administered Axokine who did not develop Axokine antibodies, weight loss occurred that was similar to what has been described with existing antiobesity drugs (50). Axokine is currently being evaluated to determine

what type of patients might best achieve weight loss with this agent, as well as its efficacy in specific patient populations, including those with type 2 diabetes (51).

Other antiobesity agents undergoing development include those that affect satiety as agonists and antagonists of hypothalamic hormones involved with food intake signaling. Decreased brain leptin/insulin activity may stimulate the neuropeptide Y (NPY)/agouti-related peptide (AgRP) axis and, conversely, decrease the proopiomelanocortin (POMC)/cocaine and amphetamine regulated transcript (CART) axis, thus increasing feeding and decreasing energy expenditure. This promotes positive caloric balance and weight (fat) gain (Figure 1). Conversely, agents that inhibit NPY and AgRP and/or stimulate the POMC and CART pathways may help create negative caloric balance and may decrease weight (fat).

NPY is a neuropeptide produced in the hypothalamus that is the most abundant neuropeptide in the brain in mammals and humans. As many as six G-protein–coupled NPY receptor subtypes have been described (Y1, Y2, Y3, Y4, Y5, Y6) (52). NPY shares structural homology with peptide YY (PYY) from the intestine and pancreatic polypeptide from the pancreas (53). Both Y1 and Y2 NPY receptors seem to be involved in feeding and may interact with one another (53), and these receptors are among the most promising antiobesity targets. NPY receptor antagonists have been evaluated and have been shown to inhibit NPY-induced feeding in animals (52,53). In humans, at least one such agent has been discontinued because of elevated liver enzymes (54). Newer NPY antagonists are in the pipeline of pharmaceutical companies and are at variable stages of development as antiobesity agents.

AgRP (also found in the hypothalamus) antagonizes melanocortin (MC) receptors, such as the MC4 (and MC3) receptors, which are found only in the brain (55) (Figure 1). Stimulation of MC4 receptors normally results in inhibition of feeding. In fact, impaired MC4 activity through MC4 receptor mutations has been described to account for 0.5% to 5.8% of severe cases of obesity (56). AgRP blocks α-melanocyte-stimulating hormone (αMSH)'s effects on MC4 receptors, resulting in weight gain (and, interestingly, decreased black and increased yellow fur pigment in mutant *agouti* strains of overweight mice that hypersecrete AgRP, which blocks the stimulation of melanin by αMSH). Inhibiting the antagonist effects of AgRP might be a promising target in the development of antiobesity agents.

POMC precursor production is a process that may be regulated by various hypothalamic hormones, neurotransmitters, and neuropeptides, including sex steroids, glucocorticoids, opioids, dopamine, GABA, corticotropin releasing hormone (CRH), and even NPY (57). POMC is cleaved to various derivatives, including an αMSH segment that stimulates MC4 receptors and promotes negative caloric balance (weight loss) (Figure 1). Thus, POMC promoters, αMSH analogues, and MC4 receptor agonists may all prove to be promising antiobesity agents.

While leptin's CNS signaling is perhaps more effective in affecting caloric balance, insulin is also an important circulating hormone with CNS signaling that affects adiposity (58). Both leptin and insulin 1) have blood concentrations that frequently correspond to adiposity, 2) enter the CNS by a receptor-mediated, saturable transport process across brain capillary endothelial cells (59), and 3) have receptors located in similar hypothalamic areas. The direct action of increased leptin and insulin activity to the brain is to decrease feeding and increase energy expenditure. Conversely, diminished CNS insulin (or leptin) activity in the brain may promote positive caloric balance and weight (fat) gain (Figure 1). Thus, there is substantial analogy, redundancy, and, in fact, interaction ("cross-talk") between CNS leptin and insulin receptors and activity (58,60).

With regard to signaling, increased leptin receptor activity seems to propagate pathways, such as 1) the JAK/STAT3 pathway, which may mediate leptin's action in the hypothalamus through effects on NPY and POMC and possibly other factors (61); 2) the mitogen-activated protein kinase pathway (60), which may have various effects on cell (adipose) growth and differentiation, inflammatory responses (62,63), and increases in plasminogen activation inhibitor-1 (64); and 3) the phosphatidylinositol 3 kinase (PI3K) pathway (60), which may affect glucose transport and endothelial nitric oxide production (65). Similarly, both the mitogen-activated protein kinase and PI3K pathways are part of insulin's cascade effect (65), and insulin may modulate leptin's signal transduction through JAK/STAT3. Thus, just as with leptin, CNS insulin activity may affect feeding (66), autonomic nervous system activity, and hormonal secretions.

Leptin binds to the extracellular portion of the leptin receptor, stimulating intracellular tyrosine kinase enzyme (JAK2) and promoting the JAK/STAT3 cascade. In an analogous way, insulin binds to the extracellular domain of the insulin receptor, which activates intracellular tyrosine kinase, which, in turn, mediates phosphorylation of the insulin receptor substrate (IRS-1) protein required for the propagation of subsequent cascade signaling to enzymes including PI3K, which, as noted before, is a kinase that may elicit cell growth and proliferation, differentiation, cell survival, protein synthesis, and lipid metabolism and which is also a crucial component of insulin signaling, glycogen synthesis, and glucose transport (through glucose transporter-4).

Leptin resistance associated with obesity results in elevated leptin blood levels. Similarly, insulin resistance results in hyperinsulinemia, which also may occur early in the onset of obesity. Acarbose is an antidiabetes treatment that improves glucose metabolism, but does not seem to affect fasting insulin levels (67). While it may not have significant

benefits in improving weight maintenance after weight loss in obese patients, acarbose has been associated with modest weight loss in some clinical trials (68). Metformin also improves glucose metabolism, but results in reduction in insulin levels when administered to patients with insulin resistance. Metformin is commonly associated with weight loss, at least partially because of a decrease in caloric intake (69). In contrast to agents that increase insulin sensitivity with no increase (or perhaps even a decrease) in insulin levels, antidiabetes drug treatments that may increase insulin levels or increase insulin production (such as insulin administration or sulfonylureas) are often associated with weight gain (70). Even without pharmacologically induced hyperinsulinemia, elevated blood levels of insulin (a growth factor), as occurs with insulin resistance, are associated with excessive body weight—particularly central obesity (71). Thus, improving glucose metabolism through increased insulin sensitivity (which may improve peripheral and central glucose metabolism) and decreased insulin levels (which may have advantages with respect to minimizing weight gain) has been, and may continue to be, a useful treatment strategy in treating obese patients with type 2 diabetes and insulin resistance.

Dysfunctional adipose tissue (adiposopathy) is a contributing cause of insulin resistance in skeletal muscle and liver (72), which results in an increase in insulin blood levels. Because adipose tissue may remain relatively sensitive to insulin in an environment of muscle and liver insulin insensitivity, increased insulin blood levels may further promote adiposity, potentially further worsen adiposopathy, and in turn, potentially further worsen insulin resistance. The hyperinsulinemia followed by worsening insulin resistance, followed by even greater hyperinsulinemia, may promote an "obesity metabolic cycle." Agents that improve insulin sensitivity and decrease insulin blood levels may prove to be promising useful antiobesity treatments, particularly in patients with type 2 diabetes or insulin resistance.

An illustrative example would be patients with type 2 diabetes who have impaired insulin-stimulated glucose transport largely because of a marked reduction in IRS-1 protein activity. Inactivation of IRS-1 may occur through protein-tyrosine phosphatase (PTP)-1B, which is a key enzyme involved in regulation of the reversible tyrosine phosphorylation. PTP-1B inactivates insulin receptors by removing phosphates from active insulin receptors and IRS-1. The effects of insulin are reduced, contributing to insulin resistance/intolerance, promoting the metabolic syndrome, and potentially leading to type 2 diabetes itself. Interestingly, PTP-1B may also dephosphorylate JAK/STAT3, decreasing leptin's effects and potentially contributing to leptin resistance as well (73).

PTP-1B levels have reportedly been found to be increased in patients with insulin resistance. Reducing the production or activity of PTP-1B may increase insulin sensitivity, reduce insulin levels, and, thus, reduce the obesity metabolic cycle of hyperinsulinemia-stimulated fat increase and may even increase energy expenditure, which would all be favorable effects in obese patients. A novel approach in accomplishing this may be through the development of an antisense inhibitor of the gene encoding for PTP-1B (74).

Peroxisome proliferator activated receptor (PPAR) activity may also affect body weight. PPARs are nuclear receptors involved in fat and glucose metabolism. PPARα receptors are preferentially found in the liver and have historically been the targets of lipid-altering drugs (fibrates), whereas PPARγ receptors are predominantly found in adipose tissue and have historically been the targets of type 2 diabetes treatments (thiazolidinediones) (75). However, this functional delineation of nuclear receptor types may not be so distinct. Animal studies have suggested that non-PPARγ agonists (i.e., PPAR agonists without γ activity, such as PPARα and δ agents) may also result in increased insulin sensitivity and weight loss (75,76).

Although PPARγ activation may reduce insulin resistance, it also promotes the differentiation and proliferation of adipocytes from fibroblasts, thus causing an increase in fat that, at least partially, explains some of the weight gain observed with these insulin-sensitizing drugs. It is theoretically possible that impairing, or in fact reversing, adipocyte differentiation through PPARγ antagonism may be the target for future antiobesity drug development. Mice treated with PPARγ antagonists have shown decreases in triglyceride content in white adipose tissue, skeletal muscle, and liver. PPARγ antagonists have also been shown to potentiate leptin's effects, and adiponectin levels may be stimulated, resulting in increase fatty acid combustion and increased energy expenditure. Finally, high-fat diet-induced obesity and insulin resistance may be decreased as well (77).

However, there are reasons to be cautious about antagonizing the potential beneficial effects of PPARγ-stimulated adipose tissue differentiation and development. An emerging concept of the pathogenesis of type 2 diabetes is that dysfunctional adipose tissue (adiposopathy) may contribute to the pathogenesis of type 2 diabetes through excessive release of free fatty acids that may be "lipotoxic" to liver, muscle, and, perhaps, pancreatic β cells, resulting in hepatic and muscle insulin resistance, and, perhaps, diminished β cell function (72). Adiposopathy may also increase adipocyte cytokine release (Table 2), which may contribute to glucose intolerance, the metabolic syndrome, and type 2 diabetes (75). These abnormalities associated with adiposopathy may be corrected with PPARγ agonism (72). Thus, the ensuing fat weight gain that frequently occurs with PPARγ agents (thiazolidinediones) could be viewed as a beneficial effect of the drugs through the recruitment and differentiation of adipose cells into a more healthy adipose organ, resulting in reduced circulating free fatty acids, im-

proved glucose metabolism, and decreased inflammatory response (72). Antagonism of these PPARγ effects has the potential to negate these beneficial effects and/or conceivably worsen adiposopathy, which would theoretically worsen fatty acid and glucose handling by fat cells, with potentially undesirable metabolic consequences.

This is an illustrative example of an important principle that the development of any effective antiobesity agent must not only reduce fat mass (adiposity) but must also correct fat dysfunction (adiposopathy) to maximize metabolic health.

Other potential antiobesity drugs that may improve insulin sensitivity and thus be promising antiobesity targets include short-acting bromocriptine (ergoset—a dopamine receptor agonist) (78) and octreotide, a synthetic somatostatin analogue that may 1) inhibit gastrointestinal gastrin and serotonin, 2) inhibit secretion of growth hormone, insulin, and glucagons, 3) modulate biliary and gastrointestinal motility, and 4) act as a neurotransmitter. Clinical trials of octreotide have shown efficacy in pediatric hypothalamic obesity (79,80).

Finally, adiponectin (adipocyte complement-related protein of 30 kDa) is a hormone produced by fat cells that is associated with fatty acid oxidation and energy release, increased insulin sensitivity, and possible antiatherogenic properties because of favorable effects on endothelial inflammation (Table 2). Adiponectin blood levels are decreased in obesity and type 2 diabetes. Increasing the activity of adiponectin may be a potential target as an antiobesity agent, with anticipated favorable effects on body weight, glucose metabolism, lipid blood levels, and reduction in atherosclerosis (81).

Investigational Antiobesity Agents that Affect the GI Pathways

Food intake may also be influenced by neural and hormonal actions of the GI tract, including the vagus neural pathways (e.g., stretch and chemoreceptors) and various endocrine factors (the gut is also among the most active of endocrine organs). Examples of hormones located in the GI system that are thought to be most promising as potential antiobesity targets include cholecystokinin (CCK), glucagon-like peptide-1 protein (GLP-1), PYY, and ghrelin (Figure 2).

CCK is produced in gall bladder, pancreas, and stomach and concentrated in the small intestine. It is released mainly in response to dietary fat and functions to regulate gallbladder contraction, pancreatic exocrine secretion, gastric emptying, and gut motility. CCK also has central nervous system effects that may increase satiety and decrease appetite. CCK-A ("alimentary") receptors are alternatively termed CCK-1 receptors, in part, because some of these receptors can also be found in the brain. Similarly, CCK-B ("brain") receptors are alternatively termed CCK-2 receptors because some of these receptors are also found in the GI/alimentary system. CCK receptor agonism inhibits gastric emptying and primarily increases central signaling of satiety through vagal afferent signals to the brain resulting in short-term inhibition of food intake. Increasing CCK activity is being evaluated as a potential antiobesity and antidiabetes treatment target (82) (Figure 2).

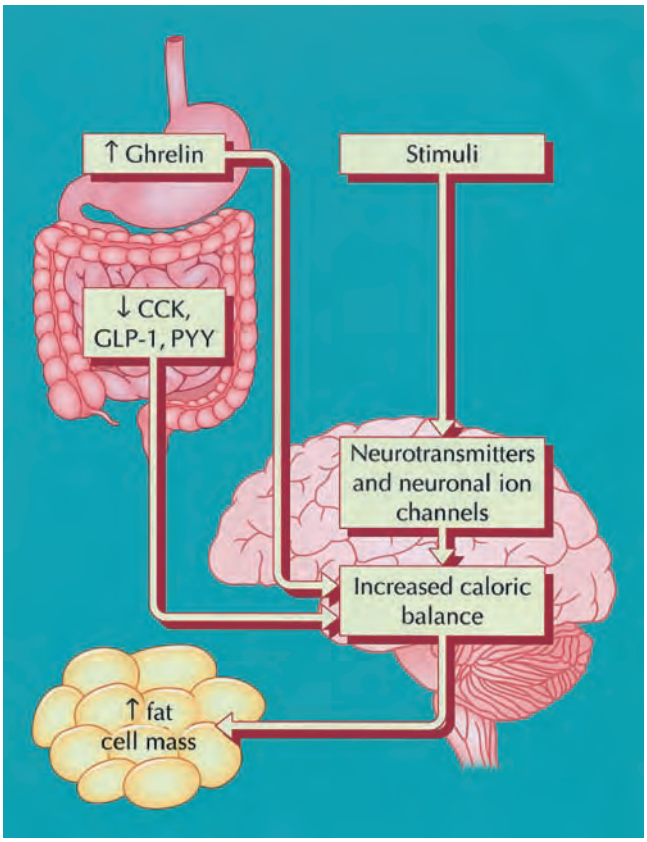

Figure 2: Simplified and illustrative select antiobesity drug targets of the gastrointestinal/CNS and neurotransmitter/neuronal ion channel pathways. Postprandial increase in CCK, GLP-1, PYY, and fasting decrease in ghrelin activity may decrease feeding. Submaximal activity or decreased effectiveness of CCK, GLP-1, PYY, or an increase in ghrelin may result in positive caloric balance (fat weight gain). Targets of antiobesity agents include the following: (1) ghrelin antagonism (or gastric bypass); (2) CCK agonism; (3) GLP-1 agonism (extendin 4, liraglutide, DPP IV inhibitors); and (4) PYY agonism. CNS drugs that may decrease appetite through a variety of effects on neurotransmitters, neuronal ion channels, and possibly other pathways, include the following: some antidepressants (bupropion), some noradrenaline reuptake inhibitors, selective 5HT receptor agonists, some antiseizure drugs (topiramate, zonisamide), some dopamine antagonists, and CB 1 receptor antagonists (rimonabant).

GLP-1 is an insulinotropic peptide gut hormone (incretin hormone) produced mainly in the distal ileum and colon that delays gastric emptying, inhibits glucagon secretion, stimulates glucose-induced insulin secretion (possibly through

restored pancreatic β cell sensitivity to exogenous secretagogues), increases insulin sensitivity, delays or prevents the decay in pancreatic β cell insulin production, improves glucose blood levels in patients with diabetes, and increases satiety. Thus, GLP-1 is another promising target for antidiabetes and antiobesity agents (83). GLP-1 agonism may be achieved through direct administration of analogues. Extendin-4 (exenatide) is a potent and long-acting GLP-1 analogue [originating in the saliva of *Heloderma suspectum* (Gila monster lizard)] that may not only inhibit gastric emptying and increase central signaling of satiety, but may also have favorable effects in the treatment of type 2 diabetes (84). Liraglutide is also a long-acting derivative of GLP-1 (85) (Figure 2).

Normally, the enzyme dipeptidyl peptidase IV (DPP IV) rapidly inactivates GLP-1. DPP IV inhibitors increase endogenous GLP-1 levels and are being evaluated as an antidiabetes agent in overweight patients with diabetes (83,86,87); however, it remains to be shown that these oral agents result in the same degree of weight loss as achieved with the GLP-1 injectable analogues.

PYY is a hormone shown to have postprandial secretion by intestinal cells that may signal satiety in the hypothalamus possibly through a decrease in NPY and an increase in POMC activity. Administration of PYY before meals has been shown to result in decreased food consumption after meals in humans (88), presumably because it provides the same sense of satiety as a postprandial snack. It has, thus, been characterized as a "third-helping hormone," in that it has been shown to result in diminished postprandial "snacking" after meals (Figure 2).

The peptide hormone ghrelin is synthesized in the stomach (as well as intestine, pituitary, and possibly hypothalamus) and may activate the growth hormone secretagogue receptor. (The "gh" portion of ghrelin originates from growth hormone.) With decreased food intake in animals and humans, ghrelin secretion may increase and stimulate food intake. Thus, the "drive to eat" after dieting may be partially because of ghrelin secretion. Reducing ghrelin activity may reduce the "drive to eat," and, in fact, it has been suggested that it is the reduction in ghrelin that partially accounts for the effectiveness of gastric bypass surgery. Therefore, ghrelin antagonism may potentially decrease or at least blunt the increased appetite that may occur with decreased feeding and, thus, be a potential adjunctive treatment for obesity (89,90) (Figure 2).

Finally, amylin is a peptide secreted by the pancreas in response to nutrients and other insulinogenic stimuli. Amylin is a neuroendocrine hormone (91) that may be a promising antiobesity or antidiabetes treatment target. Pramlintide is a subcutaneously administered synthetic analogue of amylin that is currently in development as a possible beneficial adjunct to insulin. It has been shown to improve blood sugar control and reduce weight among patients with type 2 diabetes (92–94).

Investigational Antiobesity Agents that May Increase Resting Metabolic Rate

Increasing energy expenditure through physical activity, or through an increase in resting metabolic rate (RMR) and/or thermogenesis, is another important part of the equation in achieving weight reduction in obese patients. Unfortunately, long-term compliance and commitment to routine physical exercise frequently does not occur. Therefore, the target of some investigational antiobesity drugs is to increase RMR and/or thermogenesis.

β-Adrenergic agonists selective for β3 receptors in adipose tissue may increase heat production through effects on fat cell mitochondria and, thus, theoretically increase RMR and reduce body fat (95). Unfortunately, early clinical trials have suggested that "selective" β3 receptor agonists have not always been so "selective" and stimulate other β receptors, including the β1 receptors in the heart, resulting in tachycardia. Nonetheless, studies continue in pursuit of selective agents that can promote fatty acid oxidation, especially in adipose tissue, while avoiding adverse cardiovascular effects.

Similarly, uncoupling protein (UCP) homologues are being developed that may increase thermogenesis. The mitochondria are the intracellular furnaces where fuels derived from fatty acids and glucose are oxidized (45). Energy is either stored (through creation of ATP through a respiration process coupled with oxygen consumption) or released as heat (not linked to ATP production and not coupled to oxygen consumption). UCP-1 is found in brown adipose tissue (BAT) (whose color is caused by the rich vascularization and densely packed mitochondria). BAT is present in small amounts at birth but is an important contributor to thermogenic responses and thermoregulation, as might be beneficial after birth when emerging from a warm, isothermic uterine environment to the colder outside world. In adults, UCP-1–associated BAT is negligible. However, the UCP-2, as found in adult white adipose tissue, is ubiquitous, whereas UCP-3 is found in skeletal muscle (96). UCPs serve as transporters of cations and, perhaps, anions across the mitochondrial membranes, reducing ADP phosphorylation, decreasing ATP energy storage, and increasing energy expenditure in the form of heat (referred to as "uncoupling"), and thus may increase thermogenesis. UCP-acting agents may be antiobesity targets.

Thyroid hormone is also known to increase thermogenesis. However, because of its potential adverse side effects at superphysiologic doses (cardiovascular toxicity, myopathy, and potential acceleration of osteoporosis), thyroid hormone is contraindicated as a treatment specifically for obesity

alone. Agents that target certain actions at the thyroid hormone receptor, while at the same time avoiding the undesirable side effects of current thyroid hormone drugs, are under development as an adjunct in the treatment of obesity and, potentially, dyslipidemia (97). However, an efficacy focus of thyroid receptor agonists would be to ensure that weight loss is predominantly fat, rather than lean body tissue loss, including muscle and bone.

Finally, other previously mentioned agents (such as adiponectin) may increase energy expenditure in animals (98) but have yet to be proven to do so in humans, or at least, yet to be proven to do so to a clinically significant extent.

Other Investigational Antiobesity Agents

Melanin-concentrating hormone (MCH) may increase food intake by its interaction with the G-protein–coupled receptor (somatostatin-like receptor). MCH receptor (somatostatin-like receptor) antagonism has been shown to inhibit food intake in rats and may also have antidepressant and anxiolytic effects as well. Thus, MCH receptor antagonism may prove to be an important target for antiobesity drug development (99).

Certain "natural" or nutraceutical analogues also have been suggested to have favorable effects on weight reduction. These include phytosterol analogues (including disodium ascorbyl phytostanol phosphate) (75,100), functional oils/medium-chain fatty acids (75,101–105), P57 [a cactus extract that is consumed by African tribesmen to decrease hunger during long hunting trips] (106), and various amylase inhibitors that may be derived from wheat and beans (107,108).

Last, a remaining diverse group of antiobesity drugs are currently under development. Administration of growth hormone to growth hormone–deficient patients may result in an increase in lean body mass with reduction in fat mass. Particularly in patients with Prader-Willi syndrome, growth hormone administration has been shown to result in sustained fat use and physical strength (109). However, the beneficial effects of intact growth hormone on obesity may be limited (110). Intact growth hormone may also induce insulin resistance. It is, therefore, possible that the development of growth hormone fragments (with predominant activity directed at fat) may preserve or potentially improve lean body mass benefits without adversely affecting glucose metabolism (111,112).

Other novel agents under investigation as antiobesity treatment targets include steroid drugs, including fluasterone, which is a synthetic analogue of the adrenal steroid hormone dehydroepiandrosterone (DHEAS). DHEAS has been proposed, but not proven, to increase mitochondrial respiration, augment thyroid hormone function, and possibly influence peroxisome proliferation (113); its questionable and potential benefits in patients await the outcomes of long-term clinical trials (114). Other novel agents are the antagonist of adipocyte 11β-hydroxysteroid dehydrogenase type 1 activity (pharmaceutical agents or possibly through magnolia officinalis bark extract), which is an enzyme suggested to contribute to visceral obesity, as well as the metabolic syndrome (115,116); agonists of the catabolic corticotropin releasing hormone or factor (CRH) molecule (animal studies have shown that human CRH increases thermogenesis, increases fat oxidation, and decreases food intake) (117); agents that decrease carboxypeptidase activity (an enzyme necessary for proteolytic processing and, thus, biosynthesis of insulin, MC, and NPY) (118,119); inhibitors of fatty acid synthesis (cerulenin and C75) (120,121); and a diverse variety of compounds, including indanones/indanols (122), aminosterols (Trodusquemine, formerly known as trodulamine), and other gastrointestinal lipase inhibitors (ATL962) (123).

In conclusion, this review has focused on the existing and some of the more promising investigational antiobesity agents and targets. However, examples of other molecules, enzymes, and assorted factors being evaluated in relation to obesity research include adrenomedullin, adenosine monophosphate-activated protein kinase, apolipoprotein A-IV, attractin, beacon, bombesin, bombinakinin M gene associated peptide, calcitonin receptor-stimulating peptide, dynorphin, endorphin, enterostatin, fatty acid synthase, feeding circuit-activating peptides, galanin, galanin-like peptide, gastric inhibitory polypeptide, gastrin releasing peptide, glucagons, growth hormone releasing factor, high mobility group protein isoform I-C, HS014, JKC363, myostatin, neuromedin B and U, neurotensin, neuropeptide B and W, orexins, oxytocin, oxynomodulin, pitiutary adenylate cyclase-activating polypeptide, perilipin, protein kinase A, resistin, secretin, somatostatin, thyroid-releasing hormone, tubero-infundibular peptide, and urocortin (124,125). Because studies in antiobesity research are in such a state of infancy, it is difficult to determine which of these single treatment targets, or which combination of treatment targets, has the best potential to effectively manage the worldwide epidemic of obesity. Therefore, it is impossible to predict at this point which agent or agents will eventually prove to revolutionize obesity treatment, as occurred when diuretics were introduced to treat hypertension, when insulin was introduced to treat diabetes, and when statins were introduced to treat dyslipidemia (7). However, given that medical science has almost always risen to and met epidemic challenges, there is no reason to believe that such a therapy or therapies are not forthcoming.

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Meridia® (Sibutramine) Utilization and Concurrency Analyses

CDR Vicky Borders-Hemphill, PharmD
Drug Utilization Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

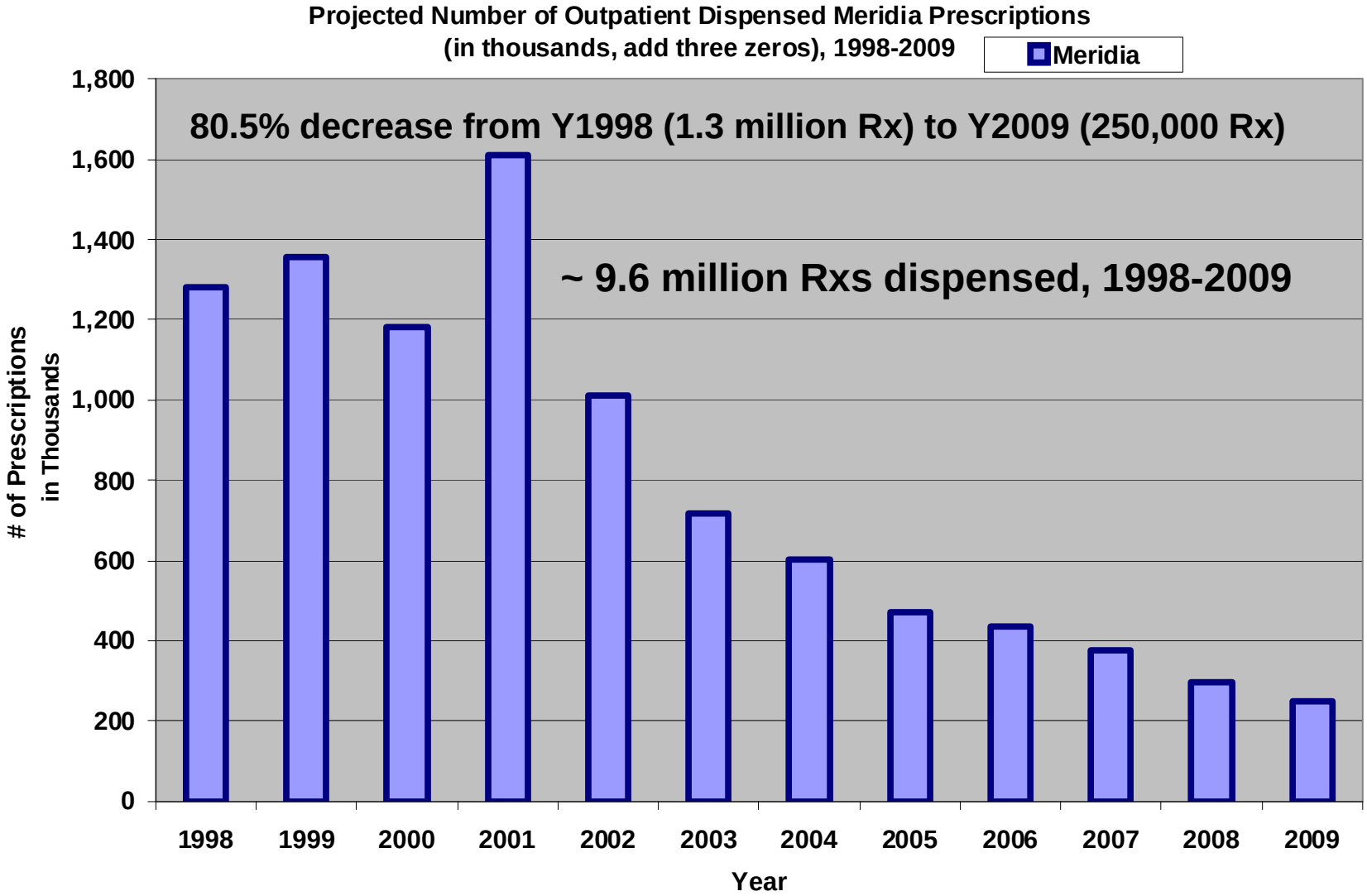
OUTLINE

- Meridia® prescription utilization in the outpatient retail setting
- Meridia® prescription utilization by prescriber specialty in the outpatient retail setting
- Meridia® patient counts by age and gender in the outpatient retail setting
- Physician reports of patient BMI by age analysis
- Concurrent Diagnosis Analysis
- Limitations
- Summary

Outpatient Utilization Data Sources

- SDI Vector One®: National (VONA) & Total Patient Tracker (TPT)
  - National-level projected prescription and patient-centric tracking service
  - 59,000 U.S. retail pharmacies
  - >2.0 billion prescription claims per year
  - >160 million unique patients

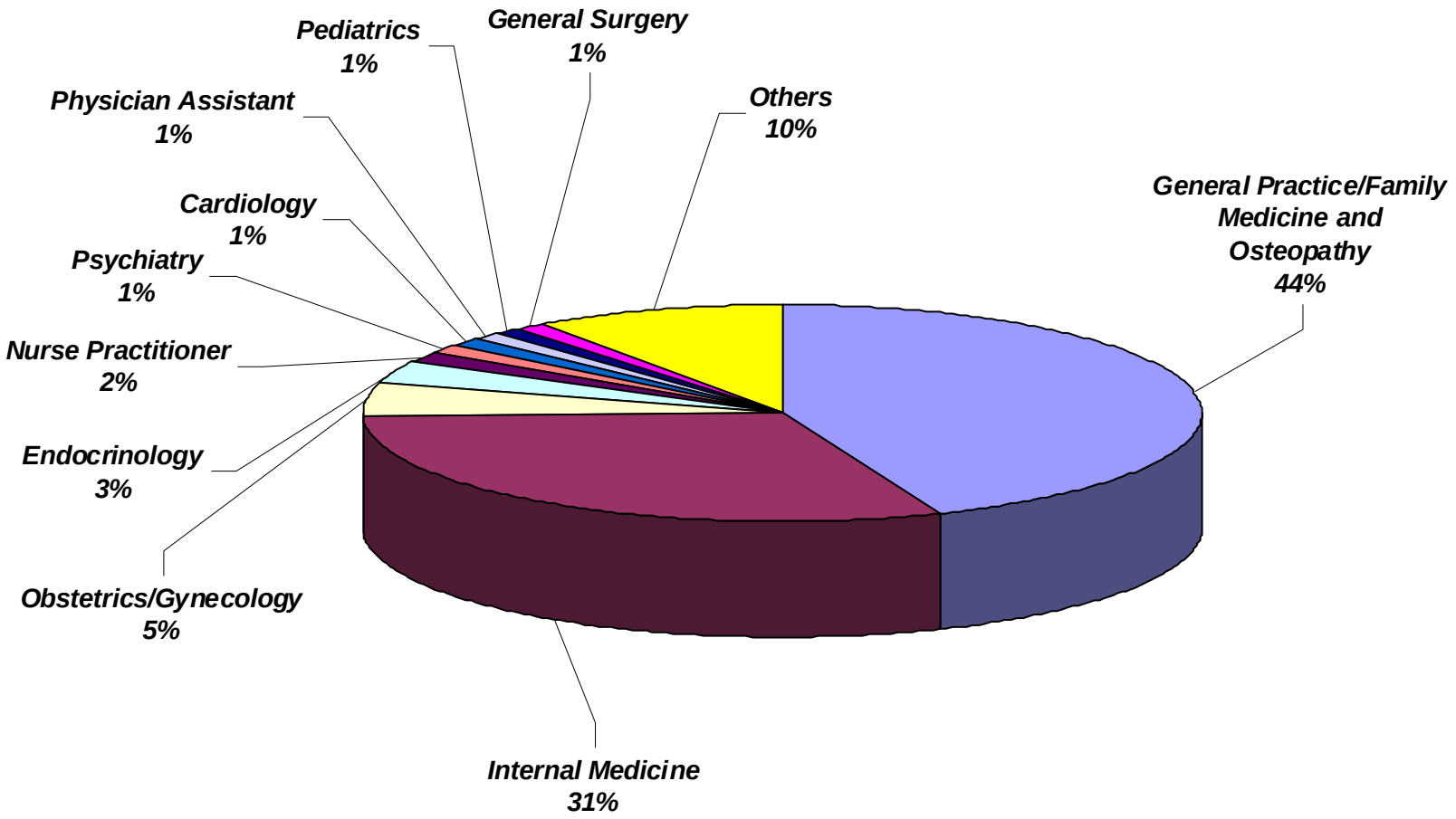
Outpatient Utilization



Source: SDI: Vector One®: National. File: VONA 2009-2201 sibutramine Trx1998-2009.xls

Outpatient Utilization

Projected Number of Dispensed Meridia Prescription by Prescriber Specialty, Cumulative Years 1998-2009

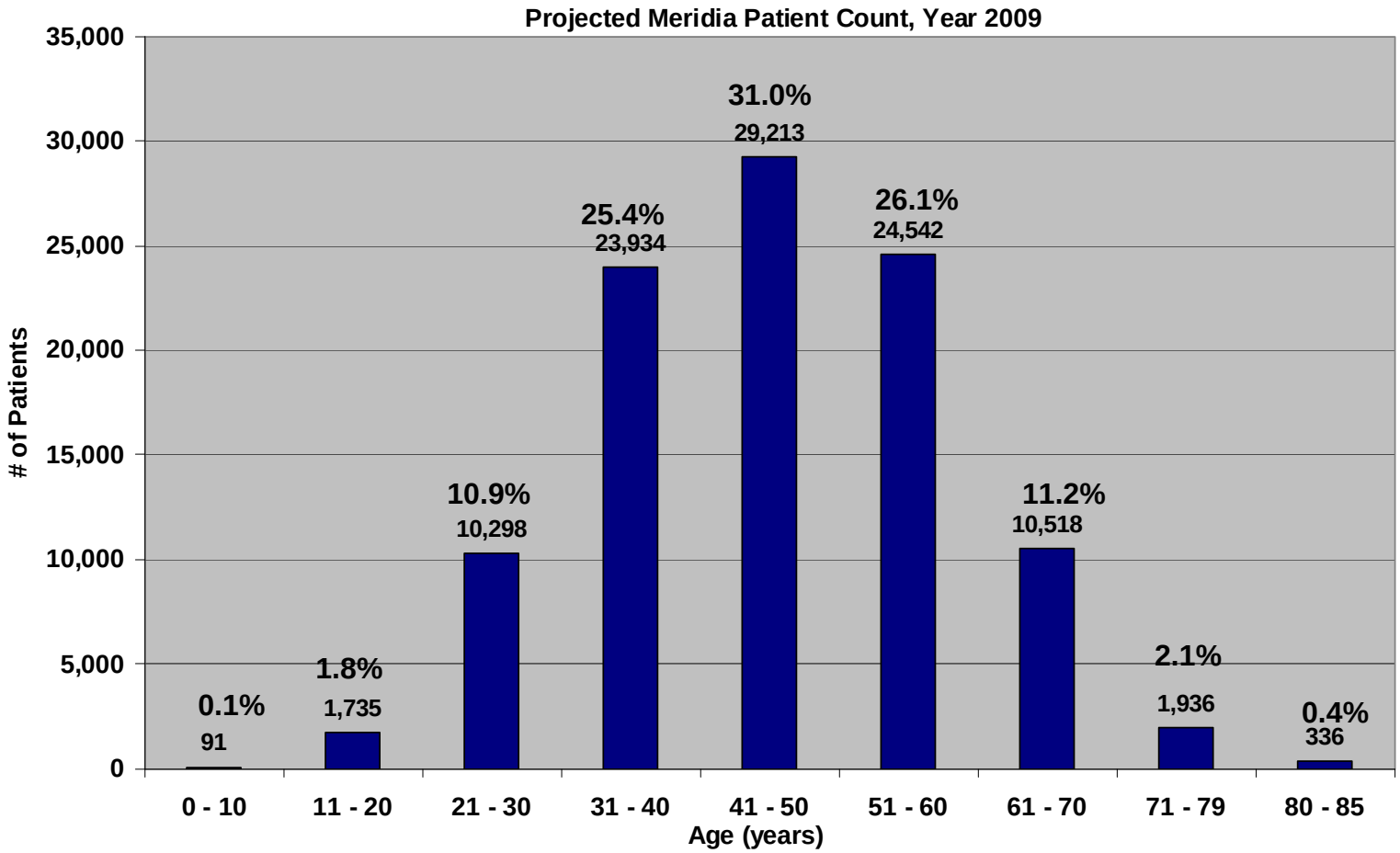


Ex. 6, Page 197

Source: SDI: Vector One®: National. File: VONA 2009-2201 sibutramine Trx specialty 1998-2009.xls

Outpatient Utilization

~ 94,000 patients in Year 2009; 83% female



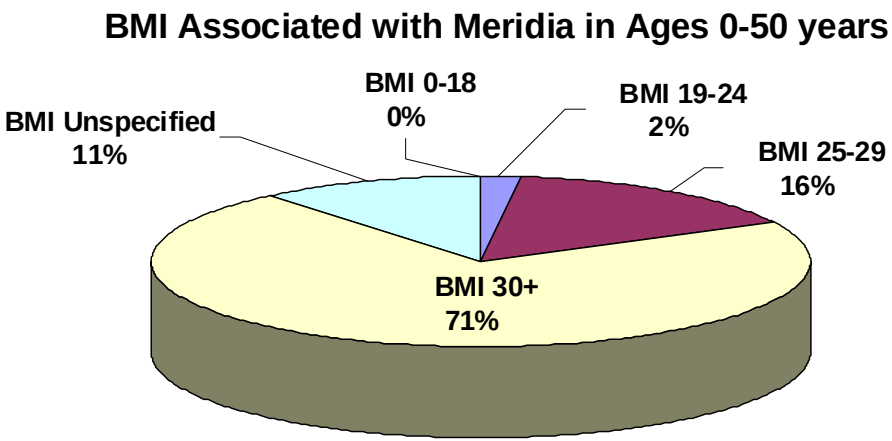
**SDI, Total Patient Tracker. Data extracted 7-29-10 and 8-31-10.*

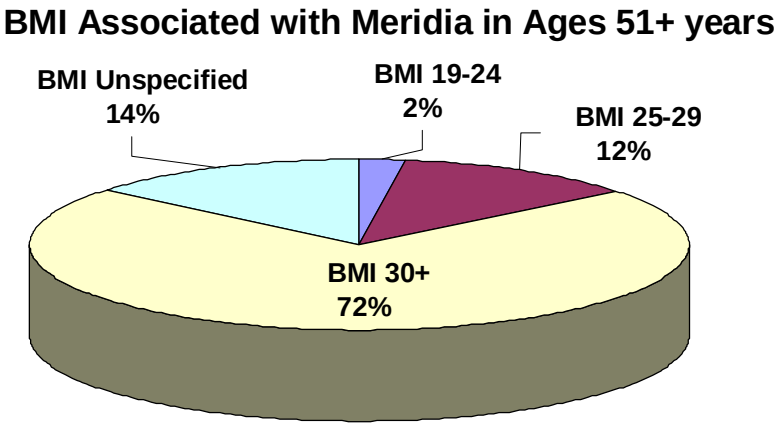
Files TPT 2009-2201 Meridia year 2009 4-15-10.xls, TPT 2009-2201 meridia age 10yr incr 2009 8-31-10.xls, TPT 2009-2201 Meridia year 2009 by gender 7-29-10.xls

Outpatient Utilization Data Sources

- SDI Physician Drug and Diagnosis Audit (PDDA)
  - Monthly survey that monitors disease states and physician intended prescribing habits on a national-level
  - 3,200 panelists, 30 specialties
  - Includes diagnoses, patients characteristics, and treatment patterns

Physician Reports of Body Mass Index (BMI), Cumulative Y1998-2009





Underweight BMI: < 18.5
Normal weight BMI:18.5 - 24.9

Overweight BMI:25 - 29.9
Obesity BMI: 30+

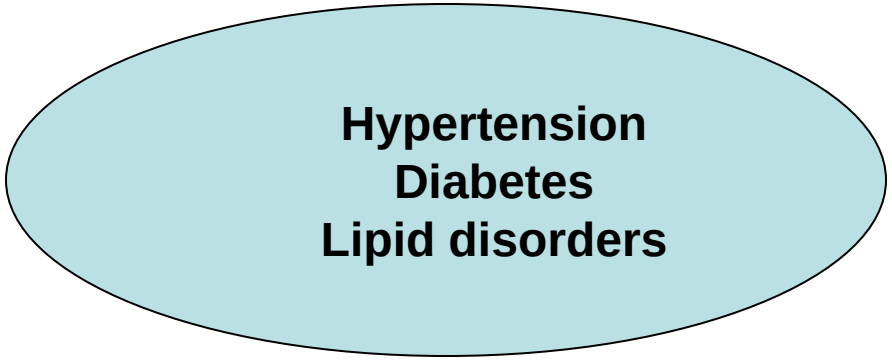
SDI's Physician's Drug and Diagnosis Audit™ (PDDA). File: PDDA 2009-2201 sibutramine by age 0-50, 51+ BMI 1998-2009.xls
Ex. 6, Page 200

Data Source: Concurrent Diagnosis Analysis

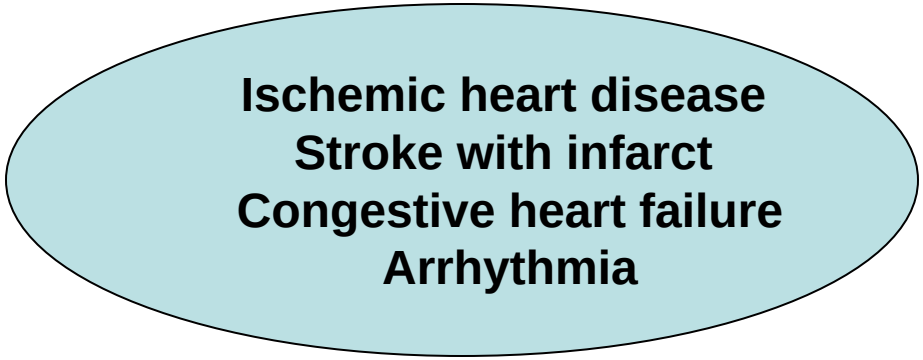
- ***Wolters Kluwer SOURCE Lx® database***
  - Longitudinal patient data source
  - U.S. adjudicated medical and prescription claims
    - commercial plans, Medicare Part D plans, Cash and Medicaid claims.
    - 4.8 billion paid, non-reversed prescriptions claims linked to over 172 million unique prescription patients
    - ICD-9 diagnosis history of which nearly 91 million prescription drug patients are linked to a diagnosis
  - The overall sample represents 27,000 pharmacies (retail/specialty/mail order), 1,000 hospitals, 800 clinics/outpatient facilities, and 80,000 physician practices.

Concurrent Diagnosis Analysis

- Obtained the number of unique patients with a Meridia® prescription claim and concurrent diagnoses* for one or more of the following:



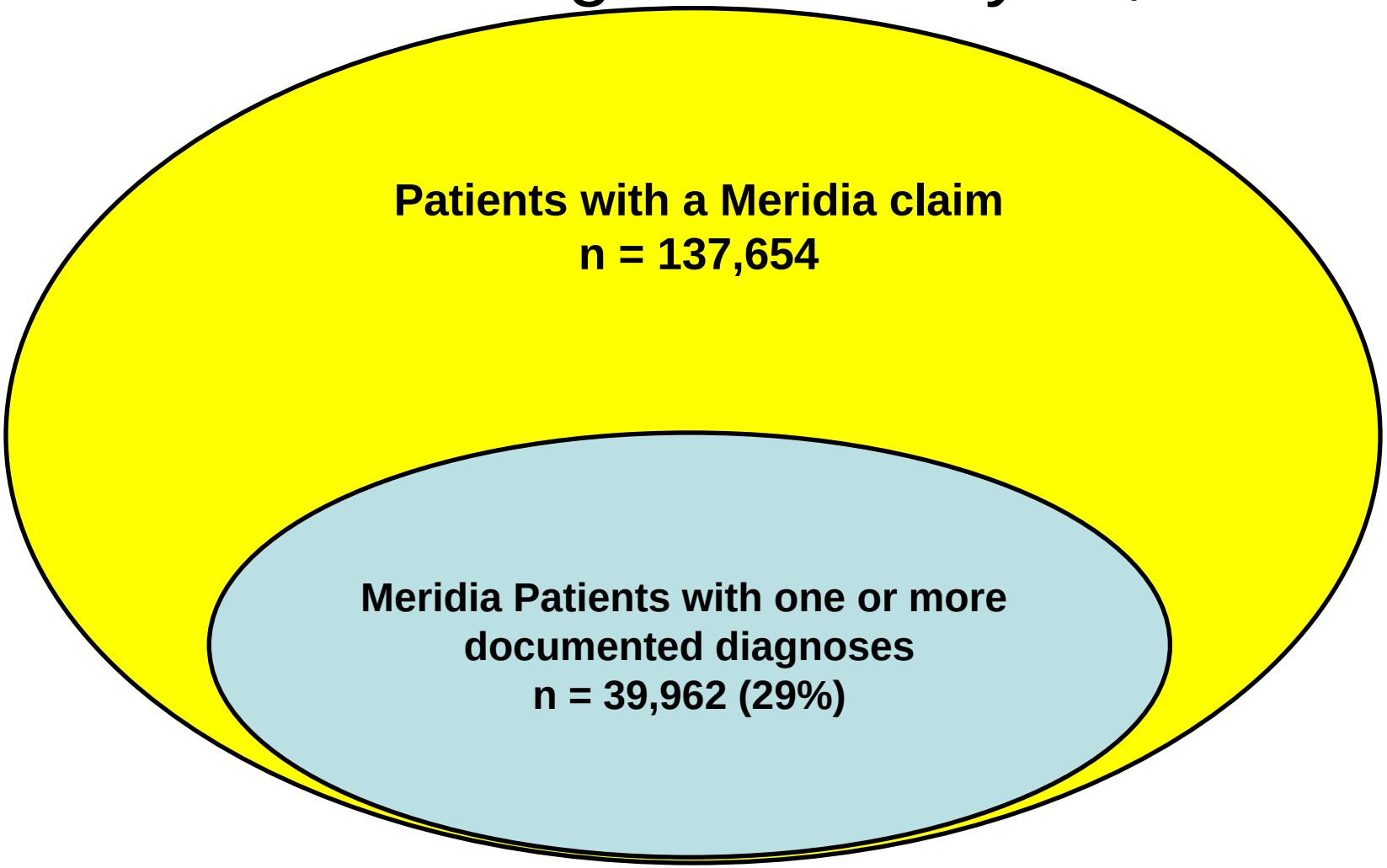
Labeling Recommends



Labeling Advised Against

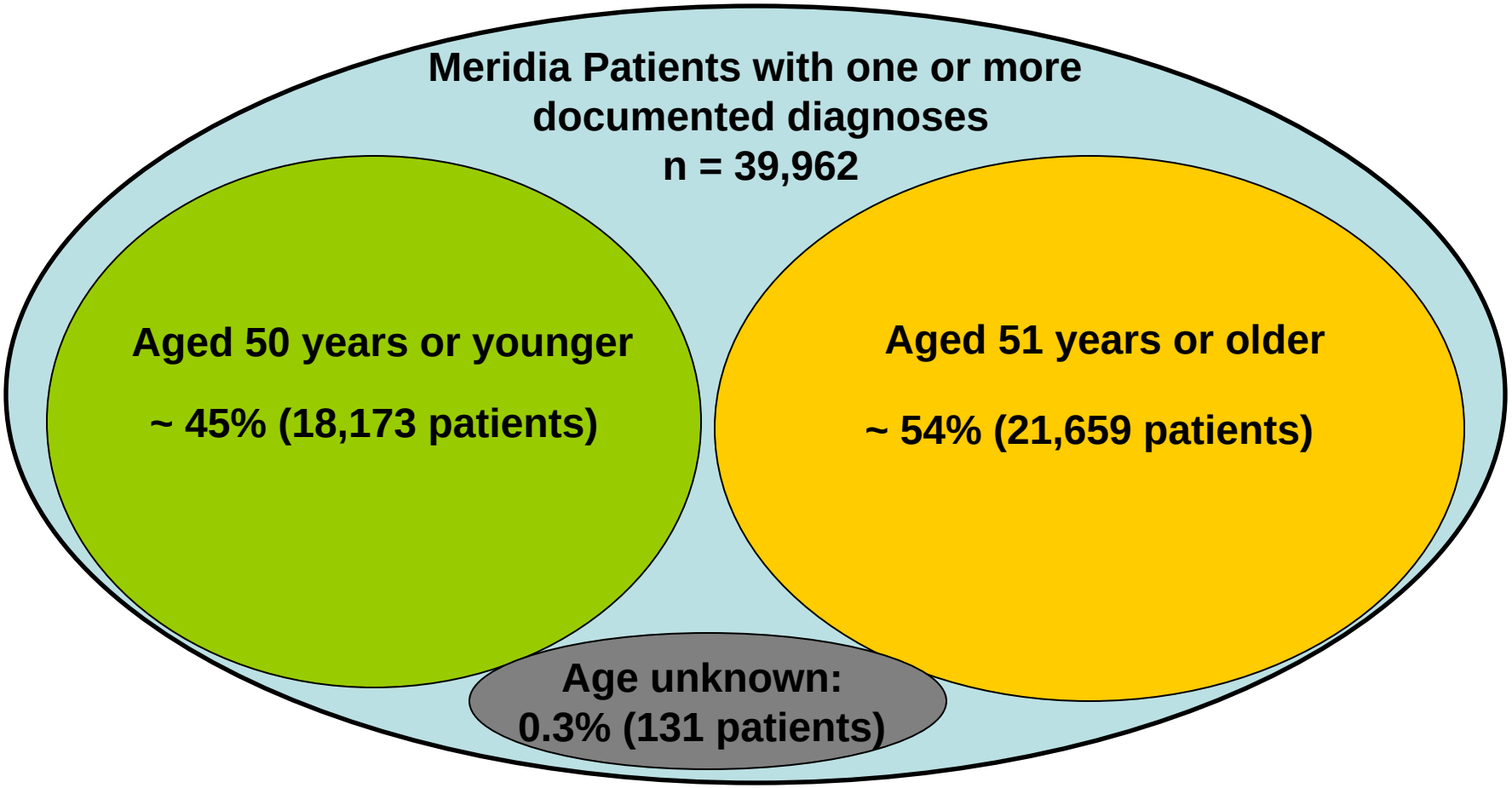
**based on selected ICD-9 codes*

Concurrent Diagnosis Analysis, Y2009



Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2009.
Extracted March 2010. File: WKCPA 2009-2201 meridia by diag TABLE working file mar10.xls

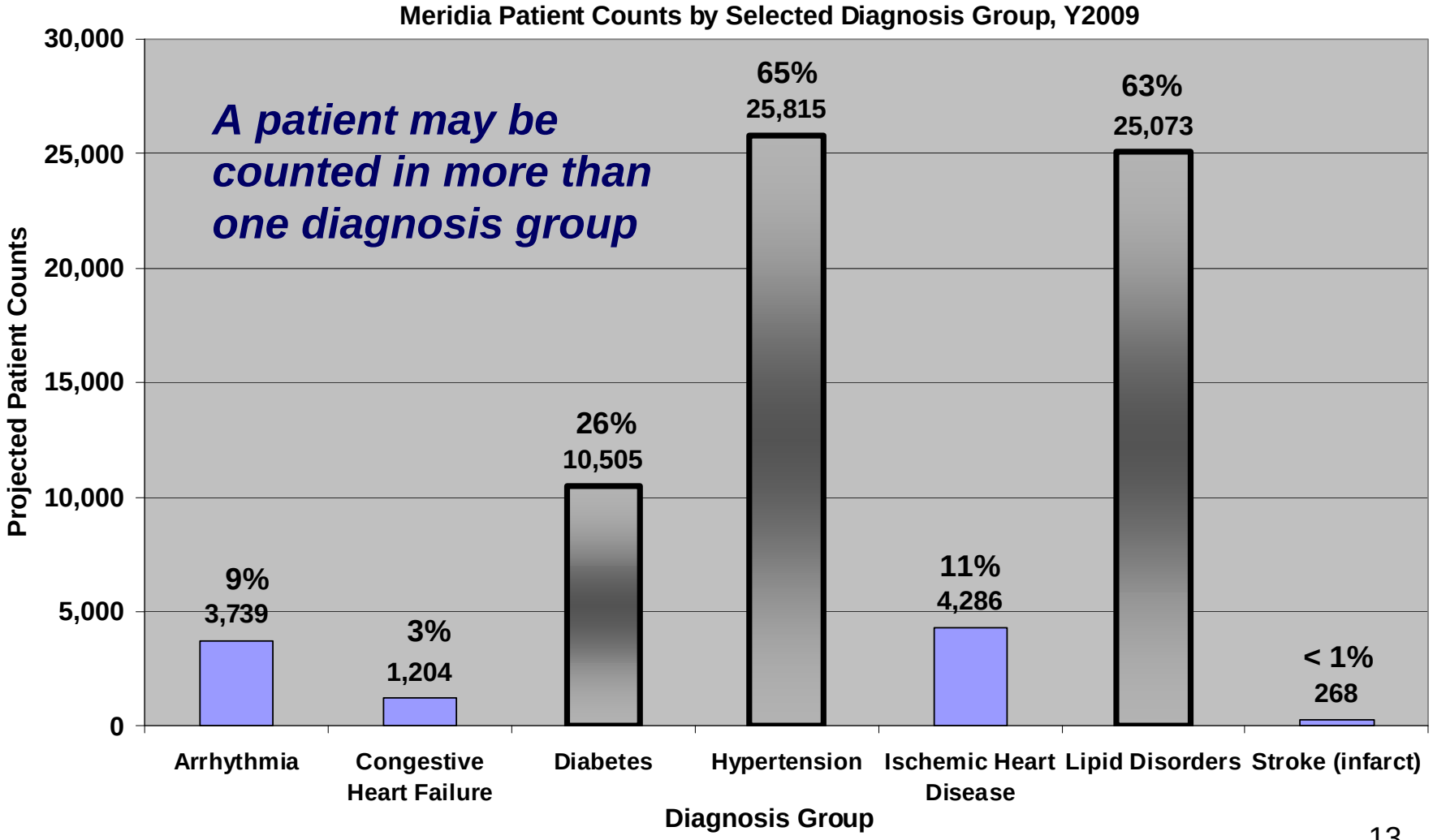
Concurrent Diagnosis Analysis, Y2009



*Age is at first claim during calendar year

Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2009.
Extracted March 2010. File: WKCPA 2009-2201 meridia by diag TABLE working file mar10.xls

Concurrent Diagnosis Analysis



Wolters Kluwer Health's Source® Lx. CPA tool Years 2007-2009. Extracted March 2010.
File: WKCPA 2009-2201 meridia by diag TABLE working file mar10.xls

Concurrent Diagnosis Analysis Summary

High rates of concurrency

Hypertension
Diabetes
Lipid disorders

Labeling Recommends

Low rates of concurrency

Ischemic heart disease
Stroke with infarct
Congestive heart failure
Arrhythmia

Labeling Advised Against

Limitations

- Concurrent Diagnosis Analysis (Wolters Kluwer Source Lx® CPA):
  - Around 30% of patients had medical diagnoses on outpatient prescription claims and pharmacy data available for analysis
  - Mail order was excluded from this analysis
  - Documented diagnoses may be a “rule out” diagnoses
  - Disease severity was not delineated

SUMMARY

- Low use in U.S.
- Prescribed by General Practitioners, Family and Internal Medicine
- Most prescribers reports were associated with obese patients
- High rates of concurrency: hypertension, diabetes, and dyslipidemia
- Low rates of concurrency: ischemic heart disease, stroke, CHF, and arrhythmia
- Further study with medical records validation is required to determine the true prevalence of concurrent disease states and drug use.

SPECIAL REPORT

Pharmacotherapy for Patients With Eating Disorders

by Timothy D. Brewerton, M.D.

Psychiatric Times •May 2004 •Vol. XXI •Issue 6

Eating disorders, including anorexia nervosa (AN), bulimia nervosa (BN) and binge-eating disorder (BED), remain one of the most complex and clinically challenging groups of mental disorders in our nomenclature. There are no easy solutions, and the bottom line of this article is that pharmacological agents are not the primary treatment of choice. Although a number of agents have been found in randomized controlled trials to be beneficial, they are by and large insufficient as stand-alone treatments. Space does not allow a comprehensive overview of this topic, but the reader is referred to a recent review by Steinglass and Walsh (2004). In addition, the revised American Psychiatric Association practice guidelines for the treatment of eating disorders (APA, 2000) and the recently released National Institute of Clinical Excellence (NICE) Guidelines (2004) are useful resources regarding the use of drug therapy within the context of a comprehensive treatment approach.

Anorexia Nervosa

No pharmacological agents have ever been shown in double-blind, placebo-controlled trials to significantly improve AN when given outside a structured, inpatient program. Food remains the "drug of choice" for this population, for reasons that will be elaborated below. Of course, administering food in the interest of weight restoration is much easier said than done, given the profound denial and resistance typical of this disorder. There are a handful of drugs found to be statistically better than placebo in randomized controlled trials, but there is little clinical significance of these findings. Lithium (Eskalith, Lithobid) was shown in one controlled trial to be statistically better than placebo in a small group of patients being treated at the National Institute of Mental Health on an intensive, highly structured, specialized treatment unit (Gross et al., 1981). However, the effect was small, and eating disorder specialists generally deem the potential risks of lithium treatment in this population to be far greater than the possible benefits, largely due to the danger of lithium toxicity secondary to dehydration and electrolyte imbalances from starvation, compulsive exercising and/or purging. Another study found amitriptyline (Elavil) statistically better than placebo for patients who are both bulimic and anorexic, while cyproheptadine (Periactin) was better for restricting anorexia (Halmi et al., 1986). However, other studies have had mixed results.

Although the use of antidepressant medications in AN seems theoretically sound, the results from randomized controlled trials have been dismal. In addition, the cardiac effects of tricyclic antidepressants include prolongation of the QT_C interval, which can already be prolonged in patients with AN, a setup for sudden death. Selective serotonin reuptake inhibitors might seem applicable given their safety profile and usefulness in major depression and obsessive-compulsive disorder, as well as the profound central serotonergic disturbances reported in AN (Brewerton, 1995; Brewerton and Jimerson, 1996). Fluoxetine (Prozac) has been shown to have absolutely no effect on weight, body image, anxiety or mood in low-weight patients with AN (Attia et al., 1998). However, once patients are weight-recovered, one controlled trial indicated that relapse (which is common) can be significantly reduced with fluoxetine in comparison to placebo, presumably due to its antiobsessional effects (Kaye et al., 2001).

It is essential for the clinician to understand that the reason fluoxetine, or any monoamine reuptake inhibitor, cannot work in low-weight patients is because central 5-HT levels are profoundly depleted in these individuals as a direct result of starvation and weight loss (Brewerton, 1995; Brewerton and Jimerson, 1996; Kaye et al., 1988). The effectiveness of SSRIs depends not only on having sufficient central 5-HT available for release and reuptake-inhibition, but also on essential amino acid precursor (l-tryptophan) availability (via a balanced meal plan) to allow continued 5-HT-synthesis following weight recovery. This is well-established as a result of many tryptophan-depletion studies.

There is excitement in the field about the possibility of using olanzapine (Zyprexa) and other atypical antipsychotics in low-weight patients with AN. Olanzapine acts in part via postsynaptic 5-HT_2-antagonism, so it bypasses the presynaptic apparatus altogether and does not depend on l-tryptophan availability. Olanzapine's propensity toward enhanced appetite and weight gain, as well as its antianxiety, antiobsessional and antidepressant properties, makes it theoretically an excellent drug for AN, especially the restricting subtype. It also increases sleep and decreases motor activity, thereby conserving energy expenditure. Open trials and case reports are promising (La Via et al., 2000; Malina et al., 2003; Powers et al., 2002), but no controlled trials have been completed as of yet. Adult patients often resist or refuse to take olanzapine because of its weight gain and soporific effects; however, in children and adolescents, parents can ensure compliance. Very low doses are usually sufficient to attain the desired effect (i.e., 0.625 mg/day to 5.0 mg/day). There are no long-term follow-up data, but once weight restoration is achieved, olanzapine can be tapered and usually stopped as fluoxetine "kicks in" for prophylaxis. If needed, a very low dose of a relatively weight-neutral atypical antipsychotic agent, such as quetiapine (Seroquel), ziprasidone (Geodon) or aripiprazole (Abilify) may be a helpful adjunct as recovery progresses, especially when there is significant comorbidity. However, this remains speculative and untested, and most patients do not need continued antipsychotic treatment following full weight recovery. The propensity for olanzapine and other atypical antipsychotics to induce hyperglycemia, diabetes mellitus and extrapyramidal side effects certainly requires monitoring and caution, but their use must be weighed against the significant psychiatric and medical morbidity and mortality associated with AN.

Bulimia Nervosa

Although cognitive-behavioral therapy (CBT) is the most empirically validated treatment for BN (APA, 2000; NICE, 2004), several randomized control trials attest to the effectiveness of antidepressant medications in reducing binge and purge frequencies in patients with BN (Steinglass and Walsh, 2004). Such antibulimic effects have been shown in several studies to be independent of the drugs' antidepressant effects per se. In general, these studies have several limitations, including short duration (generally six to eight weeks) and exclusion of patients with major, yet common, comorbidities (e.g., mood/anxiety/substance use disorders, suicidality or parasuicidality). Both imipramine (Tofranil) (Mitchell et al., 1990) and desipramine (Norpramin) have been found to be effective in short-term, randomized controlled trials. Unlike treatment for major depression or anxiety disorders, one cannot generalize from one SSRI to another because not all of them have been studied in BN, and available evidence suggests that they are not equally effective. The only SSRIs that have been seriously studied in BN using randomized controlled trials are fluoxetine and fluvoxamine (Luvox). Fluoxetine at 60 mg/day, but not 20 mg/day, was superior to placebo in reducing both binge and purge frequencies (Romano et al., 2002), so it is important that clinicians treating BN realize that higher doses (40 mg/day to 80 mg/day) are generally required for an effective antibulimic response (similar to OCD). On the other hand, fluvoxamine has not been found to be statistically different from placebo in European randomized controlled trials (unpublished data), although it may help in relapse prevention (Fichter et al., 1996).

There are no known studies using non-SSRI newer generation agents such as nefazodone (Serzone), mirtazapine (Remeron) and venlafaxine (Effexor), except bupropion (Wellbutrin). Although bupropion has been found to be effective in one randomized controlled trial to reduce bingeing and purging frequency (Horne et al., 1988), the risk of seizures far outweighs its potential benefits, therefore its use in AN or BN is contraindicated.

There is one randomized controlled trial using ondansetron (Zofran), a potent 5-HT_3 antagonist and antiemetic indicated in the treatment of chemotherapy-induced nausea and vomiting in patients with cancer (Faris et al., 2000). Ondansetron was found to be effective in reducing bingeing and purging when compared to placebo. Although this agent is very costly, it is worth considering in refractory and/or severe cases.

The anticonvulsant topiramate (Topamax) has been recently reported to be effective in reducing binge and purge frequencies in comparison to placebo (Hoopes et al., 2003). However, bothersome side effects such as paresthesias, impaired mentation, metabolic acidosis and oligohydrosis may lessen its usefulness. It appears to be an ideal adjunct treatment to other mood stabilizers in patients with BN who are also overweight or obese and have comorbid bipolar disorder and/or migraine.

Naltrexone (ReVia) is a possible adjunct in patients who are refractory to SSRIs, especially in those with comorbid alcoholism and/or self-injurious behaviors. Although naltrexone was no better than placebo in one randomized controlled trial in BN (Mitchell

et al., 1989), a double-blind, placebo-controlled crossover study in patients with AN or BN showed it to significantly reduce bingeing and purging (Marrazzi et al., 1995).

Binge-Eating Disorder

Like in BN, CBT has been demonstrated in randomized controlled trials to be the treatment of choice for BED. In two unpublished controlled studies comparing CBT and fluoxetine, CBT was superior with or without fluoxetine (Devlin, 2002; Grilo et al., 2002). Cognitive-behavioral therapy has also been combined with fluvoxamine with better results (Ricca et al., 2001). Nevertheless, randomized controlled trials suggest that bingeing is reduced by the SSRIs fluoxetine (Arnold et al., 2002), fluvoxamine (Hudson et al., 1998), sertraline (Zoloft) (McElroy et al., 2000) and citalopram (Celexa) (McElroy et al., 2003b). Recent results indicate that sibutramine (Meridia) significantly reduces binge eating and weight in BED in comparison to placebo (Appolinario et al., 2003). Finally, a randomized control trial found the anticonvulsant topiramate to be effective in reducing binge eating as well as weight (McElroy et al., 2003a).

Conclusions

Without weight restoration in AN, antidepressants are essentially useless for this condition, while olanzapine shows some promise in open studies. There is a strong case for the use of fluoxetine as an adjunct in the treatment of BN, but remission rates are low in comparison to the effects of CBT. Other SSRIs may be helpful for BED, while topiramate appears to be effective in both BN and BED. Despite its expense, ondansetron can be useful in refractory BN, as can naltrexone with or without SSRIs.

Dr. Brewerton is clinical professor of psychiatry and behavioral sciences at the Medical University of South Carolina and is in private practice in the Charleston area.

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Clinical Handbook of Eating Disorders

An Integrated Approach

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Neurotransmitter Dysregulation in Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder

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The current system of psychiatric diagnosis, DSM-IV (1), addresses two official eating disorder (ED) syndromes—anorexia nervosa (AN) and bulimia nervosa (BN)—and a third (still provisional) diagnostic entity—binge eating disorder (BED). However, BED has all but officially been recognized as a distinct eating syndrome. AN, BN, and BED are all polysymptomatic syndromes, defined by maladaptive attitudes and behaviors around eating, weight, and body image, but typically including "nonspecific" disturbances of self-image, mood, impulse regulation, and interpersonal functioning. All three syndromes are known to be associated with significant mortality and morbidity, both medical and psychiatric (2,3). Despite popular beliefs, there is no convincing evidence that cultural factors alone cause eating disorders. Indeed, during the past few years (and especially the last decade) investigations into the role of neurotransmitters and other neuromodulators in the eating disorders have been highly productive, and have implicated primary

neurotransmitter disturbances in the etiology of both AN and BN. Furthermore, recent data clearly identify strong genetic factors in AN and BN, which appear to share common genetic vulnerabilities (4,5) linked to obsessionality, perfectionism, anxiety, and/or behavioral inhibition (6,7). One powerful piece of evidence to support monoamine involvement in the eating disorders is the observation that antidepressant medications can be beneficial in controlled studies, not only in BN patients but in recovered AN patients as well (8).

However, it is also clear that some disturbances are consequences of the abnormal eating practices and nutritional disturbances that characterize these disorders (9), which in turn exacerbate or perpetuate signs and symptoms (10). This perspective, taken together with the disorders' consequences, challenges, and costs, compels us toward a better understanding of the biological mechanisms underlying all stages and types of eating disorders. The identification of the psychobiological underpinnings of these conditions may be useful in many ways, including the development of improved medical and psychopharmacological interventions, improved education and psychotherapy for patients and their families, and improved prevention efforts at a primary level.

It must be emphasized that most measurements of neurotransmitter function provide only a glimpse into the state of the organism at that moment. Sorting out what is trait and what is state related has been a challenging focus of neurotransmitter research in the eating disorders.

MONOAMINES

The classical monoaminergic neurotransmitter systems, including serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE), and dopamine (DA), have been fairly extensively studied in the eating disorders using available techniques in biological psychiatry. Most of these studies have been conducted during the active state of illness, during which severe nutritional compromise may represent an important confound. Dieting and/or semistarvation clearly depletes central monoamines and leads to altered neurotransmitter levels and receptor sensitivity in animals and humans (11–15). To avoid this problem, a more recent strategy has been to study "recovered" patients, i.e., AN and BN patients who have attained normalization of eating and weight, resumption of menses and/or normalization of gonadal hormone levels, and abatement of typical cognitive features to subclinical levels. This strategy attempts to minimize starvation state–related effects and to reveal potential trait-related disturbances or vulnerabilities. However, the long-term effects of chronic malnutrition and disordered eating behaviors on the brain (similar to substance use disorders) should not be minimized. Studies of

transmitter function in at-risk premorbid individuals as well as nonaffected identical and fraternal twins, siblings, and other first-degree relatives of ED patients could begin to confirm trait-related disturbances.

Neurotransmitter function in patients with EDs have been investigated using a variety of existing techniques and methodologies, each of which has its own advantages and disadvantages. Studies of cerebrospinal fluid (CSF) concentrations of the major metabolites have been a popular strategy and include measures of 5-hydroxyindoleacetic acid (5-HIAA) for 5-HT, 3-methoxy-4-hydroxyphenylglycol (MHPG) for NE, and homovanillic acid (HVA) for DA. Some studies have also examined actual concentrations of 5-HT and NE, but not DA. Such studies measure transmitter metabolism of the whole brain and spinal cord and lack any anatomical specificity.

Neuroendocrine and other psychobiological response measures have been studied following acute challenges with various agents, including amino acid precursors, e.g., L-tryptophan (L-TRP) and 5-hydroxytryptophan (5-HTP) for 5-HT, presynaptic receptor agonists, e.g., *dl*-fenfluramine (*dl*-FEN) or *d*-fenfluramine (*d*-FEN) for 5-HT, postsynaptic receptor agonists, e.g., *m*-chlorophenylpiperazine (*m*-CPP) for 5-HT, and isoproterenol (ISOP) for NE. Longer term challenges with receptor antagonists, e.g., antipsychotics for DA and 5-HT, and antidepressants, especially the serotonin-specific reuptake inhibitors (SSRIs), also illuminate the role of neurotransmitters in the eating disorders. Acute amino acid precursor depletion, most notably of L-TRP (16–19), has been another important source of information about the role of central 5-HT function in eating and related disorders.

Platelet (PLT) and leukocyte studies are possibly reflective of central neurotransmitter function but are always at least one step removed from the nervous system, e.g., platelet 5-HT reuptake, ^{3}H-imipramine binding, ^{3}H-paroxetine binding, platelet monoamine oxidase (MAO), platelet 5-HT content, as well as platelet receptor–mediated aggregation (5-HT_2 and α-adrenergic).

Plasma concentrations of neurotransmitter precursors, e.g., L-TRP, L-tyrosine (L-TYR), and their competing large neutral amino acids (LNAAs), neurotransmitters themselves, e.g., NE, DA, and whole-blood serotonin (WBS), as well as the usual metabolites, MHPG, HVA, and 5-HIAA.

Brain imaging receptor-binding studies are a promising avenue but remain relatively unexplored in the eating disorders.

For each neurotransmitter, the results from controlled studies in humans will be reviewed and summarized for both AN and BN. Where applicable, comparisons between restricting AN patients, bingeing–purging AN patients, and normal-weight BN patients will be made. Very little work of this nature has been done in BED patients but when available will be mentioned.

NOREPINEPHRINE

There are a number of reasons to suspect NE involvement in the eating disorders. Most notably, NE pathways at the level of the hypothalamus are known to be involved in the initiation of feeding (20). Disturbances in these pathways may therefore be involved in the pathophysiology of the profoundly altered feeding behaviors classically associated with the eating disorders. In addition, NE's role in the modulation of mood, anxiety, neuroendocrine control, metabolic rate, sympathetic tone, and temperature make it a likely candidate for study (21–26). It has been recognized for some time that low-weight anorexic patients, and to some degree bulimic patients, have reduced body temperature, blood pressure, pulse, and metabolic rate (25,27,28). Investigations in this area have shown that low-weight AN patients have reduced measures of plasma, urinary, and CSF MHPG (27,29–31). In contrast, reports of plasma NE levels in the eating disorders has been more variable (32,33), and this appears to be linked not only to weight but to the stresses associated with the illness (25). AN patients tend to have higher plasma NE levels at admission, which then decrease as treatment and weight gain progresses (25,34).

When ill, BN patients demonstrate lower values of plasma NE at baseline (21,28) and in response to abstinence (35), standing (36), test meal challenge (37), and mental challenge (37). They also have other evidence of blunted sympathetic activation in response to mental stress (38). However, despite low baseline plasma NE levels, BN patients show normal responses to exercise (39) but reduced responses to orthostasis (40).

In AN patients, depression has been found to be significantly worse in those patients with the lowest Δ change in plasma NE concentrations to orthostasis (41). Reduced urinary MHPG levels have also been related to the presence of comorbid major depression (29,42). It is therefore important in such studies to control for psychiatric comorbidity.

Like the plasma NE studies, CSF NE levels have been reported to be no different in AN patients than controls at low weight and after short-term weight gain, but then significantly lower after weight recovery of at least 6 months (26,31,32). In BN patients, reduced CSF NE levels have been reported during the active state of the illness (23,43). However, upon long-term recovery, concentrations of CSF MHPG have been reported to normalize in both AN and BN (7) despite earlier reports of lower levels (32). Given that CSF NE concentrations have not yet been reported in long-term (> 1 year) recovered AN or BN patients, the extent to which adrenergic alterations seen in the eating disorders are trait related remains unclear. Nevertheless, available evidence suggests exquisite sensitivity of this system to malnutrition or stress.

Challenge studies using the β-adrenergic agonist isoproterenol in underweight anorexic patients revealed erratic secretion of plasma NE in response to increasing doses (24). Bulimic patients demonstrated significantly increased chronotropic responses to isoproterenol (44). Challenge studies with adrenergic agents in recovered patients have not been reported.

The number of platelet α_2 receptors has been reported to be reduced in both AN and BN compared to controls (33,45), suggesting increased postsynaptic receptor sensitivity that is probably secondary to dieting or semistarvation. In summary, peripheral and central sympathetic nervous activity is reduced in both AN and BN, although it tends to normalize with recovery. Taken together, the preponderance of the evidence so far leads to the conclusion that these changes are a result of chronic starvation or intermittent dieting (26). However, a trait-related disturbance of the adrenergic system cannot be ruled out at this time (35).

Studies of adrenergic receptors on human leukocytes have been another strategy to investigate adrenergic function in the eating disorders. Buckholtz et al. (46) reported altered β-adrenergic receptor affinity on circulating lymphocytes of BN patients compared to those of controls. However, in a similar study of a mixed group of eating disorder patients, Lonati-Galligani and Pirke (40) reported lower receptor number (B_{max}) but normal affinity (K_d) in low-weight AN patients, whereas both measures were no different from controls in the BN patients and the weight-recovered AN patients. Gill and colleagues (47) reported differential changes in α- and β-adrenoceptor linked ($^{45}Ca^{2+}$) uptake in platelets from patients with AN, further documenting an adrenergic disturbance in eating disorder patients. However, the issue of cause versus effect remains unanswered in platelet and leukocyte studies.

DOPAMINE

DA is also suspect in the neuropathophysiology of the eating disorders given its reported involvement in the regulation of feeding, mood, activity, perception, sexual/social behavior, hormone and peptide release, and to some extent aggression (48–51). Notably, DA is involved in the hedonic reward responses to eating and its maintenance as well as to other pleasurable activities (52–54).

The majority of studies of DA metabolism in the eating disorders have consistently shown that low-weight AN patients have reduced measures of peripheral and central DA activity, including decreased plasma (27) and CSF HVA (31). In BN patients, reduced CSF HVA levels also have been reported in BN patients with frequent binge–purge episodes (23,50) but not in those less severely ill. Furthermore, binge frequency was inversely correlated with CSF HVA levels in one study (50). Upon long-term recovery, concentrations

of CSF HVA have been reported to normalize in BN (8), whereas a trend for decreased CSF HVA levels persisted in six restricting AN patients compared to controls and to bingeing and/or purging AN patients (7). This suggests a possible trait-related disturbance specific to restricting AN, although this finding needs replication given the small sample size. These results could also still be due to nutritional factors given that patients in this study weighed significantly less than those in the BN group and may still have been at the low end of the normal weight range.

Anecdotal reports of the successful use of dopaminergic antagonists (typical antipsychotic agents) in the treatment of AN patients (55) have been generally followed by equivocal results in controlled studies (56,57). Atypical antipsychotic agents may show more promise in the adjunctive treatment of AN given their combined antidopaminergic and antiserotonergic effects (58–60), but the results of placebo-controlled studies remain to be seen.

Genetic investigations into the role of DA have been limited to the Bal I DRD3 receptor polymorphisms in which no differences were found between AN patients and controls (61). However, the polymorphisms of other genes coding for DA receptors could be tested. Interestingly, Corcos and colleagues (62) reported significantly lower IgG and IgM autoantibodies to DA in BN patients compared to controls. There was also a trend for lower levels of IgM autoantibodies to DA in the eating-disordered group. The relevance of these findings to the pathophysiology of the eating disorders remains uncertain but invokes possible autoimmune mechanisms.

SEROTONIN

Several lines of reasoning point to disturbances of 5-HT function in the pathophysiology and neuropsychopharmacology of the EDs (8,9,63), including serotonin's role in feeding (64,65), satiety (66,67), dieting/fasting (11,12), mood regulation (16), anxiety (68), obsessive-compulsiveness/perfectionism/behavioral inhibition (69), harm avoidance (70,71), impulsivity/aggression (72,73), motor activity (74,75), gender (76,77), seasonality (66,78,79), body image/perception (80), and social behavior (81–83) (see Table 1).

Reductions in a variety of 5-HT parameters have been consistently reported in low-weight AN patients. Although no significant differences have been found in absolute plasma L-TRP levels (84–86), the plasma L-TRP/LNAA ratio is reduced in the low weight state (30,87,88) but normalizes upon short-term weight recovery (22,30). In BN, Gendal and Joyce (89) reported that the L-TRP/LNAA ratio inversely correlated with the desire to binge-eat. In addition, symptomatic bulimic relapse or worsening of symptoms has been reported following acute L-TRP depletion in BN (17–19).

TABLE 1 Monoamines and the Phenomenology of the Eating Disorders

Factor	Norepinephrine	Dopamine	Serotonin
Activity/exercise	X	X	X
Fasting effects	X	X	X
Mood regulation	X	X	X
Hormone regulation	X	X	X
Neuropeptide regulation	X	X	X
Trauma effects	X	X	X
Temperature	X		X
Anxiety	X		X
Blood pressure/pulse	X		X
Metabolic rate	X		
Feeding initiation/hunger	X		
Body image/perception		X	X
Impulsivity/aggression		X	X
Sexual behavior		X	X
Feeding maintenance/hedonic reward		X	
Novelty/sensation seeking		X	
Harm avoidance			X
Behavioral inhibition			X
Feeding termination/satiety			X
Obsessive-compulsiveness/perfectionism			X
Social hierarchy/rank			X
Gender differences			X
Seasonality/light effects			X
Circadian rhythmicity			X
Age/developmental effects			X

Other significant findings include decreased CSF L-TRP levels (90) and decreased CSF 5-HIAA levels (22,88,91) during low-weight status with normalization of these levels with short-term weight recovery (STWR, goal weight maintenance ≥3 weeks). Strikingly, Kaye and colleagues (69,92) have reported abnormally elevated CSF 5-HIAA levels following long-term weight recovery (LTWR, goal weight maintenance ≥6–12 months), and interpret these findings as indicating that AN may correspond to a primary state of excessive 5-HT tone, which is then masked by malnutrition-induced *reductions* in 5-HT activity during active illness. In other words, they propose that the pathophysiology of AN actually involves a hyperserotonergic trait and, furthermore, postulate that this trait may correspond to behavioral traits of obsessionality and inhibition. Corroborating the notion of hyperserotonergic status in AN, Kaye and colleagues have noted long-term weight-restored anorexics to display *elevated* 5-HT_{1a} receptor binding, measured by positron emission tomography (PET) (93).

In BN, reduced levels of CSF 5-HIAA are consistently reported only in the subgroup of patients displaying more frequent binge–purge episodes (23,50). Suggesting a possible link to severity of bulimic symptomatology, binge frequency has been found to correlate inversely with CSF 5-HIAA concentrations (50). In a small pilot study, Brewerton and colleagues (94) have reported no difference in CSF 5-HT levels between BN patients and controls. However, upon recovery for at least a year, BN patients have been reported to have elevated CSF 5-HIAA levels compared to healthy controls (95), much like those described earlier as being characteristic of long-term recovered anorexics. As in AN, this finding has been linked to obsessive-compulsive personality traits, perfectionism, and behavioral inhibition, associated with a hypothetical tendency toward hyperserotonergic status. However, we note, that the Kaye et al. study of recovered BN may be confounded by small weight discrepancies between their (heavier) recovered bulimics and lighter comparison controls. Such weight differentials could underlie discrepant levels of 5-HT metabolism.

Decreased prolactin (PRL) responses following *m*-CPP (96–98), L-TRP (96,97), and fenfluramine (FEN) (99–101) have been reported in AN and indicate an anatomically specific alteration in 5-HT receptor sensitivity at the level of the hypothalamus, which could conceivably also occur in other brain pathways (9). Blunting of PRL following *m*-CPP persists into short-term weight recovery, although trends toward normalization of PRL responses, after refeeding and weight gain, have been reported (97). With at least a year of recovery, neurohormonal responses to *m*-CPP normalize in restricting AN patients (92). Apparently, full normalization of PRL responsivity to serotonergic agents occurs after full weight restoration, normalization of hypothalamic-pituitary-gonadal function, and abatement of overt eating disorder symptoms (7). However, the appetite-suppressing effect of FEN is significantly diminished in recovered AN patients despite normalization of hormonal release (102).

Platelet (PLT) studies contribute to the demonstration of serotonergic dysfunction in AN. Significant increases/reductions in PLT imipramine (IMI) binding (103), but not PLT 5-HT uptake (103,104) or PLT MAO content (42), have been reported in low-weight AN patients. However, a more recent study reported decreased PLT MAO in AN (105), which was inversely correlated with impulsivity and positively correlated with persistence (which is similar to rigidity). In a related vein, Finocchiaro and colleagues (106) conducted a novel study of indole metabolism and reported altered phytohemagglutinin stimulated, light-induced [^{3}H]thymidine incorporation into the DNA of peripheral blood mononuclear leukocytes in AN patients compared to controls. The authors concluded that the white cells of AN patients show a failure in the regulation of 5-HT and melatonin metabolism in response to light.

As in AN, neurobiological indices in active BN are often consistent with reduced 5-HT tone. For example, findings in BN show a consistent pattern of PRL blunting following *m*-CPP (107–110), fenfluramine (99,101,111–113), and 5-hydroxytryptophan (5-HPT) (114), but not L-TRP (9,107). PRL responses following L-TRP are low only in the BN patients with concurrent major depression, again emphasizing the need to control for comorbidity. PRL responses following *m*-CPP are inversely correlated to baseline cortisol (CORT) (9). Self-reported binge frequency also has been shown to be inversely correlated to PRL responses following *m*-CPP (9) and fenfluramine (101,111,113) in BN patients. Given that this presumed alteration in hypothalamic postsynaptic 5-HT functioning normalizes with recovery from BN (8,95,115), these serotonergic abnormalities could be understood to be a *result* of bingeing, purging, and/or dieting rather than a *cause* of these behaviors, although other vulnerabilities of the 5-HT system may also exist and interact with these psychosomatic behaviors. There is only one serotonergic challenge study reported in BED (101), which found that PRL responses following *d*-FEN were no different in patients with BED than in controls. This lends support to the idea that purging, dieting, and weight loss (rather than bingeing per se) have greater roles in creating the serotonergic abnormalities noted above. Dieting, bingeing, and vomiting all may affect central 5-HT synthesis (13,14,22,116,117) and could conceivably result in down-regulation of postsynaptic 5-HT receptors and blunted PRL responses. In addition, these behaviors may involve activation of the HPA axis, which in turn appears to dampen 5-HT receptor sensitivity (9,107). Despite findings linking recovery from BN to normalization of blunted endocrine responses after 5-HT agonists (95,115), other findings (based on PET techniques) suggest persistent reductions in postsynaptic 5-HT_{2a} receptor activity even in fully recovered bulimics (118). Such findings associate BN with a stable reduction in 5-HT neurotransmission at some central sites—and present the possibility that such tendencies exist independently of disorder sequelae in BN patients.

In BN, platelet studies indicate reduced PLT IMI binding (119) and PLT MAO (120). PLT 5-HT uptake has been reported to be increased in one study (121) but not another (120). Steiger et al. (110,122) reported reduced PLT paroxetine binding in groups of BN patients compared to healthy controls.

Possible Trait-Linked Effects

Independently of dietary factors, personality trait variations might explain some of the variations in 5-HT status seen in eating disorder sufferers. In non-eating-disordered populations, correspondence between 5-HT function and personality trait variations has been well established. For example, impul-

sivity has been consistently linked to decreased 5-HT activity; suicide, fire setting, violence, and borderline personality disorder (BPD, for which impulsivity is pathognomonic) have all been linked to decreased 5-HT metabolism (as indicated by reduced CSF 5-HIAA) (123,124). Likewise, impulsive suicidality and aggression have been linked to low platelet 5-HT content and reduced PRL response to 5-HT agonists (123,124). On the opposite side of the same coin, findings in non eating-disordered samples have (at least inconsistently) associated anxiety or compulsivity with *increased* 5-HT tone. For example, patients with obsessive-compulsive disorder have been reported to display elevated CSF 5-HIAA (125) and increased PRL response after the 5-HT agonist fenfluramine (126). Furthermore, the partial 5-HT agonist *m*-CPP has been observed to increase obsessionality in obsessive-compulsive patients, and anxiety in patients with generalized anxiety disorder (127–129). Likewise, heightened anxiety has been associated with elevated 5-HT activity in both generalized anxiety disorder (130) and AN (131). Such findings have encouraged some theorists to propose that "impulsive" and "compulsive" traits occupy opposite poles of a continuum of 5-HT under- to overactivation (132,133). While this notion remains controversial, it is tempting to contemplate the possibility that 5-HT findings in restrictive versus bulimic ED variants may reflect variations associated with differential loadings of compulsive or impulsive traits in these ED subgroups.

In keeping with the notion outlined above, various studies report that personality trait variations account for variations of 5-HT indices in ED patients, at least when actively eating disordered. Waller and colleagues (134) observed that hostile bulimics, compared to less hostile ones (by self report), showed smaller neuroendocrine responses following buspirone (which they presumed to be a 5-HT_{1a} agonist). Likewise, Carrasco and colleagues (135) observed systematically lower platelet MAO concentrations (taken as a proxy for reduced 5-HT activity) in bulimics with impulsive or "borderline" traits. Results of several studies by Steiger and his colleagues are comparable. In one study, PRL responses after *m*-CPP were measured in bulimic women who reported, or who denied, a history of self-mutilative or suicidal impulsivity (136). (Incidentally, these two groups of women, were quite comparable on indices of binge and purge frequency and body mass). Compared to normal eaters, the self-harming bulimics were clearly blunted, as far as 5-HT function was concerned; the non-self-harming bulimics were not. In other words, an association was observed between blunting of the *m*-CPP-stimulated PRL response and self-destructiveness, comparable to that obtained in non-eating-disordered populations (137). This observation suggests that hypoactivity of the 5-HT system in BN may be more strongly linked to self-aggressive impulsivity than it is to binge–purge symptoms per se. However, in the study by Brewerton et al. (107), no such differences were found between bulimic patients with and without a history of suicidality. Another study by Steiger's

group examined platelet ^{3}H-paroxetine binding in normal women and in bulimic women, and assessed effects of "nonplanning impulsivity" (i.e., the tendency to act without considering consequences) (110). Both bulimic groups displayed reductions in density (B_{max}) of paroxetine binding sites. However, in bulimics, the extent of reduction in binding site density was inversely correlated with "nonplanning." In other words, reduced peripheral 5-HT reuptake corresponded to increased impulsivity. This effect parallels inverse relationships noted between platelet 5-HT binding and aggressive impulsivity (138) or self-mutilation (138) in personality-disordered subjects, raising the notion that in BN we could be observing a constitutional (trait-linked) susceptibility to underactivity of the 5-HT system. Furthermore, if exacerbated by effects of dieting, such susceptibilities could cause certain people to become especially impulsive and/or prone to binge eating.

Taken together, research findings from plasma, CSF, and pharmacological challenge studies suggest reduced 5-HT synthesis, uptake, and turnover, as well as altered postsynaptic 5-HT receptor sensitivity during the active phases of both AN and BN. Consequently, many reported alterations in 5-HT function appear to be state dependent, although they may have important biological roles in the perpetuation of symptoms, particularly mood dysregulation, increased anxiety, obsessionality, impulsivity, self-aggression, and perhaps the resistance to and difficulty in learning healthier coping strategies (139).

However, to avoid presenting an oversimplified, unidirectional hypothesis of 5-HT alterations in the eating disorders, it is necessary to note some findings suggesting heightened 5-HT receptor sensitivity at certain central sites in eating disorder patients with active symptoms. For example, Brewerton (9) reported enhanced temperature and migraine headache responses to *m*-CPP but not L-TRP in BN patients (regardless of the comorbid presence of AN or MD) (9,140,141). As discussed in detail elsewhere (141), the enhanced migraine-like HA responses in the BN patients may indicate enhanced 5-HT_2 receptor sensitivity in CNS vascular tissues. Enhanced 5-HT-mediated platelet aggregation, a 5-HT_2 receptor–mediated phenomenon, has also been reported in BN (142) and AN (99,112,142) and lends further support to this hypothesis. The normal cortisol responses following *m*-CPP and L-TRP in AN and BN are compatible with this view given the involvement of both 5-HT_1 (facilitative) and 5-HT_2 receptors (inhibitive) in cortisol secretion. These presumed alterations in 5-HT receptor sensitivity, whether primary or secondary, demonstrate that 5-HT receptor sensitivity can be both decreased and increased in the same subjects depending on the anatomical location of the receptor as well as the receptor subtype. We (9,143) have argued in favor of a dysregulation hypothesis of serotonin dysfunction in the eating and related disorders, proposing that there is a failure in transmitter regulation in the face of a variety of psychobiological perturbations potentially affecting

monoamine function, including dieting, fasting, purging, substance abuse, excessive exercising, medical illnesses, family stresses or losses, sociocultural pressures, traumatic events, puberty, other developmental tasks/challenges, and changes in the seasons. Certainly, evidence suggests that a model of neurotransmitter alterations in the eating disorders stated in terms of a unidirectional (high versus low activity) concept will not be adequate.

Interest in 5-HT activity in the EDs has led to quite a catalogue of studies on 5-HT system genes—controlling activity of 5-HT receptors, tryptophan hydroxylase (TPH, the rate-limiting enzyme for 5-HT synthesis), and 5-HT transporter (reuptake) mechanisms (144). Collier et al. (145) reported a statistically significant 5-HT2A-1438G/A receptor gene polymorphism in a group of restricting AN patients compared to healthy controls. This finding has been replicated in at least two other studies in AN (146,147) as well as in OCD (147), but not in BN (147). Nacmias et al. (146) reported that other serotonergic polymorphisms of the 5-HT_{2a} as well as those of the 5-HT_{2c} receptors showed no differences in AN patients compared to controls. Likewise, no differences between AN patients and controls have been reported for serotonin transporter gene–linked polymorphisms (5-HTTLPR) (148,149), tryptophan hydroxylase polymorphisms (150), and 5-HT1Dbeta and 5-HT7 gene polymorphisms (151).

For BN, there have been various association studies: Studies on 5-HT_{2c} polymorphisms in BN detect no syndrome-linked associations (144). Similarly, three of four available studies on the 5-HT_{2a} receptor gene indicate absence of association with BN (146,147,152). However, a fourth (in a heterogeneous anorexic–bulimic sample) associates the 5-HT_{2a} "G" allele with proneness to bulimic symptoms, borderline personality, and generalized impulsivity (153). Such findings imply that common genetic factors might mediate concurrence of bulimic eating patterns and traits of a borderline/impulsive type. Yet another recent study, first to examine the 5-HT transporter gene (promoter region, 5HTTLPR) in BN, indicates a short-allele variation to confer sevenfold risk of BN (154). The short (s) allele of 5HTTLPR has been linked to reduced transcription of 5-HT transporter protein, decreased 5-HT reuptake in lymphoblasts (155), and traits like suicidality (156), neuroticism, and impulsivity (157). Preliminary findings from our lab provide a second indication of relevance of the 5-HT transporter (5-HTT) gene to binge eating and impulsivity (158). Results in 48 women with binge eating syndromes showed individuals carrying the short (s) allele of 5HTTLPR (either s/s or s/l genotypes) to show more impulsivity and lower density of paroxetine-binding sites than did long (l) allele homozygotes. These results, if they hold up, would cross-validate (at a genetic level) a link between impulse control problems and hyposerotonergic status, indicating convergence among impulsive traits, low 5-HT transporter activity, and the s allele.

Evidence from Pharmacological Effects

It is well known that serotonin-specific antidepressant medications can be beneficial in controlled studies of BN patients (159) but not in low-weight AN patients (160,161). More recent data indicate a prophylactic effect of fluoxetine following weight gain in recovered AN patients (8). SSRIs don't work during the low-weight state, presumably because of central depletion of 5-HT and other monoamines with starvation. There is significantly less 5-HT centrally to be inhibited by SSRIs.

Finally, recent evidence indicates significant antibulimic responses to 5-HT_3 antagonists, such as ondansetron (162,163). Although the authors attribute this therapeutic response to the drug's ability to reduce vagal tone, the role of the 5-HT_3 receptor remains intriguing given its antianxiety effects (164). These findings open important new arenas for future research involving possible serotonergic-cholinergic mechanisms, which has been a relatively unexplored area in the eating disorders.

MAO/ISATIN

Isatin, or tribulin, is an endogenous indole associated with stress, which inhibits MAO (165). Brewerton et al. (94) reported significantly higher CSF concentrations of isatin in BN patients compared to healthy controls. There was also a trend for CSF isatin concentrations to be inversely correlated with CSF concentrations of the serotonin metabolite 5-HIAA ($n = 14$, $\rho = -0.51$, $p = 0.06$), although CSF isatin levels were not significantly correlated with CSF MHPG or HVA. The increase in isatin levels has been hypothesized to be in response to the resultant monoamine depletion secondary to the effects of the illness on monoaminergic function. As noted previously, platelet MAO has been reported to be decreased in BN (120) and in AN (105). This decrease may represent a compensatory change in response to monoamine depletion during the active state of the disorders.

RELATIONSHIP TO OTHER SYSTEMS

Neurotransmitter systems do not exist in a vacuum but are exquisitely interdependent with other brain and body systems and the environment as well. It is important to think about systems (e.g., 5-HT) and their subsystems (presynaptic, postsynaptic, receptor subtypes) in the context of larger systems (brain, environment) and interacting systems/subsystems (e.g., NE, DA, neurohormones, neuropeptides) with complex feedback and counterfeedback mechanisms at multiple anatomical levels. An extensive discussion of this

rather far-reaching topic is beyond the scope of this chapter but is discussed in more detail elsewhere (9).

CONCLUSIONS

Taken together, available findings implicate abnormalities of all monoamine neurotransmitter systems during the active phases of both AN and BN. Upon normalization of weight and neurohormonal function, most transmitter anomalies resolve or atleast improve. Some data show persistent particularities of the 5-HT system, and suggest that observed tendencies may reflect psychological traits found in both AN and BN, including obsessionality, perfectionism, high harm avoidance, and behavioral inhibition, on the one hand, and recklessness, failure to consider consequences of actions, self-destructiveness, and behavioral disinhibition, on the other. Furthermore, some evidence may be consistent with association between greater behavioral inhibition and excessive 5-HT activity (at some loci in the system), and behavioral disinhibition and reduced 5-HT neurotransmission (also at some loci in the system). The findings in question create a case for the idea that any given individuals' 5-HT functioning probably varies in function of constitutionally determined (latent or manifest) personality trait tendencies. In this light, it is intriguing to contemplate the ways in which constitutional traits associated with hypoactivity of the 5-HT system (e.g., impulsivity) may predispose to binge eating—and traits associated with elevated 5-HT tone (like compulsivity or harm avoidance) may predispose to dietary restriction.

Some evidence suggests prolonged alterations in NE metabolism, but this is most likely due to persistent low-grade dietary restraint following recovery. Preliminary data indicate a DA deficit in restricting AN patients, but this result remains to be replicated in larger samples. Recent findings also emphasize the importance of neurotransmitter precursor substrate availability to normal brain function and especially to the process of recovery from an eating disorder. Future research directions will include further exploration of neurotransmitter-related gene candidates, in vivo receptor imaging studies, and improved psychopharmacological interventions based on biological alterations characteristic of the different stages and features of these dangerous disorders.

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Psychopharmacology of Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder

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As the fundamental causes of eating disorders remain unknown, it is no surprise that development of successful treatments has not come easily. Nonetheless, much progress has been made. The current mainstays of treatment of eating disorders are psychological interventions, including cognitive therapy, behavioral therapy, family therapy, and nutritional counseling (1). Clinicians have generally looked to medication to augment the effects of psychological intervention, or as a primary intervention when such treatment is unavailable or ineffective.

The role of psychopharmacology in eating disorders has been greatly clarified in the last decade. But, as in the case of other psychiatric disorders, the limited understanding of the basic pathophysiology handicaps the ability to design psychopharmacological treatments. In the absence of a specific biological model, a range of differing perspectives has prompted attempts to identify medication treatments for anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). In general, studies of medications in AN have been disappointing. In contrast, in BN, antidepressants are clearly effective at reducing binge eating and purging behaviors. Studies of BED are

at an earlier stage but have already yielded promising findings. A consistent observation across the eating disorders is the need for double-blind, placebo-controlled studies to assess efficacy, as a medication often looks promising in case studies or open trial but fails to show superiority to placebo in a rigorously controlled trial.

This chapter will review the current data on the use of medications in the management of AN, BN, and BED with the intention of providing the clinician with information needed to make decisions about pharmacological treatment. The data will be reviewed according to what has been shown to be useful on the basis of controlled trials. Each illness—and stage of illness in the case of AN—will be considered separately and different outcome measures will be discussed when available.

ANOREXIA NERVOSA

Anorexia nervosa is characterized by a relentless pursuit of thinness and fear of becoming fat: patients starve themselves to extremes of low weight, resulting in amenorrhea and risk of death. Treatment must target multiple aspects of the disorder as patients need to gain weight, extinguish eating-disordered behaviors, and alter cognitions that foster these behaviors. Current recommendations focus on a multidisciplinary approach to treatment, including psychotherapies with cognitive–behavioral components. Inpatient treatment for patients at very low weight focuses on behavioral interventions and nutritional counseling to encourage eating and weight gain in conjunction with beginning to challenge cognitive disturbances. Nonetheless, AN has been difficult to treat and has a high relapse rate. Thus medications are under investigation both to facilitate initial treatment and to prevent relapse.

Study of the management of AN lends itself to multiple possible outcome measures. The major initial concern is weight restoration, which can be readily assessed by the amount and the rate of weight gain. In the long term, rate of relapse is an important outcome, defined as significant weight loss or reemergence of restrictive or binge–purge behaviors. Interwoven through both phases of treatment (weight gain and relapse prevention) is the complex problem of body image dissatisfaction.

Many psychopharmacological interventions have been tried, beginning with the work of Dally and Sargant on antipsychotics in the 1960s. Due to the limited understanding of the biological basis of AN, medication trials have been driven by unproven theoretical models and/or by an interest in taking advantage of medication side effects. While anecdotal reports of successful treatments have been published, only a small number of randomized controlled

trials have been conducted, and definitive psychopharmacological treatment has not been identified.

Antidepressants

Antidepressant treatment for AN is a reasonable notion given the common concomitant symptoms of anxiety and depression. Many patients with AN describe low mood, low energy, poor concentration, loss of interest, and social isolation. The ritualized behaviors around eating and the obsessive preoccupation with shape and weight can be conceptualized as on the spectrum of obsessive-compulsive disorder (OCD), a syndrome that is also responsive to antidepressant medication.

Controlled trials of several different medications to promote weight gain have been generally discouraging. Initial studies involved tricyclic antidepressants (TCAs), with the hope that the side effect of weight gain would add to the benefits of treating mood disturbance. There have been three randomized controlled trials of TCAs. In one, clomipramine was associated with a slower rate of weight gain than placebo despite increased appetite, and there were no long-term effects at 1 and 4 years (2). In a study of amitriptyline versus placebo, there was no significant difference in weight gain (3). A second study of amitriptyline, which also had a third arm in which subjects received the serotonin (5-HT) antagonist cyproheptadine, showed no major benefit of amitriptyline (4). TCAs are known to prolong the QTc interval, which is also affected by AN. These observations, coupled with concerns that TCAs in children and adolescents may be linked to sudden death (5), suggest that TCAs should be rarely used for patients with AN at low weight.

In light of their benign side effect profile and efficacy in many other disorders, selective serotonin reuptake inhibitors (SSRIs) would appear promising in the management of in AN. Initial anecdotal evidence that fluoxetine might be beneficial for weight gain and mood symptoms (6) was supported in an open trial (7). However, the single randomized placebo-controlled trial of fluoxetine did not support these results. Attia et al. (8) conducted this trial of 33 patients with AN at low weight. All patients received inpatient care in addition to either fluoxetime (60 mg/day) or placebo for 7 weeks or until they reached 90% of ideal body weight and maintained it for a week. Fluoxetine conferred no benefit on weight gain, irrespective of subtype (restricting versus binge–purge). This finding is consistent with an open trial of Strober et al. (9) who administered fluoxetine to 33 inpatients.

While the studies of medication treatment in the acute phase focused on weight gain, some studies also included measures of other dimensions of AN. Mood symptoms have been found to improve with weight gain, with no added

benefit from medication (8,34). The open trial of Strober et al. described above (9) examined severity of weight phobia and abnormal eating behaviors and found no evidence that fluoxetine treatment was of benefit. Attia and colleagues (8) assessed the effect of medication on body image dissatisfaction, a core component of AN, and noted significant improvement with weight gain in scores on Body Satisfaction Questionnaire (BSQ) in both placebo and fluoxetine groups, although not to within the normal range in either group.

Somewhat more promising results have been found in the relapse prevention phase, but there is just one randomized controlled trial. Thirty-five women with AN, restricting subtype, entered a double-blind, randomized, controlled trial after inpatient weight restoration and received either fluoxetine (10–60 mg/day) or placebo for 11 months (10). Subjects receiving medication were significantly more likely than those who received placebo to maintain near-normal weight for one year. Interpretation of data from the randomized trial is limited in that dosage of fluoxetine was not controlled for, nor was additional treatment (i.e., psychotherapy) restricted. Subjects were limited to those with restricting subtype, and there is no information on the effect of medication on parameters other than weight. In addition, a naturalistic study of Strober et al. (11) comparing relapse among patients receiving open fluoxetine treatment to relapse among a group of matched, historical controls failed to detect evidence of a benefit from fluoxetine. Nonetheless, the study of Kaye et al. (10) is virtually the only placebo-controlled examination of medication in AN that found a statistically and clinically significant impact of medication compared to placebo. Further study is needed to determine replicate and extend this finding.

In summary, there is little reason to think that antidepressants add substantially to the standard inpatient management of AN. Given the widespread benefits of antidepressant medication in other, seemingly related psychiatric disorders, the lack of impact of antidepressants is surprising. Kaye et al. (12) have shown that patients at low weight have low levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, which improve with weight gain. Low levels of 5-HIAA suggest that patients have low levels of brain serotonin, which is consistent with the finding that dieting in non-eating-disordered women reduces tryptophan levels (the amino acid that is the substrate for serotonin) and reduces serotonin production (13). Thus, it may be that antidepressants are ineffective at low weight because they have insufficient substrate (14). This is supported by the finding that tryptophan depletion has been shown to reverse the effects of SSRIs in depressed patients (13).

Notably, virtually all studies of patients at low weight have been conducted in an inpatient setting, where nonpharmacological interventions are effective in producing weight gain. At least theoretically, there is potential

for benefit from medication in an outpatient setting, where weight gain tends to be slower.

Antipsychotics

Pharmacological treatment in AN began with antipsychotics. The theoretical rationale for the use of this class of medication derives from the near-delusional quality of beliefs about shape and weight held by some patients with AN. Dally and Sargant (15) studied chlorpromazine (1600 mg/day) and found that while the rate of weight gain was enhanced compared to historical controls, there were significant negative effects including seizures and the emergence of binge–purge behavior. Furthermore, benefits were not sustained over long-term follow-up. Pimozide was studied subsequently in a randomized, controlled trial of hospitalized patients (16). The authors found a trend toward slightly higher daily weights while on pimozide, but effects on psychological symptoms were inconsistent. In a study of sulpiride among hospitalized patients receiving either medication or placebo for 3 weeks, there was no significant effect of medication on weight gain (17). Due to the known long-term side effects of the older antipsychotics and the side effects noted in some of the early studies, these medications are not generally recommended for management of AN.

With the advent of the new generation of antipsychotics, which have a lower incidence of tardive dyskinisia, extrapyramidal symptoms, and decreased likelihood of seizures, the possible usefulness of this class of medications has again been raised. Olanzapine would appear particularly promising as the prominent side effect of weight gain might be advantageous in AN. There have been several case reports of the use of olanzapine (5–10 mg/day) comprising about 10 hospitalized patients who had been refractory to other treatments (18–20). The patients described in these reports held near-delusional beliefs about their bodies, with no other psychotic symptoms. Mehler et al. (20) reported that while there was no dramatic improvement in the rate of weight gain after initiation of medication, there was a marked improvement in patient's cognitive style. One patient with a history of restricting developed binge–purge behavior while taking olanzapine (19). Olanzapine is a potentially promising intervention for AN, but its efficacy has not yet been established. In light of the research on antidepressants, where promising case reports and open studies were not born out in randomized controlled trials, further study of olanzapine and other second-generation antipsychotics is needed before definitive conclusions can be drawn. In addition, an important clinical consideration is whether patients will agree to a medication so clearly associated with weight gain.

Other Agents

A number of other medication classes have been tried, targeting primarily the weight gain phase of AN. Cyproheptadine, an antihistaminic agent that acts centrally to decrease serotonin activity, has been studied in several controlled trials after it was noted to cause weight gain in other conditions. Results have been mixed. In the first placebo-controlled trial (21), cyproheptadine did not improve weight gain. A second study found that cyproheptadine was associated with improved weight gain in a subgroup of severely ill patients (22). In a trial comparing amitriptyline, cyproheptadine, and placebo (mentioned above) (4), the authors noted no significant weight gain in the cyproheptadine group. However, they did note a difference between subtypes such that individuals with the restricting subtype showed an increased rate of weight gain with cyproheptadine whereas individuals with the binge–purge subtype showed an increased rate of weight gain with amitriptyline.

Consistent with patients' complaints about feelings of fullness and early satiety, patients with AN have been found to have slowed gastric emptying (23). Open trials of motility agents have been conducted using metoclopramide, bethanacol, cisapride, and domperidone (14). Few agents have been subjected to randomized controlled trials. Metaclopramide was found to decrease gastric emptying time (24), but a randomized controlled trial could not be completed because of the emergence of depression likely related to the CNS effects of the drug (25). Cisapride is a motility agent with mixed agonist/antagonist properties. It is an antagonist at the serotonin 5-HT_3 receptor and an agonist at the 5-HT_4 receptor. Cisapride was shown to improve gastric emptying time in a small, randomized, placebo-controlled study ($N = 12$) (26), but improvements in weight gain were not noted . In a larger study, Szmukler et al. (27) described improvement in gastrointestinal symptoms but no difference between medication and placebo groups with respect to gastric emptying or weight gain. Thus, the clinical benefits of cisapride in AN are uncertain. Furthermore, it was recently withdrawn from the market in the United States due to cardiac conduction effects, including prolonged QT interval and reports of sudden death.

Patients often describe their eating disorder symptoms as overwhelmingly strong urges to eat or to diet in a manner that bears some similarity to descriptions of drug cravings. Several studies have been conducted to examine the potential utility of opiate antagonists. Open trials of intravenous naloxone and oral naltrexone in underweight patients suggested improved weight gain (28). One placebo-controlled trial of naltrexone (200 mg daily) using a crossover design was conducted in patients with AN and BN (29). While the authors did not report results on weight gain in AN, they found that binge eating and purging rates diminished.

Zinc deficiency has notable similarities to AN. It is associated with weight loss, dysphoria, appetite and taste changes, and amenorrhea. Zinc deficiencies have been noted in low-weight AN populations (30), an unsurprising finding given the level of overall malnutrition. In contrast to most studies of AN, a number of the studies of zinc supplementation were conducted in children and adolescents. Three randomized controlled trials (30–32) and one open trial (33) of zinc supplementation (50–100 mg elemental zinc/day) have been reported. In a randomized controlled trial in children (31), there was no significant weight effect in the zinc-treated group. In adolescents, Katz et al. (30) found improvement in depression and anxiety in the adolescents who received zinc, but no effect on weight gain. In contrast, Birmingham et al. (32) found that zinc supplementation was associated with an increased rate of weight gain, even without evidence of zinc deficiency. In light of these mixed results, the utility of zinc supplementation is uncertain.

Other novel approaches to improving weight gain have included lithium, for its weight gain and mood stabilizing properties, and tetrahydrocannabinol (THC) for its appetite-enhancing effect. Lithium was associated with a small weight increase in one small, short-duration placebo-controlled trial (34). THC was compared to diazepam in a small randomized, double-blind trial using a crossover design (35). There was no benefit from THC with respect to food intake or weight gain, and THC was associated with significant side effects, including paranoia, sleep disturbance, and interpersonal sensitivity.

A major medical complication of AN is osteoporosis/osteopenia. Estrogen replacement therapy has been used to treat osteoporosis in postmenopausal women and therefore has been explored as an adjunctive treatment in AN. However, a randomized controlled trial assessing the bone densities of subjects receiving estrogen and progestin versus no medication found no significant changes in the hormone-treated group (36). Those patients who resumed menses showed improvement in bone density. These data suggest that, at present, the best documented intervention to arrest bone loss in AN is weight gain sufficient to restore regular menstruation.

BULIMIA NERVOSA

Bulimia nervosa is characterized by recurrent binge eating followed by inappropriate compensatory behaviors, such as vomiting. Because in DSM-IV, AN has diagnostic precedence over BN, patients with AN who meet criteria for BN are considered as having the binge–purge subtype of AN. Thus, most patients with BN are of normal weight. Like patients with AN,

those with BN have a disturbance of body image and unduly value their shape and weight when evaluating their self-esteem. Bulimia nervosa is more common than AN, with a prevalence of 1–5% in adolescent and young adult women (37). BN tends to be managed in the outpatient setting, making clinical trials less complicated and costly than with AN and, presumably for these reasons, more numerous. In addition, studies of medications in the management of BN have yielded more promising results, most notably with antidepressants.

Antidepressants

The study of antidepressant medications resulted from the observation that patients with BN, like those with AN, often describe depressive symptoms. Over the past 20 years, many antidepressants have been found to be more effective than placebo in reducing binge–purge episodes in normal-weight women with BN (38,39). While TCAs (40–45), monoamine oxidase inhibitors (46–48) and SSRIs (49–51) have all been shown to be effective, there are no direct comparisons to suggest superiority of one drug over another. SSRIs have come into favor due to their overall acceptable side-effect profile. Open trials of sertraline (52) and fluvoxamine (53,54) have reported good results, but only fluoxetine, at a dose of 60 mg daily, has been shown to be effective in randomized, controlled trials (49,50). Antidepressants consistently decrease eating-disordered behaviors and improve mood in patients with BN, regardless of the presence of major depressive episode (49). In addition, two randomized controlled trials have suggested efficacy of SSRIs in prevention of relapse (55,56).

While studies of antidepressants have generally been favorable, the study of bupropion must be mentioned for its significant side effects. In this trial of 55 women with BN (57), bupropion (up to 450 mg/day) was effective at reducing binge–purge behavior. The study was terminated prematurely, however, because four women experienced grand mal seizures. Because of this association, bupropion is specifically not recommended in management of BN, and the package insert indicates that bupropion is contraindicated in the treatment of patients with a current or past diagnosis of BN or AN.

The clinical significance of the difference between antidepressant medication and placebo is complicated by the broad range of effect between studies. The improvement in binge frequency reported in controlled trials ranges from 31% to 91% decrease (58,59). Remission rate (cessation of binge–purge behavior) was often not reported and when reported, ranged from 4% to 34% (58). The improvement in BN with antidepressant medication is clear, but the low remission rate suggests that there are limitations to this treatment.

Medication trials have generally focused on binge–purge behaviors as the primary outcome, but a few studies have also assessed body image dissatisfaction. Most use the BSQ or the Eating Disorders Inventory Body Dissatisfaction Scale (EDI-BD), which are self-report measures that address how patients feel about body parts or their whole body. While these measures do not address all of the dimensions of body dissatisfaction, they may serve as a crude measure of this important variable. Interestingly, some, (45,49) but not all, (60–62) studies suggest that it is possible to see change in body dissatisfaction with medication treatment alone. Thus, the impact of antidepressants on body dissatisfaction remains unclear.

Overall, the use of antidepressant medications in the management of BN is well supported but there remain some gaps in the knowledge base. The current data are mostly derived from short-term studies that range from 6 to 8 weeks duration. Most trials have been conducted with normal weight women who use self-induced vomiting to purge. Thus, it is unknown if these results can be generalized to apply to other patients, such as men, adolescents, and those who compensate for binge eating through other behaviors, e.g., excessive exercise. Areas for further study include the optimal duration of treatment and the long-term efficacy of antidepressants.

Anticonvulsants

An early clinical model conceptualized BN as a seizure disorder, with binge–purge episodes thought to represent paroxysmal events. Small trials with the anticonvulsants phenytoin (63) and carbamazepine (64) did not suggest a robust response to medication. A recent case report (65) of a woman with epilepsy and BN who was treated with topiramate and showed improvement in binge–purge behaviors and in attitude about shape and weight raised the possibility that topiramate may have benefit in the management of BN. Results from a randomized, double-blind, placebo-controlled trial of topiramate (25–400 mg/day) have been presented, showing reduction in binge and purge duration and frequency (66). Although preliminary, these results are encouraging.

Other Agents

Some agents have been studied based on biological models, as opposed to clinical models, of BN. These models have focused mainly on the potential role of serotonin, which has been shown to impact various aspects of feeding. As increased serotonergic function tends to decrease food intake, it was hypothesized that medications that increase serotonin would decrease binge eating behavior (67). L-Tryptophan, the amino acid precursor of serotonin, was examined in a randomized, placebo-controlled trial ($N = 13$), but no

drug–placebo difference was detected (68). Fenfluramine, a serotonergic agent that both blocks reuptake and increases release, was studied with mixed results. In a randomized, placebo-controlled trial using a crossover design, fenfluramine was shown to decrease binge–purge frequency (69). However, in two subsequent placebo-controlled trials, the medication showed no benefit (70,71). Fenfluramine was withdrawn from the market in 1997 due to an association with cardiac valve abnormalities.

Another model for treatment of BN focuses on the feeding behaviors of patients, specifically their difficulty in identifying satiety. This model postulates that binge eating and purging might lead to desensitization of the vagal nerve afferents, which have a key role in signaling satiety. Subjects with BN were found to have an increased somatosensory pain threshold, which may indirectly reflect altered vagal nerve activity (72). Based on these observations, Faris and colleagues (73) conducted a 4-week randomized, placebo-controlled trial in BN and found that ondansetron (24 mg/day), a medication that blocks 5-HT_3 receptors involved in visceral stimulation of the vagal nerve, was associated with a significant decrease in binge–purge behaviors.

One clinical model of BN focused on the similarities between binge–purge behaviors and addictive behaviors, drawing on the evidence that endogenous opiates may be involved in appetite changes. In a small, open trial of naltrexone, an opiate antagonist, 7 of 10 patients with BN improved with complete or partial remission (74). One randomized, controlled trial including AN and BN patients found a decrease in binge–purge behaviors with naltrexone (100–200 mg/day) (29), whereas a randomized, controlled trial using a lower dose (50 mg/day) showed no benefit (75).

Lithium has also been studied. Hsu et al. (60) conducted a randomized, placebo-controlled, 8-week trial of lithium (mean lithium level = 0.62) in patients with BN. Both placebo and medication groups improved, and there was no significant difference between the groups.

Combination Treatment

While the above data clearly support the efficacy of antidepressants in BN, controlled trials have also shown the efficacy of psychotherapy alone (see Chapters 17, 19, and 20). Seven randomized controlled trials have, in different ways, compared treatments in an attempt to assess the benefits of psychotherapy versus pharmacotherapy versus a combination of the two. Overall, the studies suggest that cognitive–behavioral therapy (CBT) alone is probably more effective in reducing binge eating and purging behaviors, but that the addition of medication provides some additional benefit.

The first study, conducted by Mitchell and colleagues (62), randomized subjects to one of four treatment arms for 10 weeks: imipramine alone,

placebo alone, intensive group therapy alone, or imipramine with intensive group therapy. The psychotherapy intervention provided was an unusually intensive group therapy, which included joint meals with the therapist on five occasions during the first week of treatment. Outcome measures assessed eating behaviors, affective symptoms, and attitudinal measures. The reduction in eating-disordered behaviors in response to intensive group therapy was impressive, and no added benefit from imipramine could be detected. On the other hand, combination treatment significantly improved affective symptoms more than either treatment alone. In a follow-up study, Keel et al. (76) found that 10 years posttreatment, all three active treatment groups showed significant improvement in social functioning as compared with placebo. There were no significant differences on measures of depression, body image, or eating disorder behavior.

A study of the combination of individual CBT with desipramine reached broadly similar conclusions. Agras and colleagues (77) randomly assigned patients to one of five treatment arms: desipramine for 16 weeks, desipramine for 24 weeks, CBT only for 16 weeks, CBT and desipramine for 16 weeks, and CBT for 16 weeks and desipramine for 24 weeks. Response to CBT was clearly superior to that for desipramine alone. There were some indications that patients receiving CBT combined with 24 weeks of desipramine had the best outcome, but these results were not statistically robust.

The finding of Mitchell et al. (62) that medication may add to the benefits of psychological treatment was also noted in a study by our own group (78). Patients were randomly assigned to one of five treatment arms for 16 weeks: medication alone, CBT and medication, CBT and placebo, supportive psychotherapy (SPT) and medication, SPT and placebo. The design allowed for a change in medication from the TCA desipramine to the SSRI fluoxetine under double-blind conditions. Patients assigned to receive active medication were given desipramine, but if response was not satisfactory or if significant side effects developed, patients were switched to fluoxetine. It was clear that CBT was more effective than SPT in reducing disturbed eating behaviors. In addition, active medication augmented the improvement in both behavioral and attitudinal measures associated with psychological treatment.

Goldbloom et al. (79) conducted a study of combination treatment with three treatment arms: fluoxetine alone, CBT alone, and fluoxetine and CBT combined. This study was limited by a significant dropout rate (43%), which contributed to an inability to detect statistically significant differences between treatments on most measures. There was a significant difference in subjective reports of binge episodes, which were most improved with combination treatment.

In another study of fluoxetine, medication or placebo was combined with 8 weeks of nutritional counseling (80). The nutritional intervention had

components similar to CBT, but with a psychoeducational focus replacing cognitive restructuring. While the authors report on this as an assessment of combined treatment, the psychotherapy intervention is sufficiently different from CBT that it is difficult to compare findings. Nonetheless, there was a rapid and significant improvement in both groups in binge eating and purging. There were few differences between fluoxetine and placebo groups, but some indications that fluoxetine augmented improvement in some psychological spheres, such as concerns with shape and weight. Bacaltchuk et al. (81) performed a meta-analysis of the studies of psychotherapy plus pharmacotherapy in BN. While their conclusions are subject to the usual limitations of meta-analyses, in the short term remission was more likely with combination of medication and psychotherapy than with either treatment alone.

Conclusions drawn from the above studies must be considered with caution. One major problem is that the largest studies were conducted before the widespread use of SSRIs, making it difficult to extrapolate from these data to current clinical practice. The limited information available suggests that CBT is likely to be more effective and more acceptable to patients than is a course of antidepressant medication. However, the data are reasonably consistent in indicating that the addition of an antidepressant to psychotherapy modestly augments improvement in psychological symptoms and, perhaps, in disturbance of eating behavior. The effectiveness of medication in reducing relapse is uncertain.

BINGE EATING DISORDER

The more recently recognized syndrome of binge eating disorder is characterized by episodes of binge eating without compensatory behaviors. Although not required for the diagnosis, BED is usually associated with obesity. As is the case with AN and BN, several clinical features of BED can be appropriately viewed as outcome measures. The ideal intervention would reduce the binge eating behavior, improve psychological disturbances such as depression and overconcern with body image, and promote weight loss. To date, most treatment studies have focused on the behavioral and psychological components, leaving weight loss as a secondary goal. As this disorder is relatively newly codified in the DSM-IV, only a small number of controlled medication studies have been published.

Antidepressants

Based on the efficacy of antidepressants in the management of BN and the similarities between these two disorders, most research has focused on antidepressants. An early placebo-controlled trial of "nonpurging BN" found

that desipramine was effective in the short-term reduction of binge eating (82). However, symptoms reemerged 4 weeks after medication discontinuation. A randomized, controlled trial has also shown imipramine to be effective (83). More recently, two studies have found benefits from SSRIs. In one randomized controlled trial of fluvoxamine (50–300 mg/day) (84) and one randomized controlled trial of sertraline (50–200 mg/day) (85), the authors reported a significant reduction in binge eating behavior as well as a decrease in BMI in the medication groups as compared with placebo. As with most of the medication trials in eating disorders, these short-term results do not provide information as to sustained benefit of medications.

Other Agents

As with AN and BN, a number of other classes of medication have received some attention as being of possible use in the management of BED. Topiramate is the latest to show promise. In one open label-study of 13 patients with BED, topiramate was associated with weight loss (86). Appolinario et al. (87) reported a case study of a patient who responded to topiramate after other treatments had been unsuccessful. McElroy et al. (88) conducted a placebo-controlled, double-blind trial of topiramate in 61 patients with BED. Topiramate-treated subjects showed significantly greater reductions in binge frequency, binge day frequency, and other measures of symptom severity, as well as significant reduction in BMI.

Trials of dexfenfluramine yielded some promising results. Dexfenfluramine was associated with a decrease in binge eating, and when used in combination with phentermine, with weight loss, as well (89,90). However, dexfenfluramine has since been withdrawn from the market due to its association with cardiac valve abnormalities. An open trial of sibutramine, an appetite suppressant approved for the management of obesity, suggested that use of this agent was associated with improvement in both binge eating and weight loss (91). A controlled trial has been conducted, but results are not yet available. The opiate antagonist naltrexone was studied in a randomized placebo-controlled trial which also included an imipramine arm (89). While both medication groups showed improvement, there was no difference from placebo.

Combination Treatment

Antidepressant medications appear to provide short-term benefit in the management of BED, but the benefits do not appear to be sustained beyond the discontinuation of the medication. Several studies have examined the benefits of combined treatment, but, at present, the data are insufficient to support clear conclusions (83,92–95).

CONCLUSIONS AND TREATMENT RECOMMENDATIONS

Anorexia Nervosa

Psychopharmacological interventions have not been shown to provide significant benefit to underweight patients with AN. The mainstays of treatment are nonpharmacological, and focus on nutritional rehabilitation and relapse prevention. There is preliminary evidence that fluoxetine may be of benefit for relapse prevention after patients have regained to a normal or near-normal weight.

Bulimia Nervosa

The data on the use of antidepressants in the treatment of BN are convincing in indicating that that fluoxetine is safe and beneficial. While it is likely that other SSRIs would be effective, only fluoxetine has been examined in placebo-controlled trials, and should be used in a dose of 60 mg/day. Most patients can be rapidly titrated to this dose over the course of a week. There are no available data to guide treatment for relapse prevention or to suggest recommended length of treatment. Bupropion is not recommended in the management of BN because of the risk of seizure. There are consistent indications that medications modestly enhance the benefits of psychological treatment.

Binge Eating Disorder

While emerging data suggest that SSRIs and, perhaps, antiobesity agents may provide some benefits, at present there is insufficient information to make firm treatment recommendations regarding the use of medication for BED.

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REVIEW

A Multidimensional Meta-Analysis of Pharmacotherapy for Bulimia Nervosa: Summarizing the Range of Outcomes in Controlled Clinical Trials

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The empirical literature on pharmacotherapy for bulimia nervosa reveals mixed results. We examined the results of controlled clinical trials of pharmacotherapies for bulimia published from 1980 to 1999. To do this, we employed a multidimensional meta-analysis, a method for aggregating a range of clinically meaningful indicators of outcome (including but not limited to effect-size estimates) across studies. We found that pharmacotherapy for bulimia yields a moderate initial effect. However, only a small minority of patients recover, and the average patient continues to meet full DSM-IV criteria for the disorder. Combined pharmacotherapy and short-term psychotherapy appears to produce better results, although most patients continue to show symptoms at termination, and few data are available on sustained recovery over time. In accordance with recent calls in the medical literature for standardization of reporting practices in clinical trials, we suggest that investigators and meta-analysts report a range of indices that bear on efficacy and generalizability to clinical practice. These include exclusion rates and reasons for exclusion, percentage recovered, percentage improved, percentage remaining improved or recovered at follow-up, and percentage seeking additional treatment at follow-up, as well as outcome data for both completer and intent-to-treat samples. (HARVARD REV PSYCHIATRY 2002;10:193–211.)

Antidepressants are a widely used component of many treatments for eating disorders. Numerous reviews of both uncontrolled and double-blind placebo-controlled studies[1–6] have concluded that such agents are superior to placebo in the treatment of bulimia nervosa. Researchers[1,7,8] have found antidepressants to be useful in reducing bingeing, purging, and depression in patients with bulimia, who often have comorbid depression as well. In a review of the longer-term outcomes of medication for bulimia nervosa, Agras[9] reported that the use of an antidepressant resulted in the recovery of an average of 25% of patients entering treatment, although over time about one-third of these patients relapsed, leading to a sustained recovery rate of about 15%. Despite evidence of efficacy, residual symptoms tend to be the norm even with appropriate pharmacotherapy: the majority of bulimic patients continue to binge and purge at termination.[6,7,10,11] Researchers[1] have also reported substantial dropout rates for subjects taking antidepressants.

Many reviews of pharmacotherapy for bulimia nervosa (see, for example, references 6, 7, 10, and 12) have concluded that medication alone is an imperfect treatment option. A

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recent meta-analysis of psychosocial and pharmacological treatments for bulimia nervosa[13] found that a combination of cognitive-behavioral therapy and medication was superior to such therapy alone for bingeing, but not purging, and was superior to medication alone for both bingeing and purging. The American Psychiatric Association's guidelines for eating disorders[14] recommend that medication not constitute the entire treatment for bulimia nervosa. Rather, medication should augment psychotherapy, particularly if the patient suffers from comorbid depression or anxiety.[7,14] Pharmacotherapy should last at least 6 months[9,15] and be flexible, since patients who do not respond to one drug may respond to dosage adjustments, the addition of a new drug, or a switch to a new medication.[7,9,14,15]

Reviews of the data thus far on the indications for and outcomes of pharmacotherapy either have been qualitative or have used meta-analysis to quantify the size of the effect of medication on bulimic symptoms. Both of these methods provide important viewpoints on the available data. Recently, we have developed a method for providing a somewhat more comprehensive meta-analytic portrait of the efficacy and generalizability of psychopharmacological and psychotherapeutic interventions tested in controlled clinical trials.[16] Here we apply this method to pharmacological treatments for bulimia nervosa, focusing on variables that bear on clinical utility and external validity and that have not previously been subjected to meta-analytic aggregation. We report the results of a multidimensional meta-analysis, which provides a variety of outcome-related statistics important in assessing the strengths and limitations of treatments for psychiatric disorders.

MEASURING EFFICACY: A MULTIDIMENSIONAL PORTRAIT

A number of outcome variables are important in drawing accurate and clinically useful inferences from data from controlled clinical trials. Measures of statistical significance provide a useful rough index of efficacy but can be misleading because of their dependence on sample size.[17,18] In outcomes research, the most common indicators of efficacy used for meta-analytic aggregation are measures of effect size. The most meaningful effect size estimate is typically some variant of Cohen's *d*,[19] which describes the difference in outcome between two groups in standard-deviation units (e.g., by dividing the difference between the posttreatment means of an experimental and a control condition by the pooled standard deviation).

Although effect size provides a crucial index of the effect an average patient can expect to achieve, it does not yield information on response variability, notably the percentage of patients who recover or experience clinically significant improvement. No single index of percentage of patients who recover or improve may be appropriate across disorders, and a more nuanced portrait of efficacy may require presentation of multiple measures. For some disorders, such as bulimia, absolute absence of symptoms is a very useful indicator,[20] because patients either do or do not stop bingeing and purging, and controlled trials of psychotherapy[16] show that roughly 40% of patients who enter controlled clinical trials are abstinent from bingeing and purging at the end of treatment; long-term follow-up data are scarce. Improvement short of recovery—for example, reduction of bingeing from ten to three times per week—may still be useful to report if the disorder is difficult to eradicate.

Determining thresholds for "improvement" has turned out to be quite challenging, as can be seen by the extensive literature on clinical significance (see, for example, references 20–22). One common solution is to identify the percentage of patients whose scores after treatment fall some number of standard deviation units below the pretreatment mean or published means for clinical samples, or some number of units away from their own pretreatment score, adjusted for standard error of measurement.[21,23] In studies of biological and psychotherapeutic treatments for bulimia and other disorders, researchers often use 50% reduction in symptoms as a rough proxy for improvement.

In addition to effect size, then, two useful indices of clinically meaningful change are percentage of patients improved and percentage of patients recovered, which can be employed either alone or together (i.e., percentage improved *or* recovered). In calculating these figures, however, one can come to very different conclusions depending on the denominator chosen (i.e., percentage improved out of what?). The most liberal estimate of percentage change uses the number of completers in the denominator and hence reflects the percentage of patients likely to improve or recover of those who complete a particular treatment. A more conservative estimate employs the number of patients randomized or the number who actually began treatment in the denominator; this estimate reflects the percentage of patients likely to improve or recover of those who agree to or begin the treatment. Neither estimate is more definitive than the other. Knowing that a treatment is highly efficacious for the subset of patients who find it useful and tolerable (and thus do not drop out) can be helpful even if the subset is relatively small, presuming the subset can be identified by a set of markers. Thus, researchers should routinely report both intent-to-treat and completer analyses.[24]

Because the intent-to-treat/completer distinction and the distinction between recovery and clinically significant improvement are both important, investigators and meta-analysts should report all four statistics created by the combination of the two (i.e., percentage recovered of the intent-

to-treat sample, percentage recovered of completers, percentage improved of the intent-to-treat sample, and percentage improved of completers). If the dropout rate is high, or if a large number of patients improve but only a small number recover with a given treatment, these four statistics can produce very different—and clinically important—outcome measures.

Another frequently overlooked measure of efficacy is the mean severity of symptoms at termination or follow-up. A treatment for bulimia might appear efficacious enough to recommend it as the treatment of choice if it produces a strong effect size and brings improvement in the majority of patients, but this conclusion may not be warranted if the average patient continues to suffer substantial, albeit substantially diminished, bulimic symptoms. Such a finding might suggest incomplete treatment and might predict relapse.

Another variable of particular importance in evaluating the usefulness of a treatment is sustained efficacy over time. A treatment that produces an initial response may or may not be an efficacious treatment for a disorder such as bulimia that tends to be longstanding and recurrent. Researchers thus need to distinguish clearly, as in other areas of medicine, between initial response and sustained efficacy (improvement or recovery) over clinically meaningful follow-up intervals, such as 1–5 years. Data on the natural course of bulimia nervosa[25] suggest that close to 100% of patients with this disorder obtain partial recovery, and approximately 75% obtain full recovery, at some point during a median of 90 months of follow-up. However, the risk of suffering additional bulimic episodes is considerable: a substantial minority of these patients relapse during the first 4 years following presentation for treatment.[25,26]

At follow-up intervals of 1 year or greater, another clinically important index of efficacy is the percentage of patients who seek additional treatment. Although percentage seeking further treatment is not an unambiguous index[24] (e.g., patients may seek further treatment because they found the treatment they received to be useful), patients who feel satisfied with their progress are presumably unlikely to seek further treatment unless they have other (comorbid) conditions that were inadequately addressed.

The variables thus far described all bear on the efficacy of a treatment in controlled clinical trials, but they say little about the external validity of the findings. One final variable essential for estimating the generalizability of findings in controlled trials pertains to the process by which patients are screened. Studies that exclude a high proportion of subjects upon screening, or that impose stringent exclusion criteria before patients are even referred for potential participation, may or may not be generalizable to patients in the community. For example, approximately 25–50% of patients with bulimia have comorbid borderline personality disorder.[26,27] Recent research from our own laboratory suggests that patients with borderline personality disorder, substantial borderline features, or symptoms (such as substance abuse or history of suicidality) of Axis I conditions that can serve as a proxy for this disorder tend to fare poorly in psychotherapy just as they often do with pharmacotherapy. Thus, excluding patients for comorbid problems such as substance abuse or suicidality (a practice common in both psychopharmacological and psychotherapeutic studies of bulimia) may have unforeseen implications for generalizability.

MULTIDIMENSIONAL META-ANALYSIS

Method

Selection of studies. To maximize the likelihood of obtaining all relevant published research reports, we employed a three-step search process. First, we identified a sample of studies on pharmacological treatments for bulimia nervosa, using a manual search of 19 high-quality, high-impact journals that routinely publish efficacy research, including research on bulimia (e.g., *American Journal of Psychiatry, Archives of General Psychiatry*). Next, we conducted an exhaustive computer search of *PsycInfo* and *Medline,* using the key word "bulim*." Finally, we manually reviewed prior meta-analyses and reviews for studies not obtained using the first two procedures. We limited the results to research published in English from 1980 to 1999. Limiting inclusion to published studies (and omitting unpublished "file-drawer" studies; see references 17 and 18) means that the findings can be generalized only to the published research literature.

Several additional inclusion criteria were established. Studies had to test the efficacy of a specific pharmacological agent against a control condition, an alternative pharmacological agent, psychotherapy, or some combination of these. We included both initial publications and follow-up studies, provided that the follow-up interval was 12 months or longer (an interval we chose because of its clinical meaningfulness for disorders that show high rates of recurrence within 4 years). We required the use of valid measures of outcome for the primary symptom, thus eliminating studies that neglected to report any direct measure of bulimic symptoms (e.g., Rossiter et al.[28] and Ong et al.[29]). The investigations had to be experimental in design (including randomized patient assignment, standardized treatments, and blind outcome assessment); hence, those on the naturalistic end of the continuum (for example, Hsu[30]) were excluded. We excluded outcome studies assessing maintenance trials, due to problems of comparability of data, although we summarize the findings of these studies in the results. We also excluded studies that involved reanalysis of data from earlier investigations already included here, those that were limited to specific subtypes of patients (e.g., those with nonpurging bulimia) who

might differ substantially from the general population of patients with the disorder, and those that included fewer than ten patients in each group.* All decisions of this sort were made a priori, before we examined any individual studies.

Twenty-one studies met inclusion criteria. Of these, 16 involved a pharmacological treatment condition, while nine (treated separately in our analyses) involved a combined pharmacotherapy/psychotherapy condition. (Some studies had both, so the numbers here do not total 21.) Three additional studies had a crossover design; they are reported separately here because of lack of comparability of data. Thirty-eight studies were excluded before we examined the data because they did not meet inclusion criteria (see Appendix for details).

Procedure. Variables assessed included number of participants, percentage of patients meeting initial criteria who passed subsequent screening and were accepted into the study, percentage of patients who completed treatment, percentage of patients who dropped out because of side effects, percentage of patients who recovered with treatment, percentage of patients who improved or recovered with treatment, effect size, and mean posttreatment symptoms (e.g., mean number of weekly binges and purges following treatment).

Tables 1 and 2 list each study, its active and control conditions, and the data we extracted and analyzed. Decisions about how to code or define variables reflected our consistent efforts to make methodological decisions prior to examining the data where possible and to give the treatments under consideration the benefit of the doubt (for example, when values or sample sizes for the same analysis differed between the text and the tables of an article) to prevent intrusion or appearance of bias.

With respect to specific variables that may require clarification, "number of subjects" refers to the number of persons who actually began treatment (i.e., the number who were randomized to any given treatment condition minus those who never attended the first treatment session). "Percent included" refers to the percentage of patients who passed the screening process. Screening typically occurred after a patient was referred or responded to advertisements for the disorder under investigation and often after a preliminary telephone screening. Researchers frequently did not indicate how many individuals responded to the initial request for subjects, passed or failed the telephone screening, or failed a final screening. Since adequate data on the initial response rate were often not available, we report here only the number of patients who passed the final screening (which usually included a semistructured interview), to provide the most generous estimate of treatment effects. "Percent completed" refers to the percentage of participants who completed the treatments.

To measure effect size, we used Cohen's *d,*[19] calculated using this formula:

$$\frac{\text{mean of treatment group} - \text{mean of control group}}{\text{pooled posttest standard deviations}}$$

The denominator places the average effect of treatment relative to control in the context of the variability of outcome in the sample at the end of treatment, thus allowing an estimate of treatment-induced change relative to random fluctuations in symptom change over time. Experimental conditions were considered controls if the authors explicitly referred to them as such. Because many studies did not include either a control group or the descriptive statistics necessary to calculate between-treatment effect sizes, we also calculated within-treatment effects using this equation:

$$\frac{\text{pretest mean} - \text{posttest mean}}{\text{pretest standard deviation}}$$

Although widely reported, this statistic is not very meaningful: actual treatment effects are confounded by placebo effects and the effects of several other factors (e.g., the passage of time, and the fact that people tend to seek treatment when their distress is very acute), so one cannot draw causal inferences. For analyses of effect size as well as posttreatment and follow-up mean symptoms, we used the measures most commonly included across studies: patients' self-reported frequency of binges and purges per week and scores on the Eating Attitudes Test (EAT).

With regard to proportion of patients who recovered or improved, "percent recovered" refers to the percentage of subjects who were no longer bingeing and/or purging for whatever time interval the investigators used to assess outcome (usually 1 week). Definitions of improvement varied substantially from study to study. (A table listing criteria for improvement in each study is available from the authors.) Thus, in recording percent improved, we used whatever definition the researchers reported, but we added a moderator variable that coded the stringency of improvement criteria. The most common definition of improvement was 50% reduction in symptoms (usually either binge or purge episodes). As described above, we provide data on percentage of

*We decided for two reasons to exclude studies with fewer than ten subjects in each experimental condition. First, we had methodological concerns about studies that build in too little power to detect effects. Second, we were concerned with the problem of maintaining blindness in investigations with few subjects. Recent studies[31,32] have demonstrated the complexity of maintaining truly double-blind conditions in pharmacological trials and the impact of such difficulties on treatment outcome. Nonetheless, when we reviewed the studies with fewer than ten patients in each group (listed in the Appendix), we found results similar to those reported in the studies included here.

TABLE 1. Studies Included in the Meta-Analysis and Summary of Descriptive Statistics

Study	Patients n	Patients % Included	Patients % Completed of entered	Treatment modalities	Duration (wk)	Mean binges/wk (SD) Pre-treatment	Mean binges/wk (SD) Post-treatment	Mean purges/wk (SD) Pre-treatment	Mean purges/wk (SD) Post-treatment
Primary studies									
Agras et al.[46]	22	—	1. 100	1. Imipramine, 300 mg	16	1. 11.6 (6.4)	1. 3.2 (2.5)	1. 10.7 (5.9)	1. 3.0 (4.1)
			2. 83.3	2. Placebo		2. 13.0 (8.4)	2. 7.4 (7.2)	2. 12.6 (7.2)	2. 8.2 (8.3)
Agras et al.[47]	71	71.0	1. 91.7	1. Desipramine, mean 168 mg	16	1. 5.5 (4.6)	1. 3.5 (6.1)	1. 9.7 (9.4)	1. 4.7 (8.6)
			2. 75.0	2. Desipramine, mean 168 mg	24	2. 5.9 (5.1)	2. 2.7 (2.8)	2. 6.3 (4.9)	2. 2.9 (3.0)
			3. 83.3	3. CBT + desipramine, mean 168 mg	16	3. 7.5 (3.4)	3. 2.4 (3.1)	3. 8.3 (4.3)	3. 2.6 (3.2)
			4. 75.0	4. CBT + desipramine, mean 168 mg	24	4. 9.3 (5.9)	4. 2.3 (4.7)	4. 11.7 (5.9)	4. 1.7 (4.7)
			5. 95.6	5. CBT	17	5. 8.7 (7.2)	5. 2.8 (5.9)	5. 10.1 (7.7)	5. 2.7 (5.9)
Beumont et al.[48]	67	—	1. 67.6	1. Fluoxetine, 60 mg, + behavioral therapy	8	1. 10.7 (10.5)	1. 1.6 (3.2)	1. 8.8 (7.4)	1. 1.2 (3.0)
			2. 78.8	2. Placebo + nutritional counseling		2. 6.2 (6.0) ("bulimic episodes")	2. 1.2 (2.0) ("bulimic episodes")	2. 7.3 (6.5)	2. 2.3 (3.3)
Fahy et al.[49]	43	61.4	1. 100	1. D-fenfluramine, 45 mg, + CBT	8	1. 6.6 (1.3)	1. 3.1 (1.2)	1. 6.2 (1.6)	1. 2.9 (1.3)
			2. 82.6	2. Placebo + CBT		2. 5.1 (0.8)	2. 2.7 (0.8)	2. 7.8 (1.6)	2. 4.6 (1.4)
Fichter et al.[50]	40	—	1. 100	1. Fluoxetine, 60 mg, + behavioral therapy	5	1. 5.6 (9.1)	1. 3.0 (4.8)	—	—
			2. 100	2. Placebo + behavioral therapy		2. 8.9 (8.0)	2. 6.6 (6.9)		
Fluoxetine Bulimia Nervosa Collaborative Study Group[51]	387	87.6	1. 76.7 2. 70.0 3. 63.0	1. Fluoxetine, 20 mg 2. Fluoxetine, 60 mg 3. Placebo	7	—	—	—	—
Goldbloom (27.2) et al.[52]	76	13.0	1. 52.2	1. Fluoxetine, 60 mg	16	1. 21.0 (12.2)	1. 10.0 (15.9)	1. 24.6 (20.4)	1. 17.3
			2. 58.3	2. CBT		2. 33.6 (29.5)	2. 7.4 (16.6)	2. 41.8 (34.4)	2. 9.0 (16.8)
			3. 41.4	3. Fluoxetine + CBT		3. 29.6 (16.5)	3. 1.8 (3.3)	3. 30.9 (29.7)	3. 3.3 (4.5)
Goldstein et al.[53]	398	82.4	1. 59.5 2. 48.0	1. Fluoxetine, 60 mg 2. Placebo	16	—	—	—	—

TABLE 1. Studies Included in the Meta-Analysis and Summary of Descriptive Statistics (*cont'd.*)

Study	Patients n	Patients % Included	Patients % Completed of entered	Treatment modalities	Duration (wk)	Mean binges/wk (SD) Pre-treatment	Mean binges/wk (SD) Post-treatment	Mean purges/wk (SD) Pre-treatment	Mean purges/wk (SD) Post-treatment
Horne et al.[54]	81	—	1. 67.3	1. Bupropion, 450 mg maximum	8	1. 12.1 (—)	1. 3.6 (—)	—	—
			2. 46.2	2. Placebo		2. 5.8 (—)	2. 5.7 (—)		
Hsu et al.[55]	91	—	1. 90.0	1. Lithium, 0.62 mEq/L/d, + psychosocial therapy	8	1. 7.5 (5.8)	1. 4.6 (4.0)	1. 7.7 (6.9)	1. 3.8 (4.4)
			2. 74.2	2. Placebo + psychosocial therapy		2. 8.1 (6.7)	2. 2.9 (3.6)	2. 10.3 (19.6)	2. 3.9 (4.2)
			3. 70.6	3. Lithium, 0.62 mEq/L/d, + psychosocial therapy*		3. 6.7 (5.8)	3. 4.0 (5.1)	3. 8.6 (8.2)	3. 4.1 (5.4)
			4. 53.9	4. Placebo + psychosocial therapy*		4. 14.6 (22.6)	4. 6.0 (8.3)	4. 13.6 (23.4)	4. 6.1 (8.4)
Hughes et al.[56]	22	—	1. 70.0	1. Desipramine, 200 mg	6	—	—	—	—
			2. 100	2. Placebo					
Kanerva et al.[57]	50	—	1. 92.0	1. Fluoxetine, 60 mg	8	1. 9.2 (—)	1. 5.3 (—)	—	—
			2. 92.0	2. Placebo		2. 10.5 (—)	2. 5.7 (—)		
Kennedy et al.[58]	36	32.7	1. 78.9	1. Brofaromine, 175 mg	7	1. 9.1 (5.7)	1. 3.5 (3.0)	1. 10.2 (12.9)	1. 2.6 (3.0)
			2. 76.5	2. Placebo		2. 8.8 (3.7)	2. 4.4 (3.9)	2. 7.5 (6.5)	2. 5.7 (6.3)
Mitchell & Groat[59]	32	—	1. 68.8	1. Amitriptyline, 150 mg, + psychosocial therapy	8	—	1. 3.5 (—)	—	—
			2. 93.8	2. Placebo + psychosocial therapy			2. 4.0 (—)		
Mitchell et al.[60]	171	67.3	1. 57.4	1. Imipramine, 200 mg	10	1. 7.3 (—)	1. 3.7 (—)	1. 8.6 (—)	1. 4.7 (—)
			2. 75.0	2. Imipramine, 300 mg, + group therapy		2. 8.4 (—)	2. 0.7 (—)	2. 9.6 (—)	2. 1.0 (—)
			3. 85.3	3. Placebo + group therapy		3. 9.2 (—)	3. 1.0 (—)	3. 13.2 (—)	3. 1.3 (—)
			4. 83.9	4. Placebo		4. 8.0 (—)	4. 7.8 (—)	4. 10.0 (—)	4. 9.9 (—)
Pope et al.[61]	22	31.4	1. 81.8	1. Imipramine, 200 mg	6	1. 10.3 (7.6)	1. 2.8 (—)	—	—
			2. 91.0	2. Placebo		2. 8.3 (6.0)	2. 8.1 (—)		
Pope et al.[62]	46	—	1. 87.0	1. Trazodone, 400 mg	6	—	—	—	—
			2. 95.7	2. Placebo					
Walsh et al.[63]	50	24.5	1. 78.3	1. Phenelzine, 60 or 90 mg/wk	8	1. 11.9 (6.4)	1. 5.4 (7.1)	—	—
			2. 77.8	2. Placebo		2. 9.2 (5.3)	2. 8.4 (5.5)		
Walsh et al.[36]	78	36.0	1. 77.5	1. Desipramine, 200 mg	6	1. 8.1 (4.6)	1. 4.3 (3.9)	1. 10.8 (12.7)	1. 7.8 (14.4)
			2. 84.2	2. Placebo		2. 8.3 (5.4)	2. 8.6 (7.2)	2. 13.0 (16.7)	2. 13.3 (17.5)
Walsh et al.[64]	38	30.7	1. 50.0	1. Phenelzine, 60 mg	8	1. 9.9 (5.8)	1. 3.4 (5.1)	—	—
			2. 72.2	2. Placebo		2. 9.7 (5.8)	2. 9.1 (6.5)		

Walsh et al.[65]	120	57.4	1. 65.2 2. 72.7 3. 57.1 4. 64.0 5. 72.7	1. CBT + desipramine 2. SPT + desipramine 3. Desipramine, 200–300 mg, or fluoxetine, 60 mg† 4. CBT + placebo 5. SPT + placebo	16	1. 7.3 (4.8) 2. 7.9 (5.6) 3. 8.3 (7.5) 4. 7.2 (4.0) 5. 6.2 (3.6)	1. 1.0 (1.6) 2. 3.6 (3.1) 3. 2.6 (3.5) 4. 2.1 (3.3) 5. 3.2 (4.0)	1. 10.8 (13.0) 2. 10.6 (9.0) 3. 10.5 (11.0) 4. 10.8 (12.0) 5. 11.9 (13.0)	1. 1.1 (2.0) 2. 5.5 (5.0) 3. 3.7 (5.0) 4. 5.6 (15.0) 5. 7.5 (10.0)
Crossover studies									
Blouin et al.[39]	36	—	1. 63.2 2. 58.8	1. Fenfluramine, 60 mg, crossover with placebo at 6 wk after 3-wk washout 2. Desipramine, 150 mg, crossover with placebo at 6 wk after 3-wk washout	6	[Only means for bingeing or vomiting given]‡			
Blouin et al.[40]	47	—	51.1	Desipramine, 150 mg, crossover with placebo at 6 wk after 3-wk washout	6	Drug: 7.5 (—) Placebo: 8.8 (—)	Drug: 4.0 (—) Placebo: 8.8 (—)	Drug: 6.8 (—) Placebo: 9.0 (—)	Drug: 3.8 (—) Placebo: 8.0 (—)
Kennedy et al.[38]	29	60.4	62.1	Isocarboxazid, 60 mg, crossover with placebo at 6 wk after 3-wk washout	6	—	—	—	—
Follow-up study									
Agras et al.[35]§							1. 5.8 (10.2) 2. 2.4 (3.6) 3. 3.4 (4.6) 4. 3.1 (7.7) 5. 2.6 (3.8)		1. 5.6 (14.3) 2. 2.6 (3.6) 3. 3.1 (4.6) 4. 2.9 (5.2) 5. 2.2 (3.5)

—, data not reported; *CBT,* cognitive-behavioral therapy; *SD,* standard deviation; *SPT,* supportive psychotherapy.

*Patients in conditions 3 and 4 had depression as well as bulimia.

†Patients were given desipramine for 8 weeks. If they experienced intolerable side effects or did not achieve at least a 75% reduction in binge frequency, desipramine was discontinued over the next 2 weeks, and they were then started on fluoxetine.

‡Before treatment: 1. Fenfluramine, mean of 18.5 (8.3) bingeing or vomiting episodes per week; placebo, 22.0 (8.3). 2. Desipramine 23.0 (6.5); placebo, 23.0 (6.5). After treatment: 1. Fenfluramine, 6.0 (2.0); placebo, 18.0 (4.0). 2. Desipramine, 7.0 (3.0); placebo, 22.0 (8.0).

§Follow-up of Agras et al.[47]

TABLE 2. Studies Included in Meta-Analysis and Summary of Recovery, Improvement, and Effect Size*

Study	% Recovered of completed			% Recovered of entered			% Improved or recovered		Effect size: Pre vs. post		Effect size: Treatment vs. control	
	Binge	Purge	Both	Binge	Purge	Both	Completed	Entered	Binge	Purge	Binge	Purge
Primary studies												
Agras et al.[46]	—	1. 30.0 2. 10.0	—	—	1. 30.0 2. 8.3	—	1. 30.0 2. 10.0	1. 30.0 2. 8.3	1. 1.7 2. 0.7	1. 1.5 2. 0.6	0.8	0.8
Agras et al.[47]	—	—	1. 45.0 2. 56.0 3. 50.0 4. 56.0 5. 41.0	—	—	1. 41.7 2. 41.7 3. 41.7 4. 41.7 5. 39.1	—	—	1. 0.4 2. 0.8 3. 1.6 4. 1.3 5. 0.9	1. 0.6 2. 0.8 3. 1.5 4. 1.9 5. 1.1	[No control group]	
Beumont et al.[48]	—	—	1. 69.6 2. 61.5	—	—	1. 47.1 2. 48.5	—	—	1. 1.2 2. 1.1	1. 1.4 2. 1.0	–0.2	0.4
Fahy et al.[49]	—	—	—	—	—	—	—	—	1. 2.8 2. 3.0	1. 2.3 2. 2.1	–0.4	1.3
Fichter et al.[50]	—	—	—	—	—	—	—	—	1. 0.4 2. 0.3	—	0.6	—
Fluoxetine Bulimia Nervosa Collaborative Study Group[51]	1. 14.0 2. 27.0 3. 13.0	1. 15.0 2. 24.0 3. 10.0	—	1. 10.9 2. 18.6 3. 8.5	1. 11.6 2. 17.1 3. 6.2	—	1. 49.0 (binge), 39.0 (vomit) 2. 63.0 (binge), 57.0 (vomit) 3. 43.0 (binge), 26.0 (vomit)	1. 38.0 (binge), 35.0 (vomit) 2. 43.4 (binge), 40.3 (vomit) 3. 27.1 (binge), 16.3 (vomit)	—	—	—	—
Goldbloom et al.[52]	—	—	1. 17.0 2. 43.0 3. 25.0	—	—	1. 8.7 2. 25.0 3. 10.3	1. 41.7 2. 64.3 3. 75.0	1. 21.7 2. 37.5 3. 31.0	1. 0.8 2. 1.1 3. 2.3	1. 0.3 2. 1.2 3. 1.3	[No control group]	
Goldstein et al.[53]	1. 18.3 2. 12.0	1. 19.0 2. 12.0	—	1. 10.8 2. 5.9	1. 11.1 2. 5.9	—	1. 51.5 (binge), 53.1 (vomit) 2. 36.0 (binge), 35.0 (vomit)	1. 30.4 (binge), 31.4 (vomit) 2. 17.6 (binge), 16.6 (vomit)	—	—	—	—
Horne et al.[54]	1. 29.7 2. 4.8	—	—	1. 20.0 2. 0	—	—	1. 56.4 2. 15.4	1. 84.1 2. 33.3	1. 1.2 2. 0	—	0.3	—
Hsu et al.[55]	—	—	—	—	—	—	—	—	1. 0.6 2. 1.0 3. 0.5 4. 0.5	1. 0.7 2. 0.5 3. 0.7 4. 0.4	0†	0†
Kennedy et al.[58]	1. 19.0 2. 13.0	1. 44.0 2. 20.0	—	1. 15.8 2. 11.8	1. 36.8 2. 17.6	—	—	—	1. 1.2 2. 1.2	1. 0.8 2. 0.3	0.3	0.6

Pope et al.[61]	1. 0 2. 0	—	—	—	—	1. 0 2. 0	1. 88.9 2. 10.0	1. 72.7 2. 9.1	1. 1.0 2. 0	—	0.8	—
Pope et al.[62]	1. 10.0 2. 0	—	—	1. 8.7 2. 0	—	—	1. 34.8 2. 0	1. 40.0 2. 0	—	—	—	—
Walsh et al.[63]	1. 44.4 2. 4.8	—	—	1. 34.8 2. 3.7	—	—	1. 61.1 2. 19.1	1. 47.8 2. 14.8	1. 1.0 2. 0.2	—	0.5	—
Walsh et al.[36]	1. 16.1 2. 9.4	—	—	1. 12.5 2. 7.9	—	—	—	—	1. 0.9 2. –0.1	1. 0.2 2. 0	0.7	0.3
Walsh et al.[64]	1. 42.9 2. 0	—	—	1. 30.0 2. 0	—	—	1. 42.9 2. 0	1. 30.0 2. 0	1. 1.2 2. 0.1	—	1.0	—
Walsh et al.[65]	1. 80.0 2. 25.0 3. 50.0 4. 37.5 5. 25.0	1. 73.3 2. 18.8 3. 43.8 4. 37.5 5. 31.3	1. 73.3 2. 12.5 3. 37.5 4. 31.3 5. 18.8	1. 52.2 2. 18.2 3. 28.6 4. 24.0 5. 18.2	1. 47.8 2. 13.6 3. 25.0 4. 24.0 5. 22.7	1. 47.8 2. 9.1 3. 21.4 4. 20.0 5. 13.6	—	—	1. 1.7 2. 1.0 3. 1.0 4. 1.3 5. 0.8	1. 1.0 2. 0.7 3. 0.8 4. 0.4 5. 0.4	[Aggregate groups]	
Crossover studies												
Blouin et al.[39]	—	—	—	—	—	—	—	—	1. 2.1 2. 3.2 (binge or vomit)	—	1. 3.8 2. 2.5 (binge or vomit)	—
Blouin et al.[40]	4.2	—	—	Drug: 2.1	—	—	Drug: 50.0	25.5	—	—	—	—
Kennedy et al.[38]	33.3	38.9	—	Drug: 20.7	Drug: 24.1	—	—	—	—	—	—	—
Follow-up study												
Agras et al.[35]	—	—	1. 18.0 2. 67.0 3. 40.0 4. 78.0 5. 54.0	—	—	1. 16.7 2. 50.0 3. 33.3 4. 58.3 5. 52.2	1. 9.1‡ 2. 55.6‡ 3. 40.0‡ 4. 55.6‡ 5. 31.8‡	1. 8.3‡ 2. 41.7‡ 3. 33.3‡ 4. 41.7‡ 5. 30.4‡	1. –0.04 2. 0.8 3. 1.0 4. 0.9 5. 1.1	1. 0.3 2. 0.9 3. 1.2 4. 1.6 5. 1.3	—	—

*Four studies (Hughes et al.,[56] Kanerva et al.,[57] Mitchell and Groat,[59] and Mitchell et al.[60]) did not provide appropriate data and were not included in this table.

†Effect sizes calculated by comparing groups 1 and 3 (depressed and nondepressed subjects receiving lithium) with groups 2 and 4 (depressed and nondepressed subjects receiving placebo).

‡Percent remaining recovered at 12-month follow-up.

TABLE 3. Meta-Analysis of Outcome of Pharmacotherapy for Bulimia: Descriptive Statistics and Effect Size Estimates*

	Overall		SSRIs		Tricyclics		MAOIs		Atypical antidepressants		Placebo	
	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†
No. of subjects	104.3 (119.1)	16	196.4 (179.3)	5	72.5 (62.7)	6	41.3 (7.6)	3	63.5 (24.7)	2	107.7 (132.4)	13
% Included	48.5 (25.4)	11	63.5 (34.4)	4	48.0 (17.1)	4	29.3 (4.3)	3			49.1 (25.7)	8
% Completed of entered	72.8 (14.7)	16	72.1 (16.4)	5	73.9 (16.3)	6	69.1 (16.5)	3	77.1 (13.9)	2	79.2 (17.1)	13
% Dropouts from side effects	9.7 (6.4)	11	7.9 (1.9)	3	9.6 (3.0)	4	14.6 (10.6)	3				
Effect size												
At termination: treatment vs. control												
Binge	0.64 (0.3)	7			0.77 (0.0)	3	0.57 (0.4)	3				
Purge	0.59 (0.2)	3			0.56 (0.3)	2						
Pre vs. post												
Binge	1.04 (0.3)	10	0.63 (0.2)	2	1.15 (0.4)	4	1.23 (0.1)	3				
Purge	0.70 (0.5)	6	0.43 (0.2)	2	0.84 (0.6)	3						

MAOIs, monoamine-oxidase inhibitors; *SD,* standard deviation; *SSRIs,* selective serotonin-reuptake inhibitors.
*In this table, data are reported only for classes of medication examined in at least two controlled clinical trials.
†Number of studies.

patients improved or recovered in two ways: as the number of patients improved or recovered divided by (a) the number who completed treatment (completer sample), and (b) the number who entered treatment, whether or not they completed it (intent-to-treat sample).

Results

Results of our primary analyses (hereafter referred to as data from the primary sample) derive from aggregated data from 16 studies, including a total of 918 patients. In secondary analyses, we provide data on four additional sets of studies: three crossover studies, two maintenance studies, one follow-up study at 1 year or beyond, and nine trials of combined pharmacotherapy/psychotherapy. Some of the combination trials also included medication-only conditions; these are included in our primary sample. Tables 3 and 4 summarize the most important findings from the primary sample.† Table 5 summarizes the most important findings from the combined pharmacotherapy/psychotherapy trials. Because of the small number of studies of each specific class of medication—selective serotonin-reuptake inhibitors (SSRIs), tricyclics, monoamine-oxidase inhibitors (MAOIs), and atypical antidepressants—we focus here on the combined data across medications and note differences between classes only when they are substantial.

Primary analyses. *Inclusion and completion rates.* Overall, approximately 50% of patients were excluded from participating in the average study, although noticeable differences appeared among the different types of medication, with inclusion rates as high as 64% for SSRIs and as low as 29% for MAOIs (the latter because of food restrictions and lethality of particular relevance to many patients with bulimia). For most studies (across all drug conditions), researchers appropriately excluded patients with comorbid psychotic or organic disorders and physical conditions such as pregnancy. Additional prototypical exclusion criteria included suicidality and substance use.

Many investigators also excluded patients with comorbid anorexia nervosa or obesity; others excluded patients with comorbid major depressive disorder, bipolar disorder, or obsessive-compulsive disorder. The exclusion criteria imposed in some of these studies effectively eliminated many troubled and difficult-to-treat patients, such as patients with borderline features (who may have been suicidal or have abused substances). Many researchers also reported excluding patients for "major" medical or psychiatric illness without stating how that determination was made or commenting on the interrater reliability of the determination of "major" illness.

The percentage of completers in these studies was high (73% on average). For investigations that included a detailed description of the reasons for not completing the trial (n = 11,

†As can be seen from the tables, the number of studies drops substantially for many analyses, particularly for the specific drug classes. We report data in the table only when such statistics are provided by at least two studies, since the aim of the meta-analysis is aggregation across studies to yield more-reliable, robust indicators.

TABLE 4. Meta-Analysis of Outcome of Pharmacotherapy for Bulimia: Recovery, Improvement, and Posttreatment Symptoms*

	Overall		SSRIs		Tricyclics		MAOIs		Atypical antidepressants		Placebo	
	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†	Mean (SD)	n†
% Recovered												
Completers												
Binge only	23.1 (15.3)	8	19.2 (1.3)	2			35.4 (14.2)	3	19.9 (13.9)	2	5.3 (6.3)	8
Purge only	28.1 (11.7)	4	19.3 (0.4)	2							13.0 (4.8)	4
Binge and purge	34.5 (17.1)	3			26.8 (15.1)	2						
Intent-to-treat sample												
Binge only	16.9 (11.3)	8	12.8 (2.7)	2			26.9 (9.9)	3	14.4 (7.9)	2	3.7 (4.6)	8
Purge only	23.1 (12.3)	4	12.7 (2.3)	2							9.5 (5.5)	4
Binge and purge	25.2 (14.9)	3			16.9 (6.3)	2						
% Improved or recovered												
Completers												
Binge only	56.9 (23.2)	10	53.7 (2.0)	3	94.4 (7.9)	2	41.0 (21.1)	3	48.2 (11.6)	2	18.2 (17.6)	10
Purge only	44.6 (10.5)	4	52.2 (1.3)	2							22.8 (10.5)	4
Binge and purge	33.2 (14.3)	4			27.6 (10.8)	3					12.4 (4.2)	2
Intent-to-treat sample												
Binge only	47.6 (21.8)	10	40.4 (9.8)	3	71.4 (1.9)	2	31.2 (16.1)	3	59.3 (34.6)	2	15.6 (14.7)	10
Purge only	33.9 (3.8)	4	34.5 (4.4)	2							14.7 (43)	4
Binge and purge	23.1 (12.9)	4			16.9 (4.5)	3					10.4 (3.5)	2
Posttreatment symptoms												
Binges/wk	4.3 (2.0)	10	6.2 (3.4)	3	3.3 (0.7)	5	4.1 (1.1)	3			7.2 (1.6)	9
Purges/wk	6.2 (5.2)	7	10.7 (9.3)	2	4.8 (2.1)	4					9.3 (3.2)	4
EAT-26 score	26.1 (3.1)	7			26.6 (4.1)	3	24.3 (1.3)	3			35.1 (7.0)	6

EAT-26, Eating Attitudes Test, 26-item version; *MAOIs,* monoamine-oxidase inhibitors; *SD,* standard deviation; *SSRIs,* selective serotonin-reuptake inhibitors.

*In this table, data are reported only for classes of medication examined in at least two controlled clinical trials.

†Number of studies.

or 55% of the total sample), only 10% of patients who entered the study dropped out because of side effects.

Effect size. With respect to effect size, initial response was moderate. For studies that included and reported data on control groups adequate to allow calculation of effect size (n = 7, or 44% of the total sample), the average effect size was 0.6 for binge episodes and 0.6 for purges. (None of the SSRI studies reported data on control groups adequate for calculating this estimate.) Pre-post effect sizes were larger, averaging 1.0 for binges and 0.7 for purges. (As noted above, however, this statistic cannot be used to make inferences about causality.)

Percentage recovered or improved. Roughly 50% of studies reported on the percentage of participants classified as recovered following treatment. Overall, of patients who completed treatment, 23% stopped bingeing and 28% stopped purging. MAOIs produced higher recovery rates (35% for binge episodes) than did SSRIs (19%) or atypical antidepressants such as trazodone or bupropion (20%); no study of tricyclics we reviewed reported data on recovery rates. Only four investigations reported the percentage of patients who completely recovered from binge and purge together. For the intent-to-treat group (that is, including those who began but did not complete the treatment, for whatever reasons), overall recovery rates were 17% for binge episodes, 23% for purge episodes, and 25% for binge and purge together.

When we broaden the definition of change to include percentage of patients either recovered or improved (with improvement typically defined as at least a 50% decrease in binges and/or purges), the percentage of patients who benefit clearly improves. Of patients who completed treatment, recovery or improvement rates were 57% for binge episodes, 45% for purge episodes, and 33% for binge and purge together. Studies of tricyclics showed higher improvement or recovery rates (94% for binge episodes) than did studies of SSRIs (54%), MAOIs (41%), or atypical antidepressants (48%). For the intent-to-treat group, overall recovery or improvement rates were 48% for binge episodes, 34% for purge episodes, and 23% for binge and purge together.

TABLE 5. Meta-Analysis of Outcome of Pharmacotherapy plus Psychotherapy*

	Overall		SSRI + psychosocial		Tricyclic + psychosocial	
	Mean (SD)	**n†**	**Mean (SD)**	**n†**	**Mean (SD)**	**n†**
Subjects	79.9 (44.1)	9	56.5 (17.7)	4	98.5 (60.3)	4
% Included	54.0 (23.5)	5	37.2 (34.2)	2	65.2 (7.0)	3
% Completed of entered	75.9 (17.9)	9	77.3 (28.4)	4	72.9 (5.1)	4
Outcome						
% Recovered—binge and purge						
Completers	54.7 (13.9)	3			47.3 (7.6)	2
Intent-to-treat sample	39.2 (9.3)	3			35.3 (9.0)	2
% Improved or recovered—binge and purge						
Completers	62.8 (19.7)	4			60.5 (23.5)	3
Intent-to-treat sample	45.8 (14.1)	4			45.3 (18.5)	3
Effect size at termination						
Combined treatment vs. pharmacological treatment only						
Binge	0.17 (0.4)	7	0.19 (0.5)	4	0.20 (0.1)	2
Purge	0.49 (0.4)	6	0.77 (0.5)	3	0.23 (0.2)	2
Combined treatment vs. psychosocial treatment only						
Binge	0.31 (0.2)	2				
Purge	0.29 (0.2)	2				
Posttreatment symptoms						
Binges/wk	2.5 (1.2)	9	2.4 (0.8)	4	2.3 (1.4)	4
Purges/wk	2.5 (1.1)	7	2.5 (1.1)	3	2.1 (1.5)	3
EAT-26 score	25.8 (3.2)	2				

EAT-26, Eating Attitudes Test, 26-item version; *SD,* standard deviation; *SSRI,* selective serotonin-reuptake inhibitor.
*In this table, data are reported only for classes of medication examined in at least two controlled clinical trials.
†Number of studies.

Posttreatment symptoms. At termination, across all types of medications, bulimic patients binged on average 4.3 times and purged 6.2 times per week. At termination the average score on the 26-item version of the EAT was 26.1. The means for both binges and purges exceeded the frequency of binge eating and compensatory behavior required for a DSM-IV diagnosis of bulimia nervosa.[33] Similarly, the average patient's score on the EAT-26 was higher than the cut-off point of 20 used to indicate clinical significance.[34]

Secondary analyses. *Follow-up and maintenance studies.* As in much of the literature on psychotherapy and pharmacotherapy for a range of disorders, one of the most striking findings with respect to pharmacotherapy for bulimia is the lack of data on follow-up at 12 months or more (see Tables 1 and 2). We could locate only one experimental study with follow-up at 12–18 months[35] and none with extended follow-up at 24 months or more. Agras and colleagues[35] reported that 50% of patients who completed the initial trial recovered; of these, 60% remained recovered at follow-up, defined as achieving abstinence for 3 months. Thus, in their sample, 30% of completers reached recovery and remained recovered. Posttreatment symptoms for the treated sample remained high, with binges averaging 4.1 per week and purges 4.1 per week at the end of the follow-up period.

We were also able to locate two maintenance trials. Walsh and colleagues[36] continued treatment for an additional 16 weeks after termination. This maintenance phase included only patients who improved (i.e., achieved reduction of 50% or more in binge episodes) during the initial phase and did not show other problems such as intolerable side effects. The maintenance trial thus included 21 out of the 40 subjects who initially entered the treatment (53%). Of these 21 patients, only 52% completed the maintenance phase, and of the completers, 55% relapsed (defined as bingeing at more than 50% of their baseline frequency for 2 consecutive weeks). Thus, of the 21 who entered the maintenance phase, only five (24%) remained in treatment and remained recovered, and of the 40 patients who initially enrolled in treatment, only 13% improved and remained improved through the maintenance phase. Comparable data were not available on purge frequency.

In another study, Pyle and coworkers[37] conducted a 6-month maintenance trial. They, too, included only patients

who had responded initially (defined as having a maximum of two binge and vomit episodes during the final 2 weeks of treatment; n = 9 out of 31, or 29%). However, only two patients completed this phase, so the results are difficult to interpret.

Crossover studies. We were able to locate three crossover studies that met our inclusion criteria.[38–40] Because of the different design of these studies, we report their findings separately here. However, due to the large variability in the information reported (e.g., only one study reported the percentage of patients who passed the screening process, and only one reported posttreatment symptom means), we were not able to perform many analyses.

The findings that could be aggregated across a minimum of two studies are consistent with the data from the primary sample. Approximately 58% of patients who entered a trial completed it. Of patients who completed treatment, 19% stopped bingeing. For the intent-to-treat group, mean recovery rate was 11% for binge episodes; data were unavailable for purge episodes.

Combined pharmacotherapy and psychotherapy. Inclusion and completion rates for the nine studies reporting a combined medication/psychotherapy condition were similar to those reported from our primary sample (54% and 76%, respectively). For effect size, the data suggest a small advantage of combined treatments over medication alone for binges but a moderate advantage for purges (d = 0.2 and 0.5, respectively, with d here referring to the difference between the standardized effects of combined treatments over medication alone). For studies that also included and reported adequate data on psychotherapy-alone conditions, the figures suggest a small to moderate advantage of combined treatments over psychotherapy alone (d = 0.3 for binges and 0.3 for purges).

With respect to percent recovered, combined treatments showed a clear advantage over medication alone. Roughly 40% of studies reported on the percentage of participants classified as recovered following treatment. Overall, of patients who completed treatment, 55% stopped bingeing and purging. For the intent-to-treat group, the figure was 39%.

Posttreatment symptoms also show a substantial benefit of combined treatments over medication alone. At termination, bulimic patients receiving both pharmacotherapy and psychotherapy binged an average of 2.5 times per week and purged an average of 2.5 times per week. The average EAT-26 score at termination was 25.8. Once again, these data point to substantial improvement over conditions prior to treatment, but they do not constitute a return to mental health. As with medication-only studies, the mean frequencies of both binges and purges following treatment exceeded the frequencies of binge eating and compensatory behaviors required for a DSM-IV diagnosis of bulimia. Similarly, the average patient's score on the EAT-26 was higher than the cutoff of 20 used to indicate clinical significance.

DISCUSSION

The data reported here support a conclusion reached in other qualitative and meta-analytic reviews—namely, that medication is useful for at least a subset of patients with bulimia but is not, on its own, an adequate treatment for the disorder.[6,12,13] They also qualify and extend this conclusion in several ways. They demonstrate that pharmacological treatments for bulimia nervosa lead to a moderate initial improvement for the average patient and clinically meaningful improvement for roughly half of patients. Recovery is seen in roughly 25% of patients who pass a series of screening criteria rigorous enough to exclude roughly half of eligible subjects. The average patient who completes a controlled trial continues to fulfill the criteria for bulimia nervosa at termination. Virtually no data exist for follow-up intervals of 1 year or more, and the data that do exist from maintenance trials suggest that the initial response in many patients is not sustained. Compared with medication alone, a combination of pharmacotherapy and brief psychotherapy (typically 16–20 sessions) yields substantially better results, at least in producing an initial response, as manifested by higher recovery rates and lower levels of symptoms following treatment. Nevertheless, the average patient in these studies of combination treatments also continues to fulfill the criteria for bulimia nervosa at termination, and the lack of follow-up data for these trials similarly limits our ability to generalize about their sustained efficacy. Thus, despite tremendous progress, we have a long way to go toward effective treatments for the majority of patients with bulimia.

Exclusion Rates and External Validity

A key variable bearing on external validity of controlled clinical trials is the extent to which researchers exclude patients who would frequently present for treatment of the disorder in clinical practice. Exclusion rates in the studies we reviewed here were substantial but not excessive. Many of the exclusion criteria, such as the presence of psychotic disorders or acute suicidality, are scientifically and ethically appropriate and do not jeopardize external validity. However, some of the common exclusion criteria may limit generalizability. Two are noteworthy.

First, most medication trials included only normal-weight women who purge. Given the high comorbidity of bulimic and anorexic symptoms (whether or not patients actually have enough anorexic symptoms for a diagnosis of anorexia, binge-eating/purging type, rather than bulimia), and the fact that bulimic patients of either abnormally high or abnormally low weight are generally sicker and have poorer treat-

ment outcomes (Thompson et al., unpublished manuscript, 2001; see also reference 2), this limits generalizability.

Second, most studies excluded patients for comorbid substance abuse or suicidality. Although these criteria are defensible for both methodological and ethical reasons, as noted above, they may jeopardize external validity because they may exclude many patients with comorbid borderline personality disorder or borderline features. Existing data[26,27] suggest that comorbidity is common between bulimia and borderline personality disorder and that comorbid borderline personality disorder can affect treatment response. For example, Johnson and colleagues[41] have shown that bulimic patients with comorbid borderline personality disorder fare worse in pharmacological trials, as manifested in lower recovery rates at termination and more-severe symptoms at 1-year follow-up. Relevant to these findings is research by Mitchell and coworkers,[42] who reviewed inclusion and exclusion criteria in 41 studies of bulimia and then examined whether 100 patients evaluated in an outpatient eating disorders clinic would have been included in the average study. They found that between one-third and one-half of patients presenting for treatment and satisfying DSM-III-R criteria for bulimia nervosa would have been excluded from these studies because of their age, their weight, comorbid substance abuse, current or prior use of psychotropic medication, or significant suicide risk. They noted that since high suicide risk, comorbid substance abuse, and inadequate response to psychotropic medications are associated with negative outcome, some of the most-difficult-to-treat patients are likely to be excluded from controlled treatment trials.

Initial Response

The data reported here bear only on initial response to treatment, which may or may not predict sustained efficacy. Compared with appropriate placebo control conditions, the studies summarized here demonstrate moderate effect sizes, with means of 0.6 for binges and 0.6 for purges. These effect sizes are clinically meaningful and within the range of those found in much research on pharmacotherapy,[13] although they are smaller than the average effect size of psychotherapy alone for bulimia, which is approximately 1.0 for binge and purge when measured by the same procedures used here (Thompson et al., unpublished manuscript; see also references 13 and 43).‡

With respect to percent recovered, as described in prior qualitative reviews, only a minority of patients recovered from bulimia as a result of pharmacotherapy. Of patients who completed treatment, roughly 25% stopped bingeing and a slightly higher percentage stopped purging. Of the intent-to-treat group, approximately 20% stopped bingeing and 25% stopped purging. If we expand the definition of clinically meaningful change to include percent recovered or improved, the data are more promising: roughly half of patients who entered or completed treatment experienced initial clinical improvement in bingeing symptoms. Substantially lower percentages of patients experienced amelioration of compensatory behaviors (purging), which seem to be more resistant to treatment. Data on cessation of both bingeing and purging together (the diagnostic criteria for bulimia) are rarely reported, so we can draw few conclusions about the efficacy of antidepressant medications for bulimia as a syndrome. Recovery rates seem to be higher for patients treated with MAOIs than for those treated with any of the other three types of medication, although studies testing the efficacy of MAOIs have not been reported in a decade.

With respect to posttreatment symptoms, the data suggest that patients can expect a significant reduction in mean levels of symptoms, which is clearly clinically meaningful. However, the average patient will maintain a clinically significant level of symptoms after treatment and will in fact continue to have symptoms well above threshold for a diagnosis of bulimia. High levels of symptoms are also evident at the termination of combined pharmacological/psychosocial treatments, although binge means and purge means are substantially lower than they are with medication alone.

Sustained Efficacy

In terms of sustained efficacy (the ability of these treatments to produce lasting symptomatic changes rather than solely an initial response), the paucity of follow-up data at 12–18 months (one study) and the nonexistence of follow-up data at 2 years or longer on specific samples (e.g., controlling for additional treatment in the intervening time) make conclusions about the general utility of these treatments difficult to draw, particularly given that bulimia tends to be a long-term, recurrent disorder.[13] The results of maintenance trials have not been particularly promising, but more studies are clearly required.

‡Although one could raise methodological questions about the comparability of effect size estimates in psychotherapy and psychopharmacololgy, we are not apologists for psychotherapy and have in fact been sharply critical of the psychotherapy efficacy literature.[16] Each type of study has substantial problems with maintaining blindness; treating therapists in psychotherapy research are obviously not blind to condition, and investigators assessing symptom changes in medication trials are typically not blind to side-effect profiles. Overall, however, on the most objective measures (such as patients' reports of whether they completely stopped bingeing and purging), the data from a multidimensional meta-analysis using precisely the same procedures as those used here (Thompson et al., unpublished manuscript, 2001), as well as the data reported here on combined medication-psychotherapy conditions, suggest, in keeping with widely accepted treatment guidelines, that at this point in time medication is not likely to be a complete treatment for bulimia.

Limitations and Implications

An important limitation to the present findings reflects a limitation of all randomized controlled trials: whereas most clinical trials compare the effects of a single pharmacological agent with those of another treatment, in real life clinicians are not limited to using a single medication. Instead, they employ trial and error to try to match the medication to the patient's particular symptoms, adjusting agents (alone and in combination) and dosages based on symptomatic response. Thus, the findings reported would be more useful in conjunction with results from large-scale naturalistic effectiveness studies to examine the relationship between bulimic symptoms and medications in everyday practice. Furthermore, many psychiatrists combine pharmacotherapy with long-term psychotherapy, a combination of treatments that has never been studied empirically and should be a focus of future research. On the other hand, the results reported here show relatively modest treatment response to all classes of medications that have been studied, with none leading to recovery in more than a small subset of patients.

Perhaps one of the most important findings of this study, consistent with the conclusions of others who have called for more complete and uniform reporting practices,[44,45] is methodological—namely, the lack of consistent criteria for reporting data in randomized controlled trials. This problem is no greater in the literature on bulimia than in any other literature we have studied and is characteristic of both the psychotherapy and the psychopharmacology literature (see, for example, references 16 and 44), but it limits the confidence with which clinicians can apply many findings from controlled trials to clinical practice. Criteria for inclusion, completion, improvement, and recovery were sometimes obscure, ad hoc, or not reported, rendering objective evaluation of findings difficult. Most authors failed to report the percentage of patients who recovered, and the vast majority who did so failed to indicate whether the patients who ceased bingeing were the same ones who ceased purging and vice versa. Similarly, data regarding exclusion rates, reasons for exclusion, and dropouts were often not provided.[3,10,13,15,44]

Our experience in attempting to meta-analyze this literature supports recent calls in the medical literature to require flowcharts for controlled clinical trials, so that readers can see how many patients were screened, how many were excluded for specific reasons, how many were randomized to each condition, how many completed the trial, how many dropped out because of side effects or inadequate response, how many recovered, how many improved, how many remained improved at follow-up, and so forth.[45] In addition, we recommend that investigators routinely report the range of efficacy estimates described here, because all of these details are important in evaluating the utility of a given treatment for patients in everyday practice.

Thus, we would recommend that primary research reports include a range of statistics and other details that are not now routinely provided but are essential for consumers of this research to judge both internal and external validity, such as numbers of patients excluded for various reasons, reliability of both pre- and posttreatment diagnosis, effect size estimates on both completer and intent-to-treat samples, percentage of patients improved or recovered (and how and when criteria for improvement and recovery were selected), comorbidity and effect sizes for patients with and without key comorbidities (even if sample size does not permit significance testing), attrition rates (and reasons for dropping out), posttreatment symptoms (not simply mean changes, as reported in many of the studies), follow-up at clinically meaningful intervals (or reasons the researchers chose not to follow up large-n studies beyond 6–12 months), percentage of patients seeking additional treatment (and reasons for seeking such treatment, kinds of treatment sought, and whether treatment or referral was sought from the investigators), and percentage of patients who remain improved at follow-up. Whether the same person made the pre- and posttreatment diagnoses, and whether the same clinician who assessed side effects also assessed outcome, should also be noted. Finally, we suggest that qualitative and meta-analytic reviews similarly routinely report such data rather than effect sizes alone. Although effect sizes are very important for assessing efficacy, they should be supplemented by a range of other data that can provide a more comprehensive picture.

APPENDIX. Studies Excluded from the Meta-Analysis

Study	Reason
Alger et al.[66]	Fewer than 10 patients per condition
Ayuso-Gutierrez et al.[67]	No comparison group
Barlow et al.[68]	Data and analyses previously reported in Blouin et al.[40]
Bossert et al.[69]	No comparison group
Brambilla et al.[70]	No comparison group
Brotman et al.[71]	Retrospective study
Collings & King[72]	Data on treatment and control groups not reported separately
Crane et al.[73]	No comparison group
Fallon et al.[74]	No comparison group

APPENDIX. Studies Excluded from the Meta-Analysis (*cont'd.*)

Study	Reason
Fava et al.[75]	No comparison group; retrospective data collection
Fichter et al.[76]	Maintenance study; original study did not include a comparison group
Geretsegger et al.[77]	No comparison group
Herzog et al.[25]	No comparison group
Hsu[30]	No comparison group
Hudson et al.[78]	No comparison group
Hudson et al.[79]	Fewer than 10 patients per condition
Joja et al.[80]	Fewer than 10 patients per condition; no randomization procedure; results reported only for treatment group; groups included mixed eating disorder diagnoses
Jonas & Gold[81]	Fewer than 10 patients per condition; no comparison group
Jonas & Gold[82]	Fewer than 10 patients per condition; study not double-blind
Kaplan et al.[83]	Fewer than 10 patients per condition
Keel et al.[84]	No comparison group
Krahn & Mitchell[85]	Fewer than 10 patients per condition
Leitenberg et al.[86]	Fewer than 10 patients per condition
Marrazzi et al.[87]	Fewer than 10 patients per condition
McCann & Agras[88]	Patients had atypical diagnosis (nonpurging bulimia)
Mitchell et al.[89]	No comparison group
Mitchell et al.[90]	Cross-over design that did not include wash-out period between phases; treatment phases lasted 3 weeks
Ong et al.[29]	Fewer than 10 patients per condition; no primary measure of bulimia outcome
Robinson et al.[91]	Fewer than 10 patients per condition; no primary measure of bulimia outcome
Rossiter et al.[28]	No primary measure of bulimia outcome; study not double-blind
Rothschild et al.[92]	Fewer than 10 patients per condition
Sabine et al.[93]	No primary measure of bulimia outcome
Stewart et al.[94]	Fewer than 10 patients per condition
Trygstad[95]	No comparison group
Walsh et al.[96]	Fewer than 10 patients per condition; no comparison group
Walsh et al.[97]	Fewer than 10 patients per condition
Wold[98]	No comparison group

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New River Pharmaceuticals Announces Third Quarter 2006 Results

RADFORD, Va., Nov. 7 /PRNewswire-FirstCall/ -- New River Pharmaceuticals Inc. (Nasdaq: NRPH) today announced its financial results for the three months ended October 1, 2006. New River recognized a net loss of $13.6 million, or $(0.38) per share, basic and diluted, for the three months ended October 1, 2006, compared to a net loss of $9.1 million, or

$(0.25) per share, for the three months ended October 2, 2005. Cash and short-term investment balances were $162.8 million at October 1, 2006.

For the three months ended October 1, 2006, New River recognized $5.0 million of revenue related to its collaboration agreement with Shire Pharmaceuticals Group plc (Shire) (LSE: SHP); (Nasdaq: SHPGY); (TSX: SHQ) with respect to NRP104, New River's lead product candidate. New River is recognizing milestone revenue from the collaboration that is not subject to refund over the estimated product development period for each of three indications for NRP104, pediatric, adult and adolescent, based on the estimated proportional effort associated with each indication. To date, New River has received $100 million under the terms of its collaboration with Shire, a portion of which is refundable under certain circumstances, and has recognized $31.9 million of the amount received as revenue.

During the third quarter, New River sold approximately $137.8 million principal amount of convertible notes due in 2013 to institutional buyers pursuant to Rule 144A under the Securities Act of 1933, as amended. The notes bear interest at 3.5% per year. In connection with the sale of the notes, New River entered into convertible note hedge transactions with respect to its common stock at a cost of approximately $43.5 million and sold warrants to acquire its common stock in private transactions for net proceeds of approximately $29.5 million. New River also concurrently purchased $41.0 million of its common stock under a prepaid forward purchase contract. These transactions were designed to offset New River's exposure to potential dilution upon conversion of the notes. In addition, New River intends to use the remaining net proceeds for working capital to develop its sales and marketing capabilities for NRP104, including the co-promotion of NRP104 under the terms of the collaboration agreement with Shire, as well as for research and development of its other product candidates and for general corporate purposes.

General and administrative expenses were $6.2 million for the three months ended October 1, 2006 compared to $4.3 million for the three months ended October 2, 2005. The increase in these expenses is due primarily to increases in shared marketing expenses with Shire under the terms of the collaboration agreement.

Research and development expenses were $13.3 million for the three months ended October 1, 2006, compared to $5.2 million for the three months ended October 2, 2005. This increase is primarily the result of increases in external development costs associated with NRP104, including manufacturing costs of validation batches, and stock-based compensation expense as a result of accelerating the vesting of certain awards in recognition of employee performance. Stock-based compensation expense was $4.0 million for the three months ended October 1, 2006, of which $3.3 million was related to equity- settled awards that have a non-cash impact on New River.

"We continue to execute on all fronts and are well positioned to build on our capabilities," said Krish Krishnan, New River's Chief Financial and Chief Operating Officer. "On October 6, 2006, we received an approvable letter from the FDA on NRP104 for the treatment of ADHD in children. We anticipate launching NRP104 in the second quarter of 2007 in collaboration with Shire. We recently completed an End-of-Phase 2 meeting with the FDA on NRP290, our second pipeline candidate, which we are developing for the treatment of acute pain. We also believe we are making good progress in other areas of our portfolio such as hormone replacement therapy and chronic pain."

New River Pharmaceuticals Inc. is a specialty pharmaceutical company developing novel pharmaceuticals that are generational improvements of

widely prescribed drugs in large and growing markets.

For further information on New River, please visit the company's website at http://www.nrpharma.com.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

This press release contains certain forward-looking information that is intended to be covered by the safe harbor for "forward-looking statements" provided by the Private Securities Litigation Reform Act of 1995. Forward-looking statements are statements that are not historical facts. Words such as "expect(s)," "feel(s)," "believe(s)," "will," "may," "anticipate(s)" and similar expressions are intended to identify forward-looking statements. These statements include, but are not limited to, financial projections and estimates and their underlying assumptions; statements regarding plans, objectives and expectations with respect to future operations, products and services; and statements regarding future performance. Such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of New River Pharmaceuticals, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include: those discussed and identified in the New River Pharmaceuticals Inc. annual report on Form 10-K, filed with the SEC on March 15, 2006; the timing, progress and likelihood of success of our product research and development programs; the timing and status of our preclinical and clinical development of potential drugs; the likelihood of success of our drug products in clinical trials and the regulatory approval process; our drug products' efficacy, abuse and tamper resistance, resistance to intravenous abuse, onset and duration of drug action, ability to provide protection from overdose, ability to improve patients' symptoms, incidence of adverse events, ability to reduce opioid tolerance, ability to reduce therapeutic variability, and ability to reduce the risks associated with certain therapies; the ability to develop, manufacture, launch and market our drug products; our projections for future revenues, profitability and ability to achieve certain threshold sales targets; our estimates regarding our capital requirements and our needs for additional financing; the likelihood of obtaining favorable scheduling and labeling of our drug products; the likelihood of regulatory approval under the Federal Food, Drug, and Cosmetic Act without having to conduct long and costly trials to generate all of the data which are often required in connection with a traditional new chemical entity; our ability to develop safer and improved versions of widely prescribed drugs using our Carrierwave (TM) technology; our success in developing our own sales and marketing capabilities for our lead product candidate, NRP104; and our ability to obtain favorable patent claims. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. New River Pharmaceuticals does not undertake any obligation to republish revised forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events. Readers are also urged to carefully review and consider the various disclosures in New River Pharmaceuticals' annual report on Form 10-K, filed with the SEC on March 15, 2006, as well as other public filings with the SEC.

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NEW RIVER PHARMACEUTICALS INC. AND SUBSIDIARY
CONSOLIDATED BALANCE SHEETS
(Unaudited)

Assets	October 1, 2006	January 1, 2006
Current assets:		
Cash and cash equivalents	$73,974,851	$3,515,572
Short-term investments	88,825,000	49,250,000
Other receivables	371,289	135,755
Prepaid expenses and other current assets	1,494,873	798,090
Total current assets	164,666,013	53,699,417
Property and equipment:		
Leasehold improvements	99,644	94,609
Machinery and equipment	1,110,950	819,472
Construction in progress	301,689	-
	1,512,283	914,081
Less accumulated depreciation and amortization	676,981	653,427
Property and equipment, net	835,302	260,654
Convertible notes issuance costs	4,414,620	-
Total assets	$169,915,935	$53,960,071
Liabilities and Shareholders' Equity (Deficit)		
Current liabilities:		
Capital lease obligation -- current	$24,252	$22,298
Accounts payable	7,743,639	1,548,473
Unpaid and accrued research and development expenses	8,406,226	3,201,732
Accrued compensation	2,254,728	2,203,898
Due to affiliates	174,460	34,138
Interest payable	879,566	-
Deferred revenue -- current	8,178,482	-
Accrued stock based compensation -- current	2,009,308	-
Total current liabilities	29,670,661	7,010,539
Capital lease obligation -- noncurrent	8,707	27,148
Accrued stock-based compensation	7,194,806	3,404,435
Deferred revenue	59,970,988	50,000,000
Convertible notes	137,750,000	-
Total liabilities	234,595,162	60,442,122
Shareholders' Equity (Deficit):		
Preferred stock, par value $0.001 per share.		
Authorized 25,000,000 shares; none		

issued and outstanding	-	-
Common stock, par value $0.001 per share. Authorized 150,000,000 shares; issued and outstanding 36,708,732 shares at October 1, 2006 and 36,367,064 shares at January 1, 2006	36,709	36,367
Additional paid-in capital	15,277,219	63,326,824
Accumulated deficit	(79,993,155)	(69,845,242)
Total shareholders' equity (deficit)	(64,679,227)	(6,482,051)
Commitments and contingencies		
Total liabilities and shareholders' equity (deficit)	$169,915,935	$53,960,071

NEW RIVER PHARMACEUTICALS INC. AND SUBSIDIARY

CONSOLIDATED STATEMENTS OF OPERATIONS

	Three months ended		Nine months ended	
	October 1, 2006	October 2, 2005	October 1, 2006	October 2, 2005
	(Unaudited)		(Unaudited)	
Collaboration revenues	$5,025,453	$-	$31,850,530	$-
Operating costs and expenses:				
Selling, general, and administrative	6,224,842	4,327,045	19,720,602	9,272,568
Research and development	13,292,263	5,247,036	24,390,172	14,072,247
Depreciation and amortization of property and equipment	34,698	41,562	115,400	116,378
Total operating expenses	19,551,803	9,615,643	44,226,174	23,461,193
Operating income (loss)	(14,526,350)	(9,615,643)	(12,375,644)	(23,461,193)
Other income (expense):				
Loss on disposal of fixed assets	(10,226)	-	(10,226)	-
Interest expense	(993,897)	(1,633)	(996,428)	(3,487)
Interest income	1,921,871	515,814	3,945,282	1,336,552
Total other income, net	917,748	514,181	2,938,628	1,333,065

Loss before cumulative effect of change in accounting principle	(13,608,602)	(9,101,462)	(9,437,016)	(22,128,128)
Cumulative effect of a change in accounting principle	-	-	(710,897)	-
Net loss	$(13,608,602)	$(9,101,462)	$(10,147,913)	$(22,128,128)
Net loss per share:				
Basic	$(0.38)	$(0.25)	$(0.28)	$(0.62)
Diluted	$(0.38)	$(0.25)	$(0.28)	$(0.62)

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July 3, 2008

One Drug, Many Uses -- Mostly a Very Good Idea

Analysis of: One drug, many uses. Good idea? | www.indystar.com

Implications: 'One drug, many uses' can make lots of sense clinically and commercially. Seeking additional FDA indications for a specific drug has obvious business benefits: greater revenue stream, improved branding, potentially longer market exclusivity, greater franchising potential of the drug into 'improved' formulations/uses (ie, Astra Zeneca's Seroquel and then Seroquel XR; or GSK's Wellbutrin family -regular, SR, XL), and less financial/regulatory risk. The costs of developing new drugs are massive and a looming unproven safety record well into development can be extraordinarily costly and even lethal to smaller companies. Take for instance Pfizer's torcetrapib which was pulled from Phase III development after safety concerns and $800M spent. Most importantly, though,'one drug, many uses' can provide valuable treatment options to patients when handled properly by pharmaceutical companies and clinicians.

Analysis: The article highlights Cymbalta – which will no doubt reward Ei Lilly heavily for its broad spectrum of uses (diabetic nerve pain, major depression, generalized anxiety) and now its newest indication, fibromyalgia, a disorder I suspect will increasingly be a target for drug development in the coming years. There is a biological basis for 'one drug, many uses': at least for central nervous system disorders, a single drug can dynamically affect a complex web of receptor targets, biologic systems, and intracellular events and produce multiple kinds of therapeutic actions. Affecting a single serotonin-specific receptor (ie, 5-HT2a) can potentially affect mood, anxiety, sleep, appetite, and cognition, and also exert effects on other brain/neurotransmitter systems like dopamine, GABA, norepinephrine, etc… Research seems increasingly to show CNS disorders as mediated by ever more complex and dynamic processes. One drug, then, may have wide biological potential.

Clinically, 'one drug, many uses' has brought improved, better studied treatments for bipolar disorder by way of several anticonvulsants (ie, valproic acid, lamotrigine, and carbamazapine) and with others coming down the pike. The class of 'atypical neuroleptics,' initially carrying FDA indications for schizophrenia, have reshaped the treatment of bipolar disorder over the past decade. Bristol Myers Squibb made an important contribution to depression treatment by executing well-designed clinical trials for its blockbuster Abilify as an 'adjunctive treatment' for depression, the first such drug approval. While a boon for BMS, the scientific and financial contributions leading to this added indication are important clinically. AstraZeneca is seeking anxiety and depression indications for Seroquel XR, building on Seroquel's success which itself made a mark with data (and an FDA indication) supporting its role in bipolar depression.

There is risk, though. Worrisome drug effects may be overlooked when the newer uses steer far from the drug's underlying central actions or the clinician's experience. For instance, if Cymbalta were approved for chronic knee and back pain, it would be important for pain specialists, orthopedists, or whichever kind of clinician is prescribing to consider certain clinical and monitoring issues. Antidepressants like Cymbalta can pose serious risk to certain kinds of patients and potentially make their illness worse, such as those with bipolar disorder or who are prone to the activating effects of such drugs.

I would take issue with the claim that one drug, many uses comes at the expense of innovation. While seeking new uses for a particular drug will never carry the scientific cache or glamour of discovering and bringing to market a new chemical entity, considering and then executing a plan to develop other uses can be quite innovative and challenging. Take for instance Jazz Pharmaceuticals, whose niche narcolepsy drug Xyrem is in the midst of Phase III fibromyalgia trials – a very innovative approach to this disorder. And if one drug/many uses makes companies a bit leaner and more successful by tapping out the potential of what they already have in hand, well then there might be more in the coffers for

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June 30, 2008

Lundbeck Reveals Mechanism of Action of its "Mixed Serotonin Modulator and Stimulator" Antidepressant LuAA21004

Analysis of: Interim report for the first quarter of 2008 - strong growth in sales and profits | www.lundbeck.com

Implications: Lundbeck has now disclosed the mechanism of action of its "mixed serotonin modulator and stimulator," albeit buried in a first quarter report. Data on LuAA21004, Lundbeck's lead antidepressant jointly in development with Takeda, was released at the Scandinavian College of Neuro-Psychopharmacology this past April. So far, the drug has been shrouded in some mystery with only speculation as to its novelty, especially when viewed against the large pool of generic SSRIs/SNRIs either in the market or soon entering it. Lundbeck and Takeda hope to advance LuAA21004 through an ambitious Phase III program with an anticipated launch by 2011 just before generic Lexapro arrives.

Analysis: Lundbeck has disclosed LuAA21004 as a mixed serotonin 5-HT3 receptor antagonist and 5-HT1 partial agonist. In prior GLG News, I have suspected serotonin 5-HT1a partial agonism for this investigational drug, which, when weighed against the latest evidence, is no longer the compelling receptor target for depression or anxiety that was once hypothesized. Drugs primarily aimed at 5-HT1a have had a couple recent development failures on the depression/anxiety front. 5-HT3 antagonists have been used primarily as anti-emetics, especially for chemotherapy induced nausea/vomiting, with a couple targeting irritable bowel syndrome. I have not seen much data on 5-HT3 receptor for depression. Lundbeck and partner Takeda appear to be advancing this compound rapidly into Phase III following positive Phase II proof-of-concept data last fall. Hopefully the Phase III data will be a bit more compelling than the receptor profile quietly announced over the last few months.

May 21, 2008

BrainCells Novel Antidepressant: Targeting Neurogenesis but not Serotonin?

Analysis of: BrainCells Inc. Initiates Phase 2 Clinical Trial With BCI-540 For Depression With Anxiety | www.medicalnewstoday.com

Implications: It's not clear just how BrainCells' BCI-540 works but the company claims the drug acts by way of promoting neurogenesis without an effect on serotonin neurotransmission. While SSRI's also promote neurogenesis, a downstream effect believed to favorably impact mood and anxiety, they obviously work by targeting serotonin. At this stage, it's hard to say what this really means for BrainCells' potentially novel drug or its proprietary platform – which aims at developing drug candidates that 'modulate neurogenesis,' presumably in brain areas like the hippocampus that may experience injury under stress or depression. But the idea of developing drugs that target downstream neurocellular events such as the production of various neurotrophic factors (i.e, BDNF) or neurogenesis itself without having all the 'upstream, start-up' actions associated with serotonin or norephineprhine reuptake inhibition is very attractive, at least in theory.

Analysis: The key question is what does BrainCells really have here, either in its drug or in its entire CNS drug development platform. Lots of drugs have potential to impact neurogenesis while helping depression/anxiety and doing so without serotonin effects. I suspect a number of them are already in the commercial market. However, if BCI-540 is doing something further 'downstream,' it may potentially carry fewer side effects or work more quickly than the standard 4-6 week trial. This could amount to something clinically very significant. Even a novel mechanism of action that can target neurogenesis, and possibly depression, in ways outside the monoamine system (i.e, serotonin, norepinephrine, or dopamine) could be compelling.

BrainCells' publicly available intellectual property platform seems largely based on 'modulating neurogenesis' with some interesting, quite novel CNS targets. Their scientific team looks good too, including the Nobel Prize winner Erik Kandel. For sure, BrainCells is certainly on the right track with early stage marketing and financing their company. I eagerly await data from this Phase II proof-of-concept study which will help determine

efficacy and safety. I also eagerly await further disclosures from the company about just how BCI-540 works to see if this is really something quite new or something old with new packaging.

Permalink

Healthcare News Feed

Report a Concern

May 13, 2008

Abbott Targets Adult ADHD with Nicotinic Drug, Shows Strong CNS Pipeline

Analysis of: Abbott Scientists Present A New Approach for Treating Attention-Deficit Hyperactivity Disorder | biz.yahoo.com

Implications: Abbott's Neuronal Nicotinic Receptor (NNR) partial agonist platform is an innovative target for ADHD and potentially other CNS disorders. The Phase II data on ABT-089 suggests efficacy for adult ADHD with good safety/tolerability. NNRs will not have the kind of effect size seen with stimulants but there is certainly a clinical need for drugs that work differently than current treatments including Eli Lilly's Strattera, a norepinephrine reuptake inhibitor. I attended the APA annual meeting in Washington DC and was impressed by Abbott's neuroscience pipeline aiming at novel treatments for Alzheimer's Disease, ADHD, and schizophrenia - beyond just the NNRs.

Analysis: Adult ADHD represents a potentially large treatment population, with an estimated prevalence of 4-5% of adults and numbers in the range of 5-10+ million individuals depending on the age range one looks at. Recent studies suggest only 1 in 5 adults that meet criteria for ADHD actually receive medication treatment for it. Stimulants are highly effective for adult ADHD but may carry certain medical risks in a subset of patients on account of the cardiovascular effects, in addition to 'perception' issues for patients and clinicians alike. Atomoxetine (Strattera; Eli Lilly) is the only non-scheduled FDA-approved treatment for adult ADHD and other off-label choices (Provigil, tricyclic antidepressants, alpha-2 agonists) carry only modest benefit, if much at all in adults. The ADHD market will likely see one or two alpha-agonists for child/adolescent ADHD in the next year or two, though hypotension and efficacy may be limitations in adults. The profile of NNRs, especially with its seeming lack of cardiovascular side effects and potential value on executive function/inattention, is attractive for adult ADHD and possibly other disorders (ie, cognitive impairment in schizophrenia, depression). We will need to await larger trials that will bear out efficacy in clearer terms but this is a positive development.

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Other Analyses of the Same Article (8)

Healthcare News Feed

Report a Concern

April 28, 2008

Glaxo Decision Moves Drug Development Forward Again

Analysis of: Federal Court Sides With GlaxoSmithKline, Strikes Down Rules Issued by Patent Office | biz.yahoo.com

Implications: The USPTO's proposed rule changes, struck down in this important Glaxo federal court decision, would have added significant burdens to pharmaceutical companies in developing their IP portfolios and ultimately their drug treatments. The proposed changes were seemingly motivated to make the patent application process run better by creating leaner applications and limiting continuations. However, the downstream result would have seriously hurt the development of new drug treatments, adversely impacting smaller biotech, academic settings, and big pharma. The federal decision, while clearly favorable to the pharmaceutical business as a whole, will also be beneficial for making better medical treatments available.

Analysis: Intellectual property forms the basis of drug development for medical illnesses. While it is possible to bring a prescription drug to market without patent protection – there is a period of 'marketing exclusivity' for FDA approved drugs – many drugs recoup their development costs (as well as costs associated with the failures a company may suffer too) while patent protected but out of the FDA's marketing exclusivity. Incentive to create new and better medical treatments has a strong basis in whether that is financially viable which, obviously, is enhanced with patent protections or a better opportunity to get there.

Narrowing claims, as was proposed by USPTO, would have limited just how much could be included in the patent but restricting continuations/requests for continued examination would have badly damaged the ability for innovators to protect their inventions. Such continuations are a way to defend the patent through its examination. It is not hard to see the repercussions if the USPTO changes were left to stand. Early stage biotech companies,

now a vital springboard to innovative treatments, would have become less attractive to potential investors; larger pharmaceutical companies might have abandoned important clinical platforms not having another chance to file for continued applications. The federal court's decision helps dampen some of the risk to drug development, itself highly risky, and ultimately helps advance medicine.

Permalink

Other Analyses of the Same Article (4)

Healthcare News Feed

Report a Concern

April 24, 2008

Corcept Therapeutics Takes Yet Another Shot at Psychotic Depression

Analysis of: Corcept Therapeutics Announces Commencement Of Next Phase 3 Study With CORLUX(R) For The Treatment Of Psychotic Depression | www.biospace.com

Implications: Corcept Therapeutics is at it again with yet another clinical trial for its lead candidate mifeprisotone (Corlux), a GR-II (glucocorticoid) receptor antagonist, hoping to show efficacy on the psychotic features of psychotic major depression (PMD). Corlux clearly offers a potentially novel paradigm unlike anything presently on the market for treating psychiatric disorders – it targets the hypothalamic-pituitary-adrenal (HPA) axis. The key question to date, however, has been whether Corlux even works at all. There are no FDA-approved treatments for psychotic depression though combination antidepressant/antipsychotic treatment or ECT is often the standard, with antipsychotic agents specifically used to treat the psychotic features.

Analysis: Corcept's latest round of financing and its partnership with MedAvante to handle clinical ratings is another breath of life for a drug that has looked on the brink of death a few times in its life. In 2006, a published clinical trial for Corlux in psychotic depression received hard criticism on multiple fronts, from study design to flawed statistical analysis, and finally the drug's efficacy itself on both psychotic and depressive symptoms. The Corcept team has mustered whatever it could from prior data and is pulling all stops to show some efficacy – higher dosing, centralized video assessments, and a sizable study group. This 4th clinical trial is designed with Corlux vs placebo for the first week, followed by antidepressant treatment.

One problem is that prior data suggests Corlux carries only modest utility against either psychotic or depressive symptoms, a rather large obstacle for an illness this challenging to treat and appearing neurobiologically closer to schizophrenia than depression. The lack of a second active comparator arm in this study will raise questions just how Corlux measures up against the kind of drugs so commonly used to treat the psychotic features of PMD nowadays – the atypical antipsychotics – which have versatility across both positive (ie, hallucinations) and negative (ie, flat affect, disorganization) symptoms of psychosis, and may help associated cognitive problems like verbal working memory. The other problem is that Corcept will require two positive studies for FDA approval. The first three trials don't look all that helpful and another large trial for a drug with a history of recruitment issues will pose time and financial burdens for Corcept especially if they plan to still learn through this trial.

Even if Corlux ultimately hits the market, there is the question of how it will fit into a clinical landscape where growing data suggests some atypical antipsychotics confer both antidepressant and antipsychotic effects, potentially with added value in combination with antidepressants. Seroquel (Astra Zeneca) and Abilify (Bristol Myers Squib) have shown antidepressant and antipsychotic properties, along with FDA-indications spanning mood and psychosis, and Seroquel XR will be aiming broadly to target psychotic, mood, and anxiety disorders. Unfortunately there is a surprising lack of data in treating psychotic major depression and Corcept has been its own guide at substantial cost. It will be hard to have another chance. Hopefully this drug will bring attention to a seriously unmet clinical need in psychiatry and even offer something clinically valuable though it may have better odds for treating weight gain associated with antipsychotic agents (like Zyprexa) and Cushing's Syndrome, other viable indications.

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Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

April 17, 2008

Another Casualty in Antidepressant Development

Analysis of: EPIX Pharmaceuticals Announces Discontinuation of PRX-00023 Clinical Development Program | biz.yahoo.com

Implications: The development of a new generation of serortinin 5HT1a agonists for major depression and anxiety disorders has met yet another failure, now from EPIX Pharmaceuticals' PRX-00023. Gepirone ER (GlaxoSmithKline), another 5HT1a partial agonist, suffered the same fate last November when the FDA rejected it as a treatment for depression. The article cites poor efficacy in depression as the reason for dropping development of PRX-00023 though lack of efficacy for generalized anxiety disorder has been reported in the past with published results this month failing to show benefit over placebo on primary endpoints. Does this failure offer any insights for what's in the antidepressant pipeline or for other, similarly acting drugs?

Analysis: Drugs acting primarily by way of this mechanism of action historically have a rather poor track record. Buspirone, available for treatment of generalized anxiety disorder, is sparsely used nowadays despite some new data shedding light on its potential value to augment antidepressants. Pindolol, an antihypertensive with 5-HT1a properties, has had mixed results in mood and anxiety studies. As far as I can tell, PRX-00023 may have been the last 5HT1a partial agonist in development for depression or anxiety and perhaps deservedly so, though a number of companies (ie, Lundbeck, Fabre-Kramer, Clinical Data, among them) are betting that this receptor profile in combination with other serotonin receptor actions will add efficacy, improve side effect profile, or speed up response over the commonly prescribed class of SSRI's. GlaxoSmithKline has an early stage 5HT1a antagonist for mood and anxiety disorders; Vilazodone, in Phase III trials, could be the first-in-class mixed SRI/5HT1a partial agonist and carries some favorable data. While a bad blow for EPIX – having lost 50% of its valuation since the bad news a few weeks ago – one of their novel early stage CNS products, a 5HT6 antagonist, looks quite interesting for memory and weight problems.

Permalink

Healthcare News Feed

Report a Concern

March 19, 2008

Another New FDA Indication For Abilify

Analysis of: U.S. Food and Drug Administration Approves Abilify (aripiprazole) for the Acute Treatment of Manic and Mixed Episodes Associated With Bipolar I Disorder in Pediatric Patients (10 to 17 Years of Age) | pharmalive.com

Implications: The FDA's approval of Abilify for treatment of acute manic and mixed episodes of pediatric Bipolar Disorder is a very important milestone. Treatment with Abilify already has had growing off-label use in the pediatric population, in both acute and chronic settings, because of its favorable profile on weight. Now data is here to support that.

Analysis: This is very good news clinically and also good news commercially for Bristol-Myers Squibb and Otsuka, coming off the Abilify adult depression augmentation approval last November. Pediatric bipolar disorder presents challenges beyond managing bipolar symptoms; children and adolescents are moving through a complex developmental period and the medical/psychological sequelae of weight gain (sometimes profound) - common to the class of atypical neuroleptics and other bipolar medications such as Depakote - cannot be overstated. While this FDA indication is for acute mood episodes, maintenance treatment with Abilify is often utilized longer term in this population because of its better side effect/metabolic profile than drugs such as Zyprexa, Risperdal and DKA, among others. I anticipate Abilify will obtain a maintenance pediatric bipolar indication though the data is not yet available, which should further support its important place in the treatment of bipolar disorder.

Permalink

Other Analyses of the Same Article (4)

Healthcare News Feed

Report a Concern

March 6, 2008

Dov's Triple Reuptake Inhibitor Enters Phase II Major Depression Trial

Analysis of: DOV Pharmaceutical, Inc. Initiates Phase II Clinical Trial in Patients With Major Depressive Disorder | www.pipelinereview.com

Implications: Triple-reuptake inhibitors (TRIs) represent an emerging class of antidepressant drugs in development with potential application for other disorders including ADHD and obesity. By potentiating all three of the main monoamine neurotransmitters implicated in depression - serotonin, norepinephrine, and dopamine – they potentially offer a degree of efficacy that will separate them from existing antidepressant treatments and may

carry an improved side effect profile (ie, less weight gain, enhanced profile on energy/motivation in the short and long term). It's too early to say much about DOV Pharmaceutical's DOV 21,947, which hopes to have this Phase II depression data within a year, but TRI's should have a significant place in the depression market in a few years.

Analysis: Looking at Triple Reuptake Inhibitors in general, we don't see anything profoundly groundbreaking or novel – we're still in the monoamine system, perhaps providing neurotransmitter effects not unlike that of the rarely used class of Monoamine Oxidase Inhbitors (MAOIs) but with a potentially better side effect and food-drug interaction profile. But longer term use of SSRIs may lead to downregulation of the dopamine system, contributing to fatigue, apathy and weight gain in some patients. TRIs may provide a built in counterbalance with their dopamine properties and, at least in theory, may be especially helpful for what is called 'atypical depression,' characterized by increased sleep, appetite, and fatigue. Also, emerging new drugs for depression treatment seem to have a litmus test of whether they cause sexual side effects or weight gain and it would appear TRIs may look good here and there is data showing weight loss with DOV 21,947.

There is no hard data to show that there is enhanced efficacy but the mechanism of action suggests the possibility; major depression still carries a full remission rate of less than 50% in most antidepressant studies, with partial responders and non-responders unfortunately all too common. How these drugs will work on anxiety symptoms, often comorbid with major depression, is not clear either and may have signficant clinical impacts - we know that SSRIs are generally favorable in this regard. A number of TRIs are in development by other companies, including a GlaxoSmithKline's 272, 475, in-licensed from Neurosearch, and Sepracor's SEP-225289, both in Phase II trials for depression.

Permalink

Healthcare News Feed

Report a Concern

March 5, 2008

An Uphill Battle Ahead – Luvox CR Approved for OCD and Social Anxiety

Analysis of: FDA Approves Luvox CR (Fluvoxamine Maleate) Extended-Release Capsules for the Treatment of Social Anxiety Disorder and Obsessive Compulsive Disorder | pharmalive.com

Implications: Fluvoxamine, the least known of the selective serotonin reuptake inhibitors in the US, will now have an FDA approved controlled release version - Luvox CR - for the treatment of OCD and Social Anxiety Disorder. The collaboration between Jazz Pharmaceuticals and Solvay will have only an uphill battle ahead to improve perception of the fluvoxamine/Luvox line. The Luvox brand once had a stronger connection to OCD treatment but that has slipped considerably over the years to all the other SSRIs, as well as to the serotonin-norepinephrine reuptake inhibitor (SNRI) Effexor XR (Wyeth) which is commonly used to treat OCD and social anxiety, as well as depression.

Analysis: While Luvox CR may offer something of a small jump start to this nearly forgotten drug line, which I see only infrequently prescribed these days for OCD, much less for social anxiety, I think the kick will be pretty small. Fluvoxamine failed to gain much traction early in its life, perhaps a consequence that it was the one SSRI that failed to obtain a major depression indication. That, along with its less than favorable drug-drug interaction profile and recommended twice daily dosing, set it well behind all the others. I doubt that will change much in the months and years ahead with Luvox CR.

What may be positive, though, is that this new CR form potentially represents an improvement on fluvoxamine, its tolerability (ie, less peak effect) and even efficacy for patients (ie, if patients are getting the proper dose rather than missing doses which often happens with twice daily dosing). Also, if this brings some added attention to the treatment of OCD or social anxiety, overshadowed by major depression and generalized anxiety disorder, there may be something else positive here.

Permalink

Other Analyses of the Same Article (5)

Healthcare News Feed

Report a Concern

March 4, 2008

Deep Brain Stimulation for Treatment Resistant Depression – The Race is On

Analysis of: St. Jude Medical Announces Clinical Study of Deep Brain Stimulation for Depression | www.pipelinereview.com

Implications: Deep brain stimulation (DBS), an FDA approved device treatment for Parkinson's Disease and essential tremor, has demonstrated quite remarkable findings in several very small pilot studies for treatment resistant depression. There is great hope among the device makers – namely Medtronics and St. Jude Medical– that this innovative approach may be but a couple years away from their own FDA approvals for refractory depression. With the FDA's Investigational Device Exemption (IDE) and clearance to begin enrollment for a DBS/refractory depression trial, St. Jude Medical takes a big step forward.

Analysis: Though DBS data so far is very limited – but a handful of cases – what's there is among the most compelling interventions in severe psychiatric illness I've come across. In some instances, patients refractory to multiple medication trials and even ECT have shown improvement of symptoms shortly after the device was turned on; even more striking is how symptoms recur when the device is switched off.

There are many unanswered questions regarding DBS and depression. Which parts of the brain are best targeted is still being worked out and whether side effects, often neuropsychiatric in nature, will present especially problematic risks for patients with severe psychiatric disorders such as refractory depression. The pioneering work of Mayberg and Lozano, which forms the neurological and patent basis for the St. Jude trial, targets Brodmann Area 25. Another area of major interest for resistant depression, also the basis of some case reports, is the nucleus accumbens (considered a key part of the brain's reward system).

Vagus nerve stimulation (Cyberonics, Inc.) has been a device disappointment for depression treatment. But the case material on DBS-treated refractory depression patients is enough to suggest something very different and promising. If indeed DBS works as well as some case reports show and makes it to market, how it will be accepted among psychiatrists and the public is the next major question.

February 27, 2008

MEM 3454, A Hopeful New Drug Treatment for Cognitive Impairment in Schizophrenia?

Analysis of: Memory Pharmaceuticals & Roche Expand Development Program for MEM 3454 in Schizophrenia | www.pipelinereview.com

Implications: The announcement of this small biomarker study for MEM 3454, an alpha-7 neuronal nicotinic receptor (NNR) partial agonist in joint development by Memory Pharmaceuticals and Roche for the treatment of cognitive impairment associated with schizophrenia (CIAS), seems like a step in the right direction in helping clarify treatment issues in this formidable clinical problem. However, despite the growing attention to find pharmacologic interventions for CIAS, the road ahead will likely carry a number of obstacles.

Analysis:
Developing effective treatments for CIAS will be challenging, in part because such cognitive deficits may be wide ranging (ie, attention, sensory filtering, linguistic function and priming, verbal working memory, etc..), may vary greatly between patients and be inextricably linked to underlying symptoms of the disorder. But that hasn't stopped interest in designing better studies or looking for experimental treatments.

The NIMH's MATRICS initiative (Measurement and Treatment Research to Improve Cognition in Schizophrenia) has been an important step to help bridge the gap between the FDA's regulatory demands and agreed upon outcome measures for evaluating cognitive function in schizophrenia. However, the jury is out (and hasn't received much evidence, either) as to whether biomarker studies carried out in clinical drug trials, in their infancy here, will provide additional guidance for assessing treatment interventions or helping the FDA make decisions. It may, however, help optimize study design and pooling of the data, so that when its time for a New Drug Application (NDA), the best picture can be set forth.

Nicotinic receptor partial agonists represent an innovative drug development platform. While varenicline (Chantix; Pfizer), an alpha4/beta2 NNR partial agonist used for smoking cessation, is the best known, there are a number of pharmaceutical companies that have nicotinic partial agonists in development for a range of cognitive disorders, among them CIAS, Alzheimer's Disease, and ADHD. Preliminary data from genetic, clinical and post-mortem studies suggest the alpha-7 receptor may play a role in some of the cognitive and attentional deficits in schizophrenia but this too warrants perspective, as such cognitive issues may have a myriad of underlying causes, much less outward presentations. Measuring P50 evoked responses has been one model of assessing such deficits.

At least on paper, MEM 3454 is intriguing. Advancing MEM 3454 to its Phase 2a trial two months ago was the key milestone for Memory and Roche, and the overall data there will be the most telling part of the equation. The 12 person biomarker pilot study can't hurt but may not shed much light on this broad problem either.

BOOKMARK

Permalink

Other Analyses of the Same Article (3)

Healthcare News Feed

Report a Concern

February 25, 2008

Lundbeck's Pipeline Advances with Lu AA34893 for Bipolar Depression

Analysis of: Lundbeck further strengthens pipeline by moving Lu AA34893 into clinical phase II | www.pipelinereview.com

Implications: Lundbeck's pipeline has been gathering some real momentum in recent months, having advanced a number of investigational CNS drugs. The initiation of this 600 person Phase II study of Lu AA34893 in bipolar depression, yet another Lundbeck drug candidate shrouded in some mystery (ie, we know that it's likely 'serotonergic' or broader yet, 'monoaminergic'), is another important milestone for Lundbeck. But what else is known about this drug or the trial?

Analysis: Lundbeck is working hard to solidify itself in a post-Lexapro/Forest era, though when that new chapter will start seems unclear on account of various generic/patent issues currently under litigation. For instance, Lu AA21004 entered Phase III for depression this past December; Lu AA24530 entered Phase II for depression in October; Lu AA 47070 and Lu AA37096 both entered Phase I since November. And now Lu AA 34893 enters Phase II for bipolar depression.

Overall, the Lu AA34893 trial looks to have a good design – randomized, double-blinded, with depressive symptoms as its primary outcome measure in patients with Bipolar I or II Disorder – and a large patient pool. In the study, different dose ranges of Lu AA 34893 will be measured against quetiapine (Seroquel; AstraZeneca) and placebo, and the drug will be studied as a monotherapy.

It's hard to say anything more substantive about Lu AA34893 at this point. How this drug actually works is not that clear and just how "new" and "novel" it is also is unclear, because Lundbeck doesn't identify specific receptor targets. Much of Lundbeck's pipeline for mood and anxiety disorders would seem to work by some combination of serotonin reuptake, partial agonist, or antagonist properties. Even if Lu AA34893 has something of this profile, it's far too speculative to say what this could mean for bipolar depression. Also, length of treatment is another potential confounding issue, as patients with Bipolar Disorder may have added risks, over time, of mania (or mixed manic/depressive states) when treated pharmacologically for depression.

What is significant clinically is that the treatment of bipolar depression is fraught with clinical challenges and there is a great need for effective, safe treatments. Seroquel now carries an FDA indication treatment, as does Eli Lilly's Symbyax (though I haven't really seen Symbyax used). Lamictal, FDA-approved for use as a maintenance treatment of adults with Bipolar Disorder to delay the time to occurrence of mood episodes, is often used to treat bipolar depression but can be slow-going due to dose-titration/side effect issues. The use (and/or augmentation) with antidepressants, Lithium and atypical neuroleptics, is common practice but with mixed data and clinical perspectives.

Needless to say I am excited to see what kind of data this trial will bear. This is a very important clinical area, with major unmet needs pharmacologically, but which unfortunately has taken a back seat to pharma's development of antidepressants.

BOOKMARK

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Healthcare News Feed

Report a Concern

February 12, 2008

Extending The Life of a Branded Drug

Analysis of: Indication Expansion: Opportunities for successful lifecycle management | www.pipelinereview.com

Implications: New clinical indications add to a drug's period of FDA market exclusivity (different than patent exclusivity) and is a common strategy used by pharmaceutical companies to generate additional revenue from a drug, in pharmaspeak referred to as creating a "successful lifecycle management" strategy.

Analysis: Bringing innovative drugs that are new-compositions-of-matter all the way through development and into the marketplace is extraordinarily costly, time-consuming, and risky. To balance this, an FDA approval for a New Drug Application is allowed 5 years of market exclusivity regardless of whether or not the new drug is patent protected. New FDA-

approved indications or an approval for pediatric use can extend such exclusivity and can make sense both clinically as well as commercially. But whether or not expanding clinical indications makes sense for any given drug involves lots of issues.

Beyond the obvious, that adding new FDA indications extends a branded drug's presence in the market, delays time against generic competitors, and thereby generates additional revenue, such "lifecycle management" strategies can reach broader. Added indications may create the perception that such drugs have broader clinical use, leading to 'off-label' prescribing of the drug for other conditions. Such strategies may also be utilized to maximize the development and commercialization of a drug well before the end of its FDA market exclusivity period, with the idea of boosting the "early" part of the lifecycle rather than "late" part which is most typically about preventing generic incursion. Take for instance AstraZeneca's Seroquel XR, FDA indicated for acute and maintenance treatment of schizophrenia. AstraZeneca is looking to expand Seroquel XR to both bipolar mania and depression indications, as well as generalized anxiety disorder. If successful, this could add significantly to AstraZeneca on multiple fronts. When 'patent protection' exclusivity issues are at hand (ie, the composition-of-matter patent may expire before the period of FDA market exclusivity ends), added indications to lengthen FDA market exclusivity or method-of-use patents (on the patent protection side) can provide added value as well, another rationale for 'lifecycle management.'

There is no bottom-line conclusion here other than managing the lifecycle of a drug can have appeal both clinically and commercially. But many factors need consideration for any prospective drug candidate.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

February 6, 2008

Somaxon and Silenor, A Win-Lose Situation?

Analysis of: Somaxon Pharmaceuticals Submits New Drug Application For SILENOR(TM) For The Treatment Of Insomnia | www.pipelinereview.com

Implications: The NDA submission of Somaxon's Silenor, a reformulation of the tricyclic antidepressant doxepin at very low doses, for the treatment of insomnia is not particularly compelling news clinically. Low doses of doxepin provide an anti-histamine effect with less norepinephrine or serotonin reuptake properties, the basis of its antidepressant effect. At first glance, this would not be a drug to have wide clinical or commercial value – perhaps an expensive version of diphenhydramine (Benardryl) or hyroxyzine (Vistaril). But that doesn't necessarily mean bad news for Somaxon….

Analysis: An FDA indication for insomnia with good marketing would still not likely make this drug anything of a winner in the insomnia market, much less a blockbuster. Its clinical value and comparative side effect profile would need to be seen but even if favorable, market perception of the drug seems to be starting at a distinct negative. And there are many good FDA-indicated treatments for insomnia, including generic zolpidem (Ambien), as well as frequent off-label uses of drugs with better market perception and clinican comfort than doxepin.

However, I doubt Somaxon's goal is to introduce a big winner here. Even a small sliver of the insomnia population could grant them a relative victory. By filing the NDA via a 505(b)(2) route, they are able to demonstrate safety based on prior data for doxepin and have their Phase III trials and results without the associated development costs and burdens. Safety is an increasingly bigger issue for investigational new drugs and the risk is obviously hedged here with a drug used clinically. An FDA indication with formulary coverage for the branded drug could create a financial base for Somaxon's pipeline, which appears more attractive than Silenor itself. Market exclusivity would protect the product for 5 years, patent and related regulatory protections would add some additional time, though I suspect prescribing of the generic 10 mg form of doxepin would occur if, by some measure, Silenor actually picked up steam. All said, I think Somaxon's strategy here may be better off than Silenor's prospects.

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Other Analyses of the Same Article (6)

Healthcare News Feed

Report a Concern

December 11, 2007

Agomelatine, An Antidepressant Without Weight Gain and Sexual

Side Effects?

Analysis of: Novel Melatonergic Antidepressant Remains Promising | www.clinicalpsychiatrynews.com

Implications: Agomelatine (Valdoxan; Servier with rights in Europe and Novartis in the US) is a mixed melatonin (MT1 and MT2) agonist and serotonin 5-HT2c antagonist in development as a treatment for major depression and generalized anxiety disorder. Its melatonergic properties make it unique among antidepressant and anxiolytic drugs in development, with a putative mechanism of action in that it helps resets desynchronized circadian rhythms. Agomelatine carries a potentially favorable profile on sleep, weight and sexual function as compared to marketed selective serotonin reuptake inhibitors (SSRIs). However, will its efficacy be significant enough to bring it to market in Europe and the US?

Analysis: In 2006, agomelatine was refused marketing authorization in Europe by the Committee for Medical Products for Human Use (CHMP) of the European Medicines Agency (EMEA) due to lack of demonstrated efficacy. However, other data including a randomized, placebo-controlled trial published last year demonstrated statistically significant results in acute depression. The data presented at the European College of Neuropsychopharmacology demonstrating a reduction for relapse in depression and significant improvement in Genaralized Anxiety Disorder (GAD) is encouraging for this drug. Preliminary research has shown agomelatine may have clinical benefit in bipolar depression as well.

In October, Novartis announced initiating two Phase III trials of agomelatine (AGO178) in the US and would plan to file its New Drug Application (NDA) for depression treatment sometime in 2008. I suspect that while the efficacy of agomelatine may not be superior to existing treatments of depression and generalized anxiety, if its side effect profile is accurately portrayed (ie, no sexual side effects, limited weight gain, favorable sleep profile), this could advantageous clinically, separate it from SSRIs, and certainly strengthen its position from a marketing point of view. The profile of this drug reminds me a bit of Serzone (nefazadone), which was pulled from the US market due to liver toxicity. Curiously, nefazodone never quite did as well as one would think from its overall profile – whether on account of (lack of) marketing or the name-branding power of SSRI's at the time. We will have to see what the final data actually shows and how agomelatine performs in treating acute depression in these US Phase III trials, which will be the basis for Novartis' NDA for depression.

November 13, 2007

What Impact Will the FDA's Rejection of GlaxoSmithKline's Gepirone ER Have for Other Experimental Serotonin 5-HT1a Partial Agonists in Depression?

Analysis of: U.S. rejects Glaxo's gepirone ER antidepressant | biz.yahoo.com

Implications: GlaxoSmithKline's Gepirone ER, a serotonin 5-HT1a partial agonist licensed from Fabre-Kramer Pharmaceuticals, was issued a non-approvable letter following an amended NDA submission to the FDA this past spring. This isn't all that surprising given gepirone's history, including a similar non-approvable letter in 2004. However, Glaxo must have been attracted to the idea of an antidepressant drug with fewer sexual side effects than SSRIs and a first-in-class serotonin 5HT1a partial agonist for depression. It's hard to imagine any life left for gepirone, at least for depression (perhaps for anxiety or as augmentation treatment?), but what will this mean for other investigational drugs targeting 5-HT1a receptors?

Analysis: Drugs acting exclusively as serotonin 5-HT1a partial agonists have been around but never quite shown robust antidepressant activity alone – buspirone and pindolol are among them. However, when added to SSRI's, there is some data to suggest a potentially quicker response, enhanced antidepressant activity and amelioration of sexual side effects (the latter two shown with buspirone). Gepirone may actually confer greater benefit as an augmentation strategy than a stand-alone treatment for depression.

There are other experimental drugs targeting 5-HT1a receptors but most of them affect more than one receptor system. Clinical Data's Vilazodone, a mixed SSRI and 5-HT1a partial agonist, leads the pack of investigational antidepressants that have an effect on 5-HT1a. Prospects appear bright for Vilazadone, with results of its recent Phase III trials looking solidly significant on primary endpoints. I suspect there is at least one such kind of drug in Lundbeck's pipeline of mystery antidepressants, so named because the company offers little description of how they work. Fabre-Kramer - despite this recent setback - has a couple of serotonergic drugs in Phase II trials that appear to have multiple mechanisms of action and that are under development for depression and anxiety. Also in the fray is Epix Pharmaceuticals, which is developing a mixed 5HT1a partial agonist/opioid antagonist for depression. All said, there are prospects for better drugs in the pipeline with Vilazodone now closest to claiming rights to a first-in-class antidepressant.

Permalink

Healthcare News Feed

Report a Concern

November 12, 2007

Is Potential Taisho-Pfizer Alliance on mGluR Schizophrenia Drug Candidate Coming Too Late?

Analysis of: Taisho and Pfizer Sign a Letter of Intent for Taisho's Schizophrenia Drug Candidate | biz.yahoo.com

Implications: Investigational drug candidates that target metabotropic glutamate receptors (mGluR) show promise as novel treatments for a range of CNS disorders which include schizophrenia, anxiety, chronic pain, Huntington's Disease, epilepsy and Parkinson's Disease. If Pfizer consummates this deal with Taisho, it will put them on the mGluR map though behind Eli Lilly and AstraZeneca which have mGluR drugs in clinical development.

Analysis: Eli Lilly's recent announcement of significant positive Phase II results for its LY2140023 mGlu2/3 receptor agonist for schizophrenia has attracted lots of attention in the field, heralding this as one of the most important advancements in schizophrenia treatment since the advent of atypical antipsychotics . Efficacy in that trial was comparable to olanzapine (Zyprexa) but with evidence of a far better metabolic profile and no extrapyramidal or prolactin effects. It is unclear just how Taisho's drug is proposed to work on mGluR (there are a number of different groups and subtypes) but my best guess would be as an mGluR2 agonist.

Pharmacologic treatments of psychotic disorders have been focused on the dopamine system, with the more widely used second-generation antipsychotics also affecting serotonin 5-HT receptors. Treatment of schizophrenia with a drug that carries a completely new mechanism of action, that may act to augment response to current drugs, and potentially have less medical morbidity (e.g. weight gain, high triglycerides, glucose abnormalities) is quite attractive though it is still too early to draw firm conclusions. Last month, AstraZeneca acquired the full rights to NPS Pharmaceuticals' mGluR intellectual property following a previous collaboration and have an mGluR drug candidate in Phase I clinical trials. Pfizer would seem wise to join in even if ultimately things don't work out or they are second or third to market – because the potential here looks very significant and assuming such drugs end up working, individual profiles may differ.

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Other Analyses of the Same Article (3)

Healthcare News Feed

Report a Concern

October 24, 2007

Just How Effective Will Orexigen's Contrave Be As An Obesity Treatment

Analysis of: OREXIGEN(TM) Therapeutics Initiates its Third Phase III Trial for Contrave(TM) to Treat Obesity | biz.yahoo.com

Implications: Obesity is a major health issue with significant associated morbidity and with rates only rising, especially among the young. OREXIGEN Therapeutics' Contrave is moving along as a potential treatment of obesity, having initiated its third Phase III trial. Contrave is a novel combination-drug concept using bupropion SR (of the Wellbutrin brand) and naltrexone SR (of the ReVia brand), drugs commonly used to treat mood disorders and alcohol dependence, respectively. But what can we expect to see with this medication approach to obesity?

Analysis: Recent clinical data suggests that low-dose naltrexone, an opioid receptor antagonist, may reduce weight gain associated with smoking cessation. Bupropion SR (a norepinephrine-dopamine reuptake inhibitor) is generally appreciated as a weight-neutral antidepressant, though sometimes will cause mild weight loss. Each drug standing alone – nothing looks groundbreaking in obesity treatment. So what does CEO Gary Tollefson, MD, PhD, know about brain circuitry to support the combination? And just how would treatment look clinically?

The dual action would appear to modulate activity in the brain's opioid-dopamine-reward system and theoretically, I suspect, dampen eating behavior that may be associated with the release of endorphins and other pleasure-type molecules. The result: a kind of stabilization of appetite and over-eating. If this concept is accurate, it has an intuitively appealing quality in that it may mitigate 'yo-yo' dieting, more rapid weight loss, and other faddish approaches that have been shown never to work in the long run. However, my gut impression (pardon the pun here) here is that efficacy may be somewhat limited, effects may take time to establish and may not be in the kind of range to attract many long-term users. The large patient numbers in each trial and the substantial trial length may reflect more modest kinds of weight loss over time. Then again, it is precisely this kind of treatment – more measured and steady that is most likely to have long term success.

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Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

October 23, 2007

Clinical Data's Vilazodone Hits Mark on Phase III Depression Trial

Analysis of: Clinical Data Announces Positive Results from Phase III Pivotal Trial of Vilazodone for Depression | www.pipelinereview.com

Implications: Clinical Data's antidepressant Vilazodone, a mixed selective serotonin reuptake inhibitor (SSRI) and serotonin 5-HT1a partial agonist, met both primary and secondary endpoints for the treatment of major depression in a pivotal phase III trial. Combining SSRIs and 5-HT1a partial agonists as separate drugs has been studied to speed up antidepressant response, enhance efficacy, and improve sexual side effects of SSRIs – Vilazodone combines both mechanisms of action in one drug. Clinical Data is also developing, under its PGx Health Division, a pharmacogenetic testing platform to determine which patients are best suited for treatment with the drug.

Analysis: Achieving statistical significance on the primary endpoint with a p=0.001, in this case mean change from baseline on the Montgomery-Asperg Depression Rating Scale, is very significant and well-below FDA thresholds for drug approvals. Another successful trial at this level would put Vilazodone in good standing for FDA approval as an antidepressant when it files its new drug application (NDA) with the FDA over the next 1-2 years. Interestingly, Vilazodone is one among a number of recycled drugs in the psychiatric pipeline that has failed prior clinical trials. Clinical Data's subsidiary Genaissance Pharmaceuticals had licensed it from Merck KGaA in 2004.

These Phase III results are an important milestone for Clinical Data, especially as Vilazodone leads the pack of antidepressants in development that have combined SSRI/ 5-HT1a partial agonist properties. Even if Vilazodone makes it to market, which probably wouldn't be for 2 or more years at the earliest, the antidepressant landscape will be competitive, facing increased generic incursion from established drugs and most likely a few new FDA antidepressant approvals, some with potentially novel mechanisms of action like Sanofi-Aventis' Saredutant, an NK2 antagonist. Assuming market entrance, Vilazodone's success will likely hinge on whether it has a more favorable side effect profile (ie, few sexual side effects, no weight gain) and is actually used with genetic profiling to improve efficacy. Based on available data from prior failed clinical trials, it doesn't look like Vilazodone by itself carries enhanced efficacy over other antidepressants (or for that matter, that it would work faster), so making Vilazodone a better, more effective depression treatment will likely require momentum on the pharmacogenetic testing front. But will the data be there to support this? And is it still a bit early for patients, clinicians, and insurers to buy into this, especially as part of an initial treatment or in a primary care setting? We will have to wait and see.

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October 22, 2007

Interpreting Preliminary Phase II-B Results for Forest Labs and Gedeon Richter's RGH-188 in Schizophrenia Treatment

Analysis of: Forest Laboratories, Inc. and Gedeon Richter Announce Results of Phase II-B Study for RGH-188 as a Treatment for Schizophrenia | www.pipelinereview.com:80

Implications: RGH-188, a dopamine D2/D3 antagonist, is a potential treatment for schizophrenia and bipolar mania developed jointly by Forest Laboratories, Inc. and Gedeon Richter. Reported top-line results of this 389 patient randomized, placebo-controlled, Phase IIb trial for RGH-188 in schizophrenia show 'nominally statistically significant' differences on primary endpoints in the low-dose arm of the study and no statistical significance compared to placebo in the high dose arm. RGH-188 is somewhat different than existing second generation antipsychotic drugs used for schizophrenia and bipolar disorder in that it strongly binds D2/D3 receptors and may have more limited serotonin (5-HT2a/2c) antagonist properties.

Analysis:

The press release issued by Forest Labs exercises some careful wording but suggests the possibility of spinning something positive when the data may be equivocal. These are just top-line results and further analyses will be borne out of the data to account for statistical adjustments. While "nominally" statistically significant differences is defined here as prior to making such adjustments, I wonder if the results in the low-dose arm were less than robust and not statistically powered with an impressive p value which might otherwise carry different language (ie, results are "very significant" or "highly significant" prior to adjusting for multiple comparisons).

In addition, the higher dose range did not meet statistical significance compared to placebo on the primary endpoint (change from baseline on PANSS). That numerical improvement was better than placebo in this arm of the study (but not statistically significant) does not paint a compelling picture for RGH-188 given the size of the study, close in range to Phase III clinical trials that would be used for an FDA approval. A larger pool of patients might be necessary to power statistical significance. While some drugs exert an inverse effect beyond certain doses, antipsychotic agents that affect dopamine receptors (though mainly D2) whether by direct antagonism or partial agonist activity have tended toward a linear dose-response pattern. Forest Labs and Gedeon Richter report plans to continue development of the RGH-188 and such results by no means imply a dead-end for the schizophrenia platform but this may be an example of euphemistically stating one's case.

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Other Analyses of the Same Article (2)
Healthcare News Feed
Report a Concern

October 16, 2007

Lundbeck's "Serotonin Modulator and Stimulator" Lu AA21004: How Novel? How Good?

Analysis of: Lu AA21004 shows highly significant results in clinical phase II trial | www.pipelinereview.com

Implications: Lundbeck's lead antidepressant in development, Lu AA21004, reportedly

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achieved 'highly significant' results on primary endpoints in a recent Phase II major depression clinical trial. This is definitely good news for Lundbeck and partner Takeda which hope to have Lu AA21004 on the market by 2011, just before a generic form of Lexapro arrives. However, Lundbeck has kept this drug under raps and offers up little publicly other than its catchy sounding labels 'serotonin modulator and stimulator' and "within the new bis-aryl-sulphanyl amine class of compounds." But what does this really mean other than good pre-market marketing?

Analysis:

Lundbeck's patent trail may provide the best evidence since no one I've spoken to can tell me exactly what a 'serotonin modulator and stimulator' is. After running a number of USPTO searches to assess IP on Lundbeck's anti-depressant pipeline, my best guess is Lu AA21004 is a mixed serotonin reuptake inhibitor (SRI)/5-HT1a serotonin partial agonist and could also have 5-HT2a antagonist properties. However, other possibilities exist. I also discovered Lundbeck has a few quite novel drug concepts in the mix as potential candidates in treating psychiatric disorders. Interestingly, other early-stage "multiple target" *(but what target?)* antidepressants carry a similar mystique though Lundbeck readily discloses the mechanism of action of its clearly novel Neuropeptide Y antagonist Lu AA44608 as a potential treatment for mood disorders.

Assuming Lu AA21004 is what I suspect, what could this mean clinically? The only sure way to tell are randomized, controlled trials and head-to-head comparisons but data exists showing 5-HT1a partial agonist augmentation to an SRI may speed up antidepressant response, enhance efficacy, and decrease sexual side effects. 5-HT1a partial agonists may independently exert antidepressant or anxiolytic effects -- Fabre-Kramer's 5HT1a partial agonist Gepirone ER is expecting the FDA's decision for a depression indication any day now and buspirone, nearly dead until the STAR-D trials, works this way. 5-HT2a/2c antagonists may confer any number of effects (ie on anxiety, sleep, weight, GI and sexual function), either a plus or minus depending on the point of view. Nothing too novel here - trazodone and mirtazapine are drugs that act, in part, on 5-HT2a/2c.

One last speculation: if the drug works, perhaps even a bit faster and better than SSRIs and enters the market in several years, how would it fit in anyway? For one, cost/insurance issues will there - Lexapro and Effexor XR will be going generic (Cymbalta too?). Second, it may not be the first such drug to claim branding rights. Vilazodone (Clinical Data Online, Inc) is a mixed SRI/5-HT1a partial agonist in Phase III trials and has recently reported positive results and good tolerability. A number of other drugs in Phase III trials, some unique like Sanofi-Aventis' Neurokin-2 antagonist Saredutant, may already be available. Then again, I may be totally wrong in my guesswork and Lundbeck can enjoy delivering a real surprise.

October 12, 2007

CX717: Cortex Pharmaceutical's Ampakine Drug for ADHD Struck Down by FDA

Analysis of: FDA's Psychiatric Division has Rejected Cortexâ€™s Request to Study CX717 in Phase IIb ADHD Study | www.pipelinereview.com

Implications: The FDA's decision to not approve the investigational new drug application for CX717 (Cortex Pharmaceuticals) in the treatment of ADHD is bad news for the class of molecules known as ampakines and certainly for Cortex, which has experienced a handful of setbacks over the years. Ampakines have recently been considered a promising and potentially safer treatment for neuropsychiatric disorders such as ADHD, Alzheimer's Disease, Fragile X syndrome, and various forms of cognitive impairment.

Analysis: Ampakines potentiate neurotransmission at AMPA-type glutamate receptors, enhance arousal and attention, and have shown potential neuroprotective effects. The FDA's denial, based on animal toxicity studies, suggests to me that there may be evidence that CX717 had some neurotoxic effects. Overexcitation of AMPA-type glutamate receptors have been shown to cause cell death.

Cortex's CX717 has had issues before around dosing and toxicity, including a hold placed on their Alzheimer's study which was recently lifted. Cortex previously dampened concerns about toxicity in their animal studies commenting that histopathologic changes were only post-mortem artifacts - the FDA's decision signals another view. Dosing seems to have been problematic for CX717 with possibly too narrow a range between effectiveness and toxicity. While Cortex states they will pursue an Alzheimer's and respiratory depression platform for CX717, the picture does not look very good. Among other setbacks for Cortex was a recent controlled trial showing no benefit over placebo for enhancing memory or cognition in Fragile X patients; and a failed clinical trial for enhancing cognitive performance and alertness in night shift work sponsored by the Defense Advanced Research Projects Agency (DARPA). Since Cortex had been featured in Business Week some several years ago with promising new treatments for Alzheimer's Disease, the trajectory has been mainly downward. Other AMPA developments: a recently published study for Eli Lilly's LY451395,

an AMPA modulator, for Azheimer's Disease showed no benefit over placebo. GSK729327 (GlaxoSmithKline) is another AMPA modulator in development for cognitive problems associated with schizophrenia and currently in Phase I trials.

October 5, 2007

Treating Adolescent Depression

Analysis of: Dual Approach Aids Depression Treatment | online.wsj.com

Implications: The study reflects growing attention to the evaluation and treatment of adolescent major depression. Untreated, the consequences can be devastating, potentially lifelong, and even fatal. While this can be the case with depression in general, adolescence is a vital period developmentally and untreated depression can negatively impact one's evolving sense of identity and day-to-day experiences as the teenager enters adulthood. The NIMH-TADS (Treatment of Adolescents Study) shows what should seem obvious - the use of combination treatment of medication (fluoxetine) and therapy (cognitive behavior therapy) provided the broadest range of benefit, over either treatment alone (ie enhanced safety/decreased suicidality; most rapid effect; modest benefit in efficacy).

Analysis: A growing body of statistics about adolescent depression is showing alarm. A study just published October's British Journal of Psychiatry (among New Zealanders) demonstrated about 1 in 3 between the ages of 16-21 met criteria for a major depressive episode; about 1 in 4 showed a pattern of recurrence; and 1 in 20 had 10 or more episodes. A CDC report just issued showed rates of teen suicide reaching its highest level in 15 years, with an 8% increase from 2003 to 2004 (it nearly doubled for girls aged 10-14). Other growingly common childhood conditions, including obesity, may be linked to depression.

One the surface, the key findings in TADS were: 1) the use of medication in treatment accelerates response; 2) CBT added to fluoxetine decreased suicidality, whether in persistent form or emerging from treatment. Why? The study did not specifically address it but providing teens with tools that may help them better navigate stressful situations and complicated emotions would seem only to help suicidal behavior.

Under the surface, the key finding is that therapy helps – the teens receiving therapy alone did as well as the medication group alone. It may have taken a bit longer than medication alone but suicidality was less. Providing depressed teens with a therapeutic channel to find better ways to resolve conflict, cope with emotions, and undue destructive ways of thinking is vital and medication alone has its limits here.

Outcome studies like this are highly valuable but further research on diagnosis, predictive measures, and differential responses to treatments, are needed. Mental illness is a dynamic entity and unfolds differently for different individuals over time, especially in adolescence - a depressive episode at one point in adolescence may be a harbinger of bipolar disorder, for another recurrent major depression, or for someone else a manifestation of other problems (psychosocial stressors, ADHD, substance abuse, etc.…). Better ways to understand and apply this clinically are particularly important in adolescence and hopefully Part II to TADS, a follow-up naturalistic study, will provide some answers.

October 2, 2007

Vanda's Iloperidone: A Genetically Targeted Pharmacotherapy for Schizoprenia

Analysis of: Vanda Pharmaceuticals Submits Iloperidone New Drug Application | www.pipelinereview.com

Implications: Vanda Pharmaceuticals has filed an NDA for iloperidone, an atypical antipsychotic agent with mixed 5-HT2a and D2 receptor antagonism, for the treatment of schizophrenia. While the drug, standing alone against others in the 'atypical' class, might not stand out that much (in particular, its efficacy) - it is unique in that the efficacy data is being submitted along with specific genetic patient profiles. Targeted pharmacotherapy for psychiatric disorders may no longer be in the future.

Analysis: There are a number of interesting issues surrounding this drug, not the least of which is its history – licensed to Titan and Novartis before Vanda acquired the rights; 2 of 3 failed major clinical trials prior to Vanda's platform; and illicit behavior by a PI in the drug's early history (and in its first successful trial, no less). But Vanda has left no stone unturned in its elaboration of the clinical data. Recent Phase III trials demonstrated generally

favorable results for both positive and negative symptoms in schizophrenia in a higher dosage range. Other lower/middle range dose trials had mixed results and doses not far off from those considered optimal had failed to separate from placebo in previous studies. The most robust results, however, appear to be for patients testing positive for a specific genetic polymorphism that affects about 3 in 4 patients diagnosed with the schizophrenia. Vanda has submitted its efficacy data for patients positive for the polymorphism and seems poised to offer a blood test to attract those likely to benefit from the drug. But with a broad range of data, some mixed results, and genetic profiling in the picture - it is unclear where this one will go. An additional regulatory hurdle may lie in potential QT interval prolongation, seen in a few patients.

Vanda had done its homework, flushing out the drug's better features in its plethora of data – possibly less akathisia and extrapyramidal side effects, and perhaps a decent metabolic profile. It seems unlikely iloperidone will be a major breakthrough in schizophrenia treatment should it enter the market, even when used for those testing positive for the polymorphism. However, if it is FDA approved and can utilize genetic profiling data, this will certainly represent an important step toward personally tailored, genetically informed treatments that may be commonplace in a couple decades.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

September 28, 2007

The Next Decade of Depression Treatment: What's New, What's Old, What Will Work?

Analysis of: DOV 21,947 Demonstrates Significant Body Weight and BMI Reductions in Drug Compliant Subjects in Phase Ib Clinical Study | www.medicalnewstoday.com

Implications: Dov Pharmaceutical's triple reuptake inhibitor ("TRI"; acts on serotonin, norepinephrine, dopamine) 21, 947 is still early in development with Phase I studies but potentially offers an antidepressant with unique features, in particular its side effect of weight loss. This may not seem like a major paradigm shift in the treatment of depression - it is yet another drug that potentiates activity on monoamines perhaps not unlike the more antiquated (yet still useful) class of MAO Inhibitors - but the potential for enhanced efficacy, weight loss, and safety may be significant.

Analysis:

The clinical and commercial landscape of pharmacotherapies for depression will be interesting to observe over the next decade, especially in light of generics and the financial burdens on healthcare. At present, there are probably near a dozen Phase III trials for new treatments of depression, with a range of novel treatments (CRF1 antagonists, serotonin partial agonists, beta-3-adrenoreceptor agonists, neurokinin antagonists) and a whole lot more in an earlier stages of development that include interesting modes of action (ie glutamate modulation, nicotine receptor agonists, and others). Dov Pharmaceuticals also has a sister-compound TRI - 216,303 - in the pipeline, along with drugs that work similarly from GlaxoSmithKline, Neurosearch, and Sepracor.

What we do know is that monoamines like serotonin, norepinephrine, and dopamine do play a role in the treatment of depression but, assuming entrance into the clinical world, how will they match up against other treatments and how safe will they be? The dopaminergic component of TRI's speculatively offers some unique features – less weight gain, enhanced arousal, improvement of symptoms like amotivation/fatigue sometimes seen in both depression as well as longer term SSRI treatment, among others; however, one must wonder could there will be abuse liability or different kinds of side effects than seen with SSRIs or SNRIs. Its hard to imagine many blockbusters emerging from the landscape but more finely tailored treatments/options would be welcome.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

September 24, 2007

5HT2 Antagonists: The Next Major Class Of Sleep Medications?

Analysis of: Sanofi and Actelion Will Dominate Insomnia Market by 2016 | www.therapeuticsdaily.com

Implications: There is a clinical need for safer, well-tolerated hypnotic agents – that work. Actelion's almorexant (an orexin antagonist) and Sanofi-Aventis' eplivanserin, a 5HT2A

receptor antagonist, are two of the lead sleep drugs that offer something new as compared to existing hypnotic agents [ie Ambien/Ambien CR(zolpidem); Lunesta (Eszopiclone); Sonata (Zaleplon)] -- most of which target GABA-A receptors.

Analysis: While further data on Actelion's Orexin antagonist, Almorexant, will ultimately prove its clinical efficacy and tolerability, and FDA approval, clinical studies so far suggest potential benefit and its on-paper profile would seem to offer advantages over existing sleep drugs. Almorexant has been a topic of considerable discussion in recent GLG NewsAnalyses. However, with a good handful (maybe half a dozen or so, I think) 5-HT2 antagonists in development for insomnia, led by Sanofi-Aventis' eplivanserin, it appears that this is the hot receptor target for the next generation of better-tolerated, effective sleep medications.

Sanofi-Aventis' eplivanserin is the midst of a Phase III trial for primary insomia, with study completion slated in the coming few months. If such 5-HT2A antagonists make it to market as effective sleep medications, the first such drug will likely have a major opportunity for branding this new class of hypnotics, much as Ambien did. Will lightning strike twice for Sanofi? Preliminary studies suggest 5HT2A antagonists may work quite well, leaving people feeling rested the next day with very limited next-day effects. Still, competing against a generic Ambien – which does work well for many – will be rate-limiting. Interestingly, blocking 5HT2A receptors is common to the class of atypical antipsychotics (now standardly used in bipolar disorder as well as psychotic disorders), which leads me to wonder whether there may be a value added feature to such drugs if they indeed work for sleep.

Permalink

Healthcare News Feed

Report a Concern

September 21, 2007

Lily's Glutumate Modulator ---Very Exciting Prospect

Analysis of: Investigational Agent Targeting Metabotropic Glutamate 2/3 Receptors Demonstrates Antipsychotic Activity in Humans, Study in Nature Medicine Finds | www.pipelinereview.com

Implications: Lily's glutamate modulator LY2140023 is an investigational new drug with favorable Phase II results in a randomized, placebo-controlled trial for treating schizophrenia in a head-to-head comparison with olanzapine and placebo. Features of this drug which make it particularly appealing at this stage of development are: 1) it introduces a novel mechanism of action (glutamate modulation) and offers potential for both independent as well as augmentation benefits in psychosis (among other possible conditions); and 2) it may carry a more favorable side effect profile as compared to currently marketed antipsychotic agents.

Analysis:

Treatment of schizophrenia and psychotic conditions has been limited to two classes of medications that primarily have targeted the dopamine system: 1) the 'conventional neuroleptics', which have fallen out of favor because of prominent extrapyramidal (ie Parkinson-like, aka, EPS) side effects and tardive dyskinesia (TD) and; 2) the newer generation of "atypical antipsychotics" like olanzapine, quetiapine, risperidone, aripirazole, and ziprasidone, which target both dopamine and serotonin (5HT)-2 receptors (and some others), and have a decreased risk of EPS and TD. However, for some of these agents, weight gain, metabolic syndrome, and increased prolactin have been problematic.

There is great demand for better tolerated antipsychotic agents and also for ones that may compliment, by virtue of an alternative mechanism of action, existing antipsychotic agents. Further studies will determine just how effective LY2140023 is in human subjects, but animal models of depression/anxiety and newer clinical data suggest that the glutamate system may play a vital role in mood, anxiety and psychosis, and that drugs which modulate this system, such as LY2140023, may potentially confer a broad range of benefit. Two noted side effects, insomnia and mood lability, suggest a possible activating effect, which will require further study and may have clinical bearing on its potential use in mood and anxiety disorders. If this drug holds up in its Phase III trial and makes it past the FDA for a schizophrenia indication, Lily indeed may have another blockbuster on its hands.

Permalink

Other Analyses of the Same Article (6)

Healthcare News Feed

Report a Concern

September 21, 2007

Actelion's Almorexant: How Close is it to the Ideal Hypnotic Agent?

Analysis of: Actelion Sleep Aid Does Well | online.wsj.com

Implications: There is significant clinical need for effective, well-tolerated, low-risk hypnotic agents that can be used safely over the long term. On the surface, Actelion's almorexant, a novel hypnotic agent acting as an orexin receptor antagonist, fits some of this profile and demonstrates statistical benefit on various sleep parameters (sleep efficiency; subjective sleep time; time to sleep onset). But just how good a sleep medication is it?

Analysis: Patients experiencing insomnia often find great relief in drugs like Ambien, Ambien CR, and Lunesta; however, part of the problem with such hypnotics is that they do indeed work very well and often leave patients cognitively/psychomotorically impaired if they might need to awake for an emergency or are concerned about dealing with young children in the middle of the night, among other things. I have seen rebound insomnia and tolerance occur with these medications though they are considered medically less risky than the benzodiazapenes ("benzo's") which can cause physiological withdrawal and dependence. Nonetheless, I often prefer benzo's or drugs like Rozerem or Trazodone for patients that either expect to be called to action in the middle of the night or fear what would happen if they were. Yet the 'hypnotic properties' of these drugs is generally not as effective and Trazodone, for instance, too often leaves people feeling hung-over in the morning. The kind of drug that would be a blockbuster, to my view, is one that can substantially improve sleep quality, leave a patient feeling rested the next day without hangover, and be perceived by patients as safe and not so cognitively impairing as Ambien or Lunesta. In addition, augmentation potential with other drugs given its unique mechanism of action would offer added-value. Based on Actelion's preliminary data, I doubt almorexant meets all these criteria, especially at the 100 mg dose range, but its purported mechanism of action and clinical profile is certainly a step in the right direction and favorable Phase III results will be a major boost for Actelion. A 'stronger' Rozerem, as it were, would be a very nice and welcome addition to insomnia treatment.

Permalink

Other Analyses of the Same Article (7)

Healthcare News Feed

Report a Concern

September 13, 2007

The Lundbeck-Takeda Alliance: A Strong CNS IP/Drug Development Platform

Analysis of: Lundbeck and Takeda form Alliance to Develop and Commercialize a Portfolio of Novel Compounds in the US and Japan for the Treatment of Mood and Anxiety Disorders | www.pipelinereview.com

Implications: Lundbeck's LUAA21004 and LU24530 are among several drugs licensed to Takeda, the others earlier in development, that may offer unique biological and clinical profiles as compared with existing antidepressants and anti-anxiety drugs. Lundbeck's platform includes about 6 drugs, covering a potentially broad spectrum of disorders (depression, bipolar, anxiety and psychosis).

Analysis:

This is an exciting drug development and intellectual property platform, among the stronger ones I've seen for psychiatric disorders, with new drug mechanisms of action (among them a bis-aryl-sulphanyl amine modulator and a neuropeptide Y receptor ligand) and with potentially significant clinical utility. Lu AA21004, Lundbeck's lead candidate, is expected to complete its 400 person Phase II clinical trial later this year, with hopes it may work more rapidly and more effective than current antidepressants. The collaboration with Takeda will move development of these drugs along much more rapidly. Though it is still early to assume much about clinical efficacy, the shared CNS pipeline is impressive with potentially broad clinical and market value.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

August 31, 2007

Wyeth's Bufeprunox –Still Some Hope Here?

Analysis of: Wyeth's Schizophrenia Pill Is Rejected by U.S. FDA | www.bloomberg.com

Implications: The FDA's conclusion that more data was required on bufeprunox's efficacy and on a death that occurred is certainly a very hard setback for Wyeth. However, I think there is some legitimacy to considering that a drug that does not cause weight gain, and even might cause weight loss, that also may confer even modest clinical benefit for psychotic disorders and possibly other conditions such as mood or anxiety disorders (which I suspect could be the case based its action) should not be underrated.

Analysis:

Bufeprunox is a partial dopamine 2 agonist, with some serotonin receptor activity, following in the footsteps of Bristol Myer Squibb's Abilify - itself bringing a kind of paradigm shift to treatment of psychotic disorders and bipolar disorder. Abilify, with its favorable weight and metabolic profile against most of its antipsychotics counterparts, has been an important addition to psychosis and bipolar treatment but BMS is now seeking to expand its clinical platform to include trials for autism, major depression (as a monotherapy and augmentation agent), dementia related psychosis, cognitive problems associated with psychosis, and others. Drugs like Eli Lilly's Zyprexa can be profoundly effective in psychosis and mania but can prove utterly intolerable over time because of massive weight gain and patient dissatisfaction, so the concept of "optimizing" medication treatment (and associated side effects) with other alternative drugs is very appealing – even if they are not the magic bullets. This would appear to be a very long road uphill for Wyeth and bufeprunox but if there is some glimpse that enough data is available for an FDA indication, even if the drug would appear substandard in some ways, there may be both clinical value and market demand.

Permalink

Other Analyses of the Same Article (5)

Healthcare News Feed

Report a Concern

August 31, 2007

Might BIOLINERX hold the next major class of antipsychotic medication?

Analysis of: BIOLINERX STARTS PHASE II TRIAL OF BL-1020 FOR SCHIZOPHRENIA. | www.therapeuticsdaily.com

Implications: BIOLINERX's BL-1020 represents a unique class of medication for the treatment of psychotic disorders – affecting the GABA system - and the prospect of a drug that might effectively treat psychotic disoders and possibly have other applications in mood or anxiety disorders, putatively due to its mechanims of action, is highly significant.

Analysis: Conceptually, it is precisely drugs like this one that could have a major clinical and market impact if efficacy is established, for several reasons : 1) tolerability and potential medical risk may be much improved (ie. weight gain, high triglycerides, glucose metabolic impairment, associated cardiovascular risk, decreased parkinsonism, and risk of tardive dyskinesia, among others); 2) that a different mechanism of action may have enhanced augmentation/combination versatility with other drugs that work in more the more conventional fashion on various monamine neurotransmitters, in particular dopamine and serotonin receptors for the atypical class of antipsychotics; and 3) that they may have a much broader range of clinical effect than just psychosis -- the GABA system has been implicated in mood and anxiety disorders, among others.

However, this is still very early stage and the study design is an open label study rather than a double blinded, randomized, placebo controlled trial; if efficacy results were to prove positive, this might bump up the company's valuation but would not imply that efficacy would be borne out in the more rigorous double blinded, randomized, placebo-controlled study design.

Permalink

Other Analyses of the Same Article (4)

Healthcare News Feed

Report a Concern

August 30, 2007

Antidepressant, Weight-Loss Drug, and ADHD Treatment, all-in-one?

Analysis of: DOV Pharmaceutical, Inc. Announces Successful Phase Ib Results for DOV 21,947 | www.pipelinereview.com

Implications: Triple Reuptake Inhibitors represent a potentially valuable new class of medications, with DOV Pharmaceuticals, GlaxoSmithKline, Neurosearch and Sepracor leading the way with Phase I and II studies in progress. While in development primarily for depression and anxiety disorders, there is interest that such drugs may benefit obesity and attention-deficit hyperactivity disorders.

Analysis: This class of drugs differs from serotonin and serotonin/norepinephrine reuptake inhibitors – which constitute pretty much most antidepressants - in that there is greater dopamine potentiation. The implications for a drug that directly involves dopamine reuptake is significant in that: 1) it may further potentiate antidepressant response, confer greater efficacy, or work more rapidly 2) it may mitigate symptoms sometimes associated with

SSRIs like weight gain/fatigue/amotivation, often associated with longer term use, and thought to have some contribution from diminished dopamine output 3) may be more stimulating and therefore enhance motivation and attention and 4) may actually curb appetite and cause weight loss, with associated benefits (ie such as lowering TGs). How such theoretical effects will play out clinically is still a way from being determined, and whether dopamine reuptake inhibition may have associated abuse liabilities (cocaine and stimulants have such effects) is unclear. But the early data from DOV's 21,947 is encouraging, along with several other triple reuptake inibitors in development.

Permalink

Other Analyses of the Same Article (4)

Healthcare News Feed

Report a Concern

August 1, 2007

Some Clinical Observations on Shire's Vyvanse

Analysis of: Shire's New ADHD medication, VYVANSE(TM) (lisdexamfetamine dimesylate) Now Available in U.S. Pharmacies Nationwide | www.eurekalert.org

Implications: My previous commentaries on Vyvanse, the pro-drug amphetamine that recently entered the US market for the treatment of ADHD, was based on readings as well as discussions with colleagues; however, now I that I have a small pool of patients taking it, I am noticing a clinical profile that does separate it from Adderall XR and Concerta, the other long-acting stimulants on the market.

Analysis: My observations:

1. The drug acts over a longer duration of time. Patients previously who had a wear out effect of Adderal XR or Concerta after 6-9 hours don't very much notice this, and feel better clinical effect into late afternoon and early evening. This has been perceived as advantageous.

2. Regarding pre-marketing concerns about slower time to efficacy; this is still hard to get a clear read on but so far not a major clinical issue as clinical effects seem to emerge not long after taking the medication.

3. Regarding patients with substance abuse concerns or histories; there are several patients I treat with prior substance abuse histories who have responded to nothing but stimulants and essentially require stimulant medication because of its pronounced clinical benefit on ADHD symptoms. This is complicated and risky population, as I have seen patients even crush Concerta and snort it. In this group, even the longer acting stimulants (Adderall XR and Concerta) have an on/off effect switch that is often clinically a problem; when the medicine wears off, there is an urge to medicate, re-enforcing addictive patterns of behavior. I have switched a couple of such patients to Vyvanse and the impact so far has been positive as the "on-off switch" doesn't seem to be there or is dampened. Taking Vyvanse once a day has relieved the daily preoccupation of when the medication will wear off and when they will have their next dose. Concerns of sniffing and toxicity, to a lesser extent, are also mitigated with Vyvanse.
Needless to say, this is a complicated clinical population but because I have seen more than a number of patients whose lives have been massively transformed, positively, with stimulant treatment when all else has failed, I am still of the mind that once substance abuse issues are adequately addressed and treated, careful use of stimulants may be clinically warranted and very helpful.

4. Dosing Issues. I have some concerns about only the 3 doses 30, 50, 70. Some variation between 30-50 mg might prove more versatile (Adderall XR and Concerta offer much more in dose range options); perhaps the 'smoother' pharmacokinetic profile will require less range than short acting stimulants or Concerta/Adderall XR – we will have to wait in see.

Conclusion: Is this the optimal kind of ADHD treatment? No, as what may be clinically advantageous to some may not be for others. I still have patients who like the fact that their Adderall XR or Concerta wears off just as they end their work day when they go for a run; or that they don't feel any effect in the evening. Some patients just like the flexibility of the shorter acting stimulants. And others who are content with their current medication will see no need to change over. But clearly, I think there is lots of room clinically for this drug and my initial impressions are more positive than my pre-marketing expectations.

Permalink

Other Analyses of the Same Article (6)

Healthcare News Feed

Report a Concern

July 25, 2007

Wyeth's Pristiq Delt a Blow On FDA request

Analysis of: Wyeth Receives Approvable Letter from FDA for PRISTIQ for the Treatment of Vasomotor Symptoms Associated with Menopause | www.pipelinereview.com

Implications: The FDA's decision for another clinical trial to establish the safety of Wyeth's Pristiq in menopausal vasomotor symptoms is a major setback. Pristiq, a derivative of Wyeth's serotonin/norepineprhine reuptake inhibitor Effexor XR, received an approvable letter from the FDA for its major depression indication early this year and will await final FDA action for that in early 2008.

Analysis: Effexor XR (venlafaxine) goes off patent in 2010, so Wyeth has hoped for the timely introduction of its successor product well before then to ease the pain of losing its blockbuster. Venlafaxine has itself been shown to be very effective for hot flashes (and broadly for depressive and anxiety spectrum disorders), so the dual indication with depression has potential to treat a very large treatment population; woman over 40 represent a very substantial portion of antidepressant usage. The issue of cardiovascular and liver toxicity could be a serious problem for Pristiq, though I am not aware such concerns were sited for the depression indication. Interestingly, Effexor XR is generally considered safe and within the camp of SSRI's, though more recent observations have cautioned its potential overdose toxicity or risk when combined with alcohol. If such concerns of toxicity with Pristiq pan out, it seems to me this would also compromise the depression platform, though the FDA is reviewing data in independent fashion for both indications. One wonders if Wyeth may try to hedge their bets and let the menopausal indication slowly pass by the wayside? The FDA is now very sensitive to drug toxicity issues, perhaps all the more for a drug that may reach very widely in its use.

Permalink

Other Analyses of the Same Article (6)

Healthcare News Feed

Report a Concern

July 24, 2007

More Bad News for Sanafi Aventis' Acomplia

Analysis of: UK Regulator: 1 Person in 10 on Acomplia Experiences Psychiatric Side Effects | www.acompliareport.com

Implications: Sanofi-Avnetis is certainly cringing as events unfold in the UK and EU around their weight-loss drug riminobant (Acomplia), a novel cannaboid 1 receptor antagonist recently withdrawn from the US FDA approval process after mounting concerns about suicidality and psychiatric side effects. The reports circulating in the news are worrisome (ie. 1 in 10 with psychiatric side effects; 1 in 100 with suicidality; two fold increase in depression, and more in patients with a history of depression), especially given the high likelihood of comorbid depression (or treatment with antidepressants) in this treatment population.

Analysis:

When rimonabant was brought before the FDA, a review of the data found over 70 incidents of suicidality in the Phase III clinical trial, significantly outnumbering the placebo arm by ~3:1 ratio. While the clinical pool for which treatment with rimonabant is indicated might, by its nature, be susceptible to symptoms of depression/suicidality, the difference as compared to placebo in the FDA review is problematic for the drug. The FDA advisory panel showed little doubt in its 14-0 vote on risks outweighing benefit. The UK and EU is taking head.

The kinds of drug effects that would naturally enhance weight loss – activation/CNS excitation – might be the same kinds of effects that could cause agitation, irritability, and anxiety (and even seizures). Such effects might dispose vulnerable patients to experience suicidal ideation/behavior or cause restlessness, anxiety or agitation (which can further fuel suicidal behavior). Ongoing warnings, and restrictions on use, in the UK and EU will certainly hamper sales forecasts and will put clinicians' on alert. Given the medical comorbidity associated with morbid obesity and the European view toward considering more generally the risk/benefit profile of the drug, it seems likelyAcomplia will have a presence in the European market, but not so broadly. Interestingly, I would add that it is not uncommon that psychiatric patients have untoward side effects to psychotropic drugs, perhaps not that different from the kinds of numbers found with Acomplia; but clinical judgement and close surveillance is the mainstay of preventing bad outcomes.

Permalink

Other Analyses of the Same Article (4)

Healthcare News Feed

Report a Concern

July 24, 2007

Depression Linked to Dementia

Analysis of: How Depression Weakens the Brain | online.wsj.com

Implications: It has long been recognized that depression may mimic a clinical picture akin to dementia, clinically dubbed “pseudodementia”; however, successful treatment of “pseudodementia” generally restores normal function while the treatment of Alzheimer’s (and other forms of) dementia is often very limited in its benefit. These new findings that link mid/late life depression to later dementia (ie. of the Alzheimer’s or vascular type), putatively due to the neurotoxic effects of depression on the brain, is indeed clinically quite significant.

Analysis: Research in the area of depression and its link to later, permanent cognitive deficits is a critically important area of investigation. From a clinical standpoint, it seems to me that the impact of these findings may be less to demand an urgency of treatment in mid/late life, as the depression itself (rather than the risk of dementia from it) would likely be the primary and conscious driving force for treatment; that said, however, such a link emphasizes yet another dimension of the devastating impact of depression, the need for ongoing surveillance for patients who have been treated, and the importance of educating patients that relapse of symptoms should be addressed aggressively to avoid an even more chronic course and other sequelae. Hopefully, such evidence pointing to the physiologic toll of depression will give further cause for clinicians, especially in primary care arenas, to be even more mindful and vigilant for addressing symptoms of depression and even actively screening for it.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

July 24, 2007

BMS’ Abilify: Seeking a Slice of the Antidepressant Market

Analysis of: ABILIFY(R) (aripiprazole) Supplemental New Drug Application Receives Priority Review by U.S. Food And Drug Administration for Adjunctive Treatment in Adults With Major Depressive Disorder | www.pipelinereview.com

Implications: There are numerous augmentation strategies to antidepressant treatment commonly utilized in clinical practice; however, larger clinical trials to establish efficacy and head-to-head comparisons are definitely lacking. The STAR-D data is now providing some important data in this regard. The FDA’s sNDA acceptance/priority review for Abilify as an adjunct is very welcome news for BMS; establishing efficacy in larger trials and obtaining an FDA-indication would be a significant milestone, clinically and commercially, for this drug.

Analysis: In my own clinical practice, I have seen a number of patients refractory to multiple medication trials, including combination antidepressant trials, respond quite favorably to the addition of Abilify to their antidepressant regimen. The observation has struck me with regard to several patients in particular; one wonders if such patients were perhaps biologically more in the bipolar camp (though not evident clinically) and as such seemed to do better with an atypical neuroleptic on board. The decreased likelihood of sedation, weight gain and metabolic side effects offer some advantage to Abilfiy’s adjunctive use over other atypical neuroleptic counterparts, though other atypical agents (such as Zyprexa, Risperdal, and Serqoeul) have been shown to confer antidepressant properties. Abilify augmentation is not without its liabilities; I have seen a number of patients become overly activated and agitated on it, but I would suspect that the BMS data looks good and no doubt an FDA-indication as an adjunct to antidepressant therapy will widely broaden the spectrum of its use. Other clinical possibilities of this drug, to my thinking, would include treatment of bipolar depression, for which Seroquel has been approved.

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Other Analyses of the Same Article (7)

Healthcare News Feed

Report a Concern

July 16, 2007

Wellbutrin XL: Is There Still Room for Improvement?

Analysis of: Once-daily Wellbutrin XL | www.ncbi.nlm.nih.gov

Implications: Bupropion (Wellbutrin immediate, SR, XL; GlaxoSmithKline) has evolved over the years to three different release forms - immediate release (three times a day dosing), intermediate release (Wellbutrin SR; twice daily dosing), and extended release (Wellbutrin XL: once daily). Compliance issues often correlate with the frequency that a medication needs to be taken, so the XL form offers some significant benefit here.

Analysis:

Wellbutrin XL offers two major advantages than its SR counterpart: once daily dosing, which cannot be underestimated, as patients who require twice daily dosing may not uncommonly miss second doses leading to lower steady state blood levels over time and potentially less antidepressant efficacy. Once daily dosing is signficantly more appealing to patients as well. Tolerability may also be enhanced with the XL form at a given dose range with decreased peak plasma values. Both of these represent advantages of Wellbutrin XL over the SR form.

However, one clinical disadvantage to Wellbutrin XL is that there are only 3 dosing options - 150, 300, 450 mg per day (as it comes in 150 mg/300 mg forms). I have sometimes found that some patients do not experience optimal efficacy at one dose but have problematic side effects at the next available dose; for these patients, I have been able to better tweak the dose with the SR form which offers more dosing flexibility (100 mg, 150 mg, 200 mg forms). A 200 mg XL dose, for instance, I think would offer an even broader range of dose versatility, efficacy, augmentation impact, and tolerability for a medication that represents an already good improvement on a good drug.

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Other Analyses of the Same Article (4)

Healthcare News Feed

Report a Concern

July 3, 2007

Janssen's INVEGA: A Better Risperdal?

Analysis of: INVEGA(TM) Receives Marketing Authorization In European Union For Treatment Of Schizophrenia | www.pipelinereview.com

Implications: Invega (Janssen), derived from Risperdal's (risperidone) active metabolite paliperidone, offers two potential advantages over its predecessor: an osmotic delivery system for once daily dosing and a potentially better side effect. But how significant are these improvements and are they worth the added cost over generic versions of Risperdal, due out in 2008?

Analysis: I do not see Invega capturing high interest in the US (though it is less clear to me the climate of the European market), especially as the cheaper generic versions of risperidone hit the US markets next year. From a clinical vantage point, the efficacy of Invega is likely comparable to Risperdal as they share the same active ingredient.

Dosing through the OROS system once-daily may be modestly advantageous, delaying peak plasma levels of paliperidone and potentially mitigating side effects. However, there is a flip side here: because risperidone reaches peak plasma levels very acutely (within a few hours, along with its active metabolite), Invega may be less effective for acute agitation, common presenting and comorbid symptoms of psychotic and bipolar spectrum disorders. As it is not uncommon for patients being started on a particular medication for the first time to remain on it if it is effective, this "first-use" phenomenon may have some impact on how these drugs will be used in longer-term maintenance treatment.

Side effect profiles do look similar. While Invega's 6 mg dose seems quite well-tolerated, it is unclear if this will have a wide range of efficacy; it is also unclear how this equivalency compares to Risperdal. Higher doses of Invega carry the same kinds of problems seen with Risperdal: extrapyramidal symptoms and hyperprolactinemia with its related symptoms. One advantage of Invega would be the lack of cytrochrome-based drug interactions. All said, Invega is not a clear winner but I suspect will have some pay-off by keeping Janssen's hand in the antipsychotic market for the next decade.

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June 29, 2007

Vyvanse, Concerta, and Adderall XR: How Will It Sort Out?

Analysis of: Shire showcases new drug Vyvanse to wary doctors | investing.reuters.co.uk

Implications: Treatment of ADHD with stimulants often requires a degree of clinical customization based on patient's subjective response, clinical comorbidities, and the varying pharmacokinetic profiles of the stimulants (short/intermediate/longer acting forms). Finding a 'superior' product above the others is inherently challenging for these reasons and while Vyvanse seems to offer some potentially strong positive features (ie. less euphorogenic properties, maybe longer duration of action, less overdose risk), it faces an uphill battle to overtake medications like Concerta and Adderall XR that have a good track record and clinician comfort for many ADHD patients.

Analysis: Adderall XR and Concerta are effective and generally safe drugs when monitored and prescribed appropriately. Despite issues of abuse liability that Vyvanse may mitigate with its pro-drug action, I don't suspect there will be a wholesale preference of Vyvanse over Adderall XR and Concerta, except for certain kinds of patients (ie. where stimulants are needed but abuse liabilities are present) – though no doubt some clinicians may favor it because of its profile.

Unless clinicians' find a visibly compelling and strongly favorable clinical profile of the drug for their patients, I think Vyvanse will develop a decent marketshare but not overshadow the other longer acting stimulants. Patients (and clinician's) may view certain features like it's slower onset of action, for instance, as both a pro and con over Concerta or Adderall XR, making it less than universally preferable over its counterparts. There is definitely solid room here clinically and in the market for Vyvanse but its will be competing against drugs that drugs that have been proven quite valuable.

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Other Analyses of the Same Article (3)
Healthcare News Feed
Report a Concern

June 28, 2007

Lyrica's Fibromyalgia Indication: A Good Break for Pfizer

Analysis of: Pfizer's Lyrica Receives FDA Approval for Fibromyalgia | www.medadnews.com

Implications: Fibromyalgia is not well understood and sometimes conceived of as having psychosomatic contributions; nonetheless, the constellation of symptoms that define it are not uncommon. Previous data I am aware of on Lyrica (Pfizer), a novel alpha-2 ligand, has demonstrated efficacy at reducing pain and fatigue and improving sleep associated with fibromyalgia.

Analysis:

As the first FDA-approved treatment of fibromyalgia treatment, this could represent a sizable market, with treatments to date being off-label and in the form of analgesics, antidepressants, muscle relaxants, and anticonvulsants. Whether or not the drug will be prescribed for 'fibromyalgia' per se, itself a diagnosis with some haziness, its FDA-indication will further add to its perception as a potentially safer, broader-spectrum, pain medication that also may carry other benefits like helping fatigue and sleep.

My own experience with Lyrica has been off-label for the treatment of anxiety disorders and

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www.guardian.co.uk

Glaxo Seeks Guidance From Health Systems
online.wsj.com

8-Year-Olds on Statins? A New Plan Quickly Bites Back
www.nytimes.com

Costly Cancer Drug Offers Hope, but Also a Dilemma
www.nytimes.com

Bill to Block Medicare-Fee Cuts
online.wsj.com

I have found it modestly effective and well-tolerated; it has been approved for the treatment for Generalized Anxiety Disorder in Europe though was denied FDA approval for the condition in 2004.

June 28, 2007

Developing Drugs with Less 'Isomeric Ballast': For Clinical Value or Commercial Profit?

Analysis of: Cephalon Receives FDA Approval of NUVIGIL(TM) for the Treatment of Excessive Sleepiness Associated with Three Disorders | www.pipelinereview.com

Implications: Reducing 'isomeric ballast', as Nuvigil (Cephalon) does compared to its predecessor Provigil, offers a cleaner vehicle for the active ingredient armodanifil and follows in the Lexapro/Celexa tradition. While developing such 'cleaner' drugs is a convenient way for pharmaceutical companies to extend patent protections and market with a different public perception, there is clinical relevance here as stereochemical variations of specific active molecules will often offer no advantage and carry added side effects. The difference between l-dopa and d-dopa isomers is a treatment of Parkinson's and toxic side effects.

Analysis: Though it is unclear whether Nuvigil will offer enhanced clinical efficacy over Provigil for the FDA-approved conditions of excessive sleepiness from narcolepsy, sleep apnea, or shift work disorder, there is data to suggest an improved pharmacokinetic profile and possibly fewer side effects. More importantly, though, Cephalon is pursuing a platform to further investigate Nuvigil in a range of psychiatric and medical conditions which has some promise and will offer a venue for this new drug to offer what modafinil (as Sparlon) could not following its failed FDA approval for ADHD.

Whether or not Nuvigil offers much of a clinical difference than Provigil, Cephalon is developing a smart clinical and marketing strategy for it. Lexapro's (Forest) strong penetration of SSRI marketshare, despite competition from its isomerically 'less-clean' generic sister compound citalopram, in part was an outcome of good timing and message. The other part of its success was that Lexapro is generally well-tolerated and effective, with fewer drug-interaction concerns than other SSRIs.

June 27, 2007

Intuniv: Potentially Good Addition but a Small-Scale Segment of the ADHD Market

Analysis of: Shire Receives Approvable Letter from FDA for INTUNIV(TM) (guanfacine) Extended Release, a Nonstimulant for the Treatment of ADHD | www.pipelinereview.com

Implications: Intuniv could expand treatment options for ADHD, especially where stimulants are problematic (substance abuse or abuse liability; tic disorders; behavioral disturbances). However, stimulants are first-line treatments because if their efficacy, which can often be dramatic and immediate, and I suspect Intuniv will not provide the kind of benefit so visible in patients properly treated with stimulant medications.

Analysis:

Intuniv would represent a smaller-scale segment in the ADHD marketplace, especially for patients where stimulants are problematic or parents/adults would prefer a drug without abuse potential. I would liken its place to Straterra (Eli Lily), which is now considered a second-line drug unless certain clinical circumstances are present, and whose status is similarly confirmed among colleagues and in a recent publication on the American Academy of Child and Adolescent's treatment parameters for ADHD.

Whether or not there is a role for Intuniv as an augmentation with stimulants to optimize treatment when maximum doses are achieved or to treat comorbid conditions (especially anxiety) would be of value to investigate. With Vyvanse in the market and other longer-acting stimulants down the road, Intuniv will probably attract only less attention and be considered a down-the-line drug choice for most ADHD patients. Nonetheless, it would be a nice compliment to Shire's broad ADHD platform and would offer another psychopharmacologic tool for the clinician.

BOOKMARK

Permalink

Other Analyses of the Same Article (11)

Healthcare News Feed

Report a Concern

May 31, 2007

The Device Playing Field in Psychiatry: rTMS, VNS, and DBS

Analysis of: Support Wavers for Brain Stimulation | www.clinicalpsychiatrynews.com

Implications: The data supporting Vagus Nerve Stimulation (VNS; Cyberonics) and repetitive Transcranial Magnetic Stimulation (rTMS; NeuroNetics) for depression is generally poor. VNS, despite its controversial and politically-laden FDA approval, risks being squeezed out of the market from insurers whose justification is that it doesn't work. Anthem began the parade and Medicare/Medicaid may likely follow suit. rTMS has a long road ahead following February's FDA review of its efficacy in depression and deciding not to approve it. Deep Brain Stimulation (DBS; Medtronics) for depression, while highly preliminary, may offer the greatest potential for devices in psychiatry.

Analysis: There are several very small case studies of DBS for refractory depression and the data seems very promising. In these studies, the patients have been extremely ill, with multiple failed treatments including electroconvulsive treatments in some cases. There is a distinct correlation between device activity (on/off) and mood/interest level, suggesting a rather immediate observable effect. At least two brain locations have been identified as target pathways, suggesting that researchers are clarifying the neuroanatomy for implantation. Treatment of Parkinson's Disease with DBS can often demonstrate dramatic effects.

While there is still a long way to go for DBS in psychiatric disorders, there is reason to think this may be a powerful treatment option for refractory depression (OCD and Tourrette's Disoder are other clinical conditions in which DBS has been studied). Besides proving clinical efficacy in larger trials, there will be the issue of patients' (and psychiatrists) accepting a treatment requiring a device to be planted in the brain, especially when that condition seems less obviously physical than a disease like Parkinson's.

BOOKMARK

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

May 23, 2007

Bristol Myer Squibb's Abilify as an Augmentation Strategy for Depression

Analysis of: Six-Week Investigational Study In Adults With Major Depressive Disorder Evaluates The Effectiveness of Adjunctive Aripiprazole Therapy With Antidepressants | www.pipelinereview.com

Implications: Abilify (Bristol Myers Squibb) as an augmentation strategy for depression is appealing from several standpoints. Its effects on the dopamine and serotonin systems suggest a sound basis for potential clinical value and its side effect profile, with less prominent weight gain/metabolic dysgregulation and sedation, is a positive.

Analysis:

This study confirms a number of case reports as well as evidence within my own clinical practice that Abilify may benefit depressive symptoms when added-on to existing antidepressant medications. Abilify is not without its problems – akathesia/restlessness can be problematic – but I have seen at least several patients who have not responded to multiple combinations of medications, including augmentation with atypical neuroleptics, that did well with Abilify.

With Abilify at nearly 20% of the 11-12 billion dollar antipsychotic drug market in 2006, data supported augmentation strategies such as this for depression (as well as other potential indications – bipolar depression; anxiety spectrum disorders) will likely lead to growing marketshare. Weight gain/metabolic and medically related side effects (ie. triglycerides; glucose abnormalities) that emerge with longer-term use of drugs like Zyprexa, and to a lesser extent, Risperdal, will lead to some attrition in the use of these drugs over time with substitution for more tolerable, less medically risky, alternatives.

BOOKMARK

Permalink

Healthcare News Feed

Report a Concern

May 22, 2007

AstraZeneca's Tries to Hedge its Bets with Serqouel XR

Analysis of: FDA Approves Astrazeneca's Once-Daily Seroquel XR Extended-Release Tablets for the Treatment of Schizophrenia | www.therapeuticsdaily.com

Implications: Seroquel XR is intended to ease patient compliance with once dialing dosing; however, Seroquel (shorter acting form) itself is very often dosed once daily at bedtime because of its highly sedating properties or with a much larger dose weighted in the evening. The BOLDER Bipolar I/II Depression trials utilized once dialing dosing (at bedtime) of Seroquel itself for these reasons, justifying its use once per day, and leading to its bipolar depression indication.

Analysis: The XR form is a way for AstraZeneca to extend its patent protection for some version of Seroquel. However, it seems unlikely that insurers will go for the costlier version once generics of quetiapine are out and especially as there is good evidence now from BOLDER that once daily dosing of Seroquel (short acting form) is clinically validated and also endorsed by the drug manufacturer.

Seroquel also carries significant off-label usage for patients with more complicated psychiatric disorders suffering from sleep problems – an XR form would not be used for this population. If it turns out that the XR form, with its longer duration of action, causes more daytime somnolence, this will be an added clinical problem. Seroquel, while not considered among the more effective antipsychotic agents when discussed among clinicians, has a substantial marketshare (>3 Billion $/year), largely because its side effect profile is soft except for sedation (which can be advantageous). All said, it seems unlikely that the XR form will be a big hit, especially once generic versions of quetiapine hit the market.

Permalink

Other Analyses of the Same Article (6)

Healthcare News Feed

Report a Concern

May 15, 2007

Shire's Broad ADHD Platform

Analysis of: Shire to Present New Scientific Data on ADHD Treatment Portfolio at APA Annual Meeting | www.shire.com

Implications: Shire's ADHD platform is impressive. Their product line will cover 'broader' spectrum ADHD treatment (Adderall, Adderall XR, Vyvanse whose market release is imminent, and prospectively, if approved for adults, SPD465, the 16 hour mixed amphetamine salt) as well as niche markets with the Daytrana patch and if approved, extended release Guanfacine (SPD503).

Analysis: Regarding the specific drugs:

Vyvanse: probably will not be the complete blockbuster it was once heralded to be due to its Schedule II status, but will certainly have a solid place in the ADHD marketplace. Unique pro-drug concept, less euphorogenic properties, potential improved safety profile in overdose, it will be clinically valuable for ADHD patients with a prior history of substance abuse (which is highly common) and potentially among college students where stimulant use for exams has nearly become the norm on some campuses. Parents may also like this version of stimulant for their children, for these reasons. Pro-drug concept and related benefits may prove clinician and liability friendly too.

SPD465 – a 16 hour duration of action should allow for once daily dosing. Despite the relatively long action of Adderall XR (extended release mixed amphetamine salts) and Concerta (extended release methylphenidate) in contrast to their shorter acting counterparts, Adderall and Ritalin, SPD465 would have the very longest duration of action. There is a need for such a long-acting drug as it is common in clinical practice that patients take Adderall XR or Concerta in the morning, only to need another shorter acting stimulant late in the afternoon. The "adult" ADHD approval would be a plus, and the longer duration of action would suggest less 'abusibilty' of the drug.

SPD503 – guanfacine has been studied in ADHD and tic disorders. Preliminary data suggests that it may help hyperactivity and inattention but highly unlikely at the level stimulants. Less perceived efficacy (like Strattera) by both patients and clincians will likely be an issue if this drug is approved. Side effects include sedation, which can be a problem for ADHD patients (as well as hypotension). I suspect if SPD503 makes its way in the ADHD marketplace, it will be used as: 1) an augmentation strategy (given its non-stimulant mechanism of action), 2) an alternative to stimulants 3) for patients with comornid tic disorders or severe behavioral disturbances and 4) for substance abusers where stimulants are contraindicated.

Daytrana patch (methylphenidate transdermal system)- for children. Basically a last line treatment, unless pills are an issue; major issue is that if the child gets a hypersensitivity reaction, stimulants may need to be permanently withheld. This is a serious clinical problem. Nonetheless, there is a need for a patch in children but it will be a niche product only.

Adderall and Adderall XR – both very good drugs. In my experience, Adderall is among the most common psychiatric medications for which I request "name brand medically necessary'. I see a good handful of patients that just don't do as well on the generics.

Permalink

Other Analyses of the Same Article (3)

Healthcare News Feed

Report a Concern

May 14, 2007

Good Times Ahead for Generics and Mylan

Analysis of: Mylan is Now Big Generic Player Player After Deal for Unit of Merck KGaA | online.wsj.com

Implications: Generic pharmaceuticals offer enormous savings on healthcare costs and are therapeutically efficacious. Pharmaceutical companies that find a solid position in the generic market over the coming years makes sense given the current healthcare and drug landscape.

Analysis: The generic market is growing rapidly, with numerous drugs coming off-patent in the next few years following the high-point of FDA drug approvals in the late 1990s.

Ever-growing focus on healthcare costs from Medicare, Medicaid, and insurance will drive movement toward generics. The Mylan acquisition from Merck KGaA may position it as the leader of generics against competitors Barr, Teva, and Watson. The issue of generic biologics is trickier – as cost saving may be minimal and regulatory concerns may hamper their penetration into the US market. However, the world market may be more amenable to generic biologics, for which Mylan may indeed have an advantage.

Permalink

Healthcare News Feed

Report a Concern

May 14, 2007

The Use of Atypical Antipsychotics in Children and Adolescents

Analysis of: Psychiatrists, Children and the Drug Industry's Role | www.nytimes.com

Implications: While some clinicians may lose neutrality and essentially become spokespeople for particular companies, pharmaceutical sponsored talks can prove educational, especially where resources may be less substantive. Yet there are real conflict of interest issues that are becoming increasingly visible in the media. Because there are few FDA drug indications for childhood psychiatric illness, considerable treatment is off-label. Marketing 'indirectly' to psychiatrists that treat children is common in drug-sponsored talks, where discussion may steer to children (as I have seen on numerous occasions in talks intended for adults).

Analysis:

The off-label use of atypical antipsychotics (among them, Zyprexa – Eli Lilly; Risperdal – Janssen; Seroquel – AstaZeneca; Abilify – Bristol-Myers Squibb; Geodon – Pfizer) in children and adolescents has increased massively in the past 5 -7 years.

Children that reach the child psychiatrist's office often present with significant behavioral disturbances. Such patients are often treated with atypicals, even if diagnostically the clinical picture is unclear, as more attention is now paid to possibly activating bipolar-prone children with antidepressants.

While atypicals can rapidly cool down behavioral problems, side effects can be highly burdensome and with medical morbidity (in particular weight gain/metabolic syndrome, most notably with Zyprexa). A number of child psychiatry colleagues I know have shifted toward drugs like Abilify or Geodon because of their side effect profile, though the clinical data is sparse and there is no data on longer term effects. Marketing/drug-sponsored talks (as described in the article) may account for some of the increased use of atypicals in children, but when children are out-of-control, atypicals may seem like the only reasonable choice. Needless to say, there is great need for more clinical data for this population as well as drugs that are both effective and well-tolerated.

Permalink

Healthcare News Feed

Report a Concern

May 10, 2007

Senate Bills Weigh in on Drug Importation, Drug Safety, Generics and FDA Changes

Analysis of: Senate Bill Would Boost FDA Powers | online.wsj.com

Implications:

The Kennedy-Enzi bill passed overwhelmingly, calling for stronger regulatory tools at the FDA, in particular to monitor drugs in their post-marketing stage.

A major fear among US pharmaceutical companies was whether the Dorgan bill would pass and allow for the legal importation of drugs from other countries. While the bill passed, its amendment from Sen. Cochran necessitates approval from the Sec. of Health & Human Services (which is not likely to happen) basically invalidating it.

Analysis: Stronger regulatory tools at the FDA and a heightened public perception about drug safety will mean a higher likelihood of drugs being issued warnings post-marketing and pharmaceutical companies having to spend more on providing data and making changes for the FDA. Making data public might raise the possibility of lawsuits. However, the key issue here is funding and while it is likely the FDA will have a broader range of regulatory tools, there will be practical limits in what it can pursue if funding remains in the expected range. 'User fees' will likely continue (via renewal package in the house) as anticipated and a large-scale overhaul at the FDA and its drug monitoring will probably be more 'perception' than actuality.

The Cochran amendment to the Dorgan bill is a big win for US pharrma. Added stipulations the the Kennedy-Enzi bill look like a potential win for generics.

Nonetheless, there is no doubt that times are changing toward tighter regulation and over time, this will have some level of impact on big pharma and biotech companies

Permalink

Healthcare News Feed

Report a Concern

May 9, 2007

Pfizer's Lyrica: On Its way to An Approved Treatment for Fibromyalgia?

Analysis of: Pfizer's Lyrica cuts fibromyalgia pain in study | www.reuters.com

Implications:

While fibromyalgia is not well understood and sometimes conceived of as having psychosomatic contributions, it is estimated to affect up to 2% of the population and still has no FDA approved medication treatments for it.

Previous data on pregabalin (Lyrica; from Pfizer), a novel alpha-2 ligand, suggests it may help reduce pain and fatigue and improve sleep associated with fibromyalgia (in a 2005 randomized controlled trial). Lyrica is approved for treatment of diabetic peripheral neuropathy, post-herpetic neuralgia, and adjunctive treatment for partial onset seizures.

Analysis: Treatment of fibromyalgia treatment could represent a very large market. Present treatments are off-label and in the form of analgesics, antidepressants, muscle relaxants, and anticonvulsants. Eli Lilly's Cymbalta has marketed toward the 'physical' symptoms of depression – not fibromyalgia itself but likely a subset this broadly conceived condition which is often characterized by mood and anxiety symptoms. Lilly is expected to file an supplemental NDA for fibromyalgia in the coming months based on positive data for the condition.

My own experience with Lyrica is that it offers some benefit as an off-label treatment of anxiety, and its non-SSRI and non-benzodiazepine mechanism of action gives it some added appeal. Should it receive a fibromyalgia indication, I think its off-label use for anxiety and other psychosomatic conditions would increase as well.

Lyrica is approved for the treatment for Generalized Anxiety Disorder in Europe and despite controlled data demonstrating its potential efficacy for the disorder, it was denied FDA approval for the condition in 2004.

Permalink

Healthcare News Feed

Report a Concern

May 4, 2007

DEA Speaks and Vyvanse Poises for Market Launch

Analysis of: Vyvanse (lisdexamfetamine dimesylate) Receives Final DEA Schedule Classification, Clearing Way for Launch of First Prodrug Stimulant for Treatment of | www.drugs.com

Implications: Vyvanse (marketed by Shire), the novel prodrug amphetamine for ADHD, has received its final DEA Schedule II status and appears on schedule to enter the market in the next couple months.

While under development, there was speculation that the drug might be listed as a Schedule IV substance, which would have expanded its market appeal considerably.

Because of the drug's need to pass through the gut to be activated, potential better safety profile in overdose, and a reported slower rate of rise to peak effect (ie. less euphorogenic potential) as compared to other stimulants (including extended release forms such as Concerta and Adderall), this drug may find a niche market as the 'preferred stimulant' for ADHD patients with a prior history of substance abuse or at risk for it. Though Strattera is sometimes used in this population, its efficacy is often lacking.

Analysis: Though Vyvanse may not be the blockbuster drug it was once touted to be, there will likely be a good place for it in the ADHD market. The produrg concept is appealing for patients with a substance abuse history (in remission) that may need stimulant treatment after other options such as Strattera (Ely Lily) or Wellbutrin (as an off-label treatment) have failed to be effective. Another prospective population for which the drug may be appealing are high school and college students, in whom shorter acting stimulants such as Ritalin and Adderall are often abused and their longer acting counterparts (Concerta and Adderall XR) may carry a higher overdose risk. Stimulant treatment for ADHD is often a trial-and-error process, with multiple dose and schedule options for the clinician to utilize, and given the pharmacokinetic profile of Vyvanse, its duration of action may be a plus for a subset of patients. How Shire is able to market the drug for these and other clinical populations will be an important part of its relative success.

Permalink

Healthcare News Feed

Report a Concern

May 4, 2007

FDA Extends Antidepressant Black Box Warning to Young Adults

Analysis of: FDA Seeks New Antidepressant Warning | www.cbsnews.com

Implications: The FDA's extended black box warning for young adults (18-24) regarding suicidality and close monitoring when starting antidepressant medication comes on the heels of the same 2004 warning for children and adolescents.

The 2004 warning has been criticized as having negative repercussions by scaring away children and parents from medication treatment (as well as clinicians for liability reasons) when it could have been otherwise highly therapeutic.

Vigilant attention when initiating antidepressants, especially younger individuals, is very important clinically as a subset of patient may experience manic activation or severe restlessness/agitation that could also intensify suicidality. However, that risk along with the public message around the presumptive dangers of antidepressants must be balanced against the potential morbidity, including suicide, which can have highly devastating consequences for individuals, families and society.

Analysis: This FDA announcement will have a much softer impact than the announcement 2 years ago that applied to children and adolescents. The news of suicidality risk has been out now for two years and considerably more focus is now being placed on the risks of untreated depression. Following the 2004 black box warning for children and adolescents, there was a dip in antidepressant prescription writing for this population while the suicide rate increased (despite a downward trend of nearly 10 years). A recent JAMA metaanalysis in April was critical of the FDA's interpretation of the data when it issued the initial black box warning and has placed the risk/benefit analysis into a more clinically appropriate context. Clinicians, I think, now have a clearer sense of the risk/benefit picture and the public is starting to understand how dangerous untreated depression can be.

Permalink

Healthcare News Feed

Report a Concern

May 2, 2007

Drugs and Devices: Will New FDA Legislation on Safety Impact Sales?

Analysis of: U.S. Senate to Consider Measure For New FDA Drug-Safety System | online.wsj.com

Implications:

Drug safety issues are in the public spotlight, with background events such as Vioxx & Bextra, antidepressants and suicidality, ADHD and cardiovascular risk still in the public consciousness, and with the foreground events such as the Kennedy Senate bill and renewal of the Prescription Drug User Free Act (PDUFA) in the fall.

There will be added political pressure for the FDA to be perceived as more accountable for its drug safety monitoring, drawn also from public criticism that the pharmaceutical industry is paying for its own drug approvals and monitoring (> 40% of the FDA's Center for Drug Evaluation and Research comes from 'user fees').

Analysis:

Funding of the drug safety monitoring program will correlate with its post-marketing impact on both pharmaceutical drugs and medical devices. Regulatory 'tools' will be limited if there is not enough money to support their implementation. Despite the fact that 1 in 5 drugs receive a black box warning after FDA approval and 1 in 20 are taken off the market altogether, preliminary reports have estimated that only ~ $30 million of the $400+ million in 'user fees' in 2008 will be used for strengthening the FDA's drug-safety system. If Congress does not step in more forcefully and with a lot of money, it is likely that the impact of any new legislation on drugs and devices will be soft, unless of course in the next year or two another Vioxx situation occurs, and then all bets are off.

For additional perspective, last week the New England Journal of Medicine (April 26, 2007; http://content.nejm.org/current.shtml) featured several articles about the issue of drug safety and its political and FDA context, which I reviewed in GLG News on April 27 in *Drug Safety Monitoring: A Changing Culture at the FDA*).

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

May 1, 2007

How Promising is Deep Brain Stimulation for Depression?

Analysis of: New Depression Therapy Gives Reason For Hope | www.medicalnewstoday.com

Implications:

Device technologies are making their way from neurologic circles to psychiatric ones for the treatment of various forms of mental illness.

Among these are deep brain stimulation and repetitive transcranial magnetic stimulation (rTMS). Vagus Nerve Stimulation (VNS) is FDA approved as a treatment for refractory depression, though its results have come into question (as I reviewed in GLG News on 4/20/07). Electroconvulsive therapy (ECT) is often used when medication options run out and can be considered the true gold standard of treatment for depression.

Despite the number of antidepressants on the market and the common use of augmentation/combination strategies when monotherapy fails, treatment resistant depression may affect nearly a quarter of a million people (possibly many more) in the US alone and is a real clinical issue. There is clearly a market for new depression treatments, including devices such as deep brain stimulation.

Analysis:

This study of deep brain stimulation is one of three clinical trials I am aware of for the treatment of depression. The other two, one presented at the American Association of Neurological Surgeons in 2006 and the other at the American Psychiatric Association's annual meeting last year, were similarly small but of longer duration and offered results that were quite promising in an extremely refractory group of depressed patients.

Medtronic's DBS device, Soletra, apparently has use-patents for depression and OCD and is in clinical trials for such conditions. There is still a long way to go for deep brain

stimulation as a treatment intervention for psychiatric disorders (besides clinical efficacy, what will come of stimulating parts of the brain that can overcome such severe depression? – if that powerful, could this induce mania, for instance?). However, clinicians know how challenging and frustrating (and of course, lethal) it can be when a chronically depressed patient remains unpresponsive to any form of treatment; while the study numbers are very low, responses in such a difficult-to-treat group is nonetheless impressive.

April 30, 2007

Restless Leg Syndrome: Diagnosis and Treatment Growing

Analysis of: XenoPort Reports Positive Top-Line Phase 3 Trial Results of XP13512 in Restless Legs Syndrome | www.pipelinereview.com

Implications:

Restless Leg Syndrome is common, with a prevalence likely greater than the estimated 10-12 million of US adults cited in some studies.

It is also underdiagnosed, as it may be conceived by clinicians as a symptom of anxiety or stress, or simply chalked up as the patient being a restless sleeper at baseline.

Dopaminergic drugs are the main for of treatment, with ropinirole (Requip ®) and pramipexole (Mirapex ®) FDA approved treatments. There is a clinical need for drugs that utilize a different mechanism of action that help this condition, for the obvious reason that it gives clinicians more to work with. Additionally, as RLS may be comorbid with various psychiatric conditions that may be exacerbated by dopaminergic agonist drugs (an area in need of further research), having other such options would be important.

Analysis: Achieving both primary endpoints in this Phase III trial of XP13512 in Restless Leg Syndrome is significant. With the first FDA approved drug (Requip) for the condition only just 2 years ago and much more discussion of it nowadays in medical circles, consideration of it in the differential diagnosis of sleep disturbances will grow as well as its diagnosis and treatment.

If XP13512 is well tolerated and effective, its use will likely be pervasive through primary care, sleep specialists, neurologists and psychiatrists. Its more targeted use may indeed occur by psychiatrists, who will be in a position to evaluate comorbidity and assess the risks/benefits of such medication treatment on the whole clinical picture. This, of course, assumes that as a group they become familiar with RLS as a clinical entity, which many are presently not.

April 30, 2007

The Diet & Wellness Trend and Its Newest Technologies

Analysis of: SenseWear ® is Accurate for Measuring Calories Burned | www.medicalnewstoday.com

Implications: The wellness and diet industry historically has evolved in the entrepreneurial spirit, and is now utilizing newer technologies to assess metabolic function. While the science hasn't always been solid, people will go to great lengths to find answers for their health, even if they are short-lived ones.

The rapid rise of 'wellness centers' and 'obesity clinics' in the last few years has indeed become creative, with 'integrated wellness programs' including metabolic rate calculations, blood testing (with seeming little medical value), customized fitness and diet plans, and even motivationally-oriented programs. Emphasis on performance in sports has extended these platforms in particular to collegiate and professional arenas.

BodyMedia, Inc.'s SenseWear ® is a portable armband used to calculate energy expenditure and therefore provides some basic information about metabolic rate that can be used for such assessments. This study of the American Journal of Nutrition may give it some perceived legitimacy as an accurate measurement of expended energy.

Analysis: BodyMedia, Inc, seems well-positioned in this wellness trend, with a range of

intellectual property, obtaining validation data such as this recent study, and establishing a scientific board that extends some level of perceived credibility for their products. Whether such devices have an overall impact on outcome is questionable at best; there is vast data about dieters and those starting wellness programs resuming their bad habits soon enough. Nevertheless, that has never prevented the countless diet and wellness books that remain at the top of best-sellers lists for months at a time, and various other related fitness or wellness technologies from their enormous success.

Permalink

Healthcare News Feed

Report a Concern

April 27, 2007

Vanda's VSF-173 for Excessive Sleepiness

Analysis of: Vanda Pharmaceuticals Initiates Phase II Clinical Trial for VSF-173 in Excessive Sleepiness | www.pipelinereview.com

Implications: Excessive Sleepiness (ES) is common condition often caused by sleep deprivation but is also a result of shift work, obstructive sleep apnea, various medical conditions (ie multiple sclerosis), and medication side effects. Narcolepsy is a primary sleep disturbance often characterized by profound “sleep attacks.” FDA approved treatments, noted below, are for ES due to one of several conditions.

Launching VSF-173 in this Phase II clinical trial for Excessive Sleepiness (ES) is an important milestone for Vanda Pharmaceuticals, which recently completed a Phase III trial for iloperidone in schizophrenia, an atypical antipsychotic with a potentially better side effect profile than some of its FDA-approved counterparts (ie less weight gain; less metabolic/glucose dysregulation).

Analysis:

Presently, modafinil (Provigil; Cephalon) is used to treat excessive daytime sleepiness due to a narcolepsy, shift work disorder, and obstructive sleep apnea/hypopnea syndrome. It is a schedule IV drug (‘limited dependence liability) and generally well-tolerated. Modafinil is sometimes used off-label to counter side effects of sedating drugs or for idiopathic hypersomnia.

Gamma-hydroxybutyrate (Xyrem; Jazz Pharmaceuticals) is used to treat excessive daytime sleepiness caused by narcolepsy, by inducing deep sleep states at night. It is tightly restricted due to its extremely rapid hypnotic effects and prescribed only by specialists with experience using it. Stimulants such as Ritalin and Adderall are approved for narcolepsy treatment as well, and like Provigil may be used to treat other forms of excessive daytime sleepiness. However, as Schedule II drugs (high abuse potential and severe dependence liability), they carry a set of clinical concerns and should be used judiciously.

Safer, effective drugs for ES conditions, in light of what’s presently available, will have an important place in the marketplace. Their off label use for medication sedation and medical conditions will likely correlate with tolerability/safety profile and they may even find their way to ‘performance-enhancing’ status, though not necessarily medically justified in this regard.

VSF-173’s use-indication is for excessive sleepiness due to shift work disorder, sleep apnea and narcolepsy (like Provigil); there is no indication at present to think it will fall in the more tightly regulated camps of stimulants and Xyrem. Other candidate drugs include Cortex Pharmaceuticals’ CX-717 which works on the ampakine system

Permalink

Other Analyses of the Same Article (3)

Healthcare News Feed

Report a Concern

April 27, 2007

Drug Safety Monitoring: A Changing Culture at the FDA?

Analysis of: Paying for Drug Approvals – Who’s Using Whom | content.nejm.org

Implications: This week the New England Journal of Medicine (April 26, 2007) featured three important editorials about the changing climate, publicly and at the FDA in particular, about the evaluation and monitoring of drugs for safety, including a piece by Dr. Mark McClellan, former commissioner of the FDA between 2002-2004.

Heightened attention to drug safety issues comes as the Prescription Drug User Fee Act (PDUFA) is up for its 5 year renewal and Congress deliberates on legislation about drug safety, including recommendations from the Institute of Medicine that found grave problems with the current FDA system for drug safety monitoring.

Under PDUFA, pharmaceutical companies pay 'user fees' to fund the FDA's Center for Drug Evaluation and Research, the division reviewing new drug applications, with payments estimated at $440 million (or 40% of the total budget) for 2008. Established in the early 1990s to help support the slow and cumbersome approval of drugs, PDUFA is now under scrutiny with critics noting that it holds the FDA's drug approval process accountable to the pharmaceutical industry itself.

In the same NEJM issue is a survey about physician-industry relationships (also highlighted in the Wall Street Journal (http://online.wsj.com/article/SB117754904637982847.html?mod=health_home_stories), bringing to light issues regarding perceived conflicts of interest.

Analysis:

The last several years has brought a number of FDA and drug safety issues into the public eye – Vioxx and Bextra, antidepressants and suicidality, ADHD stimulant drugs and cardiovascular risk, among others. In this context, numerous conflict of interest stories have circulated such as FDA advisory board members having received honoraria and consulting fees from the very pharmaceutical companies whose drugs they are evaluating. An attitude change at the FDA seems inevitable but funding will be a key factor and it would appear unlikely that Congress would assume the tab for full funding of the FDA's Center for Drug Evaluation and Research with a payment mechanism already in place.

Despite the fact that 1 in 5 drugs receive a black box warning after FDA approval and 1 in 20 are taken off the market altogether, a mere 29 million of the 400+ million in 'user fees' for 2008 will be used for strengthening the FDA's drug-safety system. Preliminary reports suggest Congress will give the FDA stronger 'regulatory tools' but without the support staff to execute them, it is unclear how effective the FDA will be in executing their action plan.

Some key questions: Will any prospective changes at the FDA ultimately affect the drug approval process? And will a higher level of vigilance post-marketing lead to even more drugs being pulled from the market or receiving warnings?

With public opinion calling for new treatments to be brought to market more quickly but complaining bitterly of safety issues when things go bad, we are caught in a Catch-22. It does appear that a change in attitude is at play, focused more on safety, but I suspect its practical impact on drug approval/monitoring will be slow until another one or two Vioxx-like cases really swing the pendulum.

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Report a Concern

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April 25, 2007

Treating Pain: What's on the Horizon?

Analysis of: Search is On to Discover 'Perfect' Pain Killer | pn.psychiatryonline.org

Implications: While opioid analgesics have established efficacy for pain, they carry a number of risks, including abuse, dependence and tolerance. Despite what appears to be a trend of increasing opioid prescriptions, establishing the frequency of such risks has been understudied and complicated to carry out. There is a clinical need to develop pain medications that work effectively and minimize such liabilities.

Targeting specific receptors that may mediate pain control while dampening other receptor systems that mediate the "reward" pathway is one interesting area of research, as cited in the article. Other prospective drug candidates would be drugs with opioid level pain control with less overdose toxity (accidental overdoses with opioids can be lethal), less risk of abuse and illegal drug trading.

Analysis: The article cities a couple groups (Center for Study of Opioid Receptors & Drugs of Abuse in L.A.; Univ of Toronto's Ctr for the Study of Pain) working to identify genes and receptors that can be targeted to develop more ideal pain medication candidates. It will likely be a number of years before such targeted candidates can be developed and adequately studied. There are publicly traded companies pursuing such platforms as well, such as Pain Therapeutics' (in alliance with King Pharmaceuticals), with their drug Remoxy, now in Phase III trials, designed to deliver oxycodone in an "abuse-resistant" capsule – no snorting or inhaling and less risk when combined with alcohol.

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Healthcare News Feed

Report a Concern

April 25, 2007

Ambien Goes Generic: What will the Market Look Like?

Analysis of: Caraco Pharmaceutical Laboratories Ltd. Announces FDA Approval To Market Generic Ambien(R) | www.medicalnewstoday.com

Implications:

Caraco Pharmaceutical Laboratories, Ltd., (Amex: CPD) is one among 13 companies approved by the FDA (on April 23) to market the generic version of the drug Ambien (zolpidem tartate) as a short-term treatment for insomnia.

The FDA's recent request that manucturers of hypnotic drugs strengthen their label to warn against complex, potentially dangerous sleep-related behaviors, has led to speculation that certain hypnotic drugs may be less commonly prescribed.

Analysis: Ambien has been a blockbuster drug for Sanofi-Aventis, dominating the sleep/insomnia market in recent years with very strong marketshare, with some 2 billion in sales last year. The generic forms should penetrate the market as easily, diminishing return on the trade brand. I do not see insurance plans paying for the name brand or physicians commonly requesting it. Sales for Caraco and the other companies will be diluted in

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online.wsj.com

comparison to the overall market, due to the 13 companies given approval, unless some are better poistioned through their distribution channels to enter quickly into the market.

Even with the FDA's recent warning on hypnotics, which will result in further investigation and study, zolpidem (Ambien) is considered an effective and generally safe drug (when used properly just for sleep) among clinicians. Ambien CR, with its bimodal release to help people stay asleep more effectively, in my view doesn't confer so distinct an advantage clinically as the marketing would have one believe.

April 24, 2007

A New Drug for Seziures, Bipolar Disorder and Pain? For Real or Wishful Thinking

Analysis of: New Drug Shows Promise For Treating Epileptic Seizures, Bipolar Disorder And Neuropathic Pain | www.medicalnewstoday.com

Implications: Despite about a dozen new antiepileptic drugs (AEDs) introduced in the past decade, nearly 1 in 3 patients treated for seizures (total est. ~ 3 million in US; nearly 50 million wordlwide) are not seizure-free. There are a number of drugs are in development, with either new mechanisms of action or derived from precursor drugs acting in a similar way. Eslicarbazepine (BIA 2-093), an investigational drug developed by the Portuguese company BIAL, is a second generation derivative of the AEDs carbamazepine (Tegretol & Tegretol XR; Novartis) and oxcarbazepine (Trileptal; Novartis). It works on voltage-gated sodium channels, just like its precurosors and various other AEDs, as well as some drugs that have been used for bipolar disorder.

This double-blind, controlled, Phase II trial (reported in Epilepsia; http://www.blackwell-synergy.com/doi/pdf/10.1111/j.1528-1167.2007.00984.x) for refractory epileptic patients on other medications, demonstrated that eslicarbazepine at once daily dosing met response criteria; additionally, 'seizure free' patients were nearly three times higher in the treatment group than the placebo arm. This is promising, though interestingly twice daily dosing did not meet statistical significance for response criteria, suggesting that dose/schedule issues may be important. The drug looks to be very well-tolerated, which would very clinically significant among this class of drugs.

Analysis:

While the original article in Epilepsia claims eslicarbazepine shows promise for "epilsepsy, bipolar disorder, and neuropathic pain," the data so far is only significant for seizures, with Phase III trials now underway. There is certainly room in the market for a prospective AED that's well-tolerated and can induce both response/remission as an adjunct treatment for epilepsy.

There is no sound data for this drug, however, in other conditions and some evidence suggesting it may not be an ideal candidate for either bipolar disorder or pain, both representing large clinical populations. Psychiatric drugs often borrow from neurology, especially as it has been proposed that bipolar disorder may arise from a 'kindling effect' not unlike seizures. However, the evidence suggests that AEDs as a class can't be assumed to necessarily work for bipolar disorder, with some successes like sodium valproate, lamotrigine, and carbamazapine (which is rarely used nowadays), and some lacking support like oxcarpazepine, topirimate, and gabapentin. Going on data from eslicarbazepine's progenitors, which itself is a spurious approach, the results are mixed, with data better for carbamazepine than for oxcarbazepine.

Among the neuropathic pain market (estimated to be near 4 billion this year in the US/Europe, with only a few drugs FDA-approved), one of the most common conditions is diabetic neuropathy. Drugs that work on sodium channels such as eslicarbazepine seem less promising than the gabapentinoid class (Pfizer's Lyrica & Neurontin) and Eli Lilly's Cymbalta. One study on oxcarbazepine, ESL's immediate progenitor, has generally faired poorly in controlled, randomized trials for pain. In contrast, Schrawz Pharama's lacosamide, a novel AED in phase III trials for epilepsy and pain, seems to show good anticonvulsant activity and has very promising results for diabetic neuropathic pain.

April 23, 2007

The Omega-3 EPA and Statins: An Healthy Combination

Analysis of: Fish Oil Added to Statin Therapy Reduces Risk For Major Coronary Events | www.medscape.com

Implications:

Though I was not able to access this article, the recent Japanese study of 18,000 men demonstrated that the addition of the Omega-3 EPA alone (1800 mg per day) to statins had a favorable, statistically significant outcome in decreasing major coronary events than with statins alone.

The Omega-3 fatty acid EPA, often used in combination with DHA in fish oil products, has been shown to have significant anti-inflammatory properties by acting on various prostaglandin and cytokine systems. The Omega-3 DHA, with less prominent anti-inflammatory effects, was not utilized in this study.

To achieve doses of 1800 mg of EPA by fish alone would be extremely difficult and be potentially toxic due to mercury, dioxin, and PCB contamination, further validating the use of Omega-3 products that can deliver high concentrations of Omega-3 fatty acids in a safe manner.

Analysis:

Omega-3 fish oil products are one of the fastest growing segments of the 20 billion dollar dietary supplement market, with annual sales well into 9 figures at present; additionally, the Omega-3 "food" market, estimated at 2 billion in 2006, is expected to grow to an 11 billion dollar industry by 2011. The FDA's approval of Omacor (Reliant Pharmaceuticals) as a prescription drug for high triglycerides is another step toward validating "fish oil" as a potentially valid medical treatment and branding Omega-3s as credible in the public view.

The scientific research on the Omega-3 fatty acids EPA and DHA is growing rapidly, with research demonstrating an important role for the Omega-3s at the cellular and immune response levels. Further, there is mounting evidence that Omega-3s have value for both preventative health issues as well as medical treatments (cardiovascular disease and high triglycerides; mood disorders and cognition; inflammatory conditions). What is not clear are the differential effects of EPA or DHA across different clinical conditions and physiologic parameters, though thus study is one step in that directions.

DISCLOSURE: I am a managing partner at Cenestra Health, a biotechnology/nutraceutical company that markets and distributes Omax3, a high-purity Omega-3 (>91%) Omega-3 supplement.

Permalink

Other Analyses of the Same Article (3)

Healthcare News Feed

Report a Concern

April 23, 2007

The Complicated Web of ADHD and Substance Abuse

Analysis of: A New Look at the Relationship and Management of ADHD and Comorbid Substance Use Disorder | cmsprepub.medscape.com

Implications: There is no doubt that substance abuse and ADHD are very often linked in a complicated web, making both diagnostic and treatment decisions challenging. The nature of this connection likely has biological underpinnings and may represent, for many, a form of self-medication for symptoms that are linked to the underlying ADHD, its sequelae (ie anxiety, depression), or other comorbid conditions.

Addressing the substance abuse issue first to 'clarify' the diagnostic picture is an important first step, helping to determine the nature of ADHD and/or whether there may be an underlying mood (such as bipolar) or anxiety disorder that may manifest with similar symptoms. Bipolar disorder is also commonly associated with substance abuse, with symptoms that may overlap those of ADHD, posing significant diagnostic challenges for adolescents, in particular, when the clinical picture is still unfolding and not so well established. The complexity of such diagnostic issues requires a sophisticated and nuanced treatment model, as well as a variety of medication considerations.

Analysis:

My own experience in treating ADHD patients with comorbid substance abuse is that it is fraught with challenges. Unless the substance abuse component has been effectively and comfortably (for the clinician) addressed, a non-stimulant medication such as atomoxetine is often utilized, or in some cases, off-label use of Wellbutrin SR/XL or Provigil (modafinil), for which there is data. Based on the outcome measures alone, it appeared that modafinil (which had been marketed as Sparlon; Cephalon) had been extremely close to FDA approval except for alarm about severe skin reactions. Guanfacine, an alpha-2 agonist, is in development as an ADHD drug by Shire (marketed as Connexyn), with a NDA filed in August 2006, and if approved, could offer another non-stimulant ADHD medication to the armamentarium. It is often used in children with comorbid tic and ADHD symptoms, with limited abuse potential, though I do not commonly prescribe it to adults.

One problem, in my view, is that non-stimulant drugs are often not as effective so at some point, consideration of their introduction makes clinical sense. The extent of the substance abuse, the kind of substance(s), the length/commitment of sobriety may factor into such treatment decisions. While there is no absolute contraindication to prescribing stimulants to ADHD patients with a history of substance abuse, there is significant risk here (to patient and clinician), of abuse as well as other liabilities such as selling of the drug, overdose, etc.… Short-acting stimulants (of the Adderall or Ritalin kind) can be especially problematic in this regard, with somewhat less liability for longer-acting forms (Adderall XR and Concerta) which have specialized delivery systems and aren't typically inhaled.

The prodrog lisdexamfetamine (Vyvanse; New River Pharmaceuticals & Shire), expected to hit the market imminently, seems to confer some advantages in that is requires biological breakdown in the gut to become active, taking longer to achieve peak affects and thereby lessening its euphoric effect. Its safety profile, in addition, might actually be preferably to the longer-acting stimulants (though this is mere speculation on my part). While likely to be listed as a schedule II drug by the DEA (to my latest knowledge), which would impact its perception among clinicians as a drug with 'high abuse potential,' knowledge of its pharmacokinetic profile might lend itself to being considered a 'first-line stimulant' for those with substance abuse histories, indeed a significant market. I suspect how the drug will be marketed, with obvious FDA/legal implications at play, will have a role in the drug's "clinician perception" and hence use in this population.

Botton-line: there is great need for effective pharmacotherapies that address this complicated comorbidity between substance abuse and ADHD. Other non-stimulant ADHD drugs in the pipeline include SGS-742 (Saegis/Novartis), CX-717 (Cortex), MEM3454 (Memory Pharm/Roche), and DOV-102, 677 (DOV Pharmaceuticals), most of which carry novel mechanisms of action.

April 23, 2007

An Effective Treatment for PTSD Sleep Problems

Analysis of: Promising Treatment For Post Traumatic Stress Disorder (PTSD) Sleep Disturbances | www.medicalnewstoday.com

Implications:

Sleep disturbances and nightmares in PTSD are notoriously difficult to manage, and can profoundly affect mood and quality of life during waking hours. Such chronic sleep disturbances in PTSD are a risk factor for serious comorbidity, including substance abuse, depression and suicidality.

This very important randomized study published in Biological Psychiatry demonstrated the alpha-1 adrenergic blocker prazosin (comes in generic; trade name: Minipres) not only significantly helped sleep quality and nightmares, but had a profoundly positive effect on the quality of life in the combat war veteran subjects. Prazosin is an anti-hypertensive agent, so can cause hypotension and dizziness, though is generally well-tolerated and was so in the study.

While the study subjects were combat veterans, my own experience with prazosin in PTSD patients (for reasons other than combat experience) is that it can be very effective for such conditions, besides being well-tolerated.

Analysis:

This study has very important and broad clinical application for the treatment of PTSD-related sleep disturbances. Prazosin is not as familiar an agent among the psychiatric community for treating sleep disturbances as are the class of hypnotics (ie. Ambien, Lunesta, Sonata) and benzodiazepines (ie. Xanax, Ativan, and Klonopin, among others). However, these sedative/hypnotic drugs can be problematic in the difficult-to-treat insomnia common in PTSD, with dose escalation, abuse and dependence a risk if they are not effective.

While it may take some time before prazosin is widely used for this indication (in part due to its being a generic and lacking the marketing arm to promulgate its use), this study should ultimately have an impact on the treatment of PTSD, even beyond that of combat veterans for which the study centered.

Report a Concern

April 22, 2007

Epix's Experimental Drug PRX-07034 Shows Potential Benefit on Cognition, Obesity

Analysis of: EPIX Pharmaceuticals Announces Statistically Signficant Results in Cognitive Function from Phase 1b Clinical Trial of Novel 5-HT6 Drug Candidate | www.pipelinereview.com

Implications: Results for this Phase 1b study of PRX-07034 (a 5-HT6 antagonist) reportedly met primary endpoints for safety/tolerability and improvement of cognitive function, now extending research observations on humans from preclinical animal studies that have demonstrated memory enhancement. Additional observations from this small-scale, early-stage trial reportedly demonstrated weight loss, also consistent with preclinical research for this 5-HT6 antagonist (as well as other such drugs in the development by other companies).

Epix is developing PRX-07034 as a treatment for obesity, Alzheimer's disease, and cognitive impairment in schizophrenia. There is evidence in animal models that the 5-HT6 serotonin receptor improves memory, with a putative mechanism of action that it translates to a rise in acetylcholine activity.

Weight loss has also been observed in preclinical studies with 5-HT6 antagonism, or partial agonism, with several other companies pursing drugs that target this receptor. Animal research would suggest that targeting this receptor my decrease adiposity and improve glycemic control.

Analysis: Novel drugs such as Epix's PRX-07034, GlaxoSmithKline's SB271046, and others (E-6837, a 5-HT6 partial agonist, and a compound from Suven Life Sciences LTD, among others) that specifically target the 5-HT6 receptor have some basis in preclinical data for benefiting memory and reducing food intake/treating obesity. While it is far too early to determine how this will translate into humans, early stage observations are encouraging. Targeting specific receptors implicated in the pathogenesis of different illnesses is the future, and the serotonin system has been implicated in quite a wide range, from depression, to appetite, to anxiety, to sexual function, and cognition/memory/attention.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

April 20, 2007

Does Vagus Nerve Stimulation for Depression Really Work?

Analysis of: Approving the Vagus-Nerve Stimulator for Depression | content.nejm.org

Implications: Despite the FDA's approval of Vagus-Nerve Stimulation (Cyberonics) for refractory depression (VNS is also approved for epilepsy), there have been significant scientific concerns about the efficacy of this device for depression.

The lack of well-controlled, replicated, randomized data has been problematic with VNS and depression, with significant criticism that its approval as a medical device was far less stringent than that of drugs. Further, its course for approval in FDA channels has been marred by politics, rancor and controversy, along with Cyberonics, the manufacturer, recently coming under heat for alleged securities fraud.

Coverage for VNS in depression has been denied by Blue Cross-Blue Shield and it appears that Medicare/Medicaid will not cover it as well.

Analysis:

Growing attention about such efficacy data poses a serious problem to Cyberonics/VNS treatment in depression. Lack of good, robust data will ultimately translate to limited use, especially with growing data around combination/augmentation drug strategies for refractory depression, a market estimated to be in the range of a quarter million people by some experts.

The cost of a VNS device, with its installation, is ~$25,000, making larger, additional studies of it to establish its efficacy quite costly. Cyberonics' platform to study VNS in anxiety, dementia, eating disorders and migraines will be subject to the same research/financing problems. Generating cash flow for Cyberonics on the depression indication will clearly be an issue with refusal of coverage by two major insurers so far.

Permalink

Healthcare News Feed

Report a Concern

April 19, 2007

The Antidepressant Market in Children and Adolescents: Heading Up?

Analysis of: Antidepressants Get a Boost For Use in Teens | online.wsj.com

Implications:

A major metaanalysis of 27 randomized trials published in JAMA (April 18; http://jama.ama-assn.org/) demonstrates a decreased risk of suicidal behavior/attempts in children and adolescents than previously determined by the FDA, while showing clinical efficacy of such medications for anxiety disorders (most effective), OCD (moderately effective) and major depression (modestly effective, with only Prozac significant for under 12).

Depressive and anxiety disorder in young people are common, though pharmacologic treatment is often complicated by a range of issues, from parental/physician perception of medication use (ie. liability/risks), diagnostic issues (are we treating depression or bipolar disorder?), and that the clinical picture will often declare itself more definitively at some later time (and which itself can be affected by the pharmacologic intervention).

In 2004, the FDA issued a black box warning about the risk of suicidal behavior in children and adolescents taking antidepressants (a two-fold higher risk), based on their own meta-analysis of 24 randomzed trials. The prevalence of antidepressant prescribing to this population decreased over the ensuing year by over 10%, followed by a leveling off in the subsequent year. Parental concerns about medication risk and physician concerns around liability likely impacted this trend.

While the 2004 FDA black box warning may have led to greater diagnostic and treatment vigilance (ie. closer follow-up when prescribing) for this population , it also had the effect of steering some children away from treatment where it would otherwise have been helpful.

Analysis:

The JAMA metaanalysis provides important risk/benefit information that will help clarify decisions around medication and give greater confidence to clinicians and parents that medications, when used properly, carry significant benefit when weighed against the potential risk of medication-induced suicidality.

This new data, along with some distance now from an amplified public response to the 2004 black box warning, will likely lead to a rebound in antidepressant usage in this clinical population. While there is value to the warning - it serves to 1) heighten awareness of such problems (ie. medication-related suicidal behavior can be a real clinical issue, with a subset of patients having a bipolar vulnerability or other underlying problem who become agitated/volatile on meds) and 2) improves follow-up/monitoring (ie. clinicians do respond to liability concerns), there are very serious costs to mental illness and this new data helps place this, and its treatment, into some perspective.

I do think the FDA should soften its black box warning, so as to not totally alienate a set of ambivalent parents/patients (and some clinicians) that read about how badly things can go on medication and run from that option before carefully assessing the risks and benefits. However, despite the FDA's more aggressive role in pediatric psychopharmacology recently (suicidality; ADHD cardiovascular risk), I think it would take some time for them to restate their position and will require their own internal analysis of the data.

Permalink

Other Analyses of the Same Article (3)

Healthcare News Feed

Report a Concern

April 19, 2007

What's Ahead for Men with Eating Disorders?

Analysis of: Men, Boys Lack Options to Treat Eating Disorders | online.wsj.com

Implications: Eating Disorders such as anorexia and bulimia have been widely perceived as female disorders, a byproduct of modern society whose physical expectations of women are dominated by the images of commercial advertising and media.

A recent Harvard survey sheds a different light on this, showing that as many as a quarter of anorectic/bulimic individuals and nearly 40% of binge-eaters are male.

Such gender bias of eating disorders is held not only in the public eye, but often among clinicians and researchers. Clinical settings and research done on eating disorders, including medication trials, are very heavily weighted toward women.

Analysis:

Because of strong cultural biases about body image and gender, it is likely that it will be some time before clinical research and treatment approaches give men the appropriate attention.

The incidence of anorexia and bulimia in men, as concluded in the survey, does admittedly come as a surprise to me, suggesting that many men are fearful of even seeking treatment. The incidence of binge-eating is less surprising, though in my experience it appears often comorbid with mood or anxiety symptoms than as a primary disorder. Regarding treatment, I am aware of numerous eating disorder groups for women, but aware of none that either have men in them or that openly invite them. And medication trials have essentially no track record for males.

The Harvard survey, articles such as this one the Wall Street Journal, and various 'male proponents' in the clinical community, can help bring attention to a very serious clinical area. But it may take some time.

Permalink

Other Analyses of the Same Article (3)

Healthcare News Feed

Report a Concern

April 17, 2007

Switching from Strattera to Stimulants Common

Analysis of: Study Shows Children With ADHD Who Start on Strattera(R) are More Likely to Change Therapies | www.drugnewswire.com

Implications: Strattera's niche in the ADHD marketplace is its non-sceduled listing, in contrast to the stimulants (and now Vyvanse), and its alternative mechanism of action as a non-stimulant which can be useful in patients with tic disorders, comorbid anxiety disorders, or substance abuse issues.

The common rate of switch from Strattera to stimulants reinforces clinical observation - while Staterra may work, it doesn't seem to work as well and it takes time.

Analysis: Prime Therapeutics' analysis/influence may well impact certain formularies away from Strattera, which will likely parallel similar clinician trends for reasons of decreased efficacy.

Staterra will retain some small portion of the ADHD marketshare but it has been basically relegated as a second-line treatment unless comorbid conditions are present or augmentation is attempted.

Some concerns of safety, for both stimulants (cardiovascular risk/sudden death) and Stattera (liver toxicity; prolonged cardiac QT prolongation), are in FDA advisory meetings and the international news, though both sets of drugs are generally considered medically safe for use by clinicians.

Permalink

Other Analyses of the Same Article (4)

Healthcare News Feed

Report a Concern

April 16, 2007

Lower Dose of Risperdal Consta FDA-Approved

Analysis of: FDA Approves New Dose of RISPERDAL(R) CONSTA(R) for Schizophrenia Treatment | biz.yahoo.com

Implications: The smaller dose of Risperdal Consta (manuf. by Alkermes; marketed by Janssen), the depot formulation of the atypical anti-psychotic agent risperidone, does afford clinicians the ability to titrate the drug from a smaller starting dose and potentially diminishes the risk of drug-interactions and clinical problems with patients having kidney/renal problems. However, the 12.5 mg dosage will likely represent a much smaller percentage of patients already taking Risperdal Consta to begin with.

Analysis: What is not clear, as their is no clinical efficacy reporting in this smaller dose range, is whether smaller dosages as such will be as effective, especially as patients taking depot medication are often more severely ill.

It is unlikely this will impact sales very much; depot formulations represent a narrow market share among the atypical antipsychotics and certainly within the use of risperidone itself.

Kidney/liver problems are not likely to account for a large percent of patients taking depot formulations, and drug-interactions don't appear to be very problematic among current dose ranges. Often, lower dose ranges are an entry point for starting a medication and improving compliance - but once the dose is titrated up, it is typically maintained at that therapeutic level.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

April 2, 2007

AACAP Treatment Guidelines for ADHD

Analysis of: Academy Releases New Parameter on Treatment of ADHD | journals.elsevierhealth.com

Implications:

The American Academy of Child and Adolescent Psychiatry issued a revision, after 10 years, of its diagnostic and treatment parameters.

The parameter was driven by new medication treatments for ADHD and a growing biological basis for the disorder.

A key feature is reporting on the superiority of medication treatment alone to other modalities, with stimulants usually the best first-line treatments.

Analysis: There is probably not much new here to those diagnosing and treating ADHD but international promulgation of the report will serves to heighten awareness of the disorder. The ADHD 'market' has grown considerably in the past decade, especially with many popularized books, on-line courses and self-help forums, and ADHD coaches. Adult ADHD has similary become recognized in the public perception, with estimates that it affects 4-5% of adults.

In the face of increasing public and FDA scrutiny about cardiovascular risk and the stimulants, the practice guideline concluded there was no higher risk of sudden death on stimulants than would be seen in the general population. Regarding other non-stimulant ADHD medications, the report adds that Strattera (Eli Lily) can be considered first-line in certain situations like comorbid anxiety or tic disorders, but stimulants remain the preferred first-line treatment.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

March 27, 2007

New FDA Indication for Cymbalta

Analysis of: FDA Approves Duloxetine for Anxiety | journals.elsevierhealth.com

Implications: Duloxetine (Cymbalta; Eli Lily), a combined serotonin and norepinephrine reuptake inhibitor (SNRI), was FDA approved in February for the treatment of Generalized Anxiety Disorder, adding to its existing FDA indications of major depression and diabetic neuropathy.

Specific Serotonin Re-Uptake Inhibitors (SSRIs) are the dominant medication for treatment of anxiety spectrum disorders (as well as depression). Theoretically, the added norepinephrine component can be considered a benefit, targeting yet an additional neurotransmitter system implicated in mood and anxiety disorders.

The other drug in the SNRI class that is presently approved for Generalized Anxiety Disorder, among other anxiety spectrum disorders and major depression, is Effexor XR. Unlike Effexor XR, whose norepinephrine properties kick in at a higher dose range, Cymbalta appears to target both serotonin and norepinephrine receptors through its entire dose range.

Analysis: With 2006 sales of Cymbalta at 1.3 billion, this added indication will only significantly strengthen the financial outlook.

With built-in norepinephrine properties and clinical efficacy (and FDA approval now) across depressive and generalized anxiety symptoms, Cymbalta can be considered with SSRIs as a first-line treatment aimed at treating the commonly depressed patient with comorbid anxiety, as well as the patient with generalized anxiety. The pain indication here also adds clinical value in contrast to SSRI's.

In addition, for patients with Generlazed Anxiety Disorder who have not responded so well to SSRIs, there is now a clear justification to consider Cymbalta as a next step switching strategy.

How well will Cymalta break into the SSRI market as a first, first-line treatment of Generalized Anxiety Disorder? With such a dominant role of SSRIs as first-line treatments of Generalized Anxiety Disorder (and other anxiety disorders) and the presence of generics, it make take some time, further clinical trials and comparisons, and hard-marketing to both psychiatrists and internists before Cymbalta strongly penetrates this arena, but it is no doubt on its way. And its dual indication for depression and gernalized anxiety is a major stride in this regard.

Permalink

Other Analyses of the Same Article (6)

Healthcare News Feed

Report a Concern

March 26, 2007

Triple Reuptake Inhibitors for Depression – the Next Big Gun?

Analysis of: Triple Reuptake Inhibitors: What to Expect from "Mega-Andipressants" | www.currentpsychiatry.com

Implications: Triple Reuptake Inhibitors aim to target all the major monoamines implicated in depression – serotonin, norepinephrine and dopamine - with an improved safety profile from Monoamine Oxidase Inhibitors (MAOIs).

Monoamine Oxidase Inhibitors (MAOIs), proven highly effective for depression though limited in their use because of potentially dangerous reactions with tyramine-rich foods, are the only currently utilized antidepressants that target all these monoamine neurotransmitters.

Analysis: Theortically, the value of such a broad-spectrum antidepressant drug with such a mechanism of action (one such investigational drug is DOV 216,303; DOV Pharmaceutical/Merck) is compelling though the clinical data is preliminary.

A Phase II trial utilizing DOV 216,303 demonstrated clinically comparable antidepressant effects to Citalopram, with a good safety profile.

Speculatively, potentiating the dopamine system more specifically may help with:

-a subset of depressive systems, such as lack of motivation, disinterest and low energy.

-offset some of the troublesome side effects like sexual difficulties common to potentiating the serotnergic system.

-jump-start the antidepressant response with a bit of a kick to the brain's motivational/reward system

Permalink

Other Analyses of the Same Article (5)

Healthcare News Feed

Report a Concern

March 15, 2007

FDA Issues Warning on Sedative-Hypnotics

Analysis of: FDA:Sleeping pills can cause 'sleep-driving' | www.cnn.com

Implications: The FDA has advised that the manufacturers of 13 sleep medications issue a warning about "sleep-driving" and other rare sleep-related problems, with "medication guides" being issued to patients later in the year.

It is likely that the warnings will serve to make clinicians and educators more vigilant about such side effects, though given the risks/benefits of hypnotic medications, the pervasive problem of insomnia, and the relative infrequency of such events (and a fairly solid clinical track record), it seems unlikely that such warnings will have any longer term or permanent effect on the use of such medications (unless gross underreporting is observed for such events).

Analysis: While such a warning will now attract a very high level of visibility due to the FDAs intervention, reports of such somnambulistic behavior (in particular with Ambien) appear to be quite rare and have been floating around the mass media for nearly a year. The FDA will recommend follow-up trials to assess the risks for such behavior and evaluate underreporting.

The drugs included are Ambien; Butisol sodium; Carbrital; Dalmane; Doral; Halcion; Lunesta; Placidyl; Prosom; Restoril; Rozerem; Seconal; and Sonata.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

March 14, 2007

Venlafaxine XR for Pediatric Generalized Anxiety Disorder

Analysis of: Efficacy and Safety of Extended Release Venlafaxine in the Treatment of Generalized Anxiety Disorder in Children and Adolescents: Two Placebo Controll | ajp.psychiatryonline.org

Implications: In this pooled analysis of two major randomized, double-blind, placebo controlled trials, Venlafaxine XR (Effexor XR; Wyeth) appears a useful and well-tolerated treatment of Generalized Anxiety Disorder in children and adolescents.

Generalized Anxiety Disorder is highly prevalent among school-age children, though to date only one small study with sertraline has looked at psychopharmacologic intervention in this specific population.

Analysis: Despite few FDA approved treatments, a paucity of large, controlled trials, and growing concerns about the 'activating' effects of antidepressants/anxiolytics in some children and adolescents, the use of psychotropic medications have increased significantly in the past decade.

The need for well-designed, controlled pharmacotherapy trials in school-age children cannot be overstated, as much pediatric psychopharmacology is off-label and with limited data. The empirical evidence for Venlafaxine XR, at least, now has some solid foundation for targeting a major anxiety disorder in this population.

While this does not mitigate concerns about medications potentially inducing mania, heightening irritability, or worsening suicidal ideation in susceptible patients, the data here is certainly a major plus.

Permalink

Healthcare News Feed

Report a Concern

March 13, 2007

Beyond Monoamines: New Neurotransmitter Targets for Depression

Analysis of: ALS Drug Appears to Ease Resistant Depression | www.clinicalpsychiatrynews.com

Implications: Riluzole (Rilutek; Sanafi-Aventis), an FDA-approved treatment for Amyotrophic Lateral Sclerosis (ALS), may benefit treatment resistant depression.

The evidence draws from a very small and highly preliminary data set, but because riluzole targets the glutamate system (a relative newcomer to psychiatric drug research), this represents a potentially important area of further clinical research.

Analysis: Riluzole dampens activity of the excitatory neurotransmitter glutamate, which in turns modulates GABA activity.

Growing evidence suggests these two neurotransmitter systems may play a significant role in depression, though presently the only treatments of unipolar depression involve monoamines (i.e., serotonin; norepinephrine; dopamine).

Early research suggests riluzole may benefit anxiety disorders as well, in particular obsessive-compulsive disorder.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

January 10, 2007

Vyvanse for ADHD: Expected to Reach Market in Second Quarter 2007

Analysis of: New River Pharmaceuticals And Shire Receive Approvable Letter For VYVANSE™ (lisdexamfetamine Dimesylate) For The Treatment Of ADHD | www.medicalnewstoday.com

Implications: According to this press release, Vyvanse is expected to reach the market in the second quarter 2007, following the FDA's recent second approvable letter, a request for 'routine' data and the DEA's review of Vyvanse's scheduling status.

The FDA has recommended to the DEA that Vyvanse receive a Schedule II status (high abuse potential; severe dependence liability) rather then the less stringent classifications of III or IV, hoped for by its collaborators Shire and New River Pharmaceuticals.

Analysis: Vyvanse has attracted significant attention for the treatment of ADHD in that the active amphetamine salts are conjugated to an amino acid, which needs to be first broken down in the GI tract before the active amphetamine salts are released in the body, potentially decreasing the risk of abuse (such as inhaling the stimulant) and overdose toxicity (slower release of drug over time).

While the perception of the drug, in its development, was that it may decrease abuse liability while maintaining the same effects as the other stimulants, the anticipated Schedule II status will likely link it to all the others unless head-to-head studies show greater efficacy than other stimulants.

There is some question as to whether clinicians and patients (and parents), despite scheduling status, will see this drug and its novel prodrug mechanism as favorable for certain sub-groups of ADHD patients and co-morbidities (ie adolescents and college students prone to abusing stimulants; substance-abusers, etc…). Presently, Lily's Statterra offers a favorable first-line treatment option for the substance-abuse/ADHD clinical population as it is not classified as an 'abusable' drug.

Permalink

Other Analyses of the Same Article (3)

Healthcare News Feed

Report a Concern

October 18, 2006

NRP104: The Next Psychiatric Blockbuster Drug?

Analysis of: FDA Issues Approvable Letter for NRP104 for the Treatment of ADHD | www.prnewswire.com

Implications:

1. Stimulants (Concerta, Ritalin, Adderall, Adderall XR, and the generic forms) are the main category of medications used to treat ADHD.
2. All stimulants are classified as Schedule II drugs (high abuse potential; severe dependence liability).
3. The prospect of scheduling NRP 104 (itself a stimulant drug), following its FDA approvable letter, to III or IV (ie less abuse/dependence liability), would have a highly significant impact on its clinical use, with new prescription marketshare likely going to NRP104 and some turnover of the existing marketshare of stimulants.

4. Final FDA approval, with a schedule III or IV, would likely position Shire as the leader in ADHD treatments.

Analysis: The article is a press release issued by Shire (in collaboration with New River Pharmaceuticals) following an approvable letter of NRP104 for ADHD. Final scheduling issues are being addressed between the FDA and DEA, though it appears the FDA is not requiring further clinical studies of NRP104 at this time. One of the key features of NRP104 is that the active amphetamine salts are conjugated to an amino acid, L-lysine, which needs to be first broken down in the GI tract before the active amphetamine salts are released in the body, thus decreasing the risk of abuse (such as inhaling the stimulants) and overdose toxicity (slower release of drug over time). Efficacy studies suggest NRP104 will be an effective treatment of ADHD, in line with various stimulant medications, as demonstrated in a Phase II study of children ages 6-12, and a larger phase III study, with up to 80 subjects responding positvely vs. 22% placebo group.

Permalink

Other Analyses of the Same Article (2)

Healthcare News Feed

Report a Concern

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Gerson Lehrman Group Healthcare Council

Gerson Lehrman Group NewsAnalysis BETA

Louis Sanfilippo, M.D.

You are currently viewing NewsAnalysis related to **Louis Sanfilippo. M.D.**. NewsAnalysis hosted by Gerson Lehrman Group is designed to present Council Member commentary on current news and articles, organized by the categories and specialties of our Council Member network. Each Council Member post is presented with a Title, News Significance Rating, URL Link to the article, and most importantly, the commentary and analysis from the Council Member. News Significance is identified by the Council Member as 'the importance of this article in the Council Member's field of expertise.

Louis Sanfilippo, MD, is an Assistant Clinical Professor of Psychiatry at Yale University in Connecticut. He also teaches courses on Psychopharmacology to Yale Psychiatry residents and psychologists with a focus on antidepressants, mood stabilizers, antipsychotics, and psychostimulants. His clinical expertise is in the treatment of anxiety, depression, ADHD, and bipolar disorder in adults and college students, as well as the treatment of athletes and executives. He has published articles, chapters and books across a wide range of topics, including psychotic disorders, mood disorders and suicide, forensic and ethical issues in psychiatry, the philosophy of mind, as well as a review of psychiatry for medical students. Dr. Sanfilippo also conducts a seminar on sports psychiatry and has been a Fellow with the American Psychoanalytic Association.

October 23, 2005

Mifepristone: Utilzing a Novel Mechanism of Action to Demonstrate Rapid and Effective Anti-Psychotic Effects in Psychotic Major Depression

Rating : 8

Flores BH, et. al. Clinical and Biological Effects of Mifepristone Treatment for Psychotic Depression. Neuropsychopharmacology. 2005 Sep 14;[Epub ahead of print].

Clinical relevance: Psychotic Major Depression (PMD) is a highly debilitating mental illness, afflicting up to 15-20% of depressed patients. Primary treatment strategies for PMD include 1) a combination of antipsychotic and antidepressant medications or 2) electroconvulsive therapy (ECT). Further, all FDA-approved pharmacologic treatment strategies utilized to treat depression, either psychotic or non-psychotic, involve the monoamine system (i.e. dopamine; serotonin; norepinephrine). Though evidence exists that the Hypothalamic-Pituitary-Adrenal (HPA) Axis may play a role in mood, anxiety and psychotic disorders (in addition to PMD), there are no psychiatric pharmacotherapies that directly target this system. Mifepristone, a glucorticosteroid receptor antagonist (developed by Corcept Therapeutics), may potentially represent a novel mechanism of action in the treatment of PMD by its “re-setting” effects on the HPA axis. While Corcept is seeking development of Mifepristone for psychotic major depression, targeting the HPA system is now of interest across a range of psychiatric disorders.

In this study, 30 patients meeting criteria for PMD were randomized to 600/day mifepristone or placebo (while maintained on their current medications) and followed for 8 days, with measurements made of depressive and psychotic symptoms. Mifespristone showed a significant improvement in psychotic symptoms (7 of 15) compared with placebo (2 of 15), with an evident biological effect on ACTH/Cortisol by blood measurements; the study authors also add that unpublished data suggests an ongoing symptom reduction beyond the 8 day study. However, there was no significant reduction in depressive symptoms compared to placebo, but this data can be difficult to interpret because the clinical effects of standard pharmacotherapy on depressive symptoms typically take considerably longer to occur (3-6 weeks) than the 8 day study would have allowed. Longer length trials might help to address this particular issue and clarify the role of antipsychotic medication treatment more acutely and as maintenance therapy (given their problematic side effects and for which mifepristone might be considered a substitute if data supported). In the short-run, mifepristone seemed well tolerated, with only one drop-out, but targeting the HPA-axis might produce side effects further down the line. Though the sample size is small and the length of the study is short, the study results are encouraging and suggest that targeting the HPA-axis may work for PMD.

Commercial relevance: The commercial value of an effective drug that also targets a different “physiologic system,” in this case the HPA-axis, is potentially quite significant. If mifepristone indeed proves to be a well-tolerated drug that rapidly reduces psychotic symptoms and speeds overall recovery of PMD, typically treated on inpatient units, its use, assuming of course FDA approval, would likely be large. A positive effect on the depressive symptoms as well would only increase its overall value and may lessen the need for combination drug strategies in PMD. One issue not addressed in the study is whether mifepristone would be administered only acutely or be part of a longer term treatment strategy (and if so, what side effects might

we see?). Lastly, while Corcept Therapeutics is seeking to develop mifepristone in the narrower clinical setting of PMD, there may be a much larger commercial market if such “HPA-axis resetting drugs” are shown effective in other mood, anxiety or psychotic disorders.

October 30, 2005

FDA Approves Rapid-Result, In-Office Lithium Test

Rating : 5

Kaplan, A. FDA-Approved Office Lithium Test Expected to Enhance Clinical Care. Psychiatric Times. 2005;22(9):6-7.

Jefferson, JW. Finger-Stick Lithium Test: In-Office Alternative to Laboratory-based Methods. Current Psychiatry. 2005;4(1):111-112.

Clinical Relevance: Lithium continues to be a commonly prescribed maintenance treatment for Bipolar Disorder, with demonstrated anti-suicidal properties beyond that of other mood stabilizing medications. However, due to its narrow range of toxicity (i.e. even small increases in blood levels can become toxic), regular monitoring of Lithium levels is required in an ongoing manner (2-3 times per year) and whenever the medication dose is changed. The InstaRead Lithium System, manufactured by ReliaLAB, uses a finger-stick to obtain Lithium levels in a matter of minutes. This is in contrast to a 24-48 hour delay typical of most outpatient laboratories. The results of the InstaRead system were found to be as reliable and accurate as those made by commercial laboratories. Rapid-response Lithium testing will likely improve overall patient care because of its convenience and the likelihood of promoting compliance (as some patients do not like to stay on Lithium because of the frequent blood tests). Whether this might actually impact psychiatrist or patient perception of, respectively, prescribing or taking Lithium, is less clear.

Commercial Relevance: The InstaRead Lithium system has the potential to become a staple of any general psychiatric or psychopharmacology practice, due to its convenience and ability to enhance clinical care. It is likely that Lithium will be utilized for some time to come, given its long track record and clinical benefits (and despite the crowding market from other Bipolar treatments from the newer generation of dopamine blocking/serotonergic agents such as Zyprexa, Risperdal, Seroquel, Abilify and Geodon as well as anticonvulsants such as Depakote and Lamictal). Other potential settings for its use would include psychiatric clinics and emergency rooms. Limitations to the system's success might be due to: 1) problems with reimbursement (i.e. for in-office blood levels) 2) lack of psychiatrist interest due to more common use of other, potentially better tolerated mood-stabilizing medications 3) the fact that immediate Lithium results aren't practically necessary unless there is acute toxicity. ReliaLAB is also developing in-office testing of low white cell and neutrophil counts for the use of clozapine.

November 05, 2005

Pregabalin : A New and Effective Approach for Treating Generalized Anxiety Disorder

Rating : 8

Rickels, K et al. Pregabalin for treatment of generalized anxiety disorder: a 4-week, multicenter, double-blind, placebo-controlled trial of pregabalin and alprazolam. Arch Gen Psychiatry. 2005;62(9):1022-1030.

Clinical Relevance: Generalized Anxiety Disorder (GAD) is a common, and often chronic, psychiatric illness. The main pharmacologic treatment strategies for GAD consist of the use of serotonin-reuptake inhibitors and/or benzodiazepines. However, one major limitation with SSRIs is that anxiolytic effects typically take several weeks to occur and anxiety may actually worsen initially. The use of benzodiazepines (i.e. alprazolam), while having a quick onset of action (within minutes to hours), can be clinically problematic due to their abuse potential, possibility for dependence and tolerance, and potential for severe withdrawal reactions. In the last few years, there has been considerable psychiatric interest in the use of pregabalin (Lyrica; manufactured by Pfizer and FDA approved for diabetic nerve pain, pain due to shingles, and adjunctive treatment for partial seizures), given its different mechanism of action than other anti-anxiety agents (it binds a subunit of voltage gated Ca channels which deceases Ca flow and release of excitatory neurotransmitters in the brain and spinal cord), good tolerability, mild drug-drug interaction profile, and lack of severe discontinuation symptoms. Although the FDA denied its approval for GAD in September, 2004, the results of this study suggest that pregabalin may be a promising treatment for GAD and possibly other anxiety spectrum disorders.

In this multi-center trial, 455 subjects were randomized to pregabalin (300 mg, 450 mg, 600 mg), alprazolam (1.5 mg), or placebo and followed over 4 weeks, with weekly ratings of anxiety symptoms. The pregabalin groups showed comparable improvement to the alprazolam group (and statistically significant over placebo) for psychic anxiety by the end of the study, but with greater therapeutic effects (at the 300/600 mg doses) than alprazolam on somatic anxiety. Also, pregabalin (at 300/600 mg doses) showed significantly greater improvement in total anxiety (via HAM-A) by end of week 1 than alprazolam. Pregabalin was very well tolerated, especially at the lower (and more effective) dose. These results, despite the short-length of trial, are very encouraging; longer-term studies addressing clinical efficacy, safety, and any potential for tolerance/abuse would be important. Based on these findings, pregabalin would seem to fit the model of an ideal anxiolytic agent – effective, fast-acting, very well-tolerated, minimal discontinuation effects, and with less abuse/dependence risk than the benzodiazepines. As a solo agent, off-label use for GAD (and also panic and social anxiety disorders based on other studies) may be justified. How pregabalin measures up against SSRIs or as an augmentation strategy with SSRIs would be important to investigate (as augmentation to SSRIs would certainly broaden its use).

Commercial Relevance: Notwithstanding the fact that pregabalin is a drug made by behemoth Pfizer, there are many clinical features to this drug that make it a potentially high impact drug in psychiatry and even primary care circles - and advantageous over the highly prescribed class of benzodiazepines - in the treatment of GAD and possibly other anxiety disorders. However, it is not clear where the FDA stands presently after its September 2004 denial.

November 13, 2005

FDA Approves Remelteon (Rozerem) : The First Sleep Medication of its Kind

Rating : 7

Rosack, J. New Sleep Drug Binds to Melatonin Receptors. Psychiatric News. 2005; Vol. 40, No. 16, pp.14, 21.

Jancin, B. Drug Improves Sleep Induction Without Sedation. Clinical Psychiatry News. 2005; Vol. 33 (October), No. 10, pp. 58-59.

Clinical Relevance: Remelteon (Rozerem; manufactured by Takeda Pharmaceuticals North America, Inc.) is the first FDA-approved (in July, 2005) long-term sleep medication that is not a schedule IV controlled substance. Its mechanism of action, as a potent melatonin agonist exclusively targeting MT1 and MT2 receptors in the hypothalamus, distinguishes it from all other hypnotic agents on the market. The drug's effect was primarily to decrease time to sleep onset, which is reflected in the FDA labeling; however, remelteon's ability to reduce multiple night-time awakenings was not notable. Two phase III, randomized, double-blinded, placebo-controlled trials, presented at the annual meeting of Associated Professional Sleep Societies, apparently showed consistent results on sleep induction across adult and geriatric populations (as noted in Jancin article).

Presently, the most commonly utilized sleep medications are hypnotics that are designated as controlled substances and which can cause CNS depression by affecting the alpha isoform of the GABA receptor (this includes the class of medications known as benzodiazepines, as well as Ambien, Sonata, and likely Lunesta). Such medications, due to their receptor profile, can also cause cognitive, memory and/or psychomotor impairment and, in some cases, a next day hangover effect. Because remelteon does not bind receptors implicated in cognitive and respiratory function, it might be a preferred agent for use in the elderly population as well as patients with chronic obstructive pulmonary disease (COPD) and sleep apnea. Moreover, the drug may have significantly more widespread appeal as a sleep agent due to the fact that there appears to be no abuse or dependence potential, no rebound insomnia upon discontinuation, and a good safety profile. The main clinical issue with remelteon was that it did not produce a significant effect on night-time awakenings, setting it at a disadvantage to its "controlled substance" counterpart Lunesta, which was recently approved for both insomnia and longer-term sleep maintenance.

Commercial Relevance: The need for a different kind of hypnotic with versatility across a range of different populations (ie. COPD, sleep apnea, elderly, substance abusers, and those concerned with abuse or dependence – the latter would include both patients and clinicians) cannot be underscored enough, making this drug a potentially important one in the class of sleep medications. Remelteon's lack of significant effectiveness against nighttime awakenings, however, is its Achilles heel, as many individuals with trouble falling asleep will often have difficulty staying asleep. Nevertheless, there would appear to be a potentially large market for this drug, based on both clinical utility and the FDA approval for long-term use.

November 19, 2005

Aripiprazole Well-Tolerated in Children and Adolescents at Adult Doses

Rating : 7

Findling R. Tolerability of Aripiprazole in Children and Adolescents with Major Psychiatric Diagnoses. Abstract C5, Joint Annual Meeting: American Academy of Child & Adolescent Psychiatry. Toronto, October 18-23, 2005.

Clinical relevance: Aripiprazole (Abilify; Bristol-Myers Squibb and Otsuka America Pharmaceutical, Inc.) is an atypical antipsychotic agent with unique dopamine (D2) partial agonist properties, presently approved for adult schizophrenia and bipolar disorder. One of aripiprazole's most favorable features in adult treatment is that it so far has not been associated with prominent metabolic side effects such as weight gain or lipid dysregulation which are common to its counterparts olanzapine (Zyprexa) and clozapine (Clozaril) and, to a lesser extent, quetiapine (Seroquel) and risperidone (Risperdal). Treatment of bipolar and psychotic conditions in children and adolescents present a significant pharmacologic challenge because of these metabolic side effects, especially weight gain, which can often be dramatic and is also associated with mood stabilizing medications such as Depakote and lithium.

This FDA-requested study was to determine the tolerability and safety profile of aripiprazole in children and adolescents. Following an initial dose escalation phase, patients were maintained at a target dose range (20 mg, 25 mg, or 30 mg per day) for an additional 14 days (these dose ranges are typical of adult dosing). Of the 19 patients (ages 10-17) enrolled, with primary diagnoses of schizophrenia or bipolar disorder, only one patient dropped out of the study due to an adverse event (dystonia); aripiprazole was otherwise quite well-tolerated. Moreover, 17 (89%) of the patients were rated as "much" or "very much" improved utilizing the Clinical Global Improvement (CGI) scale, with CGI scores moving from 3.7 (moderately ill) at baseline to 1.9 (borderline ill) at the end of the study. While it is extremely encouraging that aripiprazole was very well-tolerated in children/adolescents at adult doses, with notable clinical benefit utilizing the CGI, this was an open-label study of short duration, and longer-term controlled trials are needed to clarify the picture regarding side effects, safety and clinical benefit. In particular, the evolution of tardive dyskinesia would be important to examine, as well as the potential for mood destabilization over time given aripiprazole's serotonergic properties.

Commercial relevance: The use of aripiprazole is very rapidly growing in the adult population, largely due to its favorable metabolic side effect profile, especially around weight gain. If its clinical utility and safety is established in children and adolescents, of which this study represents an important step, the impact would be enormous. Already, child and adolescent psychiatrists are turning to aripiprazole as a first-line agent, despite its off-label use, because the side effects from other antipsychotic and antimanic drugs can be so damaging and profound.

November 26, 2005

Stathmin: A New Genetic Target for Conditioned Fear and Anxiety

Rating : 7

Shumyatsky GP et al. *stathmin*, a Gene Enriched in the Amygdala, Controls Both Learned and Innate Fear. Cell. 2005;123(4):697-709.

Clinical relevance: Stathmin, a protein that inhibits microtubule formation, is coded by the stathmin gene (also known as oncoprotein 18) and is highly concentrated in the amygdala. In this study, mice were genetically engineered to be devoid of the stathmin gene. These genetically mutant mice showed significantly less fear conditioned responses than their control counterparts, as tested on various measures. One conclusion from the study is that it appears the stathmin protein is required for the expression of innate fear and for encoding memories associated with learned fear. The direct genetic link to the stathmin gene (which codes for the protein) in the amygdala provides an actual molecular target for research on understanding fear and anxiety, as well as for potential drug therapies should these findings be borne out in clinical research.

Commercial relevance: While this is a basic science study in knockout mice, there is considerable excitement that the study's findings may represent the first major step of a revolutionary breakthrough in understanding anxiety and fear, and may lead the way toward new drug therapies for a host of mental disorders over the next decade. Collaborating on the study were neuroscientists from Columbia, Rutgers, Harvard, and Albert Einstein (including Nobel Prize winner Eric Kandel). While drug therapies based on this research would be a long way off in the future and require much further research, including its applicability to humans, it seems likely that stathmin will fuel its own research and investment industry because the implications are quite profound.

December 04, 2005

Buprenorphine (Subutex) Shows Robust Benefits for Opioid Detoxification in Adolescents

Rating : 5

Marsch, LA et al. Comparison of pharmacological treatments for opioid-dependent adolescents: a randomized controlled trial. Arch Gen Psychiatry. 2005 Oct;62(10):1157-64.

Clinical relevance: The use of heroin and prescription narcotics among adolescents is a growing public problem. However, there is little data regarding the safe and effective detoxification of opioids in this population. One major treatment strategy for opioid detoxification includes the use of buprenorphine, a partial opioid agonist providing some opioid effects but with a ceiling effect that enhances safety and avoids an extreme high. Buprenorphine comes in two forms, buprenorphine alone (Subutex, Reckitt Benckiser Pharmaceuticals, Inc.) and buprenorphine with naloxone (Suboxone; the naloxone component, as an opioid antagonist inactivated by oral ingestion but active when injected, helps prevent abuse of the medication through injection). Other detoxification strategies include the use of methadone and clonidine.

This study randomized subjects (n=36, mean age 17) to buprenorphine (Subutex) and clonidine detoxification protocols, each arm associated with 3x per week behavioral therapy, performed in an outpatient setting. Doses were variable and based on amount of narcotic use and tolerability. Outcome measures showed a significant difference between the two groups, and markedly favoring the Subutex arm. Treatment retention rates for Subutex were 72% versus 39 % for clonidine. Even more importantly, 61% of Subutex subjects continued relapse prevention treatment with Naltrexone after the acute detoxification phase verus 5% of clonidine subjects. This is likely due to the fact that patient detoxification with Subutex was physically and subjectively better tolerated (also demonstrated in the study), leading to a better perception of the treatment experience as well as the benefit on ongoing treatment after detoxification. Safety and effectiveness studies of buprenorphine have been well established in adults; there is some safety data of buprenorphine in children/adolescents taken for pain studies, but this may be the first randomized, controlled trial comparing different pharmacotherapies for opioid detoxification in adolescents and, by itself, will likely lend support to this treatment regimen. Of course, larger studies are required to confirm these results, and establish safety and efficacy, but these overall findings, nonetheless, would suggest Subutex is a reasonable primary treatment strategy for this population.

Commercial relevance: While opioid dependence in adolescents may represent a narrower population as compared to the categories of mood disorders, ADHD, and anxiety disorders, this is a growing population for which there are no well-established treatments. That the Subutex arm was so robustly more effective across the outcome measures of treatment retention and transition into relapse prevention treatment is extremely encouraging for its use as a primary detoxification drug in adolescent opioid dependence.

December 18, 2005

FDA Issues Public Health Advisory for Paxil Use in Early Pregnancy

Rating : 6

Paroxetine HCl - Paxil and generic paroxetine

Clinical Relevance: Paroxetine (Paxil and Paxil CR; GlaxoSmithKline) taken in the first trimester of pregnancy was found to increase the risk of congenital malformations in infants (most specifically cardiac anomalies) as compared to the general population as well as to other antidepressants. One unpublished study, based on the Swedish National Registry, demonstrated a two-fold risk of heart malformations with paroxetine versus the general population; the expected risk of infant cardiac malformations for those treated with paroxetine was 2% while the rate of cardiac malformations in the general population was 1%. Another study, based on data from the US insurance claims database, showed a 1.5 fold increased risk of cardiac malformations and a 1.8 fold increased risk of congenital malformations in general. Data from this latter study also showed a rate of cardiac defects at 1.5% versus 1% for other antidepressants. Based on this data, GlaxoSmithKline has changed the “pregnancy precaution rating” from Category C (uncertain safety; ho human and animal studies show an adverse event to fetus) to Category D (indicative of positive evidence of human fetal risk).

On account of this data, and the resultant public advisory, there are several potential clinical consequences. Paroxetine will likely be much less commonly prescribed to women of child-bearing age who are considering having children in the near-term future. As for women who are taking paroxetine that learn that they are pregnant or that are considering a pregnancy, the risks and benefits of continuing paroxetine (versus changing to another antidepressant or discontinuing it altogether) will need to be carefully evaluated with their health care provider.

Commercial Relevance: Paxil’s increased risk of fetal malformations and change to Category D status in pregnancy will likely lead to its more limited use in woman of child-bearing age, especially if they are considering pregnancy at some point soon. Though still widely prescribed by both the primary care community as well as by psychiatrists, this narrows the population that might be amenable to the use of Paxil. In addition to its shorter ½-life (and therefore its often more significant discontinuation syndrome), this is another development that distinguishes Paxil more negatively than its counterpart SSRI’s.

January 07, 2006

Quetiapine for Bipolar Depression

Rating : 9

Calabrese JR et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry. 2005 Jul;162(7):1351-1360.

Clinical Relevance: The depressive phase(s) of Bipolar Disorder (I or II) are associated with a high degree of morbidity and often present significant treatment dilemmas. Despite numerous approaches for treating the manic phase of Bipolar Disorder or unipolar Major Depression, well-studied and empirically validated medication options for Bipolar depression are limited. Presently, Symbyax (Lilly; combination of olanzapine and fluoxetine) is FDA-approved for the treatment of Bipolar depression, though its use as a combination drug offers much less versatility than utilizing the two drugs separately or other combinations of medications. Other approaches to treatment include the use of lamotrigine (Lamictal, GSK, approved for maintenance treatment of Bipolar Disorder) or the concomitant use of an antidepressant with a mood stabilizer. The latter approach carries the risk of emergent mania or rapid-cycling in patients either not adequately treated with a mood stabilizer or pre-disposed to activation by an antidepressant. The use of quetiapine (Seroquel; AstraZeneca), FDA-approved for the treatment of both schizophrenia and the manic phase of Bipolar Disorder, potentially offers an effective treatment for Bipolar depression with potentially less risk for activation into mania or rapid-cycling than add-on antidepressant strategies. Similarly, data suggests that Lamotrigine may also confer antidepressant properties while protecting against mania.

In this study, 542 subjects with Bipolar I or II, and in a depressive episode, were randomized to 600 mg quetiapine, 300 mg quetiapine, or placebo following a washout period of psychotropic medications. By week 1, both quetiapine groups significantly separated from placebo; by the end of the 8 week study, positive response criteria were met in 58% in each of the quetiapine groups (versus 36% for placebo) and positive remission criteria were met in 53% in each of the quetiapine groups (versus 28% for placebo). Statistically significant improvements were also seen along scales assessing anxiety, quality of sleep, quality of life, and sense of improvement. Drop out rates in the study were comparable across the three arms of treatment, though significantly more dropouts due to adverse events occurred in the quetiapine groups (26% 600mg; 16% 300 mg; 8% placebo); lack of efficacy accounted for the highest number of dropouts in the placebo group. Rates of emergent mania were similar across all groups. Replication and longer term evaluation would further clarify the role of quetiapine in this population. Further, in clinical practice, it would be helpful to clarify the role of quetiapine as an add-on to existing medications as wash-outs are often impractical and potentially hazardous.

Commercial Relevance: This is a very significant study in a clinical population where treatment strategies are still limited and fraught with clinical dilemmas. One such problem is adding an antidepressant to an existing mood stabilizer(s), which risks activating certain patients into mania or rapid-cycling states. Treating Bipolar depression with a medication such as quetiapine that might also have a protective effect against mania (“treatment from below”) represents a new paradigm in treating Bipolar Disorder and evidently would be of enormous clinical value. The use of lamotrigine in treating Bipolar depression is growing, though its slow

rate of titration due to the risk of a life-threatening rash makes its use in more severely acute depressions less than optimal.

January 15, 2006

The Selegiline Patch: Will MAOI Treatment of Depression Return?

Rating : 5

Mechcatie E. FDA Panel Backs Selegiline Patch For Depression: Majority view 20-mg formulation as safe. Clin Psych News. 2005;33(16):1,10.

Clinical relevance: Orally ingested MAO inhibitors (MAOI's) are an older class of antidepressants that are generally relegated to last-line usage due to their potential of causing an acute hypertensive crisis when tyramine-rich foods such as aged cheeses are ingested. Concerns about safety and close dietary regulation make MAOI's both worrisome and cumbersome for patients and psychiatrists. Dietary restrictions for the selegiline patch (Emsam; Somerset Pharmaceuticals; prospective treatment of major depression) were recently under review by an advisory panel to the FDA, which voted 7-4 that no dietary recommendations were warranted for the patch at a 20 mg dose (though it is likely that 30 and 40 mg dosages will require dietary restrictions due to limited safety data). Bypassing gastro-intestinal circulation with the patch allows for enzymes there to properly degrade tyramine.

Presently, the FDA is reviewing data to approve the selegiline patch for major depression, with results so far demonstrating superior effects to placebo through one year of treatment. While MAOI's are considered to be, perhaps, among the most effective class of antidepressants, it is not clear whether selegiline, which has a long track record for Parkinson's (orally; Eldepryl), will have similar robust effects on depression. Further, if higher doses may prove more effective or necessary for the treatment of major depression, then having to implement dietary restrictions will evidently be a major shortcoming, failing to distinguish it from the oral MAOIs (Parnate; Nardil) which have been used to treat depression thus far.

Commercial relevance: The option of having an MAOI in the pharmacologic armamentarium for treating major depression, without dietary worries, would likely bring the selegiline patch moderate success (assuming, of course, FDA approval), though given the growing number of pharmacologic options, its market-share would likely be limited. Unless, of course, the data bears more robust results as have been shown in the orally ingested MAOIs. What is appealing about the selegiline patch is that, should no dietary requirements be warranted, it would re-introduce the "MAOI pathway" as a treatment alternative which has long since fallen out of favor.

January 22, 2006

Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression

Rating : 7

Fitzgerald PB et al. A Randomized, Controlled Trial of Sequential Bilateral Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression. Am J Psychiatry 2006;163(1):88-94.

Clinical relevance: Repetitive transcranial stimulation (rTMS) has shown potential promise for certain psychotic disorders, but the data on treatment resistant major depression thus far has been mixed. The technical aspects of administering rTMS, and where to target the magnetic currents, are becoming much better understood, which may explain why the results of this study were so robust. Of 25 patients with treatment-resistant depression (and on stable medication regimen for the preceding month) in each treatment arm (rTMS versus sham), the rTMS group demonstrated notably better responses than the sham at 2 through 6 weeks of the study, with response rates of 44% (versus 8% sham) and remission rates of 36% (versus 0 sham) by the 6-week end point. Treatment with rTMS was extremely well tolerated. The results were significantly better than in previous studies of rTMS in treatment-resistant depression; the authors postulate that this may have to do with a bilateral (versus unilateral) stimulation, combining both left and right sided stimulation of the prefrontal cortex. Recent FDA approval of vagus-nerve stimulation (VNS) in 2005 for treatment-resistant depression has opened the door for new non-pharmacologic strategies addressing this complicated and difficult clinical population; ECT remains another option. One hopeful consequence of this study is to pave the way toward refining the method of administering rTMS, which thus far has been one of its major obstacles.

Commercial relevance: While rTMS remains a relatively cumbersome and technically challenging method of treatment, with less known about how persistent the beneficial effects of treatment are beyond acute improvement, these results suggest that rTMS may have significant value in treatment-resistant depression. It is quite possible that with newly emerging methodologies around how and where to direct the magnetic currents, rTMS may find an important place in depression treatment. One potential advantage of this form of treatment over VNS is its non-invasive nature.

January 27, 2006

Yaz, the Oral Contraceptive that Helps Premenstrual Dysphoric Disorder, Awaits Final FDA Approval

Clinical Relevance: Berlex, Inc., a US affiliate of Schering AG, received an "approvable letter" from US FDA for its oral contraceptive Yaz, pending further review of recently submitted clinical data; Yaz had received a similar "approvable letter" in 2004 as well. Yaz, a low dose version of the oral contraceptive Yasmin (manufactured by Schering), was found to be as effective as selective serotonin reuptake inhibitors (SSRIs) in the treatment of Premenstrual Dysphoric Disorder (PMDD) in a study published in the September 2005 issue of Obstetrics & Gynecology. The study, a randomized, double-blind trial conducted across 64 US medical centers, involved 450 women and demonstrated a 48% response rate for Yaz (as defined by a 50% reduction of symptoms) compared with a 36% response rate for placebo. The authors of the study indicate that these results were similar to SSRIs, the only FDA-approved treatment for PMDD at present. The study was conducted over 3 cycles, with minor attrition due to adverse events (15% Yaz versus 5% placebo). One significant clinical implication of the study, which the authors briefly suggest, is that Yaz might have a unique clinical role in women seeking both oral contraception and relief from their premenstrual dysphoric symptoms. Taking Yaz alone might avert potential side effects of concurrent SSRI/oral contraceptive treatment in women who would otherwise be taking two medications; more specifically, this might serve to avert the common SSRI side effects of sexual dysfunction and the less common, but especially detrimental, SSRI side effect of activating pre-disposed individuals into mania. PMDD is a relative common condition, afflicting up to 5% of women in their reproductive years.

Commercial Relevance: If Yaz were to receive final FDA approval for the treatment of PMDD, this would represent a unique and important treatment option for a large treatment population. Further, it is likely that much of PMDD could be treated directly out of OB-GYN offices (as some of it presently is), without referral to psychiatrists. Moreover, for women who are also seeking oral contraception (which likely represents a large portion of PMDD patients), folding treatment into a single agent has obvious benefits for both the clinician and for the patient: fewer overall side effects, better tolerability, ease of use, and less risk of the more deleterious SRRI side effects for individuals not properly screened (ie mania).

January 28, 2006

Modafinil (Sparlon) Safe and Effective for Child and Adolescent ADHD

Rating : 9

Biederman J, et al. Efficacy and Safety of Modafinil Film-Coated Tablets in Children and Adolescents with Attention-Deficit Hyperactivity Disorder: Results of a Randomized, Double-Blind, Placebo-Controlled, Flexible-Dose Study. Pediatrics. 2005 Dec;116(6):e777-84.

Clinical Relevance: Attention-Deficit Hyperactivity Disorder, one of the most common neuropsychiatric disorders in children and adolescents, is now widely treated with psychostimulants such as methylphenidate (ie. Ritalin; Concerta) and mixed amphetamine salts (ie. Adderall). Such drugs, though highly effective, carry more significant risks of abuse and are classified as Schedule II drugs. Atomoxetine (Strattera; manufactured by Lilly), a norepinephrine re-uptake inhibitor, is a non-stimulant drug FDA-approved for ADHD in children, adolescents, and adults, with far fewer concerns about abuse potential. Modafinil (Sparlon; Cephalon, Inc.), whose novel mechanism of action is putatively related to enhanced arousal and cortical activation, was shown in this study to be an effective and well-tolerated treatment of ADHD in children and adolescents. The FDA is presently reviewing clinical data on the safety and efficacy of Sparlon; Cephalon is apparently poised to launch the drug as early as the first quarter of 2006 if approved.

This study was a 9 week, double-blind, randomized, placebo-controlled trial involving 248 children/adolescents ages 6-17 years. Dosing was flexible, ranging from 170-425 mg once per day. Significant improvements were shown by week 1 and throughout the study, with 48% of Modafinil treated subjects “much” or “very much” improved by the end of the study (versus 17% for placebo). Of note, patients doing well with stimulant treatment were excluded from the study, though they may have also done well with Modafinil, possibly making the trial population an even “more difficult-to-treat” group. Modafinil was well-tolerated, with comparable drop-out rates (at 3%) to placebo (at 4%). The most common side effects were insomnia (29%), headache (20%) and decreased appetite (16%). Modafinil is FDA-approved (as Provigil, Schedule IV drug – less abuse risk than Schedule II) for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift-work problems.

Commercial Relevance: Given its unique mechanism of action (and thus potential usefulness as an augmentation strategy for ADHD in addition to a stand-alone treatment), significantly less abuse potential than the stimulants, generally good tolerability, and clinical efficacy for ADHD, Sparlon will likely find an important place in ADHD treatment, assuming its FDA-approval. It is difficult to interpret the data in this study against stimulant efficacy, as patients treated effectively with stimulants were excluded from the study. One major potential breakthrough in ADHD treatment might come from NRP104 (New River Pharmaceuticals), an amphetamine conjugated to an amino acid which allows for equal therapeutic effects as the stimulants but with notably less abuse potential. Another potential breakthrough is a methylphenidate patch (Daytrana; Shire Pharmaceuticals & Noven Pharmaceuticals), also presently under FDA review.

January 29, 2006

Methylphenidate Skin Patch for ADHD Reaches FDA Advisory Committee

Rating : 5

Mechcatie Elizabeth. Panel Supports ADHD Drug Patch with Warning. Clinical Psychiatry News 2006; Volume 34, Issue (1), p 1, 9.

Clinical Relevance: A methylphenidate patch (Daytrana; codeveloped by Shire Pharmaceuticals and Noven Pharmaceuticals) received approval support from the FDA's Psychopharmacologic Drugs Advisory Committee, but with agreement in the committee that the label should include a warning about drug sensitization. The patch, which would represent the first such transdermal delivery system of a stimulant, would be intended for children aged 6-11. Among potential benefits of a patch are allowing for stimulant delivery in children who have difficulty with pills as well as a diminished abuse risk (though the Shire is not presently planning to develop the patch for adolescents or adults). The patch was effective and well-tolerated in two studies, but failed FDA approval in 2003 due to longer pharmacokinetic activity than desired and safety concerns; such problems appear to have been resolved by wearing the patch for a shorter duration of time. Concerns of allergic contact sensitization stem from a case where a subject taking the patch developed skin irritation, discontinued the patch, but then redeveloped skin irritation after beginning an oral form of methylphenidate. While it would appear that true allergic reactions from the patch are small based on the clinical data (though skin irritations were quite common at 55%), the potential risks of not being able to ever resume stimulant treatment after an allergy likely led the committee to advise the label warning.

Commercial Relevance: With Shire and Noven pursuing the patch in a narrower clinical population (6-11 years of age) and with the recommended label warning for sensitization, the transdermal patch loses some initial momentum in the rather large ADHD pharmacology market (ADHD is estimated to occur in 5-10% of children and adolescents; and up to 4-5% in adults). Nonetheless, there appears to be a clinical need for such a drug delivery system. Moreover, the patch is likely to further establish Shire (makers of Adderall, Adderall XR) as one of the major competitors in the ADHD drug development market.

February 05, 2006

Oral Form of Nalmefene Shows Benefit in Pathological Gambling

Rating : 7

Grant JE, et al. Multicenter Investigation of the Opioid Antagonist Nalmefene in the Treatment of Pathological Gambling. Am J Psychiatry. 2006 Feb;163(2):303-12.

Clinical Relevance: There are no FDA-approved pharmacologic treatments for pathological gambling, despite its 1-2% lifetime prevalence in the US population. Naltrexone, an opioid receptor antagonist, has shown significant benefits in pathological gambling in a randomized clinical trial; however, due to the high doses required in that study, dose-dependent liver toxicity emerged in 1 in 5 patients. Oral nalmefene, an opioid receptor antagonist developed by BioTie Therapies and Somaxon Pharmaceuticals, Inc., demonstrated superior benefits to placebo in this 16 week double-blind, randomized trial, involving 207 patients. One major advantage of nalmefene is that it is not associated with liver toxicity. By the end of this 16 week study, 59% of subjects taking nalmefene at 25 mg per day were “much improved” or “very much improved” compared to 34% in the placebo arm. These would appear to be very positive findings in a notoriously difficult treatment population. Dosing at 25 mg daily was generally well-tolerated (no statistical difference to placebo) and with better clinical results, while side effects led to much higher rates of discontinuation at the 50 mg and 100 mg per day dosing, with no added clinical benefits. One limitation of the study was a very high discontinuation rate (about 2/3 of the subjects), which the authors attribute partly to the patient population but also poor management of side effects. The authors suggest that tolerability might be improved with more conservative dosing regimens that were not utilized in the study. Another limitation to this study was its relatively short-duration. Pathological gambling is often a lifelong impulse control problem, so whether the effects of nalemefene would be sustained (as well as its safety) over time would be important to clarify.

Commercial Relevance: Oral nalmefene is presently an investigational drug in the US that is attracting significant attention in the treatment of alcohol as well as impulse control disorders, due to its effects as an opioid receptor antagonist and its favorable side effect profile (as it lacks dose-dependent liver toxicity). The results of this study are very encouraging for pathological gambling, a clinical area that has yet to receive an FDA-approved pharmacologic treatment. The broader clinical implications for nalmefene in the treatment of impulse control disorders that may be mediated by the opioid system is, indeed, potentially quite important clinically with a large commercial market.

February 12, 2006

Priority Review Granted for Pfizer Smoking Cessation Drug

Rating : 9

Jim Rosack. "Med Check: Regulatory and Legal Briefs." Psychiatric News 2006; (Volume 41, Number 2): 30-31.

Clinical Relevance: Varenicline (Pfizer; trade name Champix) is a selective nicotinic-acetylcholine receptor partial agonist that has shown favorable smoking cessation results compared to its major potential competitor, bupropion (Zyban), and placebo, in a comparison, placebo-controlled, clinical trial (quit rate at 12 weeks 44%, 30%, 18%, respectively). The FDA has granted varenicline a 6 month priority review, following an NDA by Pfizer for the drug in November, 2005. Because it acts on nicotinic receptors, Varenicline targets both craving and withdrawal symptoms associated with smoking. By pharmacologically targeting nicotinic receptors in partial agonist fashion, varenicline represents a novel mechanism of action for treatment of one of the most morbidty and mortality-laden of human habits. The drug appears to be well-tolerated in clinical trials.

Commercial Relevance: With a nearly 50% greater quit rate than bupropion in a 4 month trial and a priority review (which the FDA assigns for drugs that "may provide a significant therapeutic advance over existing therapies"), varenicline would seem poised for a significant clinical and commercial impact.

February 26, 2006

Substance P Antagonist Fails Phase III Trial For Depression

Rating : 5

Keller M, et al. Lack of Efficacy of the Substance P (Neurokinin1 Receptor) Antagonist Aprepitant in the Treatment of Major Depressive Disorder. Biol Psychiatry. 2006 Feb 1;59(3):216-23. Epub 2005 Oct 24.

Analysis/Commentary: There has been considerable research interest in Susbatnce P and Neurokinin1 receptors in the pathpophysiology of depressive and anxiety disorders. Excessive binding of Substance P to neurokinin1 receptors in the limbic system has been thought to play a role in bringing about depressive symptoms, based on a large body of preclinical data. Further, Phase II studies have demonstrated antidepressant activity of the substance P (neurokinin1 receptor) antagonist aprepitant (MK-0869; proposed trade name “Emend”, Merck and Co., Inc). In this large, multicenter, randomized, 8-week, placebo-controlled trial, aprepitant failed to show any statistically difference from placebo on the HAM-D depression scale in any of the 5 trial arms; this was in contrast to paroxetine, which showed antidepressant efficacy in all three trial arms it was involved in. Dosing of aprepitant did not appear to be an issue, as PET analysis of subjects in the study demonstrated sufficient neurokinin1 receptor antagonism throughout the study. The study data looks to have come as a surprise to the authors, given previously favorable clinical data for the drug. Some explanations cited for the lack of efficacy have to do with the possibility of preferential recruitment of “responsive” patients in the phase II trials as well as the possibility of a “false positive” error in the analysis of the Phase II clinical data.

Implications: This study will likely severely dampen, if not end, what had been a significantly burgeoning interest in substance P and the neurokinin1 receptor system for the treatment of mood disorders. It is not clear where the neurokinin1 receptor system may stand with regard to anxiety disorders and whether this will be clinically investigated.

March 06, 2006

Transdermal MAO-Inhibitor Patch Approved by FDA for Depression

Rating : 6

Peggy Peck. FDA Approves First Antidepressant Transdermal Patch. MedPage Today Online. March 1, 2006.

Analysis/Commentary: The FDA has approved the monoamine oxidase inhibitor (MAOI) selegiline transdermal patch (Emsam; developed by Somerset Pharmaceuticals; marketed in US by Bristol-Myers Squibb) for major depression, the first such transdermal system utilized for major depression. Though oral MAOI's are considered among the most effective treatments for depression, the risk of a potentially life-threatening hypertensive condition with certain tryamine rich foods have relegated them to last-line usage in clinical practice. However, the 6 mg form of Emsam (which also comes in 9 & 12 mg forms) will not require any dietary restrictions and has been successful in treating major depression, in trials ranging from 6-8 weeks and through one year. Presently, it is not clear whether the selegiline patch will match remission rates of the older, orally ingested MAOI's. The higher dose strenghs (9, 12 mg) will carry recommendations for dietary restrictions, as data on interactions with certain foods has not been conclusively established; however, it is unclear whether these restrictions may be lifted with longer-term data. More significant than the delivery system (though this is the first FDA approved transdermal treatment for depression) is that this brings back MAOI treatment of depression, and with less concerns about dietary restrictions, and will likely benefit a subset of patients who have not responded to, or tolerated, more standard SSRI treatments or would prefer a non-oral form of medication (ie. some medically ill patients with difficulty swallowing).

Implications: Given the already large and expanding anti-depressant market, it is unlikely Emsem will gather a large market share unless it is shown to demonstrate superior efficacy to the more commonly used antidepressants. However, given that the antidepressant market is quite crowded with SSRIs and SNRIs (serotonin/norepinephrine reuptake inhibitors), having a more user-friendly MAOI is very appealing as a treatment option. Further, it will offer clinicians an alternative if a patient has failed, or poorly tolerated, serotonergic antidepressants. One interesting area for investigation is whether individuals who have failed trials with serotonergic drugs may respond more favorably to an MAOI, possibly due to a different underlying biology; if this were the case, this would greatly enhance the clinical usage and commercial value of an MAOI like Emsam.

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SENTIMENTS DIVIDED ON BLACK BOX WARNING ON ADHD MEDS>>>>>>>

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March 10, 2006

Intramuscular Drug Treatment for Alcohol Dependence Poised for Launch

Rating : 7

Rosenthal R. Intramuscular Naltrexone: Targeting adherence in alcohol dependency treatment. Current Psychiatry 2006, Vol 5, No. 3, 106-111.

Analysis/Commentary: Presently, pharmacologic treatments for alcohol dependency are based on oral formulations (oral naltrexone – Depade & ReVia; acamprosate – Campral); however, given the risks of early relapse and compliance problems with daily medication use, Vivitrol (Alkermes; marketing and distribution arrangement with Cephalon), an intramuscular/injectable form of naltrexone that can be dosed once monthly, may prove an effective alternative to improve compliance and prevent relapse in this population. Vivitrol received an approvable letter from the FDA in December, 2005; Alkermes submitted their response to the letter on February 17 and awaits an FDA reply, which is expected within 60 days of its filing. Vivitrol demonstrated significant benefit in alcohol dependent patients in a phase 3 trial (Garbutt JC, et al. Vivitrex Study Group. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA 2005; 293:1617-25). Patients who were abstinent before the study had very significant reductions in heavy drinking (80% greater than placebo arm), while patients who continued to drink into the study had a significant benefit over placebo, but less dramatic. Vivitrol was reasonable well-tolerated, with some early-onset mild nausea as the most common side effect. The use of Vivitrol has both clinician and patient appeal because of its monthly dosing and potential benefits for patients with compliance difficulties or who have failed other treatments. What is less clear is whether an injectable drug will be widely utilized; while clinic settings might be better positioned with an ancillary staff equipped to inject the drug, private psychiatric practices may be less inclined to take on the responsibility of administering the drug due to liability as well as staffing concerns.

Implications: Over 2 million Americans seek alcohol treatment each year, with significant rates of relapse in the illness. Offering this population an IM, once-a-month-dosing treatment is likely better-suited for compliance than oral formulations and will likely be met with some success, gathering more momentum in clinics designed for substance abuse treatment than in private community practices. While injectables are often rejected by patients, there is certainly a clinical need for them in this population as well as a willingness among clinicians who see the same patients chronically stopping their oral medications, acting out impulsively, and then relapsing on alcohol.

YAZ FDA Approved as Oral Contraceptive: Premenstrual Dysphoric Indication Pending

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Buprenorphine: Change to A Schedule II Controlled Substance?

STAR*D Data Demonstrate Clinical Benefits for Augmentation and Switching Strategies in Major Depression

Posted: 4/21/2006 7:57 AM

Implications:
These two second level STAR*D studies are extremely important in that they represent the largest controlled data examining specific outcomes with different switch and augmentation strategies. The rationale to utilize either switch or augmentation strategies now has a sound scientific basis, even when switching from one SSRI (that has failed) to another SSRI (ie. given the improvement with Zoloft). It is unlikely that these results will notably affect prescribing habits, with exception of possibly re-igniting some interest in Buspar, which did seem to hold its own against Wellbutrin for the augmentation of SSRIs, though in the end, Wellbutrin helped reduce depressive symptoms more substantially and with fewer side effects (Wellbutrin is far more utilized as an augmentation strategy than BuSpar anyway).

Mirtazapine (Remeron; manufactured by Oraganon) - a serotonergic and norepinephrine potentiator – was not included in the study, despite evidence suggesting that it might actually be quite useful as an augmentation strategy to SSRIs and would also be a reasonable switch strategy as well. Cymbalta (Eli Lilly) a norepinephrine and serotonin reuptake inhibitor, was also not included in the study and would have been a useful comparison in the switch study, especially because its norepinephrine reuptake properties kick it at a lower end dose than its counterpart, Effexor XR, and may (theoretically) have some physiologic benefit in certain SSRI non-responders due to a different underlying physiology.

Analysis:
Despite the common usage of augmentation strategies as well as switching to another medication when an SSRI has failed to effectively treat a major depression, there is a surprising lack of controlled, comparison data to evaluate the effectiveness of such pharmacologic approaches. These two second-level studies from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) demonstrate the effectiveness of both augmentation and switch strategies in such cases. In the first level of the study, over 4000 patients with major depression were treated with citalopram (Celexa; Forest Pharmaceuticals) in flexible doses; the group that did not achieve remission (about 65%; the high percentage likely a result of “remission” rather than “response” being utilized as the outcome measure) were then pooled into two second level studies.

In the augmentation study (n=565), patients were randomized to either Wellbutrin SR (GlaxoSmithKline; dopamine and norepinephrine reuptake inhibitor) or Buspar (Bristol-Myers Squibb; 5 HT1A partial agonist), to be taken with Celexa. Remission rates were similar for both groups (~30%), but the Wellbutrin SR group demonstrated a greater reduction in depressive symptoms by the end of the study, as determined by the QIDS-SR-16 rating scale. Wellbutrin SR was also better tolerated, with fewer side effects and adverse events. Though Wellbutrin SR augmentation to SSRIs is a commonly utilized clinical strategy (as it targets non-serotonin receptors and thus complement SSRIs), with results here that should not come as a surprise, the comparable effectiveness of Buspar augmentation is of notable interest as its use has largely fallen out of favor in recent years.

In the switch study (n=727), patients that failed Celexa were randomized to either Wellbutrin SR, Zoloft (Pfizer; SSRI), or Effexor XR (Wyeth-Ayerst Laboratories; serotonin and norepinephrine reuptake inhibitor). Remission rates were comparable between the groups, at roughly 1 in 4 across all medications (and depending on symptom scale utilized), as were response rates (26-28% range). Tolerability was similarly alike across all groups. Given the fact that there was no “loser” or “winner” in this study, the authors concluded that switching to any of these medications (including Zoloft, whose mechanism of action as an SSRI is like citalopram) represented a reasonable approach after an initial trial of an SSRI failed.

New Warnings Ahead for Lilly's Strattera?

Posted: 5/2/2006 8:59 AM

Implications:
The past several months have brought intense scrutiny over ADHD drugs, especially the stimulants, due to potential cardiovascular risks. Also, significant safety issues over Cephalon's Sparlon – a potential non-stimulant treatment of ADHD - have risked its FDA approval despite favorable clinical efficacy. In this setting, the British equivalent of the FDA has recommended label changes of Lilly's Strattera, a non-stimulant treatment of childhood and adult ADHD, to include risk of seizures and prolongation of the QT interval.

Analysis:
The article cites the FDA's report of 3 sudden deaths in children and 4 in adults between 1992-2004. In the US, however, there has not been much clinical attention paid to either of these risks (seizures; QT prolongation) specifically, but increased vigilance and monitoring of more serious side effects such as these will no doubt be one consequence of the FDA's heightened scrutiny of these medications. In particular, prolongation of the QT interval can increases the risk of arrhythmias, and can be compounded with other drugs that also affect the QT interval - thereby potentially introducing a whole new arena of drug-drug interactions with Strattera that have not been well explored to date. It is not clear how solid the evidence is that the British regulatory body reviewed to make such label recommendations, but to be sure, more clinical attention to will be paid to such potential serious side effects in the coming months.

Zyprexa in Prodromal Psychosis: Weighing the Risks and Benefits

Posted: 5/10/2006 2:34 PM

Implications:
This study may be regarded as somewhat controversial in that it investigates the use of antipsychotic medication, with potentially serious side effects, for symptoms in the “prodromal” category rather than more overt psychosis. This is balanced against the idea that early intervention for such prodromal patients may spare some of them the profoundly damaging and chronic course of schizophrenia. The study was not adequately powered because of its high drop-out rate, and so did not meet statistically significant conclusions, but does seem to confirm what is known in clinical practice – that some patients with symptoms suggestive of an emerging psychotic condition can benefit from treatment, but that ambivalence about treatment and side effects (in this case, significant weight gain with Zyprexa) constitute major barriers. While the pool of patients with “prodromal psychotic symptoms” is potentially quite large, there is little data to determine which subset of this pool is at greater risk and therefore more likely to benefit from (and more likely justified to receive) preventative medication treatment.

Analysis:
In this placebo-controlled study of patients with prodromal symptoms of schizophrenia (n=60), patient were randomized to either placebo or olanzapine (Zyprexa; Eli Lilly)) to determine whether medication might prevent the emergence of psychosis. The 2 year study (year 1 – treatment administered; year 2 – only follow-up with no treatment administered) had only a 20% completion rate (n=12). While only 16% of olanzapine patients converted to psychosis during the treatment year as compared with 38% converting in the place group, the results did not achieve statistical significance, likely because of the small study numbers. However, nearly 2/3 of the Zyprexa group gained weight with treatment, with a mean 19 lbs over one year. The authors conclude that 4.5 patients would need to be treated in order to prevent one conversion to psychosis over a year of treatment, noting the benefits of treatment in this population may outweigh the risks and should be clarified with further clinical trials.

Pfizer's Chantix Obtains FDA-Approval for Smoking Cessation

Posted: 5/15/2006 12:43 PM

Implications:
The FDA approved varenicline (Chantix; Pfizer) for smoking cessation treatment, following its priority review. Chantix will likely emerge as the top smoking cessation medication, given its roughly 50% higher efficacy as compared to Zyban – as demonstrated in a comparison, placebo-controlled 12 week trial, in which quit rates were 44%, 30%, and 18% respectively, for Chantix, Zyban, and placebo. The medication, a novel nicotine-acetycholine receptor partial agonist, is approved for 12 weeks of treatment, and seems to be fairly well-tolerated.

Analysis:
While quit rates were less than 50% in the 12 week trial, they were even less after one year of follow-up. The newsbrief cites data showing that cessation rates at one year of follow-up were 22% for Chantix, as compared to 16% for Zyban and 10% for placebo, bringing into question the sustained, long-term benefit from the drug. Nonetheless, with the medical morbidity of smoking as severe as it is, it would appear that Chantix may represent a big step forward and will no doubt attract a large number of users.

Topamax: An Emerging Treatment for PTSD?

Posted: 5/15/2006 9:02 AM

Implications:
While topiramte (Topamax; Ortho-McNeil Neurologics) has had mixed results across a broad range of different psychiatric disorders (ie. Bipolar Disorder, Bulimia, Alcohol Dependence, Binge-Eating Disorder and others), there is growing evidence it may be effective in Post-Traumatic Stress Disorder (PTSD). Chronic PTSD is a notoriously difficult illness to treat, in particular because of significant psychiatric comorbidity and the persistence (and intensity), of symptoms like nightmares and hyperarousal. While some SSRIs (Zoloft and Paxil) have been FDA-approved for the treatment of PTSD, their effects are often limited and introduce problematic side effects like sexual dysfunction and weight gain. Often, various medications are used concurrently, each medication intended to target specific symptoms. While this review draws on limited controlled data – only three smaller scale placebo-controlled trials – it would appear that topiramate may be effective as a treatment of PTSD as either an add-on strategy or as a monotherapy, with particular value for re-experiencing symptoms such as nightmares.

Analysis:
This review article of topiramate reviews its history as a treatment for PTSD, including early case series reports, open-label clinical trials, and placebo-controlled trials. Three smaller-scale placebo-controlled trials, two of which were monotherapy trials and one add-on study, suggest that topiramate might be most useful as an add-on (to existing pharmacotherapy regimens) strategy to address the entire range of PTSD symptoms. In the monotherapy trials, measures of total symptom reduction, while better than placebo, failed to achieve statistical significance - likely due to the small number of subjects. When pooled across studies, it appears that topiramate might be particularly helpful for re-experiencing phenomena (ie. nightmares) more than other symptoms. However, the small study numbers make it difficult to draw any firm conclusions but strongly suggest that investigating topiramate for PTSD would be clinically valuable. One potential advantage in topriamate's side effect profile is its tendency to induce weight loss.

FDA Pediatric Advisory Committee Votes Against Black Box Warning

Posted: 5/17/2006 5:14 PM

Implications:
Nissen's article "ADHD Drugs and Cardiovascular Risk" was published on www.nejm.org on March 20, 2006 - about a month after the Drug Safety and Risk Management Advisory Committee of the FDA voted 8-7 to issue the class of stimulants a black box warning for cardiovascular risks (this meeting took place on February 9, 2006, and the vote was spurned on by Nissen himself).

However, two days after Nissen's article was published at www.nejm.org, the Pediatric Advisory Committee to the FDA met (3/22/06) and voted against issuing the black box warning to stimulant medications and instead, chose to recommend certain labeling language to be included in a package insert to highlight the cardiovascular risks (http://www.medpagetoday.com/Psychiatry/AttentionDeficitDisorder/tb/2921). Though the FDA will consider recommendations from both groups, according to the Director of the FDA's Medical Policy Office Dr. Robert Temple, it is likely that the FDA would follow the recommendations from the Pediatric Advisory Committee, whose vote was against the black box warning and which was based on a risk-benefit analysis of stimulant treatments for ADHD in children and adolescents (see above link for further details). A black box warning, to be sure, would have had a profound adverse effect on prescribing habits; however, based on public information presently available, it would appear that a black box warning will not be issued.

Analysis:
The use of stimulants will likely continue as a first-line treatment of ADHD, though the heightened public awareness of cardiovascular risks will (re-)focus interest on drugs like Strattera (FDA-approved for ADHD) and Sparlon (manufact. by Cehephalon; under FDA review). In clinical practice, Strattera has come with some disappointment, with less robust and rapidly apparent benefits than the stimulants. Interestingly, the British equivalent of the FDA has issued a warning for Stratterra due to its potential effect on prolongation of the QT interval as well as seizures; also, it commented on potential cardiac risks when combined with other drugs that prolong the QT interval.

Further, a recent FDA review of Sparlon has raised questions about a potentially severe skin reaction (Stevens-Johnsons Syndrome), prompting the FDA to extend its review of Sparlon for ADHD into August (as compared to its initial timeline of mid-May). NRP104 (in development; New River Pharmaceuticals) does have appeal as the next-generation first-line treatment of ADHD, due to its potential to be declassified from a Schedule II drug; however, it is not clear whether there might be any advantage from a cardiovascular standpoint as compared to its stimulant counterparts.

Abilify Shows Efficacy in Borderline Personality Disorder

Posted: 5/22/2006 5:35 PM

Implications:
Aripiprazole (Abilify; Bristol-Myers Squibb and Otsuka America Pharmaceutical, Inc.), considered a 'third-generation' atypical neuroleptic drug due to its unique effect as partial agonist 'dopamine stabilizer,' is presently FDA approved for the treatment of Bipolar Mania and Schizophrenia. However, its broad-spectrum of action across dopamine and serotonin neurotransmitter systems, as well as its diminished risk of weight gain and lipid abnormalities (more common to its atypical neuroleptic counterparts Zyprexa, Risperdal, and Seroquel), have spurned interest in the drug across a wide range of psychiatric disorders and age groups (including in children and adolescents).

Borderline Personality Disorder (BPD) is often a complicated and difficult psychiatric condition to treat, in part because of its comorbidity with other psychiatric disorders and also because its constellation of symptoms transect so many different domains. As a result, pharmacotherapy of more severe BPD often requires multiple medications, each utilized to target specific symptoms clusters. This study is significant in that it demonstrates the efficacy of a single agent across multiple symptom clusters (though, as the authors suggest, the high success rate of the study may have something to do with its shorter duration of 8 weeks). Off-label use of Abilify for BPD is likely to gain some strength from this study, and its favorable profile on weight gain will further add momentum, given that drugs like Zyprexa and Risperdal are often utilized in BPD for targeting the range of mood, anxiety, paranoid and agressivity symptoms.

Analysis:
This European study, published in the American Journal of Psychiatry, investigated the use of aripiprazole for Borderline Personality Disorder. Though the study was relatively small (n=52) and its duration moderate in length (8 weeks), the aripiprazole arm showed significantly greater improvement across nearly every rating scale, including measures of anxiety, depression, anger expression, paranoid thinking, and aggression. The authors acknowledge that the small data pool, while enough to power statistically significant results, might also have contributed to a reduced failure rate. Nonetheless, this study is a potentially significant one in this challenging treatment population.

Revia (Naltrexone) Outperforms Campral (Acamprosate) for Alcohol Dependence

Posted: 5/22/2006 5:34 PM

Implications:
Given the superior benefit of naltrexone (Revia) alone for treating alcohol dependence, in the setting of medical management (ie addressing compliance/abstinence as well as medical problems), this study lends support for the use of naltrexone in primary care settings. Alcohol dependence treatment often takes place in more specialized clinical settings, but the results of this trial suggest an alternative paradigm for considering treatment of this large clinical population (estimated at about 8 million Americans per article). To this effect, treatment of alcohol dependence could potentially expand to include both substantially more patients as well as more clinicians who are able to provide such treatment. Surprisingly, acomprosate (Campral; Forest Labs) showed no benefit over placebo in all arms of the trial, despite its FDA approval in the US; it is not clear whether the study design may have contributed to these results. This publication comes on the heels of the FDA's recent approval of an intramuscular form of naltrexone, Vivitrol, marketed by Alkermes & Cephalon.

Analysis:
In this large multi-center study, multiple combination strategies (medication treatment with natrexone or acamprostae or placebo, with or without behavioral therapy) were investigated for the treatment of alcohol dependence. Naltrexone treatment, in combination with medical management faired best, along with a combined behavioral intervention with medical management. Interestingly, the use of behavioral therapy plus natrexone was slightly less effective, and the use of acomprosate showed no benefit over placebo (both alone as well as in combination with naltrexone or behavioral therapy). Acamprosate and naltrexone are both FDA approved treatments of alcohol dependence in the US, sharing different mechanisms of action – the former is a glutaminergic modulator, the latter an opioid antagonist.

Is There A Future for Medical Devices in Psychiatry?

Posted: 5/30/2006 6:57 PM

Implications:
Psychiatry has had a recent history of borrowing some of its treatments from neurology. While this has largely been in the area of pharmacotherapies (a number of anticonvulsants have now found their way to FDA-approved and off-label uses in psychiatric disorders), the arena of medical devices now seems to be finding its way as well. Vagus Nerve Stimulation (VNS), a treatment for epilepsy, was FDA-approved for long-term treatment of refractory major depression last July (VNS Therapy System, manufactured by Cyberonics). Now, deep brain stimulation (DBS), a treatment with demonstrated benefit for Parkinson's Disease, has shown potential value in treatment-resistant depression, more specifically the melancholic subtype. Despite the growing number of pharmacotherapies, often used in combination for more challenging cases of depression, treatment-resistant depression continues to affect a very large clinical population and is in need of more advanced therapies. The conceptualization of major depression as a chronic, disabling condition lends credence for more invasive therapies if they provide sustained benefit over time. Whether deep-brain stimulation will make its way to this clinical population is unclear, but it is likely that given these kinds of preliminary results for treatment-resistant melancholic depression, future clinical trials and interest in DBS will continue.

Analysis:
Preliminary data presented at the annual meeting of the American Psychiatric Association this past week demonstrated the potential use of deep brain stimulation for treatment-resistant major depression. Though the study pool was small (n=12), patients were considered treatment-resistant, with at least four failed prior treatment trials (ie. pharmacotherapies; ECT; evidence-based psychotherapies). 6 of 12 patients showed a significant reduction in symptoms (greater than 50% on HAM-D) over 6 months; 4 showed modest benefit and 2 had no benefit; the responders were characterized by the melancholic form of major depression (high guilt; decreased sleep; often weight loss). DBS involves placing electrodes directly in the brain – in this study, in the subgenual cingulate region - which has been linked metabolically to aberrations found in depression. DBS is a surgical procedure, with attendant risks such as intracranial bleeding, infection, stroke, and neurological impairment.

Deep Brain Stimulation: The Next Gold Standard for Intractable Depression?

Posted: 6/5/2006 10:25 AM

Implications:
Preliminary data presented at the annual meeting for the American Association of Neurological Surgeons (AANS), in April 2006, demonstrated that deep brain stimulation (DBS) might prove an effective treatment for intractable major depression. The study results demonstrate consistency with another recent, small study presented at the American Psychiatric Association's annual meeting (in May 2006), in which patients with refractory depression showed a statistically significant reduction in depressive symptoms with DBS treatment (and which I reviewed in "Is There a Future For Medical Devices in Psychiatry?").

The data from the AANS showed improvement at 12 months, while the APA study had an endpoint at 6 months. In both studies, the pool of patients was extremely impaired and essentially un-treatable, given the number of failed trials. In fact, the AANS study group had failed multiple electrconvulsive therapies (ECT) trials, placing them among the very most difficult depressed patients to treat. The device utilized in the AANS study was Medtronic's Soletra, which Medtronic recently announced it has intentions to utilize in a major clinical trial for intractable major depression (Medtronic apparently holds patents for use of DBS in depression and OCD).

Analysis:
Also, the following link provides additional information on this study:

http://www.medpagetoday.com/tbprint2.cfm?tbid=3153

This study, coming out of the Cleveland Clinic Center for Neurological Restoration, involved 9 patients with extremely severe refractory depression. All patients had failed multiple medication trials (ie. 3 failures from different classes of medication at maximum doses; 2 failed combination treatments) as well as multiple failed ECT trials. By this information alone, the pool of patients could be considered to be among the most difficult and refractory kind of patient suffering from depression. Of the 9 patients, 6 completed 12 months of follow-up, with 3 of the 6 completers demonstrating greater than 50 % reduction in symptoms (67%, 70%, 76% respectively); another one showed nearly 50% reduction. For such an intractable group, and despite the very small number of patients under study, these results are very promising, in particular as this pool of patients had failed multiple ECT trials.

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New River Pharmaceuticals Announces Third Quarter 2006 Results

RADFORD, Va., Nov. 7 /PRNewswire-FirstCall/ -- New River Pharmaceuticals Inc. (Nasdaq: NRPH) today announced its financial results for the three months ended October 1, 2006. New River recognized a net loss of $13.6 million, or $(0.38) per share, basic and diluted, for the three months ended October 1, 2006, compared to a net loss of $9.1 million, or

$(0.25) per share, for the three months ended October 2, 2005. Cash and short-term investment balances were $162.8 million at October 1, 2006.

For the three months ended October 1, 2006, New River recognized $5.0 million of revenue related to its collaboration agreement with Shire Pharmaceuticals Group plc (Shire) (LSE: SHP); (Nasdaq: SHPGY); (TSX: SHQ) with respect to NRP104, New River's lead product candidate. New River is recognizing milestone revenue from the collaboration that is not subject to refund over the estimated product development period for each of three indications for NRP104, pediatric, adult and adolescent, based on the estimated proportional effort associated with each indication. To date, New River has received $100 million under the terms of its collaboration with Shire, a portion of which is refundable under certain circumstances, and has recognized $31.9 million of the amount received as revenue.

During the third quarter, New River sold approximately $137.8 million principal amount of convertible notes due in 2013 to institutional buyers pursuant to Rule 144A under the Securities Act of 1933, as amended. The notes bear interest at 3.5% per year. In connection with the sale of the notes, New River entered into convertible note hedge transactions with respect to its common stock at a cost of approximately $43.5 million and sold warrants to acquire its common stock in private transactions for net proceeds of approximately $29.5 million. New River also concurrently purchased $41.0 million of its common stock under a prepaid forward purchase contract. These transactions were designed to offset New River's exposure to potential dilution upon conversion of the notes. In addition, New River intends to use the remaining net proceeds for working capital to develop its sales and marketing capabilities for NRP104, including the co-promotion of NRP104 under the terms of the collaboration agreement with Shire, as well as for research and development of its other product candidates and for general corporate purposes.

General and administrative expenses were $6.2 million for the three months ended October 1, 2006 compared to $4.3 million for the three months ended October 2, 2005. The increase in these expenses is due primarily to increases in shared marketing expenses with Shire under the terms of the collaboration agreement.

Research and development expenses were $13.3 million for the three months ended October 1, 2006, compared to $5.2 million for the three months ended October 2, 2005. This increase is primarily the result of increases in external development costs associated with NRP104, including manufacturing costs of validation batches, and stock-based compensation expense as a result of accelerating the vesting of certain awards in recognition of employee performance. Stock-based compensation expense was $4.0 million for the three months ended October 1, 2006, of which $3.3 million was related to equity- settled awards that have a non-cash impact on New River.

"We continue to execute on all fronts and are well positioned to build on our capabilities," said Krish Krishnan, New River's Chief Financial and Chief Operating Officer. "On October 6, 2006, we received an approvable letter from the FDA on NRP104 for the treatment of ADHD in children. We anticipate launching NRP104 in the second quarter of 2007 in collaboration with Shire. We recently completed an End-of-Phase 2 meeting with the FDA on NRP290, our second pipeline candidate, which we are developing for the treatment of acute pain. We also believe we are making good progress in other areas of our portfolio such as hormone replacement therapy and chronic pain."

New River Pharmaceuticals Inc. is a specialty pharmaceutical company developing novel pharmaceuticals that are generational improvements of

widely prescribed drugs in large and growing markets.

For further information on New River, please visit the company's website at http://www.nrpharma.com.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

This press release contains certain forward-looking information that is intended to be covered by the safe harbor for "forward-looking statements" provided by the Private Securities Litigation Reform Act of 1995. Forward-looking statements are statements that are not historical facts. Words such as "expect(s)," "feel(s)," "believe(s)," "will," "may," "anticipate(s)" and similar expressions are intended to identify forward-looking statements. These statements include, but are not limited to, financial projections and estimates and their underlying assumptions; statements regarding plans, objectives and expectations with respect to future operations, products and services; and statements regarding future performance. Such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of New River Pharmaceuticals, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include: those discussed and identified in the New River Pharmaceuticals Inc. annual report on Form 10-K, filed with the SEC on March 15, 2006; the timing, progress and likelihood of success of our product research and development programs; the timing and status of our preclinical and clinical development of potential drugs; the likelihood of success of our drug products in clinical trials and the regulatory approval process; our drug products' efficacy, abuse and tamper resistance, resistance to intravenous abuse, onset and duration of drug action, ability to provide protection from overdose, ability to improve patients' symptoms, incidence of adverse events, ability to reduce opioid tolerance, ability to reduce therapeutic variability, and ability to reduce the risks associated with certain therapies; the ability to develop, manufacture, launch and market our drug products; our projections for future revenues, profitability and ability to achieve certain threshold sales targets; our estimates regarding our capital requirements and our needs for additional financing; the likelihood of obtaining favorable scheduling and labeling of our drug products; the likelihood of regulatory approval under the Federal Food, Drug, and Cosmetic Act without having to conduct long and costly trials to generate all of the data which are often required in connection with a traditional new chemical entity; our ability to develop safer and improved versions of widely prescribed drugs using our Carrierwave (TM) technology; our success in developing our own sales and marketing capabilities for our lead product candidate, NRP104; and our ability to obtain favorable patent claims. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. New River Pharmaceuticals does not undertake any obligation to republish revised forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events. Readers are also urged to carefully review and consider the various disclosures in New River Pharmaceuticals' annual report on Form 10-K, filed with the SEC on March 15, 2006, as well as other public filings with the SEC.

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NEW RIVER PHARMACEUTICALS INC. AND SUBSIDIARY
CONSOLIDATED BALANCE SHEETS
(Unaudited)

Assets	October 1, 2006	January 1, 2006
Current assets:		
Cash and cash equivalents	$73,974,851	$3,515,572
Short-term investments	88,825,000	49,250,000
Other receivables	371,289	135,755
Prepaid expenses and other current assets	1,494,873	798,090
Total current assets	164,666,013	53,699,417
Property and equipment:		
Leasehold improvements	99,644	94,609
Machinery and equipment	1,110,950	819,472
Construction in progress	301,689	-
	1,512,283	914,081
Less accumulated depreciation and amortization	676,981	653,427
Property and equipment, net	835,302	260,654
Convertible notes issuance costs	4,414,620	-
Total assets	$169,915,935	$53,960,071
Liabilities and Shareholders' Equity (Deficit)		
Current liabilities:		
Capital lease obligation -- current	$24,252	$22,298
Accounts payable	7,743,639	1,548,473
Unpaid and accrued research and development expenses	8,406,226	3,201,732
Accrued compensation	2,254,728	2,203,898
Due to affiliates	174,460	34,138
Interest payable	879,566	-
Deferred revenue -- current	8,178,482	-
Accrued stock based compensation -- current	2,009,308	-
Total current liabilities	29,670,661	7,010,539
Capital lease obligation -- noncurrent	8,707	27,148
Accrued stock-based compensation	7,194,806	3,404,435
Deferred revenue	59,970,988	50,000,000
Convertible notes	137,750,000	-
Total liabilities	234,595,162	60,442,122
Shareholders' Equity (Deficit):		
Preferred stock, par value $0.001 per share.		
Authorized 25,000,000 shares; none		

issued and outstanding	-	-
Common stock, par value $0.001 per share. Authorized 150,000,000 shares; issued and outstanding 36,708,732 shares at October 1, 2006 and 36,367,064 shares at January 1, 2006	36,709	36,367
Additional paid-in capital	15,277,219	63,326,824
Accumulated deficit	(79,993,155)	(69,845,242)
Total shareholders' equity (deficit)	(64,679,227)	(6,482,051)
Commitments and contingencies		
Total liabilities and shareholders' equity (deficit)	$169,915,935	$53,960,071

NEW RIVER PHARMACEUTICALS INC. AND SUBSIDIARY

CONSOLIDATED STATEMENTS OF OPERATIONS

	Three months ended		Nine months ended	
	October 1, 2006	October 2, 2005	October 1, 2006	October 2, 2005
	(Unaudited)		(Unaudited)	
Collaboration revenues	$5,025,453	$-	$31,850,530	$-
Operating costs and expenses:				
Selling, general, and administrative	6,224,842	4,327,045	19,720,602	9,272,568
Research and development	13,292,263	5,247,036	24,390,172	14,072,247
Depreciation and amortization of property and equipment	34,698	41,562	115,400	116,378
Total operating expenses	19,551,803	9,615,643	44,226,174	23,461,193
Operating income (loss)	(14,526,350)	(9,615,643)	(12,375,644)	(23,461,193)
Other income (expense):				
Loss on disposal of fixed assets	(10,226)	-	(10,226)	-
Interest expense	(993,897)	(1,633)	(996,428)	(3,487)
Interest income	1,921,871	515,814	3,945,282	1,336,552
Total other income, net	917,748	514,181	2,938,628	1,333,065

Loss before cumulative effect of change in accounting principle	(13,608,602)	(9,101,462)	(9,437,016)	(22,128,128)
Cumulative effect of a change in accounting principle	-	-	(710,897)	-
Net loss	$(13,608,602)	$(9,101,462)	$(10,147,913)	$(22,128,128)
Net loss per share:				
Basic	$(0.38)	$(0.25)	$(0.28)	$(0.62)
Diluted	$(0.38)	$(0.25)	$(0.28)	$(0.62)

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Press Release

SHIRE AGREES TO ACQUIRE NEW RIVER TO GAIN FULL CONTROL OF VYVANSE™, ITS FUTURE FLAGSHIP PRODUCT FOR ADHD
All cash transaction for $2.6 billion funded by $2.3 billion new debt facilities and $800 million equity financing.

Basingstoke, UK and Philadelphia, PA, US – February 20, 2007 – Shire plc (LSE: SHP.L; NASDAQ: SHPGY; TSX: SHQ) ("Shire" or the "Company") announces today that it has agreed to acquire New River Pharmaceuticals Inc. (NASDAQ: NRPH) ("New River") for $64 per New River share, or approximately $2.6 billion in total, in an all cash transaction unanimously recommended by the Boards of both companies.

In January 2005, Shire entered into a collaborative agreement with New River to develop and co-promote NRP104, now known as VYVANSE™ (lisdexamfetamine dimesylate) for Attention Deficit and Hyperactivity Disorder ("ADHD"), before Phase 2 data were available for the drug. In December 2006, New River received a second approvable letter for VYVANSE from the US Food and Drug Administration ("FDA") and, as previously announced, Shire plans to launch VYVANSE for the pediatric indication and file a supplemental New Drug Application ("sNDA") for the adult indication in the second quarter of 2007. Shire is confident that the final terms of the expected FDA approval will provide a strong and differentiated platform for the successful launch of VYVANSE.

The acquisition of New River will allow Shire to capture the full economic value of VYVANSE, and gain control of the future development and commercialization of this product. This is consistent with Shire's already stated focus on the growing ADHD market and allows the Company to progress and benefit from its successful strategy of acquiring, developing and marketing specialty products. In addition, the acquisition will provide Shire with access to potentially attractive new specialty drug candidates and technology.

The acquisition is structured as a tender offer for all outstanding shares of New River followed by a merger. The acquisition is subject to the approval of Shire's shareholders as well as the satisfaction of certain customary conditions, including the tender of a majority of the outstanding New River shares on a fully-diluted basis and the expiration or earlier termination of the Hart-Scott-Rodino waiting period. We expect the tender offer to be commenced by March 2, 2007 and to close early in April 2007, unless extended. The tender offer is not subject to a financing contingency. Mr R.J. Kirk, New River's CEO, who beneficially owns 50.2% of the total outstanding shares of New River common stock (or 46% on a fully diluted basis) has agreed pursuant to a tender and support agreement with Shire that he will tender his shares in the tender offer.

Shire Chief Executive Officer, Matthew Emmens, said:

"This is an important and complementary acquisition that gives us full control of VYVANSE, a novel drug. We are confident and expect that the final labeling will provide patients and physicians with real benefits that differentiate this compound from other ADHD products. It will enable us to drive the launch and future development of VYVANSE and gain the full economic benefits of the drug. Based on VYVANSE's expected profile, we believe it has the potential to be the next generation stimulant product to ADDERALL XR®. This acquisition continues our leadership position in the growing US ADHD market, improves our operating margins, significantly enhances our earnings growth from late 2009 and delivers on our overall global growth strategy. The combined debt and equity financing announced today enables us to both acquire New River and retain the financial flexibility to make further acquisitions that will continue to drive Shire's growth."

Acquisition Rationale:

VYVANSE represents the future flagship product for ADHD

- Shire is confident in its ability to make VYVANSE the leading treatment in the ADHD market and, as Shire has demonstrated historically, to transition successfully the majority of patients from its current market leading product (ADDERALL XR) to the next generation prodrug ADHD product (VYVANSE)
- VYVANSE, as a New Chemical Entity (NCE), represents an important innovation in ADHD treatment with a favorable therapeutic profile for pediatric ADHD patients
- In clinical studies designed to measure duration of effect, VYVANSE provided significant efficacy compared to placebo for the full treatment day, up to, through and including 6:00 pm
- In two clinical human drug abuse studies, VYVANSE produced subjective responses on a scale of "Drug Liking Effects" (DLE) that were significantly less than d-amphetamines in the case of oral administration and less in the case of intravenous administration at equivalent dosages. DLE is used in clinical abuse studies to measure relative preference among known substance abusers
- VYVANSE has robust intellectual property with patent protection through to June 2023 in the US and through to June 2024 in Europe

Opportunity to fully control development and commercialization strategy for VYVANSE

- Shire can leverage its ADHD expertise to maximize the value of VYVANSE's development program, including pursuing further studies in ADHD and additional product indications
- Establishes a single voice to the key opinion leaders for the product, based on Shire's already strong ADHD position in the US. Consistent marketing program to be delivered through a single experienced sales organization
- Enhances Shire's existing excellent relationship with ADHD physicians and the patient community
- Opportunity to maximize VYVANSE's potential in North America and Europe

Attractive market opportunities

- Current US ADHD market worth $3.3 billion with current estimated yearly market prescription volume growth at 4% which Shire expects to rise to 6% with the introduction of new products
- Major opportunity in adult ADHD market
  - Currently makes up close to 40% of total prescriptions and adult prescription volume grew 9% over 2005
  - Market data estimates that 75% of adult ADHD patient population in the US remain undiagnosed, under-treated or untreated
- Major opportunities for ADHD in growing European markets
  - Shire plans to file VYVANSE for European approvals for pediatric indication in 2009

Acquisition allows Shire to capture fully the future profits of VYVANSE. It is expected to enhance significantly Shire's medium and long-term earnings per share (EPS) growth

- Significantly enhances Shire's operating margin through elimination of VYVANSE's profit share and royalties
- Expected to be cash EPS and US GAAP EPS neutral in 2009 and significantly earnings enhancing from late 2009
- Effective use of Shire's balance sheet and cash generation
- Shire retains financial flexibility to make further acquisitions

Adds to Shire's product pipeline and broadens technology platform

- NRP290 (phase 2 for acute pain)
- NRP409 (pre-clinical) for use in treatment of hypothyroidism
- Ownership of patented CARRIERWAVE™ platform technology, with potential application in reduced drug abusability

A circular providing further details of the acquisition and convening an Extraordinary General Meeting of Shire shareholders will be posted to Shire shareholders in due course.

Shire also announces today its results for the twelve months to December 31, 2006, which demonstrate the continued strong growth of its ADHD portfolio. Please refer to the separate press release.

Analysts' conference calls and presentation

A conference call will be held for analysts at 12noon GMT / 7am EDT today, February 20, 2007. Please dial USA / Canada toll free: 1 866 793 4279 or UK toll free 0800 358 2705 or Standard International Dial In: +44 (0) 20 8609 0205, password: 292846#.

There will also be a live audio webcast at www.Shire.com.

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Shire plc

Shire's strategic goal is to become the leading specialty pharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on ADHD, human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire believes that a carefully selected portfolio of products with a strategically aligned and relatively small-scale sales force will deliver strong results.

Shire's focused strategy is to develop and market products for specialty physicians. Shire's in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe.

For further information on Shire, please visit the Company's website: www.Shire.com.

About New River

New River Pharmaceuticals Inc. is a specialty pharmaceutical company developing pharmaceuticals that are generational improvements of widely prescribed drugs in large and growing markets. New River was founded in 1996 by R.J. Kirk, Chairman and Chief Executive Officer, who is the principal shareholder with 50.2% of the outstanding shares of New River common stock (46% on a fully diluted basis).

New River is developing new molecular entities that are derivatives of public domain active compounds using its proprietary CARRIERWAVE technology.

New River currently has three active programs in clinical or pre-clinical development stages:

- VYVANSE, New River's principal product candidate, is under FDA review for the treatment of ADHD in pediatric populations
- NRP290 (Phase 2) is being developed to treat acute pain and is intended to be a safer, more abuse-resistant and more effective alternative to currently marketed opioids
- NRP409 (pre-clinical) is being developed as a replacement or supplemental therapy in patients with primary hypothyroidism and other indications

As at October 1, 2006 New River had total assets of $169,915,935. For the nine months ended October 1, 2006 New River reported collaboration revenues of $31,850,530 and recorded an operating loss of $12,375,644 (operating loss for full year 2005: $31,751,617).

The Management of New River comprises of R.J. Kirk, Chairman and Chief Executive, Krish Krishnan, Chief Operating Officer and Chief Financial Officer, Garen Z. Manvelian M.D., Chief Medical Officer, John K. Thottathil, Ph.D. - Chief Scientific Officer, Suma M. Krishnan, Vice President, Product Development, Samir D. Roy Ph.D, Vice President, Formulation and Manufacturing, Clifton R. Hendon II, Vice President, Finance and Controller, and James P. Shaffer, Vice President, Sales and Marketing.

Background to collaboration between New River and Shire

In January 2005 Shire entered into a collaborative agreement with New River for the development of VYVANSE for the treatment of ADHD, before Phase 2 data were available for the drug. On 21 December 2006, the FDA issued a second approvable letter to New River for VYVANSE and, following this, Shire is preparing for the US launch of the pediatric indication of VYVANSE in the second quarter of 2007.

The US Prescription Drug User Fee Act date for the pediatric indication of this drug is 24 February 2007. The FDA has proposed that VYVANSE be classified as a Schedule II controlled substance under the US Controlled Substances Act. This proposal has been submitted to the US Drug Enforcement Administration (DEA) and a final scheduling decision is anticipated within two months of approval. Once VYVANSE receives final scheduling designation by the DEA, it will be available in three dosage strengths: 30 mg, 50 mg and 70 mg, all indicated for once-daily dosing.

While both companies have jointly developed VYVANSE to date, a launch strategy driven by a single organization with substantial experience in the ADHD market will maximize the potential for the product. In particular, Shire's longstanding patient and physician relationships established over the last decade through the ADDERALL franchise will be fully leveraged to ensure optimal positioning of VYVANSE in North America and Europe.

VYVANSE is an innovative drug that addresses significant medical need and its unique technology could potentially limit the absorption to doses within the therapeutic range and make it less suitable for abuse.

Shire has successfully commercialized specialty pharmaceutical products in the major pharmaceutical markets of North America and Europe and it expects to leverage this capability to realize the full potential of VYVANSE.

Shire's ADHD portfolio, VYVANSE's potential and market dynamics

The current US ADHD market is estimated to be worth $3.3 billion with yearly prescription volume market growth at 4% in 2006 which Shire expects to rise to 6% in 2007 with the introduction of new products. Shire also expects the market to grow further in the future along with the expansion into new geographic areas and new patient populations.

Shire believes that there are major opportunities for ADHD in European markets and Shire plans to file VYVANSE for European approvals in 2009.

Market data estimates that 9.9 million adults in the US suffer from ADHD, and that 75% of these people remain undiagnosed, under-treated or untreated. The adult segment now makes up close to 40% of the new prescriptions written in the market place.

VYVANSE has been developed for adult as well as for pediatric use. Shire expects to file the sNDA for the adult indication in Q2 2007. If accepted as a sNDA the review period is expected to be 180 days.

Shire has a leading position in the US ADHD market with ADDERALL XR and DAYTRANA™, and also has two additional products in registration; SPD465 (high dose mixed-amphetamine salts for adults) and SPD503 (extended release guanfacine, non-

stimulant agent for pediatric use). With VYVANSE expected to replace ADDERALL XR, Shire's portfolio of ADHD products will have a widespread position in this growing market.

Financial impact

The acquisition of New River is expected to enhance significantly Shire's medium and long-term EPS growth. It will also allow Shire to fully capture the future profits of VYVANSE and improve operating margin performance.

The acquisition is expected to be cash EPS and US GAAP EPS neutral in 2009 and significantly earnings enhancing from late 2009.

It is anticipated that the value of the pediatric indication of VYVANSE (approximately $1bn) will be recognized as an intangible asset, together with an associated deferred tax liability of approximately $0.4bn on the balance sheet. The intangible asset will be amortized over its useful economic life (approximately 20 years). There will also be a one-time charge of approximately $2 bn on closing of the acquisition relating mainly to the write-off, under US GAAP, of the intangible asset value associated with the acquired in-process R&D pipeline (including the adult indication), together with some integration and transaction costs.

The financing announced today enables Shire to both acquire New River and retain financial flexibility to make further acquisitions in other areas that will continue to drive Shire's growth.

Additional New River products

NRP290, New River's most advanced compound (Phase 2) after VYVANSE, is a Conditionally Bioreversible Derivative (CBD) of hydrocodone, an opioid widely used in combination with other non-opioid analgesics to treat acute pain

- Acute pain usually lasts for a short time, typically not more than a month. Treatment for acute pain may consist of non-opioid analgesics and non-steroidal anti-inflammatory drugs. In more severe cases of acute pain, opioids are commonly prescribed. While opioids are the most effective drugs available for treating pain, there is increasing concern with respect to their potential for abuse and propensity for addiction
- Repeated administration of opioids, including hydrocodone, can create psychological addiction as well as increased tolerance resulting in the potential for overdose. Overdose can result in respiratory depression, coma, hypotension, cardiac arrest and death
- On June 28, 2005, New River filed an Investigational New Drug Application (IND) with the FDA. On September 12, 2005, New River presented the results of its first clinical trial on NRP290. Further clinical development is ongoing

NRP409 (pre-clinical) is being developed as a replacement or supplemental therapy in patients with primary hypothyroidism and other indications

- New River's CARRIERWAVE triiodothyronine (T3) hormone is being developed as a replacement or supplemental therapy in patients with primary hypothyroidism and other indications. The leading thyroid Hormone Replacement Therapies (HRTs) are based on tetraiodothyronine (T4), and require deiodination within the patient to convert to the more active hormone (T3). Patients demonstrate significant variability

in their ability to convert the T4 hormone in the HRT into T3. This variability can arise as a function of age, stress or a variety of medical conditions. Commercially approved drugs based on T3, however, engender certain safety risks, most notably cardiovascular in nature

- NRP409 will mark a significant improvement in thyroid HRT by reducing the variability of the more active hormone's availability, while reducing the safety risk associated with other T3 based therapies
- New River filed an IND for NRP409 in the second quarter of 2006

New River patented technology

In addition to the above products, the acquisition provides Shire access to New River's CARRIERWAVE technology. This proprietary technology enables the design of proprietary compounds consisting of active pharmaceutical ingredients bound to adjuvants. The adjuvants are comprised of various substances such as peptides, amino acids, lipids and nucleic acids. New River believes that the breakdown of the active from the adjuvant occurs at specifically targeted sites of enzymatic activity in the body. In the case of its current CARRIERWAVE compounds, the site of enzymatic activity is primarily in the gastrointestinal tract. At the target site, enzymes hydrolyze or cleave the adjuvant from the active pharmaceutical ingredient, releasing the active pharmaceutical ingredient into circulation.

New River believes that the CARRIERWAVE technology has particular application in overcoming the drawbacks associated with drugs of abuse and addiction, like amphetamines and opioids while providing efficacy similar to currently marketed versions. CBDs are intended for oral delivery. In the case of amphetamines and opioids, they are designed to limit the release of the active pharmaceutical ingredient from the CBD at greater than therapeutically prescribed amounts, and to be inactive when administered other than orally.

Terms of the Transaction

The acquisition will be effected pursuant to a merger agreement (Merger Agreement). Under the terms of the Merger Agreement, a subsidiary of Shire will commence a tender offer for all outstanding shares of New River common stock at a price of $64 per share in cash no later than March 2, 2007. Following the completion of the tender offer, any remaining shares of New River will be acquired in a cash merger at the same price. The transaction values New River's share capital as of the date of the Merger Agreement, at $2.6 billion on a fully diluted basis. The acquisition price represents a premium of approximately:

- 10% to New River's closing share price of $58.35 on February 16, 2007 (being the last business day prior to this announcement); and
- 14% to $55.92, the average New River closing share price over the four weeks prior to the date of this announcement.

The transaction has been unanimously recommended by the boards of both companies. The acquisition is structured as a tender offer for all outstanding shares of New River followed by a merger. The acquisition is subject to the approval of Shire's shareholders as well as the satisfaction of certain customary conditions, including the tender of a majority of the outstanding New River shares on a fully-diluted basis and the expiration or earlier termination of the Hart-Scott-Rodino waiting period. We expect the tender offer to be commenced by March 2, 2007 and to close early in April 2007, unless extended.

The Merger Agreement contains provisions relating to the payment of break fees by Shire and New River. New River is obliged to pay Shire $70 million and reimburse Shire for up to $8 million in expenses in the event that the merger is terminated in specified circumstances. Shire is obliged to pay New River $70 million and reimburse New River for up to $8 million in expenses in the event that the Merger Agreement is terminated as a result of, among other things, (i) Shire shareholders not approving the acquisition, (ii) the board of directors of Shire changing its recommendation in respect of the transaction, or (iii) the board of directors of Shire not complying with its obligations under the Merger Agreement to convene an Extraordinary General Meeting of Shire shareholders.

R.J. Kirk, New River's CEO, owns 50.2% of the outstanding shares of New River common stock (46% on a fully diluted basis), has agreed, pursuant to a tender and support agreement with Shire that, he will tender his shares in the tender offer. If the Merger Agreement is terminated, however, including by reason of New River accepting an offer from a third party that the New River board of directors deems to be superior to the transactions contemplated by the Merger Agreement, the tender and support agreement also terminates.

Financing of the Transaction

The total consideration for the acquisition of New River amounts to approximately $2.6 billion in cash. Shire has entered into new bank facilities of $2.3 billion to provide part of the finance for the acquisition. This new facility is conditional upon, amongst other things, approval being given by Shire shareholders at an Extraordinary General Meeting for the Shire Group to exceed the limit on its aggregate borrowings set out in Shire's Articles of Association.

Shire also intends to raise approximately $800 million through an equity financing.

Financial information and current results

Shire today announced its preliminary results for the 2006 financial year. In 2006, Shire achieved total revenues of $1,796 million and net income of $278 million. Fully diluted earnings per ordinary share for 2006 were 54.6 cents. As of December 31, 2006 Shire had $1,127 million in cash and cash equivalents. For 2007 guidance and further information, please refer to Shire's 2006 year end earnings release or visit: www.Shire.com.

Goldman Sachs, Morgan Stanley and Deutsche Bank acted as financial advisors to Shire in relation to the acquisition.

Additional Information

The tender offer described in this press release has not yet commenced, and this press release is neither an offer to purchase nor a solicitation of an offer to sell New River common stock. Investors and security holders are urged to read both the tender offer statement and the solicitation/recommendation statement regarding the tender offer described in this report when they become available because they will contain important information. The tender offer statement will be filed by a subsidiary of Shire with the Securities and Exchange Commission (SEC), and the solicitation/recommendation statement will be filed by New River with the SEC. Investors and security holders may obtain a free copy of these statements (when available) and other documents filed by Shire or New River with the SEC at the website maintained by the SEC at www.sec.gov. The tender offer statement and related materials may be obtained for free by directing such requests to Shire at Hampshire International Business Park, Chineham, Basingstoke, Hampshire, England, RG24 8EP, attention: Investor Relations. The

solicitation/recommendation statement and such other documents may be obtained by directing such requests to New River at 1881 Grove Avenue, Radford, Virginia 24141, attention: Director of Corporate Communications.

General

This announcement is for information only and does not constitute an offer or invitation to acquire or dispose of any securities or investment advice in any jurisdiction. Past performance is no guide to future performance and persons needing advice should consult an independent financial adviser.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to: risks associated with the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to the impact of those on Shire's ADHD franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval dates of SPD503 (guanfacine extended release) (ADHD), SPD465 (extended release of mixed amphetamine salts) (ADHD), and VYVANSE (NRP104) (lisdexamfetamine dimesylate) (ADHD), including its scheduling classification by the Drug Enforcement Administration in the United States; Shire's ability to complete, and achieve anticipated benefits from the acquisition of New River Pharmaceuticals; Shire's ability to secure new products for commercialization and/or development; and other risks and uncertainties detailed from time to time in Shire's filings with the Securities and Exchange Commission.

Statements regarding future earnings or earnings per share or the growth of either of these should not be interpreted to mean that earnings or earnings per share will necessarily be greater in any financial period than for the relevant preceding financial period

Goldman Sachs, Morgan Stanley and Deutsche Bank are acting exclusively for Shire and no one else in relation to the matters described in this announcement and will not be responsible to anyone other than Shire for providing the protections afforded to customers of Goldman Sachs, Morgan Stanley or Deutsche Bank or for providing advice in relation to the acquisition or in relation to any transaction, arrangement or other the matters referred to in this announcement.

Definitions

The following definitions apply throughout this announcement unless the context otherwise requires:

“Deutsche Bank”	means Deutsche Bank AG, London Branch;
“Goldman Sachs”	means Goldman Sachs International;
“Morgan Stanley”	means Morgan Stanley & Co. International Limited;
“New River”	means New River Pharmaceuticals, Inc.;
“Shire”	means Shire plc, a public limited company incorporated under the laws of England and Wales;
“US GAAP”	means generally accepted accounting principles in the United States;
“United States”	means the United States of America, its territories and possessions, any state of the United States and the District of Columbia;
References to “$” are to the lawful currency of the United States of America.	

New River Acquisition and Full Year 2006 Results

20 February 2007

THE "SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to: risks associated with the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to the impact of those on Shire's ADHD franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval dates of SPD503 (guanfacine extended release) (ADHD), SPD465 (extended release of mixed amphetamine salts) (ADHD), and VYVANSE (NRP104) (lisdexamfetamine dimesylate) (ADHD), including its scheduling classification by the Drug Enforcement Administration in the United States; Shire's ability to complete, and achieve anticipated benefits from the acquisition of New River; Shire's ability to secure new products for commercialization and/or development; and other risks and uncertainties detailed from time to time in Shire's filings with the Securities and Exchange Commission.

Goldman Sachs International, Morgan Stanley and Deutsche Bank, which are authorized and regulated in the United Kingdom by the Financial Services Authority, are acting exclusively for Shire in relation to the acquisition and no one else and will not be responsible to anyone other than Shire for providing the protections afforded to its customers or for providing advice in relation to the acquisition or in relation to any transaction, arrangement or other matter referred to in this announcement.

Agenda

Acquisition Rationale	Matthew Emmens
Acquisition Financing	Angus Russell
2006 Year End Review	Matthew Emmens
2006 Financial Results	Angus Russell
Concluding Remarks	Matthew Emmens
Questions & Answers	All

Acquisition Rationale

Matthew Emmens

Chief Executive

Shire agrees to buy New River for $2.6 billion to gain control of VYVANSE - future flagship ADHD product

NEW RIVER PHARMACEUTICALS

Vyvanse (lisdexamfetamine dimesylate) capsules

Why New River

- **Logical strategic move**
- **Innovative drug – the next generation of ADHD treatment**
- **Attractiveness of the ADHD market**

New River Acquisition Terms

- All cash transaction
- $64 per share (approximately $2.6 billion total)
- 10% premium to New River' closing price on 16 February 2007
- 14% average price over the last 4 weeks prior to closing date
- RJ Kirk, New River's CEO, who beneficially owns 50.2% of the total outstanding shares of New River common stock has agreed pursuant to a tender and support agreement with Shire that he will tender his shares in the tender offer
- Subject to shareholder and regulatory approvals – anticipated to close by the end of Q2 2007
- Retain our financial flexibility to make further acquisitions

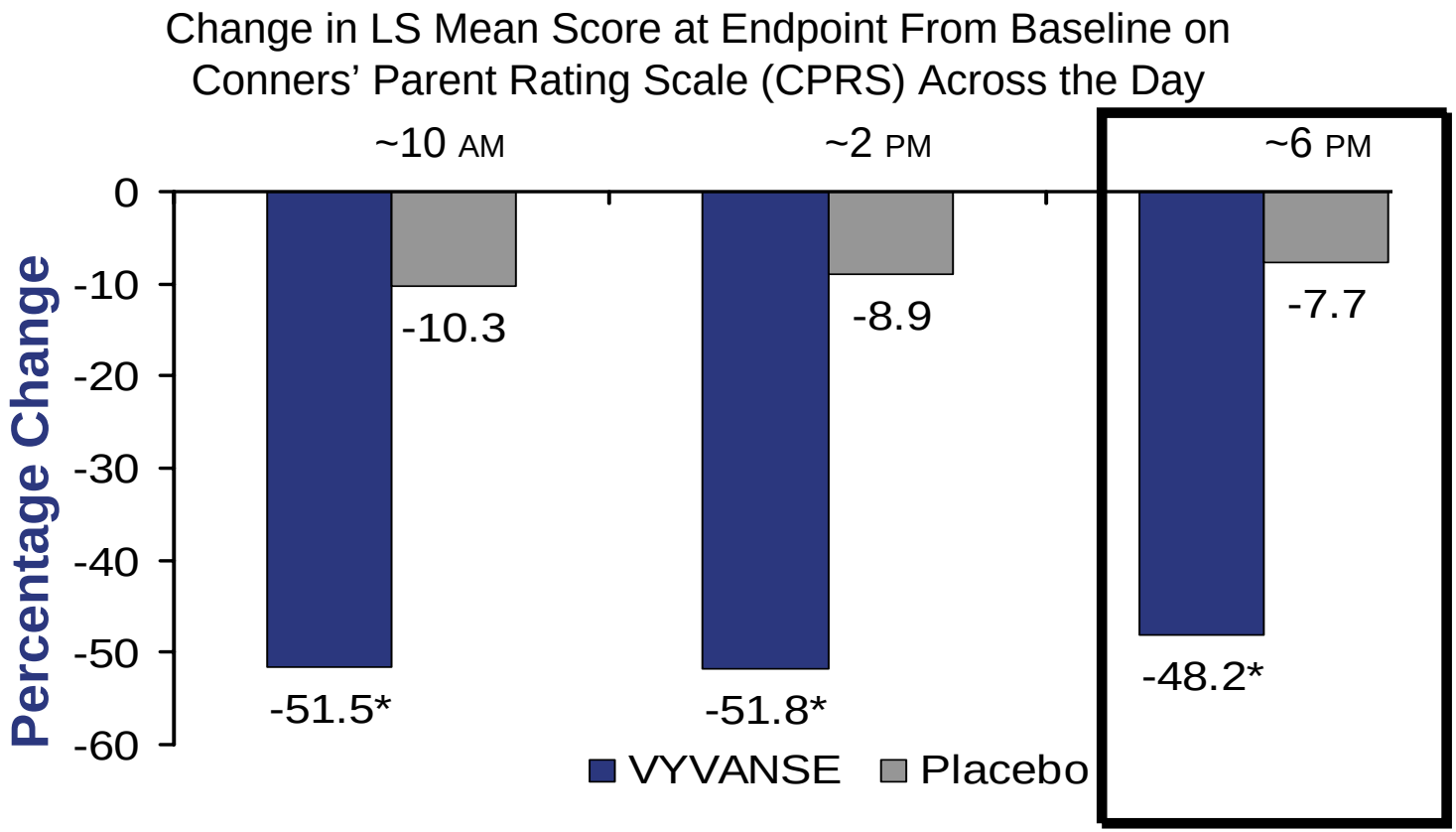
Rationale

- **Logical strategic move**
  - Transition from ADDERALL XR
  - Gain full economic benefit of the drug
  - Significantly enhances Shire's EPS growth from late 2009
  - Fully control development and commercialization strategy
  - Further studies in ADHD, additional product indications
  - Adds to Shire's product pipeline and broadens technology platform

Rationale

- **Unique drug – next generation of ADHD treatment**
  - VYVANSE innovative and future flagship product for ADHD
  - Favorable therapeutic profile; long acting, lower abuse potential
  - Confidence in FDA outcome
  - Strong IP until 2024
- **Attractiveness of the ADHD market**
  - 6% potential annual US prescription growth
  - Adult market opportunities
  - Europe – plan to file VYVANSE in 2009

VYVANSE provides duration of effect throughout the day



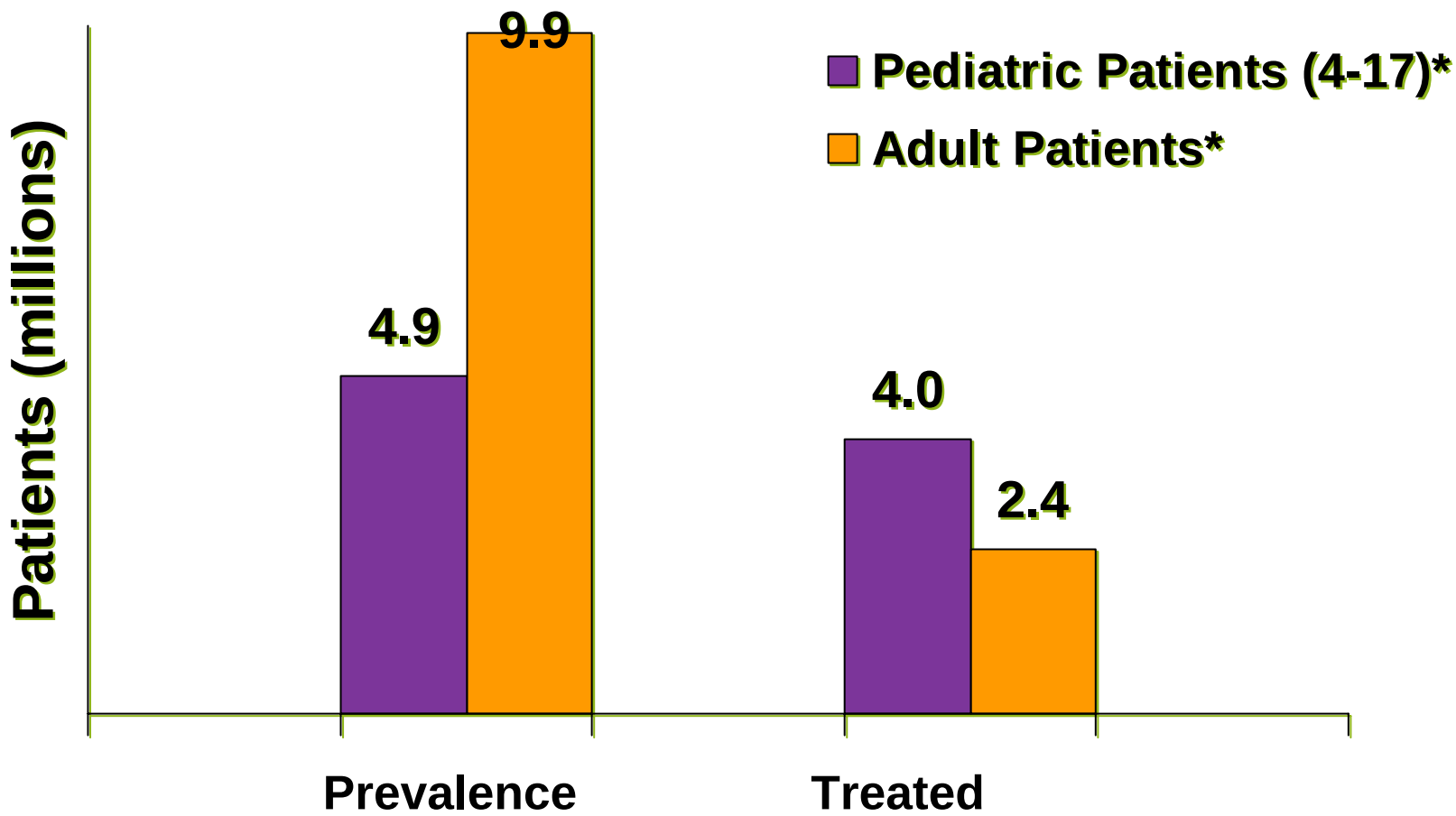
Median daily dosing time was between 7:30 AM and 8 AM.

The CPRS was used to assess the duration of therapeutic response in 285 patients by separately analyzing the assessments performed per protocol in the morning (~10 AM), afternoon (~2 PM), and evening (~6 PM).
*P<.0001 vs placebo.

Data on file, Shire US Inc.

Ex. 6, Page 412

US ADHD Prevalence and Treatment

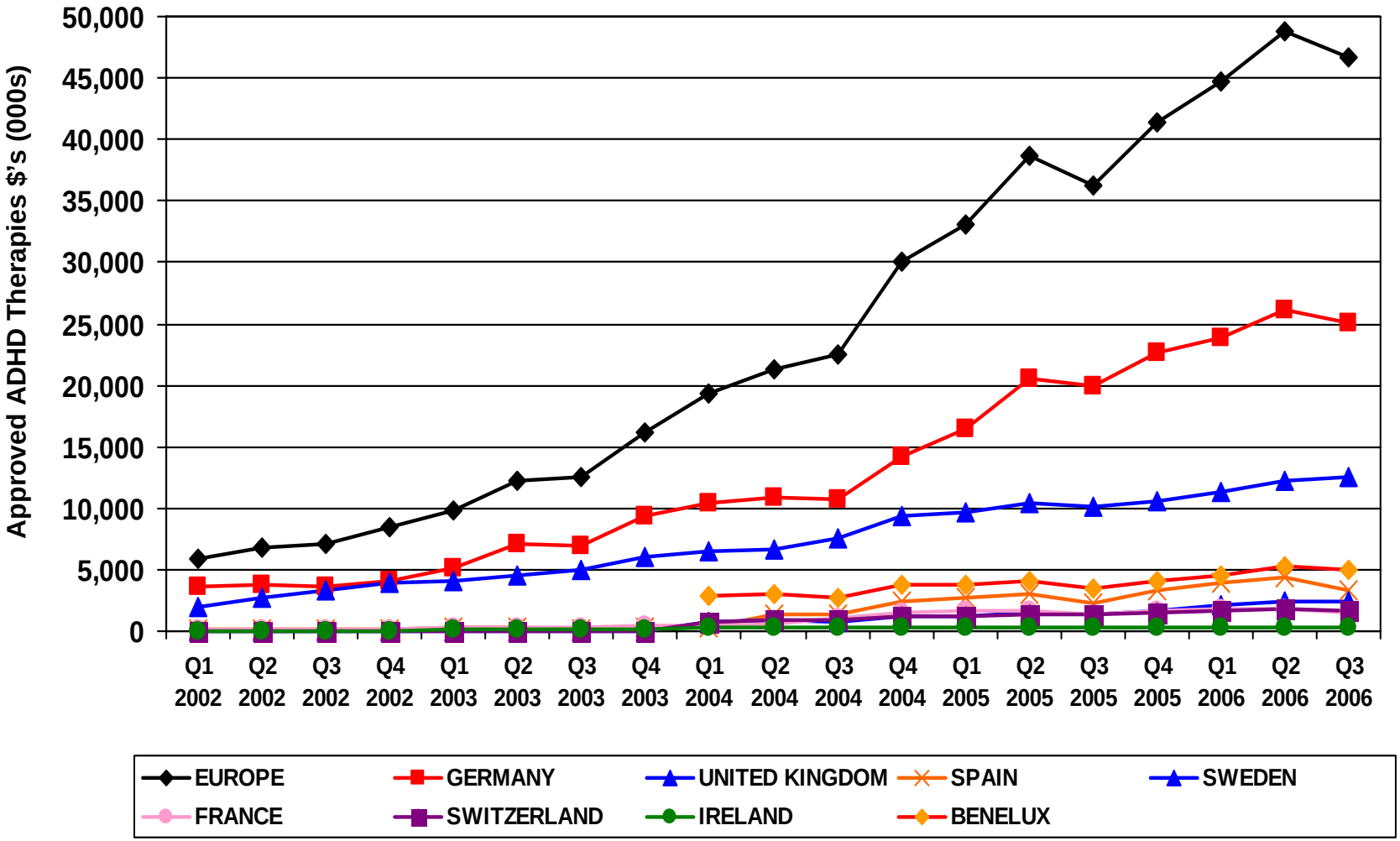


*** 2004 NHIS (National Health Interview Survey, given by CDC); Kessler et al, 2005**

Ex. 6, Page 413

Growth in European ADHD market

Circa $200 million market growing at CAGR > 70% and likely to more than double by 2010



- Source: IMS

Scientific efforts in ADHD advancing dramatically across Europe

- **Diagnosis of ADHD evolving in Europe**
  - Increasing adoption of US diagnostic criteria (DSM-IV*)
  - ADHD treatment guidelines being developed and communicated
    - Pan – European Guidelines
    - NICE – 2000; 2006; 2008/09 (planned)
    - British Association of Psychopharmacology – 2006 (ADHD in Adults)
- **Increased clinical research in ADHD in Europe**
  - Germany, UK, Netherlands leading the way

*** DSM-IV – Diagnostic and Statistical Manual of Mental Health Disorders**

Acquisition Financing

Angus Russell

Chief Financial Officer

Transaction Financing

- **All cash transaction valued at $2.6bn to be funded by cash:**
  - Committed new bank facilities of $2.3bn
    - Existing $700 million facilities to be cancelled
  - Placing of new ordinary shares to raise approximately $800 million
    - Executed by way of accelerated book built private placement to certain institutional investors
    - Launched immediately
    - Represents up to 7.5% of Shire's market value*

*Based on closing price of Shire shares on LSE on February 19, 2007 of £10.75

Financial model based on following assumptions:

- Achievement of leading US ADHD market share
- VYVANSE EU Launch in 2010/2011
- Probability risk adjusted value for NRP290/409
- Cost savings (COGS, G&A) of approximately $25 million per annum
- Full US tax rate of 37%
- Minimal level of tax losses

The Next Generation, Prodrug Stimulant for ADHD……..

ONE DOSE DAILY
ADDERALL XR™ CII

(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Dextroamphetamine Saccharate
Amphetamine Aspartate Monohydrate Amphetamine Sulfate

→

Vyvanse
(lisdexamfetamine dimesylate) capsules

Ex. 6, Page 419

2006 Year End Review

Matthew Emmens

Chief Executive

2006 Financial Highlights

- Product sales up 16% to $1,536 million
- Total revenues up 12% to $1,797 million
- Cash and cash equivalents up $470 million
- Dividends up 15%

2006 Highlights - Executing on Strategy

- **Expansion of the business through significant advancement of our late stage pipeline**
  - ADHD
    - VYVANSE – Approvable received – launch planned Q2 2007
    - DAYTRANA – transdermal patch, successful US launch in progress
    - SPD503 – non-stimulant for pediatric - June 24, 2007
    - SPD465 – long-acting stimulant for adults - May 21, 2007
  - GI
    - LIALDA / MEZAVANT – launch planned Q2 2007
  - Renal
    - FOSRENOL – now launched in Germany and France; to be launched in UK, Spain and Italy in 2007
      - US co-promote agreement with Abbott Laboratories – effective as of February 2007
    - DYNEPO – Q2 07 European launch planned
  - Human Genetic Therapies
    - ELAPRASE – US and European launches in progress: 245 patients globally on therapy at the end January 2007
    - REPLAGAL – Approval received in Japan – launch planned for Q2 2007

Ex. 6, Page 422

Executing on strategy

- **Early stage pipeline to develop future product candidates**
  - GA-GCB: phase 3 clinical program initiated in Gaucher disease
  - Three enzyme replacement projects advanced to pre-clinical development
    - Sanfililppo (Mucopolysaccharidosis IIIA)
    - Metachromatic Leukodystrophy
    - Hunter syndrome CNS
  - SPD500 (tissue protective cytokines pre-clinical): in-licensed from Warren Pharmaceuticals for renal and genetic disease areas
  - SPD493 (Valrocemide Phase 1): in-licensed from Yissum Research and Development Company for CNS disorders
  - **New** SPD491: once-a-day, non-opiate, transdermal analgesic with the goal of non-scheduled labelling to treat moderate to severe pain
  - **New** SPD535: pre-clinical evaluation of a novel compound for the treatment of platelet reduction

2006 Financial Results

Angus Russell

Chief Financial Officer

Total Revenues

	2006 $m	2005 $m	
Product Sales	1,535.8	1,327.7	+16%
Royalties	242.9	242.9	
Other Revenue	17.8	28.7	
Total Revenues	1,796.5	1,599.3	+12%

Ex. 6, Page 425

Major Product Sales

	2006 $m	2005 $m	Sales Growth	US RX* Growth
ADDERALL XR	863.6	730.8	+18%	+8%
PENTASA	137.8	136.1	+1%	+2%
REPLAGAL	117.7	**94.6	+24%	N/A
CARBATROL	68.3	72.1	-5%	-9%
XAGRID***	53.3	46.8	+14%	N/A
FOSRENOL	44.8	53.5	-16%	+34%
DAYTRANA	25.1	N/A	N/A	N/A
ELAPRASE	23.6	N/A	N/A	N/A

* Source: IMS Data

** Includes pre-acquisition sales of $53.3m

*** worldwide sales excluding US and Canada

Ex. 6, Page 426

Royalties

	2006 $m	2005 $m	Growth
3TC	150.9	159.8	-6%
ZEFFIX	34.8	30.5	+14%*
Other **	57.2	52.6	+9%
Total	242.9	242.9	0%

* Foreign exchange movements have contributed +1% to reported growth
** Includes REMINYL/RAZADYNE

Ex. 6, Page 427

Financial Ratios

(on a non-GAAP basis, excluding FAS123R)	2006	2005
COGS : Product sales	13%	13%
Gross margin	87%	87%
R&D : Revenues	17%	18%
SG&A (excl. D&A) : Product sales	52%	48%
Operating margin	22%	27%

This slide contains non GAAP financial measures. Management believes that the presentation of these non GAAP financial measures provide useful information to investors regarding Shire's performance as the excluded items are not indicative of the ongoing business in 2006 & 2005.

Net Income/EPS

	2006	2005[1]	
Net income ($m)			
- GAAP	278.2	(578.4)	
- Adjustments	10.7	892.4	
- Non GAAP[2]	288.9	314.0	-8%
EPS (diluted):			
- ADS	163.8c	(346.8c)	
Non GAAP EPS (diluted)[2]			
- ADS	170.1c	187.8c	-9%
Non GAAP EPS (diluted)[2]			
- ADS (excluding FAS123R)	187.2c	201.4c	-7%

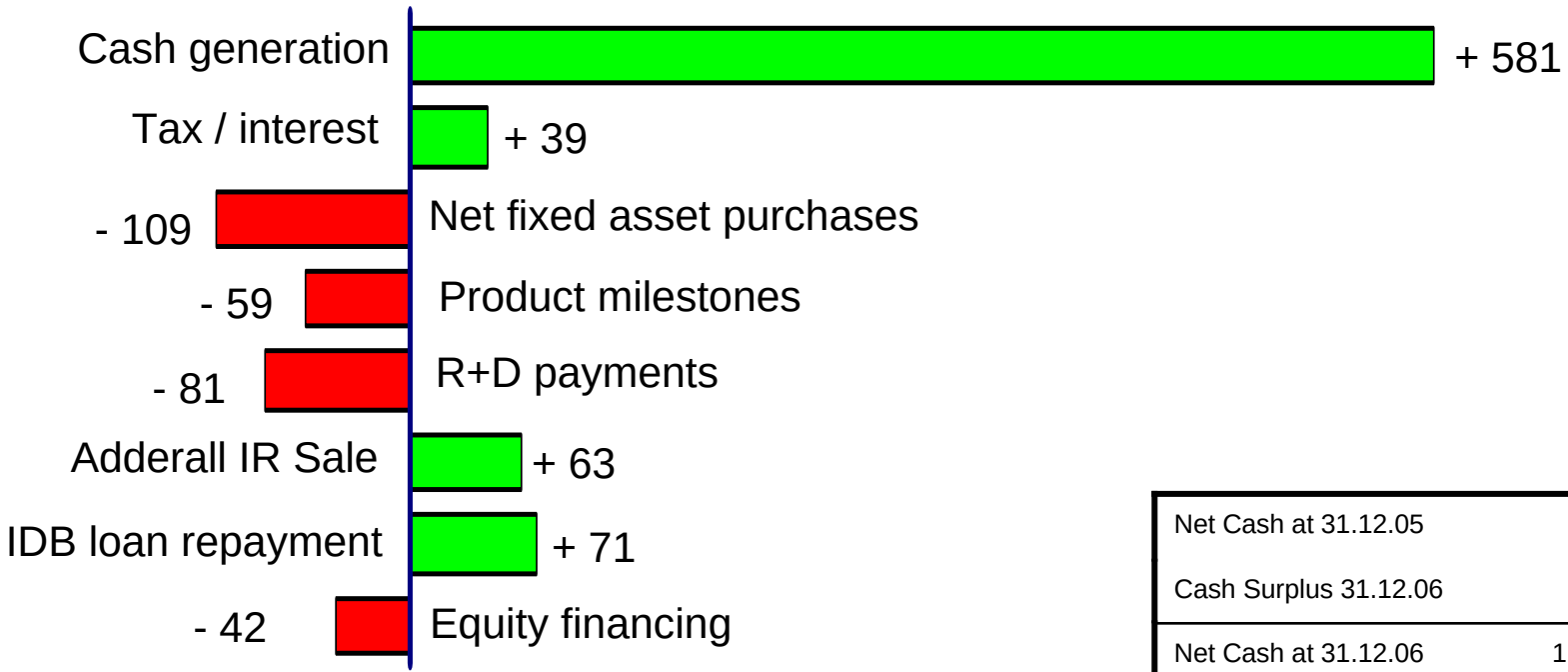
(1) Adjusted to reflect retrospective adoption of SFAS 123R and restated for the correction to the value of TKT's IPR&D

(2) These are non GAAP financial measures. They exclude items that management believe are not indicative of the ongoing business in 2006 & 2005.

Ex. 6, Page 429

Cash flow –2006

Millions of USD



Net Cash at 31.12.05	694
Cash Surplus 31.12.06	463
Net Cash at 31.12.06	1,157
Provision for amounts due for appraisal rights	(452)
Restricted cash	(30)
"Free Cash" at 31/12/06	675

Cash surplus for 2006 (1) : + 463

(1) Cash & cash equivalents up $470m less short term investments down $7m.

2006 Actual v Guidance

	Actual	Guidance
Revenue growth	12.3%	12% - 14%
R&D - GAAP ($m)	387	
Less New River milestone	(50)	
Warren up front	(6)	
Duramed up front	(25)	
FAS123R	(5)	
R&D - Non GAAP ($m)	$301	$310m to $330m
SG&A - GAAP ($m)	835	
Less: FAS123R	(34)	
SG&A - Non GAAP ($m)	$801	$770m to $800m
D&A increase	34%	30%
Tax rate	27%	28%

Ex. 6, Page 431

Outlook - 2007

Shire's Non GAAP measure for 2007 will be **Cash EPS**, being GAAP EPS excluding significant milestone payments, amortization (up approx 20% over 2006) and FAS123R (approx $45m). The following guidance excludes these costs and the impact of the New River acquisition.

- 2007 revenue growth expected to be around 20% (assuming prescription growth in the ADHD market of 4-6%).
- Earnings for 2007 will continue to be impacted by costs associated with the ongoing development and launch of new products.
  - Up to 6 new products to be launched during 2007 and H1 2008 in addition to the continued growth of DAYTRANA, ELAPRASE & FOSRENOL in the US and ELAPRASE & FOSRENOL in Europe;
  - Launches will require additional advertising and promotional spend and in some cases additional sales representatives. Consequently, SG&A expected to rise to between $930–960m for 2007;
  - Phase 3(b) and Phase 4 studies to support new product launches, the continuation of phase 3 trials on GA-GCB, the development of the Women's Health franchise, pre-clinical development of 3 HGT projects and 2 further pre-clinical projects expected to result in R&D spend in the range of $360–380m.
- Depreciation is expected to increase by approximately 20% compared to 2006; and
- Estimated tax rate - approximately 26% (down 1%).

2006 Cash EPS

	2006	2005	
Non GAAP EPS (diluted)[1]			
- ADS	170.1c	187.8c	-9%
Non GAAP EPS (diluted)[1]			
- ADS (excluding FAS123R)	187.2c	201.4c	-7%
Cash EPS (diluted)[2]			
- ADS (excluding FAS123R and amortisation)	211.2c	220.7c	-4%

(1) These are non GAAP financial measures. They exclude items that management believe are not indicative of the ongoing business in 2006 & 2005.

(2) This represents cash EPS and will be the measure which management intend to use for guidance in 2007

Concluding Remarks

Matthew Emmens

Chief Executive

Concluding Remarks

- Shire to gain control of VYVANSE, future flagship product for ADHD
  - Logical strategic move
  - Innovative drug – next generation of ADHD treatment
  - Attractiveness of the ADHD market
- Retain our financial flexibility to make further acquisitions

Concluding Remarks

- **Excellent results – the business continues to perform strongly**
  - Successful launches in 2006 with guidance for robust revenue growth
- **Continuing to demonstrate our ability to execute**
  - ADDERALL XR – leading US market share
  - DAYTRANA - strong launch
  - ELAPRASE - approved in US and EU
  - FOSRENOL - strong start in Europe
  - SPD465 - PDUFA May 21, 2007
  - SPD503 – PDUFA June 24, 2007
- **Additional product launches by mid-2007 - on track**
  - VYVANSE
  - LIALDA / MEZAVANT
  - DYNEPO
- **Early stage pipeline advancing toward clinical development**

Questions and Answers

All

APPENDIX

Appendix 1-EPS Reconciliation

	2006 $m	2006 cents/ADS	2005 (1) $m	2005 (1) cents/ADS
Net income for diluted EPS (ADS)	**278.2**	**163.8c**	**(578.4)**	**(346.8c)**
TKT in-process R&D write-off	-	-	815.0	487.5c
Cost of product sales fair value adjustment	47.0	27.7c	41.9	25.2c
New River milestone and upfront payments	50.0	29.5c	50.0	30.0c
Up-front license payments (Duramed & Warren)	30.5	18.0c	-	-
Reorganisation / integration costs	5.6	3.3c	23.6	13.8c
Gain on disposal of drug formulation business	-		(3.6)	(2.1c)
Gain on sale of product rights	(63.0)	(37.1c)	-	-
Taxes on above adjustments less dilution impact of Non GAAP adj	(18.8)	(11.1c)	(31.4)	(18.0c)
Gain on disposition of discontinued operations	(40.6)	(24.0c)	(3.1)	(1.8c)
Net income for non GAAP EPS (ADS)	**288.9**	**170.1c**	**314.0**	**187.8c**
FAS 123R effect (net of tax)	31.3	17.1c	25.6	13.6c
Net income for non GAAP EPS (ADS) (Ex FAS 123R)	**320.2**	**187.2c**	**339.6**	**201.4c**
Amortisation (net of tax)	41.2	24.0c	32.5	19.3c
Net income for non GAAP EPS (ADS) (Ex FAS123R and amortisation)	**361.4**	**211.2c**	**372.1**	**220.7c**

(1) Adjusted to reflect retrospective adoption of SFAS 123R and restated for the correction to the value of TKT's IPR&D

(2) These are non GAAP financial measures. They exclude items that management believe are not indicative of the ongoing business in 2006 & 2005.

Additional Information

The tender offer described in this presentation has not yet commenced, and this presentation is neither an offer to purchase nor a solicitation of an offer to sell New River common stock. Investors and security holders are urged to read both the tender offer statement and the solicitation/recommendation statement regarding the tender offer described in this report when they become available because they will contain important information. The tender offer statement will be filed by a subsidiary of Shire with the Securities and Exchange Commission (SEC), and the solicitation/recommendation statement will be filed by New River with the SEC. Investors and security holders may obtain a free copy of these statements (when available) and other documents filed by Shire or New River with the SEC at the website maintained by the SEC at www.sec.gov. The tender offer statement and related materials may be obtained for free by directing such requests to Shire at Hampshire International Business Park, Chineham, Basingstoke, Hampshire, England, RG24 8EP, attention: Investor Relations. The solicitation/recommendation statement and such other documents may be obtained by directing such requests to New River at 1881 Grove Avenue, Radford, Virginia 24141, attention: Director of Corporate Communications.

Shire to Buy Out Partner Shire to buy out longtime partner The maker of ADHD medications, with its U.S. base in Wayne, will pay $2.6 billion as a new drug moves toward approval.

By Thomas Ginsberg INQUIRER STAFF WRITER

POSTED: February 21, 2007

One equity analyst jokingly called it ransom - at a fair price.

Shire P.L.C., the No. 1 maker of attention-deficit medications with U.S. headquarters in Wayne, said yesterday that it would buy out its longtime partner, New River Pharmaceuticals Inc., for $2.6 billion.

They announced the deal just days before Friday's expected federal approval of their new product for attention-deficit/hyperactivity disorder, Vyvanse, which will be pitched to succeed Adderall XR as the world's top-selling treatment.

Wall Street cheered the pricey deal, calling it essentially unavoidable. Virginia-based New River owns the patent to the next-generation drug, Vyvanse. Shire faced the prospect of steep royalty payments and sharing up to 60 percent of the profit from Vyvanse.

The deal "significantly enhances Shire's operating margin through elimination of Vyvanse's profit share and royalties," Shire said in a statement.

Vyvanse has been billed as an improved ADHD medication whose method of action makes it harder to abuse. The company says it has the same safety profile as Adderall XR.

Under the deal, Shire would pay $64 for each New River share, or nearly 10 percent higher than its Friday close of $58.28. Shire said it would fund the transaction with $2.3 billion in new debt and an $800 million equity financing.

The deal would give Shire full control over Vyvanse. Shire and New River already have been collaborating for two years on the drug.

"It's a fair price," said Andrew Forman, an equity analyst at WR Hambrecht & Co. Quipping that the deal was like a "ransom," he explained: "It gives them a successor to Adderall XR. If they didn't have this, then by 2009, they'd lose their revenue" to generic rivals.

Shares in New River, of Radford, Va., closed up more than 8 percent, or $4.84, at $63.19, near the per-share purchase price. Shares in United Kingdom-based Shire rose more than 5 percent, or $3.33, to $66.61.

The acquisition also would give Shire control of New River's experimental pain reliever NRP290, now in Phase 2 trials, as well as other compounds.

Shire, based in Basingstoke, about 50 miles west of London in Hampshire County, employs about 3,000 people worldwide and 700 in Wayne, where it has been building up its headquarters functions since 2003.

With Shire's arrival in the region, Philadelphia became something of an ADHD Alley. A large share of the $3.3 billion global revenue for ADHD drugs went to companies in the region, including Shire and McNeil Consumer & Specialty Pharmaceuticals, a Johnson & Johnson subsidiary in Fort Washington that makes Concerta.

Shire has been pursuing the sometimes contradictory goals of building up its ADHD lines while trying to wean itself from dependence on ADHD revenue.

Yesterday, it said Adderall XR revenue last year rose to $864 million, 18 percent over the previous year. Total revenue was $1.8 billion, up 12 percent. Net earnings were $278.2 million, up from a loss of $578.4 million in 2005.

In a statement, Shire chief executive officer Matthew Emmens said the New River acquisition "continues our leadership position in the growing U.S. ADHD market, improves our operating margins, significantly enhances our earnings growth from late 2009, and delivers on our overall global growth strategy."

Makers of generic drugs have been nipping at Shire's revenue on Adderall. It noted that Vyvanse has "robust intellectual property with patent protection to June 2023 in the United States and to June 2024 in Europe."

The deal, already approved by both companies' boards, still needs approval of Shire shareholders. If approved, the company expects it to close by June.

The deal would be a windfall for Randal J. Kirk, New River's founder and chief executive, who owns roughly 50 percent of the outstanding stock valued at $1.3 billion in the deal. His 29-worker company reported revenue of just $31 million for the nine months ended Oct. 1.

"We have confidence in Shire's commitment and ability to optimize the therapeutic and commercial potential of the New River portfolio," Kirk said in a statement. "Shire has a proven track record of success in developing and commercializing products, as evidenced by the success of the Adderall XR franchise."

The deal is the second major move for relatively small Shire. In 2005, Emmens led Shire in buying the biotech firm Transkaryotic Therapies Inc. for $1.6 billion.

Contact staff writer Thomas Ginsberg at 215-854-4177 or tginsberg@phillynews.com.

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Press Release

Shire and New River Pharmaceuticals Announce FDA Approval of the First and Only Stimulant Prodrug VYVANSE™ (lisdexamfetamine dimesylate) as a Novel Treatment for ADHD

Basingstoke, U.K., Philadelphia, PA and Radford, VA – FEBRUARY 23, 2007 – Shire plc (LSE: SHP, NASDAQ: SHPGY, TSX: SHQ) and its collaborative partner New River Pharmaceuticals Inc. (NASDAQ: NRPH) announced today that the U.S. Food and Drug Administration (FDA) has granted marketing approval for VYVANSE (lisdexamfetamine dimesylate, formerly known as NRP104), for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).

On February 20, 2007 Shire and New River announced an agreement whereby Shire will acquire New River for approximately $2.6 billion in an all cash transaction unanimously recommended by the Boards of both companies. The transaction is the subject of another press release issued February 20, 2007.

VYVANSE is a prodrug that is therapeutically inactive until metabolized in the body. In clinical studies designed to measure duration of effect, VYVANSE provided significant efficacy compared to placebo for a full treatment day, up through and including 6:00 pm. Furthermore, when VYVANSE was administered orally and intravenously in two clinical human drug abuse studies, VYVANSE produced subjective responses on a scale of “Drug Liking Effects” (DLE) that were less than d-amphetamine at equivalent doses. DLE is used in clinical abuse studies to measure relative preference among known substance abusers.

“The FDA approval of VYVANSE is exciting news for Shire as well as for patients, their families, and healthcare providers as it’s an important, novel approach for the treatment of ADHD,” said Matthew Emmens, Shire Chief Executive Officer. “The label we received with the approval letter includes information about the extended duration of effect and abuse-related drug liking characteristics of VYVANSE which illustrate benefits that differentiate this compound from other ADHD medicines. The addition of VYVANSE to our ADHD portfolio reaffirms Shire’s commitment to continue to address unmet medical needs and advance the science of ADHD treatment. Beginning with product launch in Q2 2007, Shire will make VYVANSE our top promotional priority within our ADHD portfolio.”

Randal J. Kirk, New River’s Chairman and Chief Executive Officer, remarked, “VYVANSE’s approval signals a new era in the treatment of ADHD. Upon product launch, patients will have a novel treatment option combining the effectiveness of a stimulant – long considered the gold standard in ADHD medicines – with other potential benefits.”

The FDA has proposed that VYVANSE be classified as a Schedule II controlled substance. This proposal was submitted to and accepted by the U.S. Drug Enforcement Administration (DEA). A final scheduling decision is expected from the DEA following a 30-day period for public comment. Once VYVANSE receives final scheduling designation, the label will be available. Pending final scheduling designation, product launch is anticipated in Q2 2007. VYVANSE will be available in three dosage strengths: 30 mg, 50 mg and 70 mg, all indicated for once-daily dosing.[1]

New River developed VYVANSE as a new ADHD medication designed to provide lower potential for abuse, in which *d*-amphetamine is covalently linked to *l*-lysine, a naturally occurring amino acid. The combination is rapidly absorbed from the gastrointestinal tract and converted to *d*-amphetamine, which is responsible for VYVANSE's activity.

Joseph Biederman, MD, director of Pediatric Psychopharmacology at Massachusetts General Hospital, was lead investigator on the pivotal clinical studies testing lisdexamfetamine dimesylate for the treatment of ADHD. These large multi-site studies showed that the drug significantly reduced ADHD symptoms throughout the day with a predictable tolerability profile. "Our studies showed that this next-generation stimulant medication's unique chemical profile offers an option for physicians and their patients in the treatment of ADHD, with outstanding efficacy and duration of action" said Dr. Biederman.

Additional information about VYVANSE and other Shire treatments for ADHD is available at www.ShireADHDTreatments.com.

VYVANSE Significantly Controls ADHD Symptoms

Data from phase II and phase III clinical trials demonstrated statistically significant improvements in ADHD symptoms for patients aged 6 to 12 years treated with VYVANSE compared to patients treated with placebo. These studies demonstrated that all doses of VYVANSE (30 mg, 50 mg and 70 mg) provided significant efficacy at all time points tested, including 6pm.[2]

In the phase II, analog classroom study, patients demonstrated significantly improved behavior when receiving either VYVANSE or ADDERALL XR® (mixed salts of a single-entity amphetamine product) as measured by the Swanson, Kotkin, Agler, M. Flynn and Pelham (SKAMP) deportment rating scale, a standardized, validated classroom assessment tool used for evaluating the behavioral symptoms of ADHD.[3] Both treatments resulted in significantly improved behavior versus a placebo (P <.0001, for both).[4] Patients also demonstrated significantly improved academic productivity with both treatments, compared to placebo (P <.0001 for both medications) as measured by Permanent Product Measure of Performance (PERMP), an age-adjusted collection of math problems that measures a child's ability to pay attention and stay on task as demonstrated by an increase in the number of attempted and successfully completed problems.[4]

In the phase III, randomized, double-blind placebo-controlled study, all three doses of VYVANSE demonstrated significant improvements in ADHD Rating Scale (ADHD-RS-IV) scores compared with placebo (P <.0001) after four weeks of once-daily treatment.[5] ADHD-RS-IV is a standardized, validated test for assessing symptoms of ADHD in children and for assessing their response to treatment.[6,7] This scale, which contains 18 items, is based on the ADHD diagnostic criteria as defined in the APA's *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision®, a publication of the American Psychiatric Association.[8]

Additionally, in a study presented in October at a major scientific meeting, VYVANSE yielded a 60 percent improvement in the primary rating scale scores for symptoms of ADHD in children aged 6 to 12 years who received six months of treatment in an open-label phase III study. Results also demonstrated that at 6 months, 95 percent of children taking VYVANSE produced a "much improved" or "very much improved" rating on the Clinical Global Impressions – Improvement score.[9]

About VYVANSE and ADDERALL XR

Tell your doctor about any heart conditions, including structural abnormalities, that you, your child, or a family member, may have. Inform your doctor ***immediately*** if you or your child develops symptoms that suggest heart problems, such as chest pain or fainting.

VYVANSE or Adderall XR should not be taken by patients who have advanced disease of the blood vessels (arteriosclerosis); symptomatic heart disease; moderate to severe high blood pressure; overactive thyroid gland (hyperthyroidism); known allergy or unusual reactions to drugs called sympathomimetic amines (for example, pseudoephedrine); seizures; glaucoma; a history of problems with alcohol or drugs; agitated states; taken a monoamine oxidase inhibitor (MAOI) within the last 14 days.

Tell your doctor ***before*** using VYVANSE or Adderall XR if you or your child are being treated for or have symptoms of depression (sadness, worthlessness, or hopelessness) or bipolar disorder; have abnormal thoughts or visions, hear abnormal sounds, or have been diagnosed with psychosis; have had seizures or abnormal EEGs; have or have had high blood pressure; exhibit aggressive behavior or hostility. Tell your doctor ***immediately*** if any of these conditions or symptoms develop while using VYVANSE or Adderall XR.

Abuse of amphetamines may lead to dependence. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events. These events have also been reported rarely with amphetamine use.

VYVANSE and Adderall XR were generally well tolerated in clinical studies. The most common side effects in studies of VYVANSE included: *children* - decreased appetite, difficulty falling asleep, stomachache, and irritability. The most common side effects in studies of Adderall XR included: *children* - decreased appetite, difficulty falling asleep, stomachache, and emotional lability; *adolescents* - loss of appetite, difficulty falling asleep, stomachache, and weight loss; *adults* - dry mouth, loss of appetite, difficulty falling asleep, headache, and weight loss.

Aggression, new abnormal thoughts/behaviors, mania, growth suppression, worsening of motion or verbal tics and Tourette's syndrome have been associated with use of drugs of this type. Tell your doctor if you or your child have blurred vision while taking VYVANSE or Adderall XR.

The Collaboration Agreement

In January 2005, New River Pharmaceuticals signed a collaborative agreement with Shire to develop and commercialize VYVANSE. Details on the collaboration agreement are available in previous filings with the U.S. Securities and Exchange Commission.

Planned Acquisition Additional Information
The tender offer described in this press release has not yet commenced, and this press release is neither an offer to purchase nor a solicitation of an offer to sell New River common stock. Investors and security holders are urged to read both the tender offer statement and the solicitation/recommendation statement regarding the tender offer described in this report when they become available because they will contain important information. The tender offer statement will be filed by a subsidiary of Shire with the Securities and Exchange Commission (SEC), and the solicitation/recommendation statement will be filed by New River with the SEC. Investors and security holders may obtain a free copy of these statements (when available) and other documents filed by Shire or New River with the SEC at the website maintained by the SEC at www.sec.gov. The tender offer statement and related materials may be obtained for free by directing such requests to Shire at Hampshire International Business Park, Chineham, Basingstoke, Hampshire, England, RG24 8EP, attention: Investor Relations. The solicitation/recommendation statement and such other documents may be obtained by directing such requests to New River at 1881 Grove Avenue, Radford, Virginia 24141, attention: Director of Corporate Communications.

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About ADHD
Approximately 7.8 percent of all school-age children, or about 4.4 million U.S. children aged 4 to 17 years, have been diagnosed with ADHD at some point in their lives, according to the U.S. Centers for Disease Control and Prevention (CDC). [10] ADHD is one of the most common psychiatric disorders in children and adolescents. [11] ADHD is a neurobiological disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development.[8] To be properly diagnosed with ADHD, a child needs to demonstrate at least six of nine symptoms of inattention; at least six of nine symptoms of hyperactivity/impulsivity; the onset of such symptoms before age 7 years; that some impairment from the symptoms is present in two or more settings (e.g., at school and home); that the symptoms continue for at least six months; and that there is clinically significant impairment in social, academic or occupational functioning.[8]

Although there is no “cure” for ADHD, there are accepted treatments that specifically target its symptoms. The most common standard treatments include educational approaches, psychological or behavioral modification, and medication.[12]

New River
New River Pharmaceuticals Inc. is a specialty pharmaceutical company developing novel pharmaceuticals that are generational improvements of widely prescribed drugs in large and growing markets. For further information on New River, please visit the Company's Web site at http://www.nrpharma.com.

“SAFE HARBOR” STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

This press release contains certain forward-looking information that is intended to be covered by the safe harbor for “forward-looking statements” provided by the Private Securities Litigation Reform Act of 1995. Forward- looking statements are statements that are not historical facts. Words such as “expect(s),” “feel(s),” “believe(s),” “will,” “may,” “anticipate(s)” and similar expressions are intended to identify forward-looking statements. These statements include, but are not limited to, financial projections and estimates and their underlying assumptions; statements regarding plans, objectives and expectations with respect to future operations, products and services; and statements regarding future performance. Such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of New River Pharmaceuticals, that could cause actual results to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include: those discussed and identified in the New River Pharmaceuticals Inc. annual report on Form 10-K, filed with the SEC on March 15, 2006, as well as other public filings with the SEC; the timing, progress and likelihood of success of our product research and development programs; the timing and status of our preclinical and clinical development of potential drugs; the likelihood of success of our drug products in clinical trials and the regulatory approval process; our drug products’ efficacy, abuse and tamper resistance, resistance to intravenous abuse, onset and duration of drug action, ability to provide protection from overdose, ability to improve patients’ symptoms, incidence of adverse events, ability to reduce opioid tolerance, ability to reduce therapeutic variability, and ability to reduce the risks associated with certain therapies; the ability to develop, manufacture, launch and market our drug products; our projections for future revenues, profitability and ability to achieve certain threshold sales targets; our estimates regarding our capital requirements and our needs for additional financing; the likelihood of obtaining favorable scheduling and labeling of our drug products; the likelihood of regulatory approval under the Federal Food, Drug, and Cosmetic Act without having to conduct long and costly trials to generate all of the data which are often required in connection with a traditional new chemical entity; our ability to develop safer and improved versions of widely prescribed drugs using our Carrierwave (TM) technology; our success in developing our own sales and marketing capabilities for our lead product candidate; and our ability to obtain favorable patent claims. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. New River Pharmaceuticals does not undertake any obligation to republish revised forward-looking statements to reflect events or circumstances after the date hereof or to reflect the occurrence of unanticipated events. Readers are also urged to carefully review and consider the various disclosures in New River Pharmaceuticals’ annual report on Form 10-K, filed with the SEC on March 15, 2006, as well as other public filings with the SEC.

Shire plc
Shire's strategic goal is to become the leading specialty pharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit and hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire believes that a carefully selected portfolio of products with a strategically aligned and relatively small-scale sales force will deliver strong results.

Shire's focused strategy is to develop and market products for specialty physicians. Shire's in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe.

For further information on Shire, please visit the Company's website: www.shire.com.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to the impact of those on Shire's Attention Deficit and Hyperactivity Disorder (ADHD) franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval dates of SPD503 (guanfacine extended release) (ADHD), SPD465 (extended release triple-bead mixed amphetamine salts) (ADHD); Shire's ability to secure new products for commercialization and/or development; Shire's planned acquisition of New River Pharmaceuticals announced February 20, 2007; and other risks and uncertainties detailed from time to time in Shire's and its predecessor registrant Shire Pharmaceuticals Group plc's filings with the Securities and Exchange Commission, particularly Shire plc's Annual Report on Form 10-K for the year ended December 31, 2005.

# # #

[1] data on file
[2] New River Pharmaceuticals Inc. CONFIDENTIAL CLINICAL STUDY REPORT PROTOCOL NO.; LDX.301 "A Phase 3, Randomized, Multi-Center, Double-Blind, Parallel-Group, Placebo-Controlled Study of LDX in Children Aged 6-12 Years with Attention Deficit Hyperactivity Disorder (ADHD)," Final (4.0), 02 November 2005.
[3] Wigal SB, Gupta S, Guinta S, Swanson JM. Reliability and Validity of the SKAMP Rating Scale in a Laboratory School Setting. Psychopharmacol Bull. 1998l 34 (1): 47-53.
[4] "Improvements in Symptoms of Attention-Deficit/Hyperactivity Disorder in School-aged Children with Lisdexamfetamine (NRP104) and Mixed Amphetamine Salts, Extended-Release Versus Placebo," presented at the American Psychiatric Association, Toronto, Ontario, Canada, May 24, 2006.
[5] "Efficacy and Safety of Lisdexamfetamine (NRP104) in Children Aged 6 to 12 Years With Attention-Deficit/Hyperactivity Disorder (ADHD)," presented at the American Psychiatric Association, Toronto, Ontario, Canada, May 24, 2006.
[6] DuPaul G. Parent and Teacher Ratings of ADHD Symptoms: Psychometric Properties in a Community-Based Sample. Journal of Clinical Child Psychology. 1991; 20(3): 245-53.
[7] Collett BR, Ohan JL, Meyers KM. Ten Year Review of Rating Scales. V: Scales Assessing Attention-Deficit/Hyperactivity Disorder. Journal of American Academic Child Adolescent Psychiatry. 2003; 42(9): 1015-37.
[8] *Diagnostic and Statistical Manual of Mental Disorders*: Fourth Edition, Text Revision. DSM-TR-IV®. Washington, DC: American Psychiatric Association; 2000: 85.
[9] Childress AC, Krishnan S, McGough JJ, Findling RL. Interim Analysis of a Long-Term, Open-Label, Single-Arm Study of Lisdexamfetamine (LDX), an Amphetamine Prodrug, in children with ADHD. American Academy of Child

and Adolescent Psychiatry Annual Meeting; 2006 Oct. 27; San Diego, CA: American Academy of Child and Adolescent Psychiatry; 2006.
[10] Mental health in the United States: Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder, United States, 2003. *MMWR*, September 2, 2005;54(34):842-847. Available at: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5434a2.htm. Accessed September 27, 2005.
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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2006

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Commission file number 0-29630

SHIRE PLC

(Exact name of registrant as specified in its charter)

England and Wales	**98-0484822**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
Hampshire International Business Park, Chineham, Basingstoke, Hampshire, England, RG24 8EP	**+44 1256 894 000**
(Address of principal executive offices and zip code)	(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of exchange on which registered**
American Depositary Shares, each representing three Ordinary Shares 5 pence par value per share	NASDAQ Global Market

Securities registered pursuant to Section 12(g) of the Act:

None
(Title of class)

Indicate by check mark whether the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act

Yes ☒ No ☐

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act

Yes ☐ No ☒

Indicate by check mark whether the Registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days.

Yes ☒ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the Registrant's knowledge, in definitive proxy or information statements incorporated by reference to Part III of this Form 10-K or any amendment to this Form 10-K.

☒

Indicate by check mark whether the Registrant is a large accelerated filer, an accelerated filer, or a non-accelerated filer. See definition of "accelerated filer and large accelerated filer" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☒ Accelerated filer Non-accelerated filer

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

Yes ☐ No ☒

As at June 30, 2006, the last business day of the Registrant's most recently completed second quarter, the aggregate market value of the ordinary shares, £0.05 par value per share of the Registrant held by non-affiliates was approximately $6,806 million. This was computed using the average bid and asked price at the above date.

As at February 21, 2007, the number of outstanding ordinary shares of the Registrant was 508,020,510.

THE "SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialise, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to: risks associated with the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialisation; the impact of competitive products, including, but not limited to the impact of those on Shire's ADHD franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval dates of SPD503 (guanfacine extended release) (ADHD) and SPD465 (extended release of mixed amphetamine salts) (ADHD); Shire's ability to complete, and achieve anticipated benefits from, the acquisition of New River Pharmaceuticals, Inc.; Shire's ability to secure new products for commercialisation and/or development; and other risks and uncertainties detailed from time to time in Shire's filings with the Securities and Exchange Commission.

The following are trademarks of Shire or companies within the Shire Group, which are the subject of trademark registrations in certain territories.

ADDERALL XR ® (mixed salts of a single entity amphetamine)
ADDERALL ® (mixed salts of a single entity amphetamine)
AGRYLIN ® (anagrelide hydrochloride)

CALCICHEW ® range (calcium carbonate with or without vitamin D_3)
CARBATROL ® (carbamazepine extended-release capsules)
COLAZIDE ® (basalazide)
DAYTRANA™ (methylphenidate transdermal system)
ELAPRASE™ (idursulfase)
EQUETRO™ (carbamazepine extended release capsules)
FOSRENOL ® (lanthanum carbonate)
GENE-ACTIVATED ®
LIALDA™ (mesalamine)
LODINE ® (etodolac)
MESAVANCE™ (mesalamine)
MEZAVANT™ (mesalazine)
REMINYL ® (galantamine hydrobromide) (UK and Republic of Ireland)
REMINYL XL™ (galantamine hydrobromide) (UK and Republic of Ireland)
REPLAGAL ® (agalsidase alfa)
SOLARAZE ® (3% gel diclofenac sodium (3%w/w))
TROXATYL ® (troxacitabine)
VANIQA ® (eflornithine hydrochloride)
VYVANSE™ (lisdexamfetamine dimesylate)
XAGRID ® (anagrelide hydrochloride)

The following are trademarks of third parties referred to in this Form 10-K.

3TC (trademark of GlaxoSmithKline (GSK))
AGENERASE (trademark of GSK)
APTIVUS (trademark of Boehringer Ingelheim)
CEREZYME (trademark of Genzyme)
CONCERTA (trademark of Alza Corporation)
CRIXIVAN (trademark of Merck)
DYNEPO (trademark of Sanofi-Aventis)
EMTRIVA (trademark of Gilead Sciences).
EPIVIR (trademark of GSK)
EPIVIR-HBV (trademark of GSK)
EPZICOM/KIVEXA (EPZICOM) (trademark of GSK)
FABRAZYME (trademark of Genzyme)
FOCALIN XR (trademark of Novartis)
FORTOVASE (trademark of Roche)
FUZEON (trademark of Roche)
HEPTODIN (trademark of GSK)
HEPTOVIR (trademark of GSK)
HIVID (trademark of Roche)
KALETRA (trademark of Abbott Laboratories)
METADATE CD (trademark of UCB)
MICROTROL (trademark of Supernus)
MMX Multi Matrix Systems (trademark of Cosmo Technologies)

NORVIR (trademark of Abbott Laboratories)
PENTASA (trademark of Ferring)
RAZADYNE (trademark of Johnson & Johnson)
REMINYL (trademark of Johnson & Johnson, excluding UK and Republic of Ireland)
RETROVIR (trademark of GSK)
REYATAZ (trademark of Bristol Myers Squibb Company (BMS))
RITALIN LA (trademark of Novartis)
SEASONIQUE (trademark of Barr Laboratories, Inc.)
STRATTERA (trademark of Eli Lilly)
SUSTIVA (trademark co-owned DuPont Pharmaceuticals and Merck)

TRIZIVIR (trademark of GSK)
TRUVADA (trademark of Gilead Sciences)
VIDEX (trademark of BMS)
VIRACEPT (trademark of Agouron Pharmaceuticals)
VIRAMUNE (trademark of Boehringer-Ingelheim)
VIREAD (trademark of Gilead Sciences)
ZEFFIX (trademark of GSK)
ZERIT (trademark of BMS)
ZIAGEN (trademark of GSK)
ZEMPLAR (trademark of Abbott Laboratories)

SHIRE PLC
2006 Form 10-K Annual Report
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PART I

ITEM 1: Business

General

Shire plc and its subsidiaries (collectively referred to as either “Shire” or the “Company”) is a leading specialty pharmaceutical company that focuses on meeting the needs of the specialist physician.

Shire plc was incorporated under the laws of England and Wales on June 27, 2005 and is a public limited company. Following the implementation of a Scheme of Arrangement, on November 25, 2005 Shire plc replaced Shire Pharmaceuticals Group plc (SPG) as the holding company for Shire plc and its subsidiaries.

Historically, the Company has grown through acquisition, completing seven major mergers or acquisitions in a twelve-year period from 1994 to 2006. Divestments of non-core assets over the past three years have streamlined the Company’s operations. The Company will continue to evaluate companies, products and project opportunities that offer a good strategic fit and enhance shareholder value in the future.

Strategy

Shire’s strategic goal is to become the leading specialty pharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit and hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire believes that a carefully selected portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

Shire’s focused strategy is to develop and market products for specialty physicians. Shire’s in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe.

In accordance with this strategy, Shire completed the acquisition of Transkaryotic Therapies, Inc. (TKT) on July 27, 2005. TKT was renamed Shire Human Genetic Therapies, Inc. (Shire HGT) with effect from January 17, 2006.

On February 20, 2007, consistent with its stated focus on the growing ADHD market, Shire announced that it had agreed to acquire New River Pharmaceuticals Inc. allowing Shire to progress and benefit from its successful strategy of acquiring, developing and marketing specialty pharmaceutical products. For further information see Item 1: Business - Recent Developments in this Form 10-K.

2006 Product and Pipeline Highlights

- DAYTRANA: On April 6, 2006 the FDA approved DAYTRANA and it was launched in the US in June 2006.
- ELAPRASE: The US Food and Drug Administration (FDA) approved ELAPRASE in the US on July 24, 2006 and it was

launched in the US in August 2006. By December 31, 2006 over 110 patients in the US had received treatment. The EU pre-approval process commenced in July 2006 and by December 31, 2006 over 100 patients were receiving treatment on a named-patient basis.

- SPD465: On July 21, 2006 the Company submitted a New Drug Application (NDA) to the FDA for SPD465 for the treatment of ADHD in the adult population. The Prescription Drug User Fee Act (PDUFA) date for the FDA to issue a formal response to this application is May 21, 2007.

- SPD503: The Company filed a NDA with the FDA on August 24, 2006 for the use of SPD503 as a treatment of ADHD in children and adolescents. The PDUFA date for the FDA to issue a formal response to this application is June 24, 2007.

- GA-GCB: The Phase 3 clinical program was initiated in January 2007.

- Enzyme Replacement Therapies: The Company has completed proof of concept studies and has advanced into pre-clinical development three projects for the treatment of lysosomal storage disorders; namely enzyme replacement therapies for Sanfilippo syndrome (Mucopolysaccharidosis IIIA), metachromatic leukodystrophy and intrathecal delivery of ELAPRASE for Hunter syndrome patients with significant central nervous system symptoms (Hunter CNS)

- SPD491 - A once-a-day, non opiate, transdermal analgesic being developed with the goal of non-scheduled labeling to treat moderate to severe pain, will enter Phase 1 testing in the first quarter of 2007.

- SPD535 - Pre-clinical evaluation has begun for development of a novel platelet-lowering agent.

In addition Shire in-licensed:

- Rights to the transvaginal ring technology of Duramed in a number of markets outside of North America, including the larger European markets in August 2006, together with a license in the same countries to Duramed's oral contraceptive, SEASONIQUE (levonorgestrel/ethinyl estradiol).

- Global rights to SPD500 (Tissue Protective Cytokine technology), from Warren Pharmaceuticals, Inc. (Warren) in September 2006. SPD500 is being developed pre-clinically in non-nervous system indications, including renal and genetic disease areas.

- Global rights to SPD493 (Valrocemide) and other related compounds, from Yissum Research and Development Company in July 2006. SPD493 is being developed at Phase 1 for the treatment of a number of central nervous system disorders.

2006 Business Highlights

ADDERALL XR – Settlement of Barr Laboratories, Inc. (Barr) Litigation

On August 14, 2006 Shire and Barr announced that all pending litigation in connection with Barr's Abbreviated New Drug Application (ANDA) and its attempt to market generic versions of Shire's ADDERALL XR had been settled. As part of the settlement, Barr entered into consent judgments and agreed to permanent injunctions confirming the validity and enforceability of Shire's US Patents Nos. 6,322,819 (the '819 Patent), 6,601,300 (the '300 Patent) and 6,913,768 (the '768 Patent). Barr has also admitted that any generic product made under its ANDA would infringe the '768 patent. Under the terms of the settlement, Barr will not be permitted to market a generic version of ADDERALL XR in the US until April 1, 2009, except in certain limited circumstances, such as the launch of another party's generic version of ADDERALL XR. No payments to Barr are involved in the settlement agreement.

Sale of ADDERALL IR to Duramed

In September 2006, Duramed Pharmaceuticals, Inc. (Duramed) purchased the product rights to Shire's ADDERALL product for $63.0 million.

ID Biomedical Corporation (IDB) loan repayment

On February 10, 2006 Shire received notice from IDB that it intended to repay in full all of its loan drawings for injectable flu development of $70.6 million, together with accrued and capitalized interest of $8.1 million (see Note 6 to the Company's consolidated financial statements contained in Part IV of this Annual report). The Company received the $78.7 million outstanding on February 14, 2006. The amounts outstanding in respect of IDB's drawings for pipeline development (principal drawings of $29.4 million) are unaffected by this repayment.

FOSRENOL

In December 2006 the Company entered into an agreement with Abbott Laboratories (Abbott) for the co-promotion of FOSRENOL in the US. Abbott's US renal care sales team will co-promote FOSRENOL with its own renal product ZEMPLAR. The Company's US renal sales force will also continue to promote FOSRENOL. This agreement began in the first quarter of 2007 and will continue for a term of five years.

Recent developments

Acquisition of New River

On February 20, 2007 Shire announced that it has agreed to acquire New River Pharmaceuticals Inc. (New River) for $64 per New River share, or approximately $2.6 billion for the fully diluted equity interest, in an all cash transaction unanimously recommended by the Boards of both companies. The acquisition is structured as a tender offer for all outstanding shares of New River followed by a merger. The acquisition is subject to the approval of Shire plc's shareholders as well as the satisfaction of certain customary conditions, including the tender of a majority of the outstanding New River shares on a fully-diluted basis and the expiration or earlier termination of the Hart-Scott-Rodino waiting period. For accounting purposes, the acquisition of New River will be accounted for as a purchase business combination in accordance with Statement of Financial Accounting Standards (SFAS) No. 141 "Accounting for Business Combinations" (SFAS No. 141).

The total consideration for the acquisition of New River amounts to approximately $2.6 billion in cash. Shire has entered into new bank facilities of $2.3 billion to provide part of the financing for the acquisition. This new facility is conditional upon, amongst other things, approval being given by Shire plc's shareholders at an Extraordinary General Meeting for Shire plc to exceed the current limit on its aggregate borrowings set out in Shire plc's Articles of Association.

Shire plc has also raised approximately $900 million through the private placement of 42,883,721 new ordinary shares to certain institutional investors at a price of 1075 pence per share. The newly issued shares represent approximately 8.4 per cent of Shire plc's issued ordinary share capital prior to the placing.

For further information see Exhibit 99.2 to the 8-K filed on February 23, 2007.

VYVANSE (previously known as NRP104)

On February 23, 2007 the FDA approved VYVANSE, indicated for the treatment of ADHD. The FDA has proposed that VYVANSE be classified as a Schedule II controlled substance. This proposal was submitted to and accepted by the US Drug Enforcement Administration (DEA). A final scheduling decision is expected from the DEA following a 30-day period for public comment. Pending final scheduling designation, product launch is anticipated in the second quarter of 2007.

ELAPRASE

On January 8, 2007 the European Medicines Agency (EMEA) granted marketing authorization for the use of ELAPRASE for the long-term treatment of patients with Hunter syndrome. Pricing and reimbursement procedures are already underway for ELAPRASE in many European countries and it will be launched across the majority of European countries in 2007.

LIALDA/MEZAVANT

On January 16, 2007 the FDA approved LIALDA, indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. LIALDA is the first and only FDA-approved once-daily oral formulation of mesalamine. Once-daily LIALDA contains the highest mesalamine dose per tablet (1.2g), so patients can take as few as two tablets once daily. The Company anticipates launching LIALDA in the US during the first quarter of 2007.

In Europe, Shire has received core labelling information approval for MEZAVANT in 15 EU countries (including UK, Germany, France and Spain) following the decentralised registration procedure. Associated national approvals should follow in the first quarter of 2007 and have already been received in Austria, Denmark and the UK.

SPD754

Shire licensed the US and Canadian rights for the investigational HIV compound, SPD754 (also known as apricitabine), to the Australian biotechnology company Avexa Limited (Avexa) on January 23, 2007. Shire received an up-front cash payment of US$10 million, 8 million additional Avexa shares (taking its shareholding in Avexa to just over 8%) and may receive further milestones and royalties.

Financial information about operating segments

Substantially all of the Company's revenues, operating profits or losses and net assets are attributable to the research and development (R&D), manufacture, sale and distribution of pharmaceutical products within two operating segments: Pharmaceutical products and Royalties. Segment revenues, profits or losses and assets for 2006, 2005 and 2004 are presented in Note 25 to the Company's consolidated financial statements contained in Part IV of this Annual Report.

Sales and marketing

At December 31, 2006, the Company employed 1,260 sales and marketing staff to service its operations throughout the world, which included its major markets in the US, Europe and Canada.

Currently marketed products

The table below lists the Company's key currently marketed products as at December 31, 2006, indicating the owner, licensor and the key territories in which Shire markets the product.

Products	Disease area	Owner/licensor	Key territory
Treatments for central nervous system (CNS) disorders			
ADDERALL XR (mixed salts of a s ingle-entity amphetamine product)	ADHD	Shire	US and Canada
DAYTRANA (methylphenidate transdermal system)	ADHD	Shire/Noven Pharmaceuticals, Inc.	US
CARBATROL (carbamazepine extended-release capsules)	Epilepsy	Shire	US
Treatments for GI diseases			
PENTASA (mesalamine)	Ulcerative colitis	Ferring A/S	US

COLAZIDE (balsalazide)	Ulcerative colitis	Shire	UK [1]

Treatments for Human Genetic Diseases

REPLAGAL (algalsidase alfa)	Fabry disease	Shire	Europe, Canada and Argentina; [2]
ELAPRASE (idursulfase)	Hunter syndrome (Mucopolysaccha-ridosis Type II)	Shire	US

Treatments for diseases in the general products (GP) area

AGRYLIN (anagrelide hydrochloride)	Thrombocythemia secondary to a myeloproliferative disorder	Shire	US and Canada [3]
XAGRID (anagrelide hydrochloride)	Elevated platelet counts in at risk essential thrombocythemia patients	Shire	Europe [3]
FOSRENOL (lanthanum carbonate)	Hyperphosphatemia in end stage renal disease	Shire [6]	US and Europe [2][4]
REMINYL/REMINYL XL (galantamine hydrobromide)	Alzheimer's disease	Synaptech, Inc.	UK and Republic of Ireland [5]

CALCICHEW (calcium carbonate range)	Adjunct in osteoporosis	Nycomed Pharma AS	UK and Republic of Ireland
LODINE (etodolac)	Rheumatoid arthritis and osteoarthritis	Shire	UK and Republic of Ireland
SOLARAZE (diclofenac sodium 3% gel)	Actinic keratosis	Jagotec A.G.	Europe [1]
VANIQA (eflornithine 11.5% cream)	Facial hirsutism in women	Skinmedica, Inc.	Europe [2]

[1] Marketed in certain European markets by distributors
[2] Marketed in certain European and other markets by distributors
[3] AGRYLIN/XAGRID is marketed in certain European and other markets by distributors
[4] Sold as FOZNOL in the Republic of Ireland
[5] Marketed in ROW under license from Shire by Janssen Pharmaceutica N.V. (part of the Johnson & Johnson group of companies)
[6] Shire has the right to acquire the patents in Japan

Treatments for CNS disorders

ADDERALL XR

ADDERALL XR is a treatment for ADHD. ADHD is estimated to affect 7.8% of US children aged 4 to 17. Symptoms present

themselves as impulsivity/hyperactivity, inattention or both. In up to 65% of children affected by this disorder, symptoms will persist into adulthood, with estimates of up to 9.9 million adults in the United States having ADHD. According to IMS Health (IMS), a leading global provider of business intelligence for the pharmaceutical and healthcare industries, the US market for ADHD treatments was approximately $3.3 billion for the year to December 31, 2006.

ADDERALL XR is a patented formulation which uses MICROTROL drug delivery technology and is designed to provide an all-day treatment with one morning dose. It is available in 5mg, 10mg, 15mg, 20mg, 25mg and 30mg capsules and can be administered as a capsule or sprinkled on soft food. In the ADHD market, a once-a-day formulation provides the following important patient benefits:

- all-day control of symptoms;
- avoids the need for medication to be taken at school;
- reduces the risk of diversion;
- allows parental control of medication; and
- offers potential for improved patient compliance.

The FDA approved ADDERALL XR as a once-daily treatment for children with ADHD in October 2001, for adults in August 2004 and for adolescents (aged 13 to 17) in July 2005.

During October 2005 the Company filed a Citizen Petition with the FDA requesting that the FDA require more rigorous bioequivalence testing or additional clinical testing for generic or follow-on drug products that reference ADDERALL XR before they can be approved. The Company received correspondence from the FDA in April 2006 stating that, due to the complex issues raised requiring extensive review and analysis by the FDA's officials, a decision cannot yet be reached by the FDA. The FDA did not provide any guidance as to when that decision may be reached.

On January 19, 2006 the Company and Impax Laboratories, Inc. (Impax) announced that all pending litigation in connection with Impax's ANDA had been settled. As part of the settlement, Impax confirmed that its proposed generic products infringe Shire's 819, 300 and 768 Patents.

On August 14, 2006 Shire and Barr announced that all pending litigation in connection with Barr's ANDA and its attempt to market generic versions of Shire's ADDERALL XR had been settled. As part of the settlement, Barr entered into consent judgments and agreed to permanent injunctions confirming the validity and enforceability of Shire's 819, 300 and 768 Patents. Barr has also admitted that any generic product made under its ANDA would infringe the 768 patent.

Under the terms of the settlement, Barr is not permitted to market a generic version of ADDERALL XR in the United States until April 1, 2009, except for certain limited circumstances (such as the launch of another party's generic version of ADDERALL XR).

Litigation proceedings relating to the Company's ADDERALL XR patents are in progress. For further information see ITEM 3: Legal Proceedings.

DAYTRANA

DAYTRANA is a methylphenidate transdermal delivery system for the once daily treatment of ADHD. DAYTRANA is the first and only patch medication approved by the FDA to treat the symptoms of paediatric ADHD. It is available in four dosage strengths of 10mg, 15mg, 20mg and 30mg, all designed for once-daily use. When worn for the recommended nine hours, efficacy has been demonstrated from the first time point measured (two hours) through the 12-hour time point.

In February 2003 the Company in-licensed from Noven Pharmaceuticals, Inc. (Noven) the worldwide royalty-free sales and marketing rights to DAYTRANA. DAYTRANA was approved by the FDA on April 6, 2006 and was launched in the US in June

2006.

CARBATROL

CARBATROL is a treatment for epilepsy. Approximately 2.7 million people in the United States suffer from epilepsy, a disorder that is characterised by a propensity for recurrent seizures and is defined by two or more unprovoked seizures.

CARBATROL is an extended release formulation of carbamazepine that uses MICROTROL drug delivery technology. It is available in 100mg, 200mg and 300mg capsules and can be administered as a capsule or sprinkled on food and delivers consistent blood levels of the drug over 24 hours, when taken twice daily. When administered in an immediate release formulation, carbamazepine requires dosing three to four times a day. CARBATROL's extended release formulation therefore provides potential compliance advantages for patients. Carbamazepine is one of the most widely prescribed anti-epileptic drugs.

The FDA approved CARBATROL in September 1997 for marketing in the US and it was launched in the US in June 1998. A promotional services agreement for CARBATROL for the US market was signed with Impax in January 2006. This took effect from July 2006.

Patent litigation proceedings relating to CARBATROL are in progress. For further information see ITEM 3: Legal Proceedings.

Treatments for GI diseases

PENTASA

PENTASA controlled release capsules are indicated for the induction of remission and for the treatment of patients with mild to moderately active ulcerative colitis. Ulcerative colitis is a serious chronic inflammatory disease of the colon in which part, or all of the large intestine becomes inflamed and often ulcerated. Typically, patients go through periods of relapse and remission and can suffer from diarrhoea, bleeding and abdominal pain. Once diagnosis is confirmed, patients are usually treated for life. The worldwide diagnosed population for ulcerative colitis is expected to reach 1.4 million by 2015. The first line treatment for inflammatory bowel disease is with mesalamine (5-aminosalicylic acid 5-ASA) based products

PENTASA is an ethylcellulose-coated, controlled release capsule formulation designed to release therapeutic quantities of mesalamine throughout the gastrointestinal tract. In the US, PENTASA is available in 250mg and 500mg capsules.

Pursuant to an agreement with Ferring A/S, the Company has in-licensed the exclusive royalty-bearing rights to PENTASA in the US. The co-promotion agreement with Solvay Pharmaceuticals, Inc. ended with effect from January 1, 2006 and PENTASA has since been exclusively promoted by the Company.

COLAZIDE

COLAZIDE is indicated for the treatment of mild to moderately active ulcerative colitis and maintenance of remission. It is a mesalamine derivative in which mesalamine is linked to an inactive carrier. The link is cleaved by colonic bacteria, delivering 99% of the mesalamine dose to the colon.

Treatments for human genetic diseases

REPLAGAL

REPLAGAL is a treatment for Fabry disease. Fabry disease is a rare, inherited genetic disorder resulting from a deficiency in the activity of the lysosomal enzyme alpha-galactosidase A, which is involved in the breakdown of fats. Although the signs and symptoms of Fabry disease vary widely from patient to patient, the most common include severe pain of the extremities, impaired kidney function often progressing to full kidney failure, early heart disease,

stroke and disabling gastrointestinal symptoms. The disease is estimated to affect 1 in 40,000 males and is less frequent in

females.

REPLAGAL is a fully human alpha-galactosidase A protein that replaces the deficient alpha-galactosidase A with an active enzyme to stop or ameliorate the clinical manifestations of Fabry disease. In August 2001, REPLAGAL was granted marketing authorization and co-exclusive orphan drug status in the European Union (EU) with up to 10 years market exclusivity.

ELAPRASE

ELAPRASE is a treatment for Hunter syndrome (also known as Mucopolysaccharidosis Type II or MPS II). Hunter syndrome is a rare, inherited genetic disorder mainly affecting males that interferes with the body's ability to break down and recycle waste substances called mucopolysaccharides, also known as glycosaminoglycans or GAGs. Hunter syndrome is one of several related lysosomal storage diseases. In patients with Hunter syndrome, cumulative buildup of GAGs in cells throughout the body interferes with the way certain tissues and organs function, leading to severe clinical complications and early mortality.

ELAPRASE was approved by the FDA on July 24, 2006 and launched in the US during August.

On January 8, 2007 the EMEA granted marketing authorization for the use of ELAPRASE for the long-term treatment of patients with Hunter syndrome. Pricing and reimbursement procedures are already underway for ELAPRASE in many European countries and it will be launched across the majority of European countries in 2007.

Prior to the grant of marketing authorization in the EU, early access was granted to patients with Hunter syndrome in a number of European countries that have mechanisms for pre-approval access including Italy, Germany, Spain, France, Sweden, Denmark and Norway.

ELAPRASE has been granted orphan drug status by both the FDA and the EMEA, providing it with up to seven and ten years market exclusivity in the US and EU, respectively, from the date of the grant of the relevant marketing authorization.

Treatments for diseases in the GP area

AGRYLIN/XAGRID

Myeloproliferative disorders (MPDs), including essential thrombocythemia (ET) and polycythemia vera, are a group of diseases in which one or more blood cell types are overproduced. In the case of platelets, which are involved in the blood clotting process, excess numbers can result in abnormal blood clot formation giving rise to events such as heart attack and stroke. Excessive platelet production can also lead to the formation of abnormal platelets, which may not be as effective in the clotting process. This can lead to events such as gastrointestinal bleeding.

Anagrelide hydrochloride is marketed in the US (under the trade name AGRYLIN) for the treatment of thrombocythemia secondary to a MPD. AGRYLIN's paediatric marketing exclusivity expired in September 2004 in the US. The FDA subsequently approved several generic versions of AGRYLIN, which, as expected, adversely affected the Company's sales of this product in North America in 2005 and 2006.

In Europe anagrelide hydrochloride is marketed as XAGRID for the reduction of elevated platelet counts in at risk ET patients. It was granted a marketing authorization in the EU in November 2004. XAGRID has also been granted orphan drug status in the EU, providing it with up to 10 years market exclusivity from November 2004.

FOSRENOL

FOSRENOL is a phosphate binder for use in end-stage renal failure patients receiving dialysis. It is estimated that there are around 1.8 million patients worldwide with end-stage renal disease. In this condition the kidneys are unable to regulate the balance of phosphate in the body. If untreated, the resultant retention and elevated blood phosphate levels (hyperphosphatemia) can combine with other biochemical disturbances and result in bone disorders described as renal osteodystrophy. Research also suggests that hyperphosphatemia is associated with the development of cardiovascular disease which accounts for nearly 50% of deaths in dialysis patients.

FOSRENOL binds dietary phosphate in the gastrointestinal tract to prevent it from passing through the gut lining and, based upon this mechanism of action, phosphate absorption from the diet is decreased. Formulated as a convenient chewable tablet,

FOSRENOL received FDA approval for the 250mg and 500mg dosage strengths in the US in October 2004 and was launched in the US in January 2005. In November 2005, the Company received FDA approval for the higher dose strengths of 750mg and 1000mg.

In December 2006 the Company entered into an agreement with Abbott for the co-promotion of FOSRENOL in the US. Abbott's US renal care sales team will co-promote FOSRENOL with its own renal product ZEMPLAR. The Company's US sales force will also continue to promote FOSRENOL. This agreement began in the first quarter of 2007 and will continue for a term of 5 years. FOSRENOL has been approved in a number of European countries in 2006 and has now been launched in Germany, France, the UK and a number of other European countries. Launches will continue throughout 2007 in Europe including, Italy and Spain, subject to the finalization of national licensing and conclusion of pricing and re-imbursement negotiations.

REMINYL and REMINYL XL

REMINYL and REMINYL XL are indicated for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer type. It is estimated that approximately 500,000 people in the UK suffer from Alzheimer's disease (AD), which affects the ability to carry out normal daily activities and affects memory, language and behaviour. The disease is progressive, with death usually occurring within eight to ten years following the onset of symptoms.

REMINYL and REMINYL XL are marketed by the Company in the UK and Republic of Ireland under a royalty-bearing licence from Synaptech Inc. (Sypnaptech). In the rest of the world, it is marketed by Janssen Pharmaceutica N.V. (Janssen), an affiliate of Johnson & Johnson (under the name RAZADYNE and RAZADYNE ER in the US). The Company receives royalties on Janssen's sales. REMINYL XL is a once-daily prolonged release formulation of REMINYL, which was launched by the Company in the UK and Republic of Ireland in June 2005 and by Janssen in the US in May 2005 as RAZADYNE ER.

In May 2006, the National Institute for Health and Clinical Excellence (NICE) in England and Wales issued its Final Appraisal Determination (FAD) which recommended that REMINYL and REMINYL XL, together with other drugs in the same class, be reimbursed by the National Health Service (NHS) when used for the treatment of either (i) patients with existing AD already being treated with one of these drugs; or (ii) newly diagnosed patients once their disease has progressed to a moderate stage. The FAD confirmed that the NHS would not reimburse treatment of patients newly diagnosed with mild AD. The Company and other consultees to the NICE process appealed against the FAD, but the appeals were unsuccessful. A pharmaceutical company with a product in this class has given notice of its intention to apply for a judicial review of the decision of NICE's Appeal Panel. The Company intends to participate in the judicial review proceedings as an interested party.

In June 2006 Janssen and Synaptech filed a law suit against Barr for infringement of their patent rights relating to RAZADYNE ER as a result of Barr filing an ANDA with the FDA for a generic version of RAZADYNE ER. No court date has been set.

Barr and other companies have filed ANDAs with the FDA for generic versions of RAZADYNE and Janssen and Synaptech have filed law suits against some of those ANDA filers. The court date for the first of these proceedings is May 2007.

CALCICHEW range

The Company is licensed by Nycomed Pharma AS (Nycomed) until December 31, 2007 to distribute the CALCICHEW range of calcium and calcium/vitamin D3 supplements for the adjunctive treatment of osteoporosis in the UK and Republic of Ireland. The Company is negotiating an extension of this license with Nycomed.

Osteoporosis is characterised by a progressive loss of bone mass that renders bone fragile and liable to fracture. More than 4.5 million people in the UK are estimated to suffer from this condition.

LODINE

LODINE SR contains etodolac 600mg in a sustained release formulation and is indicated for use in the treatment of rheumatoid arthritis and osteoarthritis in the UK and Republic of Ireland. More than seven million adults in the UK have long-term health problems associated with arthritis and related conditions.

The Company has exclusive UK sales and marketing rights to LODINE. In November 2006, a generic company was granted a marketing authorization for a 600mg etolodac tablet in the UK and launched the product shortly after approval.

SOLARAZE

SOLARAZE is a topical preparation for the treatment of Actinic Keratosis (AK). AK is a common form of pre-malignant skin tumor. AK is caused primarily by long-tem exposure to the sun (UV radiation) and may progress to squamous cell carcinoma in up to 10% of cases. The reported incidence of AK is up to 25% in the northern hemisphere increasing to 60% in Australian adults.

On November 29, 2006 the Australian Government Department of Health and Ageing Therapeutic Goods Administration approved the registration of Solaraze for the management of AK.

VANIQA

VANIQA Cream is a novel topical prescription-only medicine indicated for the treatment of facial hirsutism (also known as unwanted facial hair) in women. Approximately 1 in 10 women remove unwanted facial hair on a weekly basis.

Royalties received from antiviral products

The Company receives royalties on antiviral products based on certain of the Company's patents licensed to GSK. These antiviral products are for Human Immunodeficiency Virus (HIV) and Hepatitis B. The table below lists these products, indicating the principal indications, marketer of the product and the territory in which the product is being marketed.

Products	Principal indications	Marketed by/relevant territory
3TC/EPIVIR	HIV	Shire & GSK / Canada; GSK / RoW
COMBIVIR	HIV	Shire & GSK / Canada; GSK / RoW
TRIZIVIR	HIV	Shire & GSK / Canada; GSK / RoW
EPZICOM/KIVEXA	HIV	Shire & GSK / Canada; GSK / RoW
ZEFFIX/EPIVIR - HBV/ HEPTOVIR [1]	Hepatitis B infection	Shire & GSK / Canada; GSK / RoW

[1] This is not a comprehensive list of trademarks for this product. The product is marketed under other trademarks in some markets.

HIV/AIDS

HIV is a retrovirus that has been isolated and recognized as the causative agent of Acquired Immunodeficiency Syndrome (AIDS). There are many strains of HIV throughout the world, although they all exhibit the same disease mechanism.

According to UNAIDS (a joint United Nations program on AIDS), in 2006 there were 39.5 million people worldwide living with HIV/AIDS, including 17.7 million women and 2.3 million children under the age of 15. In 2006 4.3 million people became newly infected with HIV, including 0.6 million children. Of these, 2.8 million new infections occurred in Sub-Saharan Africa. In an effort to combat the AIDS epidemic in Africa and reduce the cost of medicines used to treat AIDS in sub-Saharan Africa, the Company has waived a significant proportion of its royalty entitlements on sales of products containing lamivudine in this region.

According to IMS the World-Wide antiretroviral (anti-HIV) market reached $8.2 billion in annual sales in the year to November 2006, with nucleotide/nucleoside transcriptase inhibitors (such as 3TC) representing 51.7% of the market ($4.22 billion). The vast majority of sales were generated in North America and Western Europe.

Lamivudine was originally discovered by Shire BioChem Inc. (BioChem), a wholly-owned subsidiary of the Company. Since 1990, the Company has licensed to GSK the worldwide rights, with the exception of Canada, to develop manufacture and sell lamivudine (now marketed in various single and combination formulations including 3TC/EPIVIR, COMBIVIR, TRIZIVIR and EPZICOM). In Canada 3TC is sold by the Company in partnership with GSK.

3TC/EPIVIR

3TC (lamivudine) is indicated for the treatment of HIV infection and AIDS and was first approved in the US in November 1995. It is now marketed in the US as EPIVIR. Approval in Canada followed shortly after in December 1995 and in the EU in August 1996.

The safety and efficacy of 3TC together with 3TC's ease of administration has successfully established 3TC as the cornerstone of combination therapy in HIV infection. In combination with other anti-retrovirals, 3TC is used in the majority of triple and quadruple combination therapies with other nucleoside analog, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI). It was also part of the pivotal clinical trials used as the basis for approval of five other HIV anti-retroviral agents: the nucleoside analog abacavir, the NNRTI efavirenz, and the protease inhibitors indinavir, nelfinavir and amprenavir.

COMBIVIR

In September 1997, the FDA authorized the marketing of COMBIVIR, the first product to combine two anti-retroviral drugs in a single tablet formulation. Each tablet of COMBIVIR contains 3TC and zidovudine (AZT) and can be taken twice daily, offering the advantage of reducing significantly the number of tablets a person on a 3TC/AZT based treatment regimen needs to take. COMBIVIR was approved for use in Europe in March 1998 and in Canada in December 1998.

TRIZIVIR

In November 2000, the FDA authorized the marketing of TRIZIVIR in the US. Each tablet of TRIZIVIR contains 3TC, AZT and abacavir (ABC) and can be taken twice daily. TRIZIVIR was the first tablet to combine three anti-HIV agents. TRIZIVIR was approved for use in the EU in January 2001 and in Canada in October 2001.

EPZICOM/KIVEXA

In August 2004, the FDA authorized the marketing of EPZICOM in the US. Each tablet of EPZICOM contains 3TC and ABC and can be taken once a day. EPZICOM, in combination with other antiretroviral agents, is indicated for the treatment of HIV-1 infection in adults. In December 2004, EPZICOM was granted a marketing authorization in the EU.

Hepatitis B infection

Hepatitis B virus (HBV) is the causative agent of both acute and chronic forms of Hepatitis B, a liver disease that is a major cause of death and disease throughout the world. Two billion people worldwide have been infected with HBV. Of those infected, over 350 million people are chronically infected. Although vaccines to prevent infection by HBV are currently available, they have not been shown to be effective in those already infected with the virus.

ZEFFIX/EPIVIR-HBV/HEPTOVIR

ZEFFIX (lamivudine) is an orally available treatment for chronic hepatitis B infection and for the prevention of liver graft reinfection.

The Company has licensed to GSK the worldwide rights, with the exception of Canada, to develop manufacture and sell ZEFFIX, EPIVIR, HBV and HEPTOVIR. In Canada HEPTOVIR is sold by the Company in partnership with GSK.

Products under development

The Company focuses its development resources on projects within its core therapeutic areas of CNS, GI, HGT and GP.

The table below lists the Company's key products under development by therapeutic area, at December 31, 2006, indicating the most advanced development status reached in any market for each and the Company's territorial rights.

Product	**Principal indications**	**Most advanced**	**The Company's**

		development status	territorial rights
Treatments for CNS disorders			
VYVANSE (lisdexamfetamine dimesylate)	Paediatric and adult ADHD	US: FDA Approval on February 23, 2007 for paediatric ADHD. Adult ADHD in Phase 3.	Global [(1)]
SPD503 (extended release guanfacine)	ADHD	US: Registration	US
SPD465 (extended release of mixed amphetamine salts)	ADHD	US: Registration	Global
SPD493 (Valrocemide)	Various	Phase 1	Global
SPD491	Pain	Phase 1 from Q1 2007	Global
Treatments for GI diseases			
LIALDA (mesalamine) / MEZAVANT (mesalazine) with MMX Technology (previously known as MESAVANCE)	Ulcerative colitis	US: FDA approved the NDA for ulcerative colitis on January 17, 2007. Canada: Registration EU: Agreed core labelling information on December 14, 2006 for ulcerative colitis through EU consensus (decentralized procedure).	Key major markets worldwide
Treatments for Human Genetic diseases			
Gene-activated glucocerebrosidase (GA-GCB)	Gaucher disease	Phase 1/2 completed Phase 3 from Q1 2007	Global

Enzyme replacement therapies	Sanfilippo Syndrome (Mucopoly-saccharidosis IIIA), Metachromatic Leukodystrophy and Hunter CNS	Pre-clinical	Global
Treatments for diseases in the GP area			
DYNEPO (epoetin delta)	Anemia related to chronic renal failure	Approved EU	Global (excluding US)
SPD500 (Tissue protective cytokine technology)	Various [(2)]	Pre-clinical	Global

SPD535	Disorder of platelet level	Pre-clinical	Global
SEASONIQUE	Woman's health	Pre-registration	Key European markets
Transvaginal Ring Technology	Woman's health	Various	Key European markets

(1) In collaboration with New River
(2) Non-nervous system indications only.

Treatments for CNS disorders

VYVANSE (previously known as NRP104)

The Company signed a collaborative agreement (the "Collaborative Agreement") with New River on January 31, 2005, for the new chemical entity NRP104, which is being developed for the treatment of ADHD. VYVANSE is an amphetamine pro-drug where lysine is linked to d-amphetamine. VYVANSE is therapeutically inactive until metabolised in the body.

On February 23, 2007, the FDA approved VYVANSE, indicated for the treatment of ADHD. The FDA has proposed that VYVANSE be classified as a Schedule II controlled substance. This proposal was submitted to and accepted by the DEA. A final scheduling decision is expected from the DEA following a 30-day period for public comment. Pending final scheduling designation, product launch is anticipated in the second quarter of 2007. VYVANSE will be available in three dosage strengths: 30 mg, 50 mg and 70 mg, all indicated for once-daily dosing.

New River has completed enrolment for its Phase 3 clinical trial examining the safety and efficacy of VYVANSE as a treatment for ADHD in the adult population (ages 18-52). Studies for the treatment of ADHD in adolescents (ages 13-18) will commence after the adult ADHD studies are completed.

Under the terms of the Collaborative Agreement, the Company will collaborate with New River to develop, manufacture, market and sell VYVANSE in the US. In the rest of the world, the Company has an exclusive royalty-bearing license to develop and commercialize VYVANSE.

On February 20, 2007 the Company announced that it had agreed to acquire New River for $2.6 billion in cash. For further information see Item 1: Business - Recent Developments in this Form 10-K.

SPD503

SPD503 is a non-stimulant "non-scheduled" compound for use in ADHD. The Company filed a NDA with the FDA on August 24, 2006 for the use of SPD503 as a treatment of ADHD in children and adolescents. The PDUFA date for the FDA to issue a formal response to this application is June 24, 2007.

SPD465

On July 21, 2006 the Company submitted a NDA to the FDA for SPD465 for the treatment of ADHD in the adult population. The PDUFA date for the FDA to issue a formal response to this application is May 21, 2007. SPD465 has the same active ingredient as ADDERALL XR, but is designed to provide ADHD symptom control for up to 16 hours.

SPD493

The Company intends to study SPD493 (Valrocemide) in a number of CNS disorders and efficacy as an anti-epileptic agent has been demonstrated in a small proof of concept clinical study.

SPD491

SPD491, a once-a-day, non-opiate, transdermal analgesic being developed with the goal of non-scheduled labelling to treat moderate to severe pain, will enter Phase 1 testing in Q1 2007.

Treatments for GI diseases

LIALDA/MEZAVANT with MMX Technology (previously known as MESAVANCE)

On January 16, 2007 the FDA approved LIALDA, indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. LIALDA is the first and only FDA-approved once-daily oral formulation of mesalamine. Once-daily LIALDA contains the highest mesalamine dose per tablet (1.2g), so patients can take as few as two tablets once daily. The Company anticipates launch of LIALDA in the US during the first quarter 2007.

In 2006, the Company submitted applications for this product to a number of European regulatory agencies (to be called MEZAVANT) and filed a New Drug Submission with Health Canada. On December 14, 2006 the Company announced that core labelling information, part of Shire's Marketing Authorization Application for MEZAVANT, had been agreed by the regulatory agencies for the 15 EU countries (including UK, Germany, France and Spain) participating in the decentralised registration procedure. Following completion of the decentralised procedure, associated national approvals should follow in the first quarter of 2007, enabling the Company to start a phased launch of MEZAVANT in Europe. Marketing authorizations have been granted in the UK, Denmark and Austria in the first quarter of 2007.

The Company has in-licensed the exclusive royalty-bearing rights to LIALDA/MEZAVANT in the US, Canada, Europe (excluding Italy) and the Pacific Rim from Giuliani S.p.A.

Treatments for human genetic diseases

Gene-Activated Glucocerebrosidase

Gene-Activated Glucocerebrosidase (GA-GCB) is being developed for the treatment of Gaucher disease. Gaucher disease is the most common of the inherited lysosomal storage diseases and is caused by a deficiency of the enzyme glucocerebrosidase. As a result of this deficiency, certain lipids accumulate in specific cells of the liver, spleen and bone marrow causing significant clinical symptoms in the patient, including enlargement of the liver and spleen, hematological abnormalities and bone disease.

In April 2004, TKT (which was acquired by the Company on July 27, 2005) initiated a clinical trial to evaluate the safety and clinical efficacy of GA-GCB, its enzyme replacement therapy for the treatment of Gaucher disease. Results from this study were announced during the last quarter of 2005 and based upon these positive results the Company has commenced a Phase 3 clinical program in 2007.

Patent litigation proceedings in Israel with Genzyme Corporation (Genzyme) relating to GA-GCB were dismissed in January 2006. For further information see ITEM 3: Legal Proceedings.

Enzyme Replacement Therapies

The Company has completed proof of concept studies and has advanced into pre-clinical development on three projects for the treatment of lysosomal storage disorders; namely enzyme replacement therapies for Sanfilippo syndrome (Mucopolysaccharidosis IIIA), metachromatic leukodystrophy and intrathecal delivery of ELAPRASE for Hunter syndrome patients with significant central nervous system symptoms (Hunter CNS).

Treatments for other diseases in the GP area

DYNEPO

DYNEPO was approved in the EU in March 2002 and is indicated for the treatment of anemia in patients with chronic renal failure. It may be used in patients on dialysis as well as patients not on dialysis. The Company is preparing for commercial manufacture in

Europe and expects to commence a staged launch in Europe of the product in the first half of 2007.

The Company has in-licensed the exclusive royalty-bearing global (excluding US) rights to DYNEPO from Sanofi-Aventis.

Patent litigation proceedings relating to DYNEPO are in progress in the US. For further information see ITEM 3: Legal Proceedings.

SPD500

Global rights to SPD500 (Tissue Protective Cytokine Technology) were in-licensed from Warren Pharmaceuticals, Inc. (Warren) in September 2006. SPD500 is being developed pre-clinically in non-nervous systems indications, including renal and genetic disease areas.

SPD535

Pre-clinical evaluation has commenced for development of a novel platelet lowering agent.

SEASONIQUE

Shire has been granted a license to Duramed's oral contraceptive, SEASONIQUE (levonorgestrel/ethinyl estradiol tablets 0.15 mg/0.03 mg and ethinyl estradiol tablets 0.01 mg). Duramed recently launched SEASONIQUE in the US. Shire has the rights to market this product in a number of markets outside of North America, including the larger European markets. Shire is currently assessing Duramed's FDA registration package relating to SEASONIQUE for suitability for regulatory filing in the EU.

Women's Health Products

Shire and Duramed have entered into an agreement under which Shire has the rights to develop a number of products using Duramed's transvaginal ring technology and other oral products. Shire has the rights to market these products in a number of markets outside of North America, including the larger European markets. The transvaginal ring technology products and other products are in various stages of clinical development.

Manufacturing and distribution

Active pharmaceutical ingredient sourcing

ADDERALL XR: Boehringer-Ingelheim Chemicals, Inc. is currently the sole supplier of amphetamine salts from two separate facilities in Virginia, US.

CARBATROL: Orgamol SA (part of BASF) is currently the sole supplier of carbamazepine from two separate facilities located in Switzerland and in France.

DAYTRANA: Mallinkrodt, Inc. is the current sole supplier of methylphenidate. A second source is in development and should be available in 2007.

PENTASA: Bayer HealthCare AG is currently the sole supplier of mesalamine from a single site in Germany. The Company protects supply by carrying significant inventories.

AGRYLIN/XAGRID: Cambridge Major Laboratories, Inc. is currently the sole supplier of anagrelide from its facility in Wisconsin, US. The Company protects supply by carrying significant inventories.

FOSRENOL: Farchemia S.R.L is the worldwide supplier of lanthanum carbonate for FOSRENOL. A second source is in development.

REMINYL/REMINYL XL: The active pharmaceutical ingredient is solely supplied by Janssen, from its European based facility.

REPLAGAL: The sole source of agalsidase alpha is the Company's protein manufacturing plant in Cambridge, Massachusetts, US. The Company protects its supply by carrying significant inventories.

ELAPRASE: The sole source of idursulfase is the Company's protein manufacturing plant in Cambridge, Massachusetts, US. The Company protects its supply by carrying significant inventories.

Manufacturing

ADDERALL XR: DSM Pharmaceuticals, Inc. (DSM) is the primary manufacturer of ADDERALL XR, with Shire's Owings Mills manufacturing facility (Owings Mills) being the secondary manufacturer.

CARBATROL: Owings Mills is the sole manufacturer of the beads used in the delivery of CARBATROL and the primary manufacturer for encapsulation with DSM being the secondary manufacturer for encapsulation and packaging.

DAYTRANA: Noven is currently the sole finished product supplier of DAYTRANA. A back up site is in early development. The Company protects its supply by carrying significant inventories.

PENTASA: Owings Mills is the primary manufacturer of PENTASA, with Aventis approved as a backup manufacturer.

AGRYLIN/XAGRID: Tyco is the sole supplier of AGRYLIN/XAGRID. The Company protects its supply by carrying significant inventories.

FOSRENOL: DSM provides finished product for the US. Reckitt-Benckiser based in Europe, is currently approved to supply finished product to the US and Owings Mills is in the process of being approved as a finished product manufacturing site for the US. Finished product for Europe and the rest of the world is currently supplied by Reckitt-Benckiser. DSM is also approved to supply Europe and Canada.

REMINYL: Finished product is supplied by Janssen, from its European based facility. It is the sole supplier of the product.

REPLAGAL: Finished drug product is supplied by two contract manufacturers.

ELAPRASE: Finished product is currently single sourced from a contract manufacturer. As the market matures, there are plans to dual source.

Other: The Company's other products marketed in the US and Canada are manufactured and packaged by third party contract manufacturers.

All products marketed by the international sales and marketing operation are either manufactured and supplied by the licensor of the product under supply arrangements or are manufactured for Shire by third parties under contract.

Distribution

The Company's US distribution center, which includes a large vault to house DEA-regulated Schedule II products, is located in Kentucky. From there, the Company distributes its CNS, GI and GP products to all the wholesale distribution centers and the three major warehousing pharmacy chains that stock Schedule II drugs in the US, providing access to nearly all pharmacies in the US.

The distribution and warehousing of certain HGT products are contracted out to specialist third party contractors in the US and Europe. Distribution agreements are in place for other export territories where the Company does not have local operations.

Physical distribution in the UK, Spain, Italy, France, Germany and the Republic of Ireland is contracted out to third parties and distribution agreements are in place for certain other export territories where the Company does not have local operations.

Material customers

The Company's three largest trade customers are Cardinal Health Inc., McKesson Corp., and Amerisource Bergen Corp., all of which are in the US. In 2006, these wholesale customers accounted for approximately 43%, 29%, and 11% of total product sales, respectively.

During 2005, the Company entered into 'fee for service' agreements with two of its three significant wholesale customers. These agreements, which are commonplace in the US pharmaceutical industry, change the way wholesalers are compensated. Under the agreements, the wholesalers receive a distribution fee from pharmaceutical suppliers. These 'fee for service' agreements eliminate wholesalers' incentives to acquire and hold excess inventories. The Company believes this will reduce the significant impact of wholesaler stocking and de-stocking on its product sales. Further, each wholesaler will provide data regarding its inventories of the Company's products that it has on hand. The Company is negotiating a 'fee for service' agreement with its remaining significant wholesale customer. 'Fees for service' are treated as a sales deduction, thus affecting revenues.

Intellectual Property

An important part of the Company's business strategy is to protect its products and technologies through the use of patents and trademarks, to the extent available. The Company also relies on trade secrets, unpatented know-how, technological innovations and contractual arrangements with third parties to maintain and enhance its competitive position where it is unable to obtain patent protection or where marketed products are not covered by specific patents. The Company's commercial success will depend, in part, upon its ability to obtain and enforce strong patents, to maintain trade secret protection, to operate without infringing the proprietary rights of others and to comply with the terms of licenses granted to it. The Company's policy is to seek patent protection for proprietary technology whenever possible in the US, Canada, major European countries and Japan. Where practicable, the Company seeks patent protection in other countries on a selective basis. In all cases the Company endeavors to either obtain patent protection itself or support applications by its licensors.

In the regular course of business, the Company's patents may be challenged by third parties. The Company is a party to litigation or other proceedings relating to intellectual property rights. Details of ongoing litigation are provided in ITEM 3: Legal Proceedings.

The degree of patent protection afforded to pharmaceutical inventions around the world is uncertain. If patents are granted to other parties that contain claims having a scope that is interpreted by the relevant authorities to cover any of the Company's products or technologies, there can be no guarantee that the Company will be able to obtain licenses to such patents or make other arrangements at reasonable cost, if at all.

The existence, scope and duration of patent protection varies among the Company's products and among the different countries where the Company's products may be sold. It may also change over the course of time as patents grant or expire, or become extended, modified or revoked. The following non-exhaustive list sets forth details of the granted US and EU patents pertaining to the Company's key currently marketed products, material products from which the Company receives a royalty and major products under development, or technology relating to those products, which are owned by or licensed to the Company and that are material to an understanding of the Company's business taken as a whole. The Company also holds patents in other jurisdictions, such as Canada and Japan and has patent applications pending in such jurisdictions, as well as in the US and the EU.

	Granted US and EP Patents	Expiration Date
ADDERALL XR	US 6,322,819	October 21, 2018
	US 6,605,300	October 21, 2018
	US 6,913,768	January 29, 2023
CARBATROL	US 5,326,570	July 23, 2011
	US 5,912,013	June 15, 2016
	EP 0660705	July 23, 2012
DAYTRANA	US 6,210,705	September 30, 2018

	US 6,348,211	September 30, 2018
	EP 591432	June 22, 2012
	EP 1037615	December 14, 2018
DYNEPO	US 5,641,670	June 24, 2014
	US 5,733,761	March 31, 2015
	US 6,270,989	March 31, 2015
	US 6,565,844	November 5, 2011
	EP 0750044	November 5, 2012
ELAPRASE	US 5,728,381	March 17, 2015
	US 5,798,239	August 25, 2015
	US 5,932,211	August 3, 2016
	US 6,153,188	November 12, 2011
	US 6,541,254	November 12, 2011
FOSRENOL	US 5,968,976	October 26, 2018
	US 7,078,059	July 5, 2021
	EP 0817639	March 19, 2016
GA-GCB	US 5,641,670	June 24, 2014
	US 5,733,761	March 31, 2015
	US 6,270,989	March 31, 2015
	US 6,565,844	November 5, 2011
	US 6,566,099	September 12, 2017
	US 7,138,262	August 18, 2020
	EP 0750044	November 5, 2012
GUANFACINE (SPD503)	US 4,847,300	November 7, 2006
	US 5,854,290	September 21, 2015
	US 6,287,599	December 20, 2020
	US 6,811,794	December 20, 2021

LAMIVUDINE: EPIVIR/EPIVIR-ZEFFIX/3TC	US 5,047,407	May 17, 2010
	US 5,693,787	December 2, 2014
	US 5,663,320	September 2, 2014
	US 5,696,254	December 9, 2014
	US 6,180,639	July 30, 2018
	US 5,532,246	January 2, 2014
	US 7,119,202	February 8, 2009
	EP 382 526	February 8, 2010
	EP 565 549	January 3, 2012
	EP 515 157	May 20, 2012
COMBIVIR	US 5,047,407	May 17, 2010
	US 5,693,787	December 2, 2014
	US 5,663,320	September 2, 2014
	US 5,696,254	December 9, 2014
	US 6,180,639	July 30, 2018
	US 7,119,202	February 8, 2009
	EP 382 526	February 8, 2010
	EP 565 549	January 3, 2012
	EP 515 157	May 20, 2012
TRIZIVIR	US 5,047,407	May 17, 2010
	US 5,693,787	December 2, 2014
	US 5,663,320	September 2, 2014
	US 5,696,254	December 9, 2014
	US 6,180,639	July 30, 2018
	US 7,119,202	February 8, 2009
	EP 382 526	February 8, 2010
	EP 565 549	January 3, 2012

	EP 515 157	May 20, 2012
EPZICOM	US 5,047,407	May 17, 2010
	US 5,693,787	December 2, 2014
	US 5,663,320	September 2, 2014
	US 5,696,254	December 9, 2014
	US 6,180,639	July 30, 2018
	US 7,119,202	February 8, 2009
	EP 382 526	February 8, 2010
	EP 565 549	January 3, 2012
	EP 515 157	May 20, 2012
LIALDA	US 6,773,720	June 8, 2020
(SPD476)	EP 1198226	June 8, 2020
	EP 1183014	June 9, 2020

REMINYL & REMINYL XL	US 4,663,318	December 14, 2008
	US 6,099,683	June 6, 2017
	US 6,358,527	June 6, 2017
	EP 236684	January 15, 2007
	EP 915701	June 6, 2017
	EP1140105	December 20, 2019
REPLAGAL	US 5,641,670	June 24, 2014
	US 5,733,761	March 31, 2015
	US 6,270,989	March 31, 2015
	US 6,565,844	November 5, 2011
	US 6,083,725	September 12, 2017
	US 6,395,884	September 12, 2017
	US 6,458,574	September 12, 2017
	EP 0750044	November 5, 2012
SPD465	US 6,322,818	October 21, 2018
	US 6,605,300	October 21, 2018
VYVANSE (NRP104)	US 7,105,486	June 29, 2023

Note:

- The EP patents listed above do not necessarily have a corresponding national patent registered in each EU member state. In some cases, national patents were obtained in only a limited number of EU member states. The rights granted to an EP patent are enforceable in any EU member state where the EP patent has been registered as a national patent.

- The EP patents listed above do not reflect term extensions afforded by supplementary protection certificates (SPC's) which are available in many EU member states.

The loss of patent protection following a legal challenge may result in third parties commencing commercial sales of their own versions of the Company's products before the expiry of the patents. The Company's sales of such product(s) may decrease in consequence. In many cases, however, the Company's products have more than one patent pertaining to them. In such cases, or where the Company enjoys trade secrets, manufacturing expertise, patient preference or regulatory exclusivity, the Company may continue to market its own products without its commercial sales of those products being adversely affected by the loss of any given patent.

Competition

Shire believes that competition in its markets is based on, among other things, product safety, efficacy, convenience of dosing, reliability, availability and price. Companies with more resources and larger R&D expenditures than Shire have a greater ability to fund the research and clinical trials necessary for regulatory applications, and consequently may have a better chance of obtaining approval of drugs that would then compete with Shire's products. Other products now in use or being developed by others may be more effective or have fewer side effects than the Company's current or future products. The market share data provided below is sourced from IMS.

ADHD market

Competition in the US ADHD market has continued to increase as several products that do or will compete with the Company's products have been launched in recent years. Among the new entrants to the market in 2006 was DAYTRANA, the Company's methylphenidate product.

Many of these products contain methylphenidate. In 2000, Johnson & Johnson (in conjunction with ALZA) launched CONCERTA, a once-daily formulation of methylphenidate. At December 31, 2006, CONCERTA had a 22.2% share of the US ADHD market. In 2001, UCB Pharma launched METADATE CD, a once-daily formulation of methylphenidate. At December 31, 2006, METADATE CD had a 3.1% share of the US ADHD market. In 2002, Novartis (in conjunction with Elan) launched RITALIN LA, an extended release formulation of methylphenidate, and in 2005 Novartis launched FOCALIN XR in conjunction with Celgene Corporation, a long-acting formulation of dexmethylphenidate, the active ingredient of traditional methylphenidate preparations. At December 31, 2006 RITALIN LA and FOCALIN XR had a 2.8% and 5.2% share, respectively, of the US ADHD market.

In 2002, Barr launched a generic version of ADDERALL. Subsequently, five additional generic companies have launched generic versions. Total ADDERALL generic prescriptions accounted for about 12.2% of the market as at December 31, 2006. In September 2006, Duramed (a subsidiary of Barr) purchased the product rights to the Company's ADDERALL product for $63 million. For further information see ITEM 7: Management's Discussion and Analysis.

In 2003, Eli Lilly launched STRATTERA, a non-stimulant, non-scheduled treatment for ADHD. At December 31, 2006, STRATTERA had a 10.7% share of the US ADHD market . The Company's non-stimulant product, SPD503 is in registration in the US.

The Company is also aware of clinical development efforts by GSK, Gliatech Inc., Cortex Pharmaceuticals Inc., Boehringer-Ingelheim, Eisai Inc., Bristol-Myers Squibb (in collaboration with Elan) and Abbott to develop additional indications and new non-stimulant treatment options for ADHD.

Generic and other possible competition to the Company's ADHD franchise is separately discussed in "Intellectual Property" above.

Market for the treatment of rare genetic diseases

The Company believes that in general rare genetic diseases have markets that are too small to attract the resources of most larger pharmaceutical and biotechnology companies. As a result, the Company believes that the primary competition with respect to its products for rare genetic diseases is from smaller pharmaceutical and biotechnology companies. Competitors for lysosomal storage disorders include BioMarin Pharmaceutical Inc., Actelion Ltd., and Genzyme. Specifically, REPLAGAL competes with Genzyme's FABRAZYME, and, if approved, GA-GCB would compete with Genzyme's CEREZYME. Shire does not know of any party developing an enzyme replacement therapy for the treatment of Hunter syndrome.

The markets for some of the potential products for rare genetic diseases caused by protein deficiencies are quite small. As a result, if competitive products exist, the Company may not be able to successfully commercialize its products. Some jurisdictions, including EU and the United States, may designate drugs for relatively small patient populations as "orphan drugs". Generally, if a product that has an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to orphan drug exclusivity. Orphan drug exclusivity means that applications to market the same drug for the same indication may not be approved, except in limited circumstances, for a period of up to 10 years in the EU and for a period of seven years in the United States.

Both REPLAGAL and FABRAZYME were granted co-exclusive orphan drug status in the EU for up to 10 years. Genzyme has orphan drug exclusivity for FABRAZYME in the United States until April 2010. ELAPRASE has orphan drug designation in the United States and the EU.

HIV Market

The HIV competitive landscape is becoming more crowded and complicated as treatment trends evolve.

3TC/EPIVIR

In the Nucleoside/Nucleotide Reverse Transcriptase Inhibitor (NRTI) market of which 3TC/EPIVIR is a part, there are a number of anti-HIV drugs which are currently sold.

Of the branded drugs available, TRUVADA (tenofovir/emtricitabine), VIREAD (tenofovir) and EMTRIVA (emtricitabine) all sold by Gilead Sciences Inc. (Gilead), ZIAGEN (abacavir) and RETROVIR (zidovudine) each sold by GSK, ZERIT (stavudine, d4T) and VIDEX (didanosine) sold by Bristol-Myers Squibb (BMS) and HIVID (zalcitabine) sold by Roche represent the most direct competition.

TRIZIVIR/COMBIVIR/EPZICOM

In the Combined NRTI market of which TRIZIVIR, COMBIVIR and EPZICOM are a part, there is one major competitor - TRUVADA sold by Gilead.

Other HIV competition

In addition to the two NRTI HIV markets in which Shire operates, there is competition from:

- *Non-Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NNRTIs)* . Of the branded NNRTIs available, SUSTIVA (efavirenz) sold by BMS and VIRAMUNE (nevirapine) sold by Boehringer-Ingelheim represent the most significant competition.

- *Protease Inhibitors (PIs)* . Of the branded PIs available, AGENERASE (amprenavir) sold by GSK, REYATAZ (atazanavir) sold by BMS, CRIXIVAN (indinavir sulfate) sold by Merck, KALETRA (lopinavir/ritanaovir) and NORVIR (ritonovir) sold by Abbott, VIRACEPT (nelfinavir) sold by Pfizer, FORTOVASE (saquinavir) sold by Roche and APTIVUS (Tipranavir) sold by Boehringer-Ingelheim represent the most significant competition.

- *Fusion or entry inhibitors* . Of the branded drugs available, FUZEON (enfuvirtide), an injectable integrase inhibitor sold by Roche/Trimeris, represents the most significant competition.

Generic HIV competitors

BMS's VIDEX EC (didanosine) became the first generic HIV product in the United States in 2004. GSK's RETROVIR (AZT) came off patent in the US in September 2005 and in Europe in March 2006. Although in September 2005 several generic formulations of zidovudine were approved by the FDA, these generic competitors have yet to fully ramp-up production and distribution. As a result, the full effect of this on the overall market for HIV products is unknown, but price decreases for all HIV products may result.

Government regulation

The clinical development, manufacturing and marketing of Shire's products are subject to governmental regulation in the US, the EU and other territories. The Federal Food, Drug, and Cosmetic Act, the Prescription Drug Marketing Act and the Public Health Service Act in the US, and numerous directives and guidelines in the EU, govern the testing, manufacture, safety, efficacy, labeling, storage, record keeping, approval, advertising and promotion of the Company's products. Product development and approval within these regulatory frameworks take a number of years and involves the expenditure of substantial resources.

Regulatory approval is required in all markets in which Shire, or its licensees, seek to test or market products. At a minimum, such approval requires the evaluation of data relating to the quality, safety and efficacy of a product for its proposed use. The specific types of data required and the regulations relating to this data will differ depending on the territory, the drug involved, the proposed indication and the stage of development.

In general, for a new chemical entity, the product needs to undergo rigorous preclinical testing. Clinical trials for new products are

typically conducted in three sequential phases that may overlap. In Phase 1, the initial introduction of the pharmaceutical compound into healthy human volunteers, the emphasis is on testing for safety (adverse effects), dosage tolerance, metabolism, distribution, excretion and clinical pharmacology. Phase 2 involves studies in a limited patient population to determine the initial efficacy of the pharmaceutical compound for specific targeted indications, to determine dosage tolerance and optimal dosage and to identify possible adverse side effects and safety risks. Once a compound is found to be effective and to have an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to evaluate more fully clinical outcomes.

It is the Company's responsibility to ensure that it conducts its business in accordance with the regulations of each relevant territory.

Information generated in this process is susceptible to varying interpretations that could delay, limit or prevent regulatory approval at any stage of the approval process. The failure to demonstrate adequately the quality, safety and efficacy of a therapeutic drug under development could delay or prevent regulatory approval of the product . There can be no assurance that, if clinical trials are completed, either the Company or its collaborative partners will submit applications for required authorizations to manufacture and/or market potential products (including a marketing authorization application or NDA) or that any such application will be reviewed and approved by the appropriate regulatory authorities in a timely manner, if at all.

In order to gain marketing approval the Company must submit a dossier to the relevant regulatory authority for review. The format is usually specific and laid out by each authority, although in general it will include information on the quality (chemistry, manufacturing and pharmaceutical) aspects of the product as well as the non-clinical and clinical data. The FDA undertakes the review for the US; in the EU the review may be undertaken by members of the Committee for Medicinal Products for Human Use (CHMP) on behalf of the EMEA as part of a centralized procedure or by an individual country's agency, followed by "mutual recognition" of this review by a number of other countries' agencies, depending on the process applicable to the drug in question. Under medicines legislation a third option in now available with the introduction of the decentralized procedure enacted in November 2005. The new procedure provides an alternative authorization procedure to the "mutual recognition" procedure for those drugs that are ineligible for a "centralized" review.

Approval can take from several months to several years, or be denied. The approval process can be affected by a number of factors - for example additional studies or clinical trials may be requested during the review and may delay marketing approval and involve unbudgeted costs. The agency may conduct an inspection of relevant facilities or review manufacturing procedures, operating systems and personnel qualifications. In addition to obtaining approval for each product, in many cases each drug manufacturing facility must be approved. Further inspections may occur over the life of the product. An inspection of the clinical investigation sites by a competent authority may be required as part of the regulatory approval procedure. As a condition of approval, the regulatory agency may require post-marketing surveillance to monitor for adverse effects, or other additional studies as deemed appropriate. After approval for the initial indication, further clinical studies are usually necessary to gain approval for any additional indications. The terms of any approval, including labeling content, may be more restrictive than expected and could affect the marketability of a product.

In the US, the Drug Price Competition and Patent Restoration Term Act of 1984, known as the US Hatch-Waxman Act, established a period of marketing exclusivity for brand name drugs as well as abbreviated application procedures for generic versions of those drugs. Approval to manufacture these drugs is obtained by filing an ANDA. As a substitute for conducting full-scale pre-clinical and clinical studies, the FDA will accept data establishing that the drug formulation, which is the subject of an abbreviated application, is bio-equivalent and has the same therapeutic effect as the previously approved drug, among other requirements. European guidelines also allow for the submission of abridged applications using bioeqivalence criteria.

For both currently marketed and future products, failure to comply with applicable regulatory requirements after obtaining regulatory approval can, among other things, result in the suspension of regulatory approval, as well as possible civil and criminal sanctions. Periodic marketing authorization renewals in Europe may require additional data, which, if unfavorable, may result in an authorization being withdrawn. In the US, the FDA has the authority to revoke or suspend approvals of previously approved products, to prevent companies and individuals from participating in the drug-approval process, to request recalls, to seize violative products, to obtain injunctions to close manufacturing plants not operating in conformity with regulatory requirements and to stop shipments of violative products. The branch of the FDA responsible for drug marketing oversight routinely reviews company marketing practices and also may impose pre-clearance requirements on materials intended for use in marketing of approved products. Changes in government regulation could have a material adverse effect on the Company's financial condition and results of operation.

In recent years, in the US, various legislative proposals at the federal and state levels could bring about major changes in the affected health care systems. Some states have passed such legislation, and further federal and state proposals are possible. Such proposals and legislation include, and future proposals could include, price controls or patient access constraints on medicines and increases in required rebates or discounts. Similar issues exist in the EU. The Company cannot predict the outcome of such initiatives, but will work to maintain patient access to its products and to oppose price constraints. Additionally, legislation is being debated at the federal level in the US that could allow patient access to drugs approved in other countries - most notably Canada. This is generally referred to as drug re-importation. Although there is substantial opposition to this potential legislation within areas of the federal government, including the FDA, the Company cannot predict the outcome of such legislative activities pertaining to drug re-importation.

In the US, federal legislation has created substantial changes in the Medicare program, including the December 2003 enactment of the Medicare Prescription Drug Improvement and Modernization Act. Beginning in 2006, Medicare beneficiaries were able to purchase prescription drug coverage from a private sector provider. It is difficult to predict the long-term impact of this legislation on pharmaceutical companies. Usage of pharmaceutical products may increase as the result of expanded access to medications afforded by partial reimbursement under Medicare. However, such potential sales increases may be offset by increased pricing pressures due to enhanced purchasing power of the private sector that will negotiate on behalf of Medicare beneficiaries.

Additionally, federal and state proposals have called for substantial changes in the Medicaid program. US law requires the Company to give rebates to state Medicaid agencies based on each state's reimbursement of pharmaceutical products under the Medicaid program. Rebates potentially could be viewed as price discounts without appreciable increases in Shire's product sales volume as an offset. The Company must also give discounts or rebates on purchases or reimbursements of pharmaceutical products by certain other federal and state agencies and programs.

Similar regulatory and legislative issues are encountered in Europe and other international markets where governments regulate pharmaceutical prices and patient reimbursement levels. The differing approach to price regulation has led to some parallel trade within the EU where Shire's products are imported into markets with higher prices from markets with lower prices. Exploitation of price differences between countries in this way can impact sales in those markets with higher prices.

The US DEA also controls the national production and distribution in the US of Scheduled drugs (i.e. those drugs containing controlled substances) by allocating production quotas based, in part, upon the DEA's view of national demand. As Schedule II drugs, the production and sale of Shire's ADHD products are strictly controlled.

EU legislation also contains data exclusivity provisions. All products will be subject to an "8+2+1" exclusivity regime. A generic company may file a marketing authorization application for that product with the health authorities eight years after the innovator has received its first community authorization for a medicinal product. The generic company may not commercialize the product until after either ten (8+2) or eleven years (8+2+1) have elapsed from the date of grant of the initial marketing authorization. The one-year extension is available if the innovator obtains an additional indication during the first eight years of the marketing authorization that is of significant advancement in clinical benefit.

Third party reimbursement

The Company's revenue depends, in part, upon the price third parties, such as health care providers and governmental organizations are willing to reimburse patients and physicians for the cost of the Company's, or the

Company's competitors', similar products and related treatment. These third party payers are increasingly challenging the pricing of pharmaceutical products and/or seeking pharmaco-economic data to justify their negotiated reimbursement prices. In the US, several factors outside Shire's control could significantly influence the sale prices of pharmaceutical products, including: Medicare Part D prescription drug plans; new Medicare Part B reimbursement rules; the increase in states seeking supplemental Medicaid rebates; the ongoing trend toward managed healthcare; and the renewed focus on reducing costs and reimbursement rates in Medicaid, Medicare and other government insurance programs. For example, revisions or clarification from the Centers for Medicare and Medicaid Services (CMS) related to Medicaid and other government reimbursement programs may have retroactive application which may result in changes to management's estimated rebate liability reported in a prior period. At the time of sale, revenues from the Company's products are reasonably estimable with the aid of historical trend analysis and consideration of any current period changes in pricing practices. The rebates can be reasonably determinable at the time of sale to the initial customers.

These factors would not impact our revenue recognition policy under generally accepted accounting principles.

The Medicare Prescription Drug Improvement and Modernization Act of 2003 established a voluntary drug benefit for Medicare beneficiaries and created the new Medicare Part D and Medicare Part B. Medicare Part D gives elderly and disabled people, already on Medicare, access to prescription drug coverage from January 2006 onwards. Medicare Part B establishes new rules to lower Medicare's reimbursement rate for physician administered drugs. Shire has not seen a material financial impact from the Medicare Part D or Medicare Part B coverage to date. However, since the programs are new, the impact and rules could change as a result of further government rule-making or competitive practices. Shire cannot predict the impact of those policies but Shire's drugs, with the exception of Fosrenol, are generally not prevalently used by the elderly who qualify for Medicare.

Similar developments may take place in the EU markets, where the emphasis will likely be on price controls and non-reimbursement for new and highly priced medicines for which the economic as well as the therapeutic rationales are not established. Significant uncertainty exists about the reimbursement status of newly approved pharmaceutical products in the EU. There can be no assurance that reimbursement will be available for any of Shire's future product launches or that reimbursement won't change for currently commercialized products. Limits on reimbursement available from third party payers may reduce the demand for the Company's products. Price applications in Europe have delayed product launches in some countries for up to two years and, as a consequence, dates for product launches and associated recognition of revenue cannot be predicted with accuracy.

Corporate Responsibility (CR)

The Company continues to develop its approach to CR; the Shire CR Committee guides the overall direction and sets and monitors objectives. Members of the Committee include representatives from R&D, HR, Environment Health & Safety, Compliance, Risk Management, Facilties, Marketing, Community Relations and Communications. The Chairman of the Committee is Shire's Chief Financial Officer, Angus Russell. The Committee meets at least three times a year to discuss and monitor progress. An annual CR report is published in hard copy and is also available on the Company's website in June.

Employees

In the pharmaceutical industry, the Company's employees are vital to its success. The Company believes that it has a good relationship with its employees. As at December 31, 2006 the Company had 2,868 employees.

Available information

The Company maintains a website on the World Wide Web at www.shire.com. The company makes available on its website its annual report on Form 10-K, quarterly reports on Form 10-Q, Current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as soon as reasonably practicable after such reports are electronically filed with, or furnished to, the SEC. Shire's reports filed with, or furnished to, the SEC are also available on the SEC's website at www.sec.gov. The information on the Company's website is neither part of nor incorporated by reference in this Annual Report on Form 10-K.

ITEM 1A: Risk Factors

The Company has adopted a risk management strategy that enables it to identify, assess and manage the significant risks that it faces. While the Company aims to identify and manage such risks, no risk management strategy can provide absolute assurance against loss.

Set out below are the key risk factors, associated with the business, that have been identified through the Company's approach to risk management. These risk factors apply equally to the Company and, therefore, they should all be carefully considered before any investment is made in Shire.

Any decrease in the sales of ADDERALL XR will significantly reduce revenues and earnings

In 2006, sales of ADDERALL XR were $863.6 million, representing approximately 48% of the Company's revenues. Any factors that decrease sales of ADDERALL XR could significantly reduce revenue and earnings and have a material adverse effect on the Company's financial condition and results of operations. These include:

- issues impacting the production of ADDERALL XR or the supply of amphetamine salts;
- development and marketing of competitive pharmaceuticals, including generic versions;
- technological advances (including the approval of new competing products for ADHD treatments);
- loss of patent protection or ability of competitors to challenge or circumvent the Company's patents (See ITEM 3 of this Form 10-K for details of current patent litigation);
- changes in reimbursement policies of third-party payers;
- government action/intervention;
- marketing or pricing actions by competitors;
- public opinion towards ADHD treatments;
- any change in the label or other such regulatory intervention;
- product liability claims; or
- changes in prescription-writing practices.

Any decrease in the sales of 3TC could significantly reduce revenues and earnings

The Company receives royalties from GlaxoSmithKline plc (GSK) on the worldwide sales of 3TC. In 2006, the Company's royalty income relating to 3TC sales was $150.9 million, representing approximately 8% of total revenues. This income stream generates a larger proportion of net income relative to the Company's own product sales as there are minimal costs associated with this income.

Any factors that decrease sales of 3TC by GSK could significantly reduce the Company's revenues and earnings. These include:

- reduction in production of 3TC;
- development and marketing of competitive pharmaceuticals;
- technological advances;
- loss of patent protection or ability of competitors to challenge or circumvent patents;
- government action/intervention;
- marketing or pricing actions by GSK's competitors;
- any change in the label or other such regulatory intervention;
- public opinion towards AIDS treatments; or

- product liability claims.

VYVANSE and the Company's other new products may not be a commercial success.

The commercial success of the Company's new products will depend on their approval and acceptance by physicians, patients and other key decision-makers, as well as the timing of the receipt of marketing approvals, the scope of marketing approval as reflected in the product's label, the countries in which such approvals are obtained,

the authorization of price and reimbursement in those countries where price and reimbursement is negotiated, and safety, efficacy, convenience and cost-effectiveness of the product as compared to competitive products.

In particular, the Company may not be able to transition patients successfully from ADDERALL XR to VYVANSE, especially if any or all of the following occur:

- if physicians who are comfortable with an existing product are unwilling to prescribe a new product in its place;
- if patients who are comfortable with an existing product do not wish to take a new product in its place;
- if parents or caregivers who are comfortable with an existing product do not want their children to take a new product in its place;
- if third-party payors are unwilling to pay for a new product;
- if the sales and marketing efforts behind VYVANSE are not effective in positioning VYVANSE and differentiating it from ADDERALL XR;
- if the FDA approved label for VYVANSE is not seen as significantly differentiating VYVANSE from currently marketed treatments for ADHD; or
- if competitive products are genericised and the impact on the market negatively affects the prescribing of branded treatments for ADHD.

Further, if VYVANSE is not a commercial success, Shire will not experience the anticipated economic benefits from VYVANSE or from Shire's proposed acquisition of New River.

If the Company is unable to commercialize VYVANSE or any other new product successfully, there may be an adverse effect on the Company's revenues, financial condition and results of operations.

The introduction of new products by competitors may impact future revenues

The manufacture and sale of pharmaceuticals is highly competitive. Many of the Company's competitors are large, well-known pharmaceutical, biotechnology, chemical and healthcare companies with considerable resources. Companies with more resources and larger R&D expenditures have a greater ability to fund clinical trials and other development work necessary for regulatory applications. They may also be more successful than the Company in acquiring or licensing new products for development and commercialisation. Further, they may also have an improved likelihood of obtaining approval of drugs that may compete with those marketed or under development by the Company. If any product that competes with one of the Company's principal drugs is approved, the Company's sales of that drug could fall.

The pharmaceutical and biotechnology industries are also characterised by continuous product development and technological change. The Company's products could, therefore, be rendered obsolete or uneconomic, through the development of new products,

technological advances in manufacturing or production by its competitors.

The failure to obtain and maintain reimbursement, or an adequate level of reimbursement, by third-party payers in a timely manner for certain of the Company's products may impact future revenues

The prices for certain of the Company's products when commercialised, including, in particular, products for the treatment of rare genetic diseases, may be high compared to other pharmaceutical products. The Company may encounter particular difficulty in obtaining satisfactory pricing and reimbursement for its products, including those that are likely to have a high annual cost of therapy. The failure to obtain and maintain pricing and reimbursement at satisfactory levels for such products may adversely affect revenues.

A disruption to the product supply chain may result in the Company being unable to continue marketing or developing a product or may result in the Company being unable to do so on a commercially viable basis

The Company has its own manufacturing capability for certain products and has also entered into supply agreements with third party contract manufacturers. In the event of either the Company's failure or the failure of any third party contract manufacturer to comply with mandatory manufacturing standards (often referred to as 'Current Good Manufacturing Standards' or cGMP) in the countries in which the Company intends to sell or have its products sold, the Company may experience a delay in supply or be unable to market or develop its products.

The Company dual-sources certain key products and/or active ingredients. However, there is currently reliance on a single source for production of the final drug product for each of CARBATROL, AGRYLIN, XAGRID, REMINYL, DYNEPO, DAYTRANA and ELAPRASE and reliance on a single active ingredient source for each of PENTASA, REPLAGAL, FOSRENOL, AGRYLIN, XAGRID, DAYTRANA, DYNEPO, ELAPRASE and REMINYL.

In the event of financial failure of a third party contract manufacturer, the Company may experience a delay in supply or be unable to market or develop its products. This could have a material adverse affect on the Company's financial condition and results of operations.

There is no assurance that suppliers will continue to supply on commercially viable terms, or be able to supply components that meet regulatory requirements. The Company is also subject to the risk that suppliers will not be able to meet the quantities needed to meet market requirements

The Company has its own warehousing and distribution capability for certain products and has entered into distribution agreements with third party distributors for certain services. The failure of either the Company's or a third party's service could result in the Company being unable to continue to distribute its products.

The development and approval of the Company's products depends on the ability to procure active ingredients and special packaging materials from sources approved by regulatory authorities. As the marketing approval process requires manufacturers to specify their own proposed suppliers of active ingredients and special packaging materials in their applications, regulatory approval of a new supplier would be required if active ingredients or such packaging materials were no longer available from the supplier specified in the marketing approval. The need to qualify a new supplier could delay the Company's development and commercialisation efforts.

The Company uses bovine-derived serum sourced from New Zealand and North America in some of its manufacturing processes. The discovery of additional cattle in North America or the discovery of cattle in New Zealand with bovine spongiform encephalopathy, or mad cow disease, could cause the regulatory agencies in some countries to impose restrictions on certain of the Company's products, or prohibit the Company from using its products at all in such countries.

Fluctuations in wholesale buying patterns may influence net sales and growth comparisons

A significant portion of the Company's product sales are made to major pharmaceutical wholesale distributors as well as to large pharmacies in both the United States and Europe. Consequently, product sales and growth comparisons may be affected by fluctuations in the buying patterns of major distributors and other trade buyers. These fluctuations may result from seasonality,

pricing, wholesaler buying decisions, or other factors.

In the event of financial failure of certain customers, the Company may suffer financial loss and a decline in revenues

For the fiscal year to December 31, 2006, the three largest trade customers, McKesson Corp., Cardinal Health Inc., and Amerisource Bergen Corp., accounted for approximately 43%, 29%, and 11% of the Company's product sales, respectively. The financial failure of any one of these customers could have a material adverse effect on the Company's financial condition and results of operations.

The actions of certain customers can affect the Company's ability to sell or market products profitably

A small number of large wholesale distributors control a significant share of the United States and European markets. In 2006, for example, approximately 83% of the Company's product sales were attributable to three customers. In addition, the number of independent drug stores and small chains has decreased as retail pharmacy consolidation has occurred. Consolidation or financial difficulties could cause customers to reduce their inventory levels, or otherwise reduce purchases of the Company's products. Such actions could have an adverse effect on the Company's revenues, financial condition and results of operations.

A significant portion of the Company's revenues for certain products for treatment of rare genetic diseases are concentrated with a small number of customers. Changes in the buying patterns of those customers may have an adverse effect on the Company's financial condition and results of operations.

The actions of governments, industry regulators and the economic environments in which the Company operates may adversely affect its ability to develop and market its products profitably

Changes to laws or regulations impacting the pharmaceutical industry, which are made in any country in which the Company conducts its business, may adversely impact the Company's sales, financial condition and results of operations. In particular, changes to the regulations relating to orphan drug status may affect the exclusivity granted to products with such designation. Changes in the general economic conditions in any of the Company's major markets may also affect the Company's sales, financial condition and results of operations.

The Company's revenues are partly dependent on the level of reimbursement provided to the Company by governmental reimbursement schemes for pharmaceutical products. Changes to governmental policy or practices could adversely affect the Company's sales, financial condition and results of operations. In addition, the cost of treatment established by health care providers, private health insurers and other organisations, such as health maintenance organisations and managed care organisations are under downward pressure and this, in turn, could impact on the prices at which the Company can sell its products.

The market for pharmaceutical products could be significantly influenced by the following, which could result in lower prices for the Company's products and/or a reduced demand for the Company's products:

- the ongoing trend toward managed health care, particularly in the United States;

- legislative proposals to reform health care and government insurance programs in many of the Company's markets; or
- price controls and non-reimbursement of new and highly priced medicines for which the economic and therapeutic rationales are not established.

Parallel importation occurs when an importer finds a cheaper price for a product or equivalent product on the world market and imports that product from the lower price jurisdiction to the higher price jurisdiction. If the parallel importation of lower priced drugs is permitted in the United States, it could have the effect of reducing sales of equivalent drugs in the United States. To the extent that parallel importation increases, the Company may receive less revenue from its commercialised products.

The parallel importation of prescription drugs is relatively common within the EU.

If the Company's projects or clinical trials for the development of products are unsuccessful, its products will not receive authorisation for manufacture and sale

Due to the complexity of the formulation and development of pharmaceuticals, the Company cannot be certain that it will successfully complete the development of new products, or, if successful, that such products will be commercially viable.

Before obtaining regulatory approvals for the commercial sale of each product under development, the Company must demonstrate through clinical and other studies that the product is of appropriate quality and is safe and effective for the claimed use. Clinical trials of any product under development may not demonstrate the quality, safety and efficacy required to result in an approvable or a marketable product. Failure to demonstrate adequately the quality, safety and efficacy of a therapeutic drug under development would delay or prevent regulatory approval of the product. In addition, regulatory authorities in Europe, the United States, Canada and other countries may require additional studies, which could result in (a) increased costs and significant development delays, or (b) termination of a project if it would no longer be economically viable. The completion rate of clinical trials is dependent upon, among other factors, obtaining adequate clinical supplies and recruiting patients. Delays in patient enrolment in clinical trials may also result in increased costs and program delays. Additional delays can occur in instances in which the Company shares control over the planning and execution of product development with collaborative partners. The Company cannot be certain that, if clinical trials are completed, either the Company or its collaborative partners will file for, or receive, required authorisations to manufacture and/or market potential products in a timely manner.

If the Company is unable to meet the requirements of regulators in relation to a particular product, it may be unable to develop the product or obtain or retain the necessary marketing approvals

Drug companies are required to obtain regulatory approval before manufacturing and marketing most drug products. Regulatory approval is generally based on the results of:

- quality testing (chemistry, manufacturing and controls);
- non-clinical testing; and
- clinical testing.

The clinical development, manufacture, marketing and sale of pharmaceutical products is subject to extensive regulation, including separate regulation by each member state of the EU, the EMEA itself and federal, state and local regulation in the United States. Unanticipated legislative and other regulatory actions and developments concerning various aspects of the Company's operations and products may restrict its ability to sell one or more of its products or to sell those products at a profit. The generation of data is regulated and any generated data is susceptible to varying interpretations that could delay, limit or prevent regulatory approval. Required regulatory approvals may not be obtained in a timely manner, if at all. In addition, other regulatory requirements for any such proposed products may not be met.

Even if the Company obtains regulatory approvals, the terms of any product approval, including labelling, may be more restrictive than desired and could affect the marketability of its products. Regulatory authorities have the power amongst other things, to:

- revoke or suspend approvals of previously approved products;
- require the recall of products that fail to meet regulatory requirements; and
- close manufacturing plants that do not operate in conformity with cGMP and/or other regulatory requirements or approvals.

Such delays or actions could affect the Company's ability to manufacture and sell its products.

The failure of a strategic partner to develop and commercialise products could result in delays in approval or loss of

revenue

The Company enters into strategic partnerships with other companies in areas such as product development and sales and marketing. In these partnerships, the Company is dependent on its partner to deliver results. While these partnerships are supported by contracts, the Company does not exercise direct control. If a partner fails to perform or experiences financial difficulties, the Company may suffer a delay in the development, a delay in the approval or a reduction in sales or royalties of a product.

The failure to secure new products or compounds for development, either through in-licensing, acquisition or internal research and development efforts, may have an adverse impact on the Company's future results

The Company's future results will depend, to a significant extent, upon its ability to in-license, acquire or develop new products or compounds. The failure to in-license or acquire new products or compounds, on a commercially viable basis, could have a material adverse effect on the Company's financial position. The Company also expends significant resources on research and development. The failure of these efforts to result in the development of products appropriate for testing in human clinical trials could have a material adverse effect on the Company's revenues, financial condition and results of operations.

The Company may fail to obtain, maintain, enforce or defend the intellectual property rights required to conduct its business

The Company's success depends upon its ability and the ability of its partners and licensors to protect their intellectual property rights. Where possible, the Company's strategy is to register intellectual property rights, such as patents and trademarks. The Company also relies variously on trade secrets, unpatented know-how and technological innovations and contractual arrangements with third parties to maintain its competitive position.

Patents and patent applications covering a number of the technologies and processes owned or licensed to the Company have been granted, or are pending in various countries, including the United States, Canada, major European countries and Japan. The Company intends to enforce vigorously its patent rights and believes that its partners intend to enforce vigorously patent rights they have licensed to the Company. However, patent rights may not prevent other entities from developing, using or commercialising products that are similar or functionally equivalent to the Company's products or technologies or processes for formulating or manufacturing similar or functionally equivalent products. The Company's patent rights may be successfully challenged in the future or laws providing such rights may be changed or withdrawn. The Company cannot assure investors that its patents and patent applications or those of its third party manufacturers will provide valid patent protection sufficiently broad to protect the Company's products and technology or that such patents will not be challenged, revoked, invalidated, infringed or circumvented by third parties. In the regular course of business, the Company is party to litigation or other proceedings relating to intellectual property rights. (See ITEM 3 of this Form 10-K for details of current patent litigation).

Additionally, the Company's products, or the technologies or processes used to formulate or manufacture those products may now, or in the future, infringe the patent rights of third parties. It is also possible that third parties will obtain patent or other proprietary rights that might be necessary or useful for the development, manufacture or sale of the Company's products. If third parties are the first to invent a particular product or technology, it is possible that those parties will obtain patent rights that will be sufficiently broad to prevent the Company or its strategic partners from developing, manufacturing or selling its products. The Company may need to obtain licences for intellectual property rights from others to develop, manufacture and market commercially viable products and may not be able to obtain these licences on commercially reasonable terms, if at all. In addition, any licensed patents or proprietary rights may not be valid and enforceable.

The Company also relies on trade secrets and other un-patented proprietary information, which it generally seeks to protect by confidentiality and nondisclosure agreements with its employees, consultants, advisors and partners. These agreements may not effectively prevent disclosure of confidential information and may not provide the Company with an adequate remedy in the event of unauthorised disclosure of such information. If the Company's employees, scientific consultants or partners develop inventions or processes that may be applicable to the Company's products under development, such inventions and processes will not necessarily become the Company's property, but may remain the property of those persons or their employers. Protracted and costly litigation could be necessary to enforce and determine the scope of the Company's proprietary rights. The failure to obtain or maintain patent and trade secret protection, for any reason, could allow other companies to make competing products and reduce the Company's product sales.

The Company has filed applications to register various trademarks for use in connection with its products in various countries including the United States and countries in Europe and Latin America and intends to trademark new product names as new

products are developed. In addition, with respect to certain products, the Company relies on the trademarks of third parties. These trademarks may not afford adequate protection or the Company or the third parties may not have the financial resources to enforce any rights under any of these trademarks. The Company's

inability or the inability of these third parties to protect their trademarks because of successful third party claims to those trademarks could allow others to use the Company's trademarks and dilute their value.

If a marketed product fails to work effectively or causes adverse side effects, this could result in damage to the Company's reputation, the withdrawal of the product and legal action against the Company

The Company's ability to sell pharmaceutical products after the receipt of regulatory approval will depend on the acceptance of those products by physicians and patients. Unanticipated side effects or unfavourable publicity concerning any of the Company's products, or those of its competitors, could have an adverse effect on the Company's ability to obtain or maintain regulatory approvals or successfully market its products. Future results of operations will also depend on continued market acceptance of current products and the lack of substitutes that are cheaper or more effective.

The testing, manufacturing, marketing and sales of pharmaceutical products entails a risk of product liability claims, product recalls, litigation and associated adverse publicity. The cost of defending against such claims is expensive even when the claims are not merited. A successful product liability claim against the Company could require the Company to pay a substantial monetary award. If, in the absence of adequate insurance coverage, the Company does not have sufficient financial resources to satisfy a liability resulting from such a claim or to fund the legal defence of such a claim, it could become insolvent. Product liability insurance coverage is expensive, difficult to obtain and may not be available in the future on acceptable terms. Although the Company carries product liability insurance, this coverage may not be adequate. In addition, it cannot be certain that insurance coverage for present or future products will be available. Moreover, an adverse judgment in a product liability suit, even if insured or eventually overturned on appeal, could generate substantial negative publicity about the Company's products and business and inhibit or prevent commercialisation of other products.

Monitoring or enforcement action by regulatory authorities or law enforcement agencies in the highly regulated markets in which the Company operates may result in the distraction of senior management, significant legal costs and the payment of substantial compensation or fines

The Company engages in various marketing, promotional and educational activities pertaining to, as well the sale of, pharmaceutical products in a number of jurisdictions around the world. The promotion, marketing and sale of pharmaceutical products is highly regulated and the operations of market participants, such as the Company, are closely supervised by regulatory authorities and law enforcement agencies, including the FDA, the US Department of Justice and the DEA in the US. Any inquiries or investigations into the operations of, or enforcement or other regulatory action against, the Company by such regulatory authorities could result in the distraction of senior management for prolonged periods of time, significant defence costs and substantial monetary penalties.

The outsourcing of services can create a significant dependency on third parties, the failure of whom can affect the ability to operate the Company's business and to develop and market products

The Company has entered into many agreements with third parties for the provision of services to enable it to operate its business. If the third party can no longer provide the service on the agreed basis, the Company may not be able to continue the development or commercialisation of its products as planned or on a commercial basis. Additionally, it may not be able to establish or maintain good relationships with the suppliers.

The Company has also entered into licensing and co-development agreements with a number of parties. There is a risk that, upon expiration or termination of a third party agreement, the Company may not be able to renew or extend the agreement with the third party as commercial interests may no longer coincide. In such circumstances, the Company may be unable to continue to develop or market its products as planned and could be required to abandon or divest a product line.

Loss of highly qualified management and scientific personnel could cause the Company subsequent financial loss

The Company faces intense competition for highly qualified management and scientific personnel from other companies, academic institutions, government entities and other organisations. It may not be able to successfully attract and retain such personnel. The Company has agreements with a number of its key scientific and management personnel for periods of one year or less. The loss of such personnel, or the inability to attract and retain the additional, highly skilled employees required for its activities could have an adverse effect on the Company's business.

In the event of breakdown, failure or breach of security on any of the Company's IT systems, the Company may be unable to maintain its business operations

The Company operates several complex information systems upon which it is dependent. The Company has back-up procedures and disaster recovery plans in place to enable the business to continue its normal operations and to mitigate any loss in the event of a failure. However, in the event of breakdown, failure or breach of security of any of these systems or the associated suppliers, the Company may be unable to maintain its business operations.

This could lead to loss of revenue and delay in product development. In addition, the Company is in the process of installing enterprise-wide information systems in its operations throughout the world. Any failure in the operation of these systems could have an adverse effect on the Company's business operations.

The Company may incur unexpected expenditure in order to comply with US environmental laws

The Company's manufacturing sites are situated in the United States and are subject to national, state and local environmental laws. Compliance with environmental laws requires ongoing expenditure and any spillage or contamination found to be caused by the Company may result in clean up costs and financial penalties for the Company which could adversely affect the Company's revenues, financial condition and results of operations.

Contracts are used in all areas of operation of the business. They may contain provisions that do not protect the Company's position or with which it cannot comply

Contracts form the basis of agreement in many key activities such as mergers and acquisitions, arrangements with suppliers, outsourcing, product licensing and marketing. These contracts may contain provisions that impose duties on the parties involved or may fail to contain adequate conditions to protect the Company's position. The Company may be unable to meet its obligations under a contract or may be unable to require other parties to comply with their obligations and, therefore, may suffer financial loss or penalty.

ITEM 1B: Unresolved Staff Comments

None.

ITEM 2: Properties

The following are the principal premises of the Company, as at December 31, 2006:

Location	Use	Approximate Square Footage	Owned or Leased
Basingstoke, Hampshire, UK	Office accommodation (Global Headquarters)	65,000	Owned
Wayne, Philadelphia Pennsylvania, USA	Office accommodation (US Headquarters)	220,000	Leased

Florence, Kentucky, USA	Warehousing and distribution facility	65,000	Leased
Owings Mills, Maryland, USA	Manufacturing facility	90,000	Leased
Dublin, Ireland	Office accommodation	16,000	Leased
Ville Saint-Laurent, Quebec, Canada	Office accommodation (Shire BioChem Inc.)	23,000	Leased
Cambridge, Massachusetts, USA	Office accommodation (Shire Human Genetic Therapies Headquarters) and laboratories	181,000	Leased
Cambridge, Massachusetts, USA	Office accommodation, laboratories and manufacturing facility	44,000	Leased
Cambridge, Massachusetts, USA	Office accommodation	16,000	Leased
Belmont, Massachusetts, USA	Warehousing facility	16,000	Leased

The Company also has other smaller locations in some of the countries listed above and in several other countries around the world. At December 31, 2006 all the above sites were utilized by the Company. In addition, Shire has properties at Newport, Kentucky; Rockville, Maryland; and Randolph, Massachusetts which are not fully utilized.

ITEM 3: Legal Proceedings

General

The Company accounts for litigation losses and insurance claims and provisions in accordance with SFAS No. 5, "Accounting for Contingencies" (SFAS No. 5). Under SFAS No. 5, loss contingency provisions are recorded for probable losses when management is able to reasonably estimate the loss. Where the estimated loss lies within a range and no particular amount within that range is a better estimate than any other amount, the minimum amount is recorded. In other cases management's best estimate of the loss is recorded. These estimates are developed substantially before the ultimate loss is known and the estimates are refined in each accounting period in light of additional information becoming known. In instances where the Company is unable to develop a reasonable estimate of loss, no litigation loss is recorded at that time. As information becomes known a loss provision is set up when a reasonable estimate can be made. The estimates are reviewed quarterly and the estimates are changed when expectations are revised. Any outcome upon settlement that deviates from the Company's estimate may result in an additional expense in a future accounting period.

ADDERALL XR

(i) Barr Laboratories, Inc.

Shire's extended release "once daily" version of ADDERALL, ADDERALL XR is covered by the '819 Patent and the '300 Patent. In January 2003 the Company was notified that Barr had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic versions of the 5mg, 10mg, 15mg, 20mg, 25mg and 30mg strengths of ADDERALL XR (Barr's ANDA products) prior to the expiration date of the Company's '819 Patent, and alleging that the '819 Patent is not infringed by Barr's ANDA products. In August 2003 Shire was notified that Barr also was seeking permission to market its ANDA products prior to the expiration date of the '300 Patent and alleging that the '300 Patent is invalid. Shire Laboratories, Inc, (Shire Laboratories) filed suit against Barr for infringement of the '819 Patent in February 2003 and for infringement of the '300 Patent in September 2003. The schedules for the lawsuits against Barr with respect to the '819 and '300 Patents were consolidated in December 2003. The

Company sought a ruling that Barr's ANDA and ANDA products infringe the '819 and '300 Patents and that its ANDA should not be approved before the expiration date of the patents. The Company also sought injunctions to prevent Barr from commercializing its ANDA products before the expiration of the '819 and '300 Patents, damages in the event that Barr should engage in such commercialization, and its attorneys' fees and costs. On September 27, 2004 Barr filed an amended Answer, Affirmative Defense and Counterclaim in which Barr added the following counterclaims: invalidity of the '819 patent, non-infringement of the '300 Patent and unenforceability of the '819 and '300 Patents due to inequitable conduct. Shire asserted affirmative defenses, alleging, among other things, that Barr has waived its right to assert the counterclaims set forth in its September 27, 2004 amended Answer. Under the Court's schedule summary judgment motions were to be filed and fully briefed by October 14, 2005. Neither Shire nor Barr filed summary judgment motions. On December 9, 2005, the Court continued the final pre-trial conference to March 10, 2006.

Shire's lawsuits triggered stays of final FDA approval of Barr's ANDA of up to 30 months from the date of the Company's receipt of Barr's notice letters. The second and final 30 month stay related to the lawsuit regarding the '300 Patent expired on February 18, 2006. As the stay has expired, the FDA may approve Barr's ANDA, subject to satisfaction by Barr of the FDA's requirements. The FDA has not approved Barr's ANDA at this time.

On October 19, 2005 Shire brought another lawsuit against Barr in the Southern District of New York alleging infringement of US Patent No. 6,913,768 (the '768 Patent), which issued on July 5, 2005. The Company sought an injunction to prevent Barr from infringing the '768 Patent, damages in the event that Barr should commercialize its ANDA products, attorneys' fees and costs. Barr moved to dismiss this action asserting that there was no subject matter jurisdiction. A hearing on this motion was held on February 17, 2006. The Court never ruled on this motion.

During October 2005 Shire filed a Citizen Petition with the FDA requesting that the FDA require more rigorous bioequivalence testing or additional clinical testing for generic or follow-on drug products that reference ADDERALL XR before they can be approved. Shire believes that these requested criteria will ensure that generic formulations of ADDERALL XR or follow-on drug products will be clinically effective and safe. In January 2006 Shire filed a supplemental amendment to its original Citizen Petition, which included additional clinical data in support of the original filing. On April 20, 2006 Shire received correspondence from the FDA informing Shire that the FDA has not yet resolved the issues raised in Shire's pending ADDERALL XR Citizen Petition. The correspondence states that, due to the complex issues raised requiring extensive review and analysis by the FDA's officials, a decision cannot be reached at this time. The FDA's interim response is in accordance with FDA regulations concerning Citizen Petitions.

On August 14, 2006, Shire and Barr announced that all pending litigation in connection with Barr's ANDA and its attempt to market generic versions of Shire's ADDERALL XR had been settled. As part of the settlement agreement, Barr entered into consent judgments and agreed to permanent injunctions confirming the validity and enforceability of Shire's '819, '300 and '768 Patents. Barr has also admitted that any generic product made under its

ANDA would infringe the '768 patent. Under the terms of the settlement, Barr will not be permitted to market a generic version of ADDERALL XR in the United States until April 1, 2009, except for certain limited circumstances, such as the launch of another party's generic version of ADDERALL XR. No payments to Barr are involved in the settlement agreement.

Shire and Duramed, a subsidiary of Barr entered into an agreement related to Duramed's transvaginal ring technology that will be applied to at least five women's health products, as well as a license to Duramed's currently marketed oral contraceptive, SEASONIQUE (levonorgestrel/ethinyl estradiol tablets 0.15 mg/0.03 mg and ethinyl estradiol tablets 0.01 mg) (the product development and license agreement). Shire was granted exclusive rights to market these products on a royalty-free basis in a number of markets excluding US and Canada (including Japan and the major European Countries). Duramed will market these products in North America. SEASONIQUE is already marketed in the United States by Duramed but Shire will need to obtain appropriate regulatory authorisations to commence marketing this product in Europe. Under this agreement, Shire made an initial payment of $25 million to Duramed on September 13, 2006 for previously incurred product development expenses, and will reimburse Duramed for development expenses incurred going forward up to a maximum of $140 million over eight years, with the amount capped at $30 million per annum.

The settlement agreement and the product development and license agreement became effective upon the Courts signing the last of the consent judgments for the litigations on September 6, 2006.

Duramed agreed to purchase Shire's ADDERALL (immediate-release mixed amphetamine salts) product for $63 million. Shire

reported the transaction to the FTC and the DOJ under the Hart Scott Rodino (HSR) Act on August 28, 2006. The HSR Act's 30-day waiting period expired on September 27, 2006 and the transaction closed on September 29, 2006.

As required by law, Shire submitted to the FTC and the DOJ all of the agreements with Barr and it subsidiaries that were entered into on August 14, 2006. On October 3, 2006, the FTC notified Shire that it is reviewing the settlement agreement with Barr. While the Company has not received any requests for information regarding the settlement agreement, Shire intends on cooperating with the FTC should it receive any such requests. The FTC's review should not be considered to be an indication that Shire or any other company violated any law, and Shire believes that the settlement agreement is in compliance with all applicable laws.

(ii) Impax

In November 2003, Shire was notified that Impax had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic version of the 30mg strength of ADDERALL XR (Impax's ANDA product) prior to the expiration date of the '819 and '300 Patents. In December 2003, Shire Laboratories filed suit against Impax for infringement of the '819 and '300 Patents.

In December 2004, Shire received an additional notification from Impax advising of the filing of an amendment to its ANDA for a generic version of the 5mg, 10mg, 15mg, 20mg and 25mg strengths of ADDERALL XR in addition to the 30mg strength, the subject of Impax's initial ANDA submission. In January 2005, Shire Laboratories filed suit against Impax for infringement of the '819 and '300 Patents by these lower strength dosage forms; this suit was consolidated with the earlier case against Impax.

As part of the October 19, 2005 lawsuit against Barr, Shire also brought suit in the Southern District of New York against Impax for infringing the '768 Patent. Impax filed a declaratory judgment action in Delaware alleging that the '768 Patent was invalid and that its ANDA did not infringe the '768 Patent.

On January 19, 2006, Shire and Impax announced that all pending litigation in connection with Impax's ANDA had been settled. As part of the settlement, Impax confirmed that its proposed generic products infringe Shire's '819, '300 and '768 Patents and that the three patents are valid and enforceable.

Under the terms of the settlement agreement, Impax will be permitted to market generic versions of ADDERALL XR in the United States no later than January 1, 2010 and will pay Shire a royalty from those sales. In certain situations, such as the launch of another generic version of ADDERALL XR, Impax may be permitted to enter the market as Shire's authorized generic. No payments to Impax are involved in the settlement agreement. The settlement agreement, which was effective immediately, has been submitted to the United States Federal Trade Commission for its review, as required by law.

(iii) Colony Pharmaceuticals, Inc.

In December 2004, Shire was notified that Colony Pharmaceuticals, Inc. (Colony) had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic versions of the 5mg, 10mg, 15mg, 20mg, 25mg and 30mg strengths of ADDERALL XR prior to the expiration date of the Company's '819 and '300 Patents. Shire has chosen not to sue Colony.

(iv) Teva Pharmaceuticals USA, Inc.

In February 2005, Shire was notified that Teva Pharmaceuticals, Inc. (Teva Pharmaceuticals) had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic versions of the 10mg and 30mg strengths of ADDERALL XR prior to the expiration date of the Company's '819 and '300 Patents. In June 2005, Shire was notified that Teva Pharmaceuticals had amended its ANDA to seek permission to market additional strengths of 5mg, 15mg and 20mg of its generic ADDERALL XR prior to the expiration of the '819 and '300 Patents. In January 2006, Shire received a third notice letter that Teva Pharmaceuticals had further amended its ANDA to seek permission to market the 25mg strength generic version of ADDERALL XR prior to the expiration of the '819 and '300 Patents. On March 2, 2006 Shire filed a lawsuit in the Eastern District of Pennsylvania against Teva Pharmaceuticals Industries Ltd. (Teva Israel) and Teva Pharmaceuticals USA, Inc. (Teva USA) (collectively Teva) alleging that all of Teva's ANDA products infringe both the '819 and the '300 Patents. The lawsuit triggered a stay of FDA approval of Teva's 25 mg strength product for 30 months from the date of the Company's receipt of Teva's third notice letter. There is no such stay with respect to Teva's 5mg, 10mg, 15mg, 20mg and 30 mg strengths versions of ADDERALL XR. On January 30, 2007, the case was

transferred to the civil suspense docket with an Order requiring the parties to notify the Court of the status of the case on the first business day of every month. No trial date has been set.

(v) Andrx Pharmaceuticals, LLC

In September 2006, Shire was notified that Andrx Pharmaceuticals, LLC (Andrx) had submitted a ANDA under the Hatch-Waxman Act seeking permission to market its generic versions of the 5mg, 10mg, 15mg, 20mg, 25mg and 30mg strengths of ADDERALL XR prior to the expiration date of the Company's '819 and '300 patents. Shire Laboratories and Shire LLC. have filed lawsuits in the US District Court for the District of New Jersey and the Southern District of Florida against Andrx Pharmaceuticals, LLC. and Andrx Corporation (collectively "Andrx") for infringement of the Company's '819 and '300 Patents. Watson Pharmaceuticals, Inc., the recent acquiror of Andrx, is also named in the lawsuits. The lawsuits allege that all of Andrx's generic strengths infringe the patents in suit. Pursuant to Hatch-Waxman legislation, there will be a 30-month stay with respect to Andrx's proposed generic products.

(vi) Sandoz Inc.

In December 2006, Shire was notified that Sandoz Inc. (Sandoz) had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic versions of the 5mg, 10mg, 15mg, 20mg, 25mg, 30mg strengths of ADDERALL XR prior to the expiration of the Company's '819 and '300 patents. On January 26, 2007, Shire filed suit in the US District Court for the District of Colorado for infringement of the '819 and '300 patents. The lawsuit triggers a stay of FDA approval of up to 30 months from the Company's receipt of Sandoz's notice. The court has ordered a scheduling and planning conference for March 21, 2007. No trial date has been set.

None of Colony, Andrx, Teva or Sandoz may launch their generic versions of ADDERALL XR before they receive final FDA approval of their respective ANDAs and before the expiration of the first to file's exclusivity rights.

CARBATROL

(i) Nostrum Pharmaceuticals, Inc.

In August 2003, the Company was notified that Nostrum Pharmaceuticals, Inc. (Nostrum) had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic version of the 300mg strength of CARBATROL (Nostrum's ANDA product) prior to the expiration date of the Company's US patents for CARBATROL, US patent No. 5,912,013 (the '013 Patent) and US patent No. 5,326,570 (the '570 Patent). The notification alleges that the '013 and '570 Patents are not infringed by Nostrum's ANDA product. On September 18, 2003, Shire filed suit against Nostrum in the United States District Court for the District of New Jersey alleging infringement of these two patents by Nostrum's ANDA and ANDA product. The Company was seeking a ruling that Nostrum's ANDA infringes the '013 and '570 Patents and should not be approved before the expiration date of the '013 and '570 Patents. The Company was also seeking an injunction to prevent Nostrum from commercializing its ANDA product before the expiration of the '013 and '570 Patents, damages in the event that Nostrum should engage in such commercialization, as well as its attorneys' fees and costs. On January 23, 2004, the Company amended the complaint to drop the allegations with respect to the '013 Patent while maintaining the suit with respect to the '570 Patent. By way of counterclaims Nostrum is seeking a declaration that the '570 and '013 Patents are not infringed by Nostrum's ANDA product. Nostrum also was seeking actual and punitive damages for alleged abuse of process by Shire. On July 12, 2004, the Court dismissed Nostrum's abuse of process counterclaim for failure to state a claim upon which relief can be granted. On December 10, 2004, Nostrum filed a summary judgment motion seeking a declaration of non-infringement of the '570 Patent, which Shire opposed. The Court heard arguments with respect to Nostrum's motion on July 15, 2005. At the conclusion of the hearing the Court denied Nostrum's motion for summary judgment of non-infringement. On July 17, 2006 the Court entered an order staying discovery in this case until and through September 15, 2006. The parties requested, and the Court granted, an extension of the stay

of discovery until and through December 29, 2006. On January 8, 2007 the parties requested a further stay discovery until March 30, 2007, which has not yet been granted by the Court. No trial date has been set.

Nostrum may not launch a generic version of CARBATROL before it receives final approval of its ANDA from the FDA. The lawsuit triggered a stay of FDA approval of up to 30 months from Shire's receipt of Nostrum's notice letter. The 30 month stay expired on February 6, 2006. Following expiry of the stay, Nostrum could be in a position to market its 300mg extended-release

carbamazepine product upon FDA final approval of its ANDA.

(ii) Corepharma LLC

On March 30, 2006 the Company was notified that Corepharma LLC (Corepharma) had filed an ANDA under the Hatch-Waxman Act seeking permission to market its generic version of carbamazepine extended release products in 100mg, 200mg and 300mg strengths prior to the expiration date of the '013 and the '570 Patents. On May 17, 2006, Shire filed suit against Corepharma in the United States District Court for the District of New Jersey alleging infringement of these two patents by Corepharma's ANDA and ANDA products. The Company was seeking a ruling that Corepharma's ANDA infringes the '013 and '570 Patents and should not be approved before their expiration dates. The Company was also seeking an injunction to prevent Corepharma from commercializing its ANDA products before the expiration of the '013 and '570 Patents, damages in the event that Corepharma should engage in such commercialization, as well as its attorneys' fees and costs. On September 1, 2006, the Company amended the complaint to drop the allegations with respect to the '013 Patent while maintaining the suit with respect to the '570 Patent. By way of counterclaims, Corepharma is alleging noninfringement and invalidity of the '570 Patent, noninfrngement of the '013 Patent and federal and state antitrust violations. The parties have agreed to, and the court has accepted, a dismissal without prejudice of the antitrust counterclaims until a final judgment has been entered in the patent case. Corepharma has also filed a motion for a judgment on the pleadings of noninfringement of the '013 Patent, which Shire has opposed, including moving to dismiss the '013 Patent noninfringement counterclaim for lack of subject matter jurisdiction. The Court heard oral argument on these two motions on February 26, 2007, immediately after which the Court granted Shire's motion to dismiss for lack of subject matter jurisdiction, rendering moot Corepharma's motion for noninfringement of the '013 Patent.

The parties exchanged written discovery on January 26, 2007, and will appear before the Court for a status conference on March 13, 2007. No further discovery schedule or trial date has been set.

Corepharma may not launch a generic version of CARBATROL before it receives final approval of its ANDA from the FDA. The lawsuit triggered a stay of FDA approval of up to 30 months from Shire's receipt of Corepharma's notice letter.

GENE ACTIVATION

In 1996, Applied Research Systems Holding N.V., a wholly-owned subsidiary of Serono S.A. (Serono) and Cell Genesys became involved in a patent interference involving Serono's US Patent No. 5,272,071 (the '071 Patent), which purportedly covers certain methods of gene activation. In June 2004, the Board of Patent Appeals and Interferences of the US Patent and Trademark Office (PTO) held that both Serono and Cell Genesys were entitled to certain claims in their respective patent and patent application, and Serono and Cell Genesys each appealed the decision of the interference to the US District Court of Massachusetts and the US District Court of the District Court of Columbia, respectively. Shire HGT (formerly known as TKT) was not a party to this interference. The District of Columbia action was subsequently transferred and consolidated with the District of Massachusetts action (the Appeal).

In August 2004, Serono served Shire HGT with an amended complaint in the Appeal. The amended complaint alleges that Shire HGT infringes Serono's 071 Patent. In August 2005, the US District Court of Massachusetts severed and stayed the infringement action pending resolution of the interference claim of the Appeal at the District Court level.

Pre-trial proceedings concerning the Appeal between Serono and Cell Genesys are ongoing and Serono's infringement action against the Company remains stayed pending resolution of those proceedings. In view of the stay, the Company has not yet answered Serono's complaint.

GA-GCB

In January 2005, Genzyme Corporation (Genzyme) filed suit against Shire HGT in the District Court of Tel Aviv-Jaffa, Israel, claiming that Shire HGT's Phase 1/2 clinical trial in Israel evaluating GA-GCB for the treatment of Gaucher disease infringes one or more claims of Genzyme's Israeli Patent No. 100,715. In addition, Genzyme filed a motion for preliminary injunction, including a request for an ex parte hearing and relief on the merits, to immediately seize and destroy all GA-GCB being used to treat patients and to prevent Shire HGT from submitting data generated from the clinical trial to regulatory agencies. In March 2005 the District Court refused to grant Genzyme's motion for a preliminary injunction. The lawsuit was dismissed in January 2006.

DYNEPO

Since 1997, Shire HGT and Sanofi-Aventis have been involved in ongoing patent litigation regarding Amgen's allegations that DYNEPO infringes claims of five of Amgen's patents. In 2001, the United States District Court of Massachusetts concluded that DYNEPO infringed certain claims of the patents that Amgen had asserted. This decision was appealed to the United States Court of Appeals for the Federal Circuit (the Federal Circuit) which affirmed in part, reversed in part, and remanded the action to the United States District Court of Massachusetts for further proceedings.

In 2004, the United States District Court of Massachusetts issued a decision on the remanded issues, finding that certain claims related to four of the patents asserted by Amgen are infringed by Shire HGT and Sanofi-Aventis. This decision was subsequently appealed to the Federal Circuit which affirmed in part, reversed in part, and once again remanded certain issues to the District Court. Recently, Amgen has filed a request for an extension of time to file a petition for certiorari with the Supreme Court.

Under the most recent Federal Circuit decision, the Company and Sanofi-Aventis would be precluded from making, using and selling DYNEPO in the United States until the expiration of the relevant patents. The Company is required to reimburse Sanofi-Aventis, which controls the litigation and is paying the litigation expenses, for 50% of the expenses incurred in connection with the litigation from and after March 26, 2004. This litigation has no impact on Shire's ability to make, use and sell DYNEPO outside of the United States.

Appraisal Rights

In connection with Shire's merger with TKT, former holders of approximately 11.7 million shares of TKT common stock submitted written demands to the Delaware Court of Chancery for appraisal of these shares and, as a result, elected not to accept the $37 per share merger consideration. On October 10, 2005, at the request of one of the holders to tender 365,000 shares at the merger price of $37 per share, TKT filed a motion to dismiss the holder's demand. On October 12, 2005, the Delaware Court of Chancery granted this motion, and the holder tendered the shares at the merger consideration of $37 per share. Therefore, as at December 31, 2006, former holders of approximately 11.3 million shares of TKT common stock maintained written demands for appraisal of these shares and have elected not to accept the $37 merger consideration. In November 2005, the Delaware Court of Chancery approved a consolidation order filed by Shire HGT whereby actions brought by all petitioners have been consolidated as one case. In April 2006, Shire filed a motion for partial summary judgment in respect of approximately 8 million shares, claiming that the petitioners were not entitled to assert appraisal rights in connection with such shares.

To the extent that petitioners' demands were validly asserted in accordance with the applicable requirements of Delaware law and the former holders perfect their rights thereunder, such former holders will be entitled to receive the fair value of these shares as determined by the Delaware Court of Chancery. The determination of fair value will be made excluding any element of value arising from the transaction, such as cost savings or business synergies. The Delaware Court of Chancery may ascribe a valuation to the shares that is greater than, less than or equal to $37 per share and may award interest on the amount determined in the appraisal process.

The total consideration for the acquisition of TKT, including amounts payable in respect of stock options and convertible securities, is approximately $1.6 billion at the merger price of $37 per share. This could change if Shire is required to pay a different amount of consideration in respect of the approximately 11.3 million shares for which holders have asserted appraisal rights. For every dollar increase/decrease in the merger consideration applicable to those TKT shareholders who have asserted appraisal rights, the total estimated purchase price would increase/decrease by approximately $11.3 million. Until such time as the appraisal process is complete, the Company is unable to determine the extent of its liability. The trial date has been set for April 23, 2007.

Class Action Shareholder Suit

In January and February 2003, various parties filed purported securities fraud class action lawsuits against TKT and Richard Selden, TKT's former Chief Executive Officer, in the United States District Court for the District of Massachusetts. In April 2003, the Court appointed a Lead Plaintiff and Lead Counsel and consolidated the various matters under one matter: In re Transkaryotic Therapies, Inc., Securities Litigation, C.A. No. 03-10165-RWZ.

In July 2003, the plaintiffs filed a Consolidated and Amended Class Action Complaint (the Amended Complaint) against TKT; Dr Selden; Daniel Geffken, TKT's former Chief Financial Officer; Walter Gilbert, Jonathan S. Leff, Rodman W. Moorhead, III, and Wayne P. Yetter, then members of TKT's board of directors; William R. Miller and James E. Thomas, former members of TKT's board of directors; and SG Cowen Securities Corporation, Deutsche Bank Securities Inc., Pacific Growth Equities, Inc. and Leerink

Swann & Company, underwriters of TKT's common stock in prior public offerings.

The Amended Complaint alleges that the defendants made false and misleading statements and failed to disclose material information concerning the status and progress for obtaining United States marketing approval of REPLAGAL during the period between January 4, 2001 and January 10, 2003. The Amended Complaint asserts claims against Dr. Selden and TKT under Section 10(b) of the Securities Exchange Act of 1934 and Rule 10b-5 promulgated thereunder; and against Dr. Selden under Section 20(a) of the Exchange Act. The Amended Complaint also asserts claims based on TKT's public offerings of June 29, 2001, December 18, 2001 and December 26, 2001

against each of the defendants under Section 11 of the Securities Act of 1933 and against Dr. Selden under Section 15 of the Securities Act; and against SG Cowen Securities Corporation, Deutsche Bank Securities Inc., Pacific Growth Equities, Inc., and Leerink Swann & Company under Section 12(a)(2) of the Securities Act. The plaintiffs seek equitable and monetary relief, an unspecified amount of damages, with interest, and attorneys' fees and costs.

In May 2004, the Court granted in part and denied in part TKT's motion to dismiss In particular, the Court dismissed allegations against TKT to the extent they arose out of certain forward-looking statements protected by the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995 and dismissed claims based on the public offerings of June 29, 2001 and December 18, 2001. The Court allowed all other allegations to remain. In July 2004, the plaintiffs voluntarily dismissed all claims based on the third public offering dated December 26, 2001.

In November 2005, the court granted the plaintiffs' motion for class certification. On May 23, 2005, the court entered judgment on all claims alleged against SG Cowen Securities Corporation, Deutsche Bank Securities Inc., Pacific Growth Equities, Inc., and Leerink Swann & Company. On June 5, 2006, the court entered judgment on all claims alleged against Messrs. Gilbert, Leff, Moorhead, Yetter, Miller, and Thomas. On November 9, 2006, Mr. Geffken filed an Agreement for Judgment on all claims alleged against him. The Company is obligated to indemnify Dr Selden for his costs incurred in connection with the SEC Action.

ITEM 4 : Submission of matters to a vote of security holders

Shire did not submit any matters to the vote of security holders during the 4 th quarter of 2006.

PART II

ITEM 5 : Market for Registrant's common equity, related stockholder matters and issuer purchases of equity securities

Ordinary shares

Shire plc's ordinary shares are traded on the London Stock Exchange (LSE). On November 25, 2005 a Scheme of Arrangement, approved by the High Court of Justice in England and Wales, became effective. Under the terms of the Scheme, holders of ordinary shares of SPG received one ordinary share of Shire plc for each ordinary share of SPG held at 5.30pm (GMT) on November 24, 2005.

Ordinary shares of Shire plc were admitted to the Official List and to trading on the LSE at 8.00am (GMT) on November 25, 2005. The listing of ordinary shares of SPG was cancelled at the same time.

The following table presents the per share closing mid-market quotation for ordinary shares of Shire plc (or, as applicable, prior to November 25, 2005, ordinary shares of SPG) as quoted in the Daily Official List of the LSE for the periods indicated.

	High £ per ordinary share	Low £ per ordinary share
Year to December 31, 2006		
1 st Quarter	9.61	7.38
2 nd Quarter	8.99	6.99
3 rd Quarter	9.38	7.72
4 th Quarter	10.90	8.57
Year to December 31, 2005		
1 st Quarter	6.42	5.62
2 nd Quarter	6.28	5.39
3 rd Quarter	7.08	6.11
4 th Quarter	7.53	6.31

The total number of record holders of ordinary shares of Shire plc as at February 21, 2007 was 5,927. Since certain of the ordinary shares are held by broker nominees, the number of holders of record may not be representative of the number of beneficial owners.

American Depositary Shares

American Depositary Shares (ADSs) each represent three ordinary shares of Shire plc. An ADS is evidenced by an American Depositary Receipt (ADR) issued by Morgan Guaranty Trust Company of New York as depositary, and is quoted on the NASDAQ National Market. As at February 21, 2006 the proportion of ordinary shares represented by ADRs was 32% of the outstanding ordinary shares.

In consequence of the implementation of the Scheme of Arrangement, ADSs representing ordinary shares of SPG were replaced by ADSs representing ordinary shares of Shire plc on a one-for-one basis. Dealings in ADSs representing ordinary shares of Shire plc on NASDAQ commenced at 9.30am (EST) on November 25, 2005. ADSs representing ordinary shares of SPG were cancelled at the same time.

The following table presents the high and low market quotations for ADSs quoted on the NASDAQ National Market for the periods indicated (prior to November 25, 2005, the ADSs represented ordinary shares of SPG).

	High $ per ADS	Low $ per ADS
Year to December 31, 2006		
1 st Quarter	50.30	38.61
2 nd Quarter	48.31	38.33
3 rd Quarter	52.26	42.50
4 th Quarter	64.44	48.51
Year to December 31, 2005		
1 st Quarter	36.15	31.28
2 nd Quarter	35.08	30.82
3 rd Quarter	39.32	32.32
4 th Quarter	39.24	33.92

The number of record holders of ADSs in the United States as at February 21, 2006 was 369. Since certain of the ADRs are held by broker nominees, the number of record holders may not be representative of the number of beneficial owners.

Dividend policy

A first interim dividend for the first half of 2006 of 1.9346 US cents (1.0475 pence) per ordinary share, equivalent to 5.804 US cents per ADS and 6.584 Canadian cents per exchangeable share, was paid in October 2006. The Board has resolved to pay a second interim dividend of 5.2455 US cents (2.6933 pence) per ordinary share equivalent to 15.736 US cents per ADS and 18.4086 Canadian cents per exchangeable share for the six months to December 31, 2006.

A first interim dividend for the first half of 2005 of 1.8246 US cents (1.0475 pence) per ordinary share equivalent to 5.4738 US cents per ADS and 6.7629 Canadian cents per exchangeable share was paid in October 2005. A second interim dividend for the second half of 2005 of 4.419 US cents (2.5356 pence) per ordinary share equivalent to 13.257 US cents per ADS and 15.2217 Canadian cents per exchangeable share was paid in April 2006.

This is consistent with Shire plc's stated policy of paying a dividend semi-annually, set in US cents per share / ADS, with the first interim payment in each year being maintained at a consistent level. Any growth will come through increasing the second interim dividend in a financial year. Shire intends to pursue a progressive dividend policy.

As a matter of English law, Shire plc may pay dividends only out of its distributable profits, which are the accumulated realized profits under generally accepted accounting principles in the United Kingdom (including reserves arising from a reduction of share capital), of Shire plc and not the consolidated Group, so far as not previously utilized by distribution or capitalization, less accumulated realized losses, so far as not previously written off in a reduction or reorganization of capital duly made. At December 31, 2006, Shire plc had distributable profits of $2,899 million. Future dividend policy will be dependent upon distributable profits, financial condition, the terms of any then existing debt facilities and other relevant factors existing at that time.

NASDAQ Corporate Governance Exemption

NASDAQ has granted Shire plc an exemption from the quorum requirement of its corporate governance standards in Marketplace Rule 4350 as Shire complies with the relevant quorum standards applicable to companies in the UK.

ITEM 6 : Selected financial data

The selected consolidated financial data presented below as at December 31, 2006 and 2005 and for each of the three years in the period ended December 31, 2006 were derived from the audited consolidated financial statements of the Company, included herein. The selected consolidated financial data presented below as at December 31, 2004, 2003 and 2002 and for each of the two years in the period ended December 31, 2003 were derived from the audited financial statements of the Company, which are not included herein. Certain amounts reported in previous years have been reclassified to conform to the 2006 presentation.

The consolidated financial data in respect of the year ended December 31, 2005 has been restated in respect of the value ascribed to in-process research and development (IPR&D) acquired with the acquisition of TKT. For further information, see note 3(a) to the Consolidated Financial Statements contained in Part IV of this Annual Report.

The selected consolidated financial data should be read in conjunction with "ITEM 7: Management's discussion and analysis of financial condition and results of operations" and with the consolidated financial statements and related notes appearing elsewhere in this report.

Year to December 31,	2006 $'M	[1] [2] Adjusted and restated 2005 $'M	[1] Adjusted 2004 $'M	[1] Adjusted 2003 $'M	[1] Adjusted 2002 $'M
Statement of Operations:					
Total revenues	1,796.5	1,599.3	1,363.2	1,211.6	1,023.3
Total operating expenses [3] [4]	(1,513.3)	(2,124.2)	(950.3)	(824.6)	(698.4)
Operating income/(loss)	283.2	(524.9)	412.9	387.0	324.9

Total other income/(expense), net [5]	33.6	33.2	13.5	(13.2)	(2.2)
Income/(loss) from continuing operations before income taxes, equity in earnings/(losses) of equity method investees and discontinued operations	316.8	(491.7)	426.4	373.8	322.7
Income taxes	(84.9)	(88.8)	(128.3)	(106.8)	(88.4)
Equity in earnings/(losses) of equity method investees	5.7	(1.0)	2.5	(1.1)	1.7
Income/(loss) from continuing operations	237.6	(581.5)	300.6	266.0	236.0
Gain/(loss) from discontinued operations, net of tax	40.6	-	(20.1)	(21.9)	(11.7)
Gain/(loss) on disposition of discontinued operations, net of tax	-	3.1	(44.2)	-	2.1
Net income/(loss) [3]	278.2	(578.4)	236.3	244.1	226.4

ITEM 6: Selected financial data (continued)

Year to December 31,	**2006**	**[1] [2] Adjusted and restated 2005**	**[1] Adjusted 2004**	**[1] Adjusted 2003**	**[1] Adjusted 2002**
Earnings per share - basic					
Income/(loss) from continuing operations	47.2c	(116.2c)	60.6c	53.4c	47.1c
Loss from discontinued operations	-	-	(4.1c)	(4.4c)	(2.3c)
Gain/(loss) on disposition of discontinued operations	8.1c	0.6c	(8.9c)	-	0.4c
	55.3c	(115.6c)	47.6c	49.0c	45.2c
Earnings per share - diluted					
Income/(loss) from continuing operations	46.6c	(116.2c)	59.4c	52.2c	46.2c
Loss from discontinued operations	-	-	(3.9c)	(4.2c)	(2.2c)
Gain/(loss) on disposition of discontinued operations	8.0c	0.6c	(8.6c)	-	0.4
	54.6c	(115.6c)	46.9c	48.0c	44.4c
Weighted average number of Shares (millions):					
Basic	503.4	500.2	496.3	498.2	500.7
Diluted	509.3	500.2	511.3	519.0	522.4
Cash dividends declared and paid per ordinary share	6.3536c	5.6746c	1.8246c	-	-

December 31,	**2006**	**[5] Restated 2005**	**2004**	**2003**	**2002**
	$'M	**$'M**	**$'M**	**$'M**	**$'M**
Balance sheets:					
Total current assets	1,810.3	1,312.2	1,928.9	1,794.1	1,467.1
Total assets	3,326.4	2,656.2	2,714.9	2,585.2	2,208.6
Total current liabilities	1,332.0	965.4	432.0	253.7	214.5
Total liabilities	1,384.1	1,008.9	464.2	662.1	635.5
Total shareholders' equity	1,942.3	1,647.3	2,250.7	1,923.1	1,573.2

(1) Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 to the Company's consolidated financial statements contained in Part IV of this Annual Report for additional information.

(2) Restated for a correction to the value of IPR&D acquired with the acquisition of TKT; see note 3(a) to the Company's consolidated financial statements contained in Part IV of this Annual Report.

(3) Total operating expenses include an in-process research and development (IPR&D) write-off of $815 million (restated) resulting from the acquisition of TKT in 2005, integration costs of $5.6 million and $9.7 million in 2006 and 2005 respectively, and reorganization costs of $9.4 million, $48.5 million and $23.9 million in 2005, 2004 and 2003, respectively. These reorganization costs were in respect of the implementation of the new business model in 2005 and 2004 and the closure of Lead Optimization together with the exit of certain properties in 2003.

(4) Total operating expenses in 2006 include a gain on sale of product rights of $63.0 million. See note 7 to the consolidated financial statements in Part IV of this Annual Report.

(5) Total other income/(expense), net includes interest income and expense, the gain or loss on the sale of assets, impairment of long-term investments and transactional foreign exchange. In 2005 it includes $3.9 million on the sale of a portfolio investment and $3.6 million on the sale of the drug formulation business. In 2004 it includes $14.8 million on the sale of a portfolio investment. See note 26 to the consolidated financial statements in Part IV of this Annual Report.

ITEM 7: Management's discussion and analysis of financial condition and results of operation

The following discussion should be read in conjunction with the Company's consolidated financial statements contained in Part IV of this Annual Report.

As described in Note 3(a) of Part IV of this Annual Report, the financial statements for the year to December 31, 2005 have been restated in respect of the value ascribed to IPR&D, acquired as part of the TKT acquisition and subsequently written off as required under US GAAP in the quarter ended September 30, 2005. IPR&D represented those assets which, at the time of the acquisition, had not been approved by the FDA or other regulatory authorities, including I2S (now known as ELAPRASE) and GA-GCB. The Company has determined that the value ascribed to IPR&D acquired as a result of the TKT acquisition did not include the benefit of tax amortization as required by the American Institute of Certified Public Accountants (AICPA) Practice Aid, *Assets Acquired in a Business Combination to Be Used in Research and Development Activities: A Focus on Software, Electronic Devices, and Pharmaceutical Industries* . The effect of this omission was to understate the value of IPR&D expensed in the year to December 31, 2005 by $142 million, with a corresponding overstatement of goodwill as at December 31, 2005.

Overview

Shire's strategic goal is to become the leading specialty pharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on ADHD, HGT, GI and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire believes that a carefully selected portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

Shire's focused strategy is to develop and market products for specialist physicians. Shire's in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe.

On February 20, 2007, consistent with its stated focus on the growing ADHD market, Shire announced that it had agreed to acquire New River Pharmaceuticals Inc. allowing Shire to progress and benefit from its successful strategy of acquiring, developing and marketing specialty pharmaceutical products.

Substantially all of the Company's revenues, expenditures, operating profits or losses and net assets are attributable to the R&D, manufacture, sale and distribution of pharmaceutical products within two operating segments: Pharmaceutical Products and Royalties.

Revenues are derived primarily from two sources - sales of the Company's own products and royalties (where Shire has out-licensed products to third parties):

- 85% (2005: 83%) of total revenues are derived from product sales, of which 48% is from ADDERALL XR (2005: 46%). All product sales fall within the Pharmaceutical Products segment;

- 14% of total revenues are derived from royalties (2005: 15%). All royalty income falls within the Royalties segment.

Shire's strategic objectives are set using a balanced scorecard approach. Objectives are also set at the functional, market and therapeutic area levels and are aligned with the Group-wide strategic objectives. The Company therefore takes a fully integrated approach to strategic management. Key performance indicators (KPIs) are used to measure achievement of the objectives. Strategic objectives are categorized into fields - 'financial', 'products & markets', 'people & capabilities' and 'operational excellence'. For 2006, Shire's corporate objectives included: defined levels of revenue growth; target sales and contributions for core products and markets; execution of defined therapeutic area strategic and operational plans; product in-licensing targets; drug application filing and launch targets for new products; maintenance of a stable and effective supply chain; implementation of an effective leadership development program; implementation of defined IT systems; and maintenance of robust risk management practices including internal controls.

The markets in which the Company conducts its business are highly competitive and highly regulated. The health care industry is experiencing:

- pressure from governments and healthcare providers to keep prices low while increasing access to drugs;

- increased R&D costs as clinical studies are typically larger and take longer to get approval from regulators;

- challenges to existing patents from generic manufacturers;

- low cost generic drugs entering the market on expiration of patent protection; and

- higher marketing costs due to the use of direct to consumer campaigns and competition for market share.

Shire's strategy to become the leading specialty pharmaceutical company has been developed to address these industry-wide competitive pressures. This strategy has resulted in a series of initiatives in the following areas:

Markets

Historically, Shire's portfolio of approved products has been heavily weighted towards the North American market. With the acquisition of TKT in 2005, Shire substantially increased its presence in Europe and thereby diversified the risk associated with being reliant on one geographic market. Through the TKT acquisition, Shire acquired ELAPRASE (global rights), REPLAGAL (which is presently sold only outside the US) and DYNEPO (to which the Company has exclusive marketing rights outside the US). In addition, 2005 and 2006 saw the European launches of XAGRID and FOSRENOL respectively. For 2006, sales outside North America represented approximately 21% of total net product sales (2005: 17%) and Shire expects this upward trend to continue in 2007. Shire's late stage development pipeline contains a number of products with global rights, including GA-GCB (acquired as part of the TKT acquisition), DAYTRANA and VYVANSE. The Company intends to launch these products in both the US and Europe, thus furthering the Company's European expansion.

Shire's continued expansion in Europe will be driven by the development of products with patent protection in both the North American and European markets wherever possible. In 2007 and the first half of 2008, Europe should see:-

- the continued roll out of FOSRENOL;

- the launch of ELAPRASE;

- the launch of DYNEPO;
- the launch of MEZAVANT.

In 2007 and the first half of 2008, the US should see:

- the continued roll out of DAYTRANA and ELAPRASE;
- the launch of LIALDA;
- the launch of VYVANSE;
- a regulatory response on the NDAs for SPD503 and SPD465, which were filed in 2006.

This program of new product launches will require significant investment in advertising, promotional spend and in some cases, additional sales representatives leading to an increase in overall SG&A costs for 2007. SG&A costs as a proportion of product sales are expected to be similar to 2006.

The specialist nature of HGT products means that relatively low SG&A and infrastructure investment is required, making them ideal products for Shire to launch into new markets. 2006 saw the expansion of REPLAGAL in Argentina. Shire will continue to consider launching products in new markets where entry barriers are low. In markets outside North America and Europe where products require significant SG&A and infrastructure investment, Shire will continue to seek out-licensing partners. In 2004, the Company successfully out-licensed the Japanese marketing and development rights for AGRYLIN and FOSRENOL to two companies with an established presence in this market. Shire's partner Dainippon Sumitomo Pharma Co., Limited launched REPLAGAL in Japan in the first quarter of 2007.

R&D

Over the last three years Shire has significantly refocused its R&D efforts on products in its core therapeutic areas, which meet the needs of the specialist physician. The Company has also concentrated its resources on obtaining regulatory approval of its later-stage pipeline products within its core therapeutic areas.

Evidence of the successful execution of this strategy can be seen from the progression of the Company's development pipeline over the last three years. Since January 2004, eight products have received regulatory approval in the US (including DAYTRANA and ELAPRASE in 2006, LIALDA in January 2007 and VYVANSE in February 2007) and four in Europe (including ELAPRASE and MEZAVANT in January 2007), the Company has another two products in registration in the US (SPD 503 and SPD 465).

Shire's strategy is focused on the development of product candidates that have a lower risk profile. Shire's acquisition of TKT was driven, in part, by the comparatively low risk of developing protein replacement therapies for genetic disease compared to other drug discovery approaches.

R&D costs in 2007 will be affected by Shire's Phase 3(b) and Phase 4 studies to support new product launches, development of new projects (including the Women's Health franchise), the continuation of Phase 3 trials on GA-GCB and pre-clinical development of three new HGT projects.

Patents and Market Exclusivity

The loss or expiration of patent protection or market exclusivity with respect to any of the Company's major products could have a material adverse effect on future revenues and net income as generic manufacturers may produce similar drugs and generally be able to sell the Company's drugs at a lower price as their costs of development are

significantly lower than Shire's. As ADDERALL XR is, in revenue terms, Shire's most significant product, representing 48% of total revenues (2005: 46%), the loss, expiration or circumvention of patent protection on this product in particular will be material to the Company's revenues and earnings.

Shire is engaged in various legal proceedings with generic manufacturers with respect to its ADDERALL XR patents and the patents for certain other products. These are discussed in more detail in ITEM 3: Legal Proceedings.

The potential impact of the introduction of generic products is illustrated by the approval in April 2005 of several generic versions of AGRYLIN, which as expected, adversely affected Shire's sales of this product from this date. US prescriptions for AGRYLIN in 2006 were 91% less than in 2005.

In consequence of the issues associated with the loss or expiry of patent protection or market exclusivity, Shire seeks to focus its business development activity on the acquisition and in-licensing of products and projects which have the benefit of long-term patent protection and market exclusivity.

Business Development

The Company remains active in seeking out opportunities to acquire new products or companies that fit its business strategy and existing therapeutic areas, as well as new complementary therapeutic areas.

In the therapeutic area of CNS, Shire in-licensed the global rights to Valrocemide (SPD493) and other related compounds from Yissum Research and Development Company in July 2006. SPD493 is being developed for the treatment of a number of CNS disorders.

In the therapeutic areas of renal and HGT, Shire in-licensed the global rights to Tissue Protective Cytokines (SPD500) from Warren in September 2006. SPD500 is being developed pre-clinically in non-nervous systems indications, including renal and genetic disease areas.

In August 2006, Shire entered the Women's Health therapeutic area with the acquisition of rights to the transvaginal ring technology of Duramed, a subsidiary of Barr, in a number of markets outside North America including the larger European markets together with a license in the same countries to Duramed's oral contraceptive, SEASONIQUE. SEASONIQUE, which is in Phase 3 studies in Europe, is already approved and marketed by Duramed in the US.

As part of its strategy of focusing on drugs with long term patent protection in its core therapeutic areas, the Company continued its disposal program of non-core assets with the sale to Duramed of ADDERALL for $63 million in August 2006. ADDERALL was Shire's immediate-release ADHD product which has been subject to generic competition since 2002.

Shire also licensed the US and Can adian rights for the investigational HIV compound, SPD754 (also known as apricitabine), to the Australian biotechnology company Avexa on January 23, 2007. Shire received an up-front cash payment of $10 million, 8 million additional Avexa shares (taking its shareholding in Avexa to just over 8%) and may receive further milestones and royalties.

Organization and Structure

During 2006, Shire completed the integration of TKT into the Company. Total integration costs from acquisition to December 31, 2006 totaled $15.3 million.

Recent developments

Acquisition of New River

On February 20, 2007 Shire announced that it has agreed to acquire New River for $64 per New River share, or approximately $2.6 billion for the fully diluted equity interest, in an all cash transaction unanimously recommended by the Boards of both companies. The acquisition is structured as a tender offer for all outstanding shares of New River followed by a merger. The acquisition is subject to the approval of Shire plc's shareholders as well as the satisfaction of certain customary conditions, including the tender of a majority of the outstanding New River shares on a fully-diluted basis and the expiration or earlier

termination of the Hart-Scott-Rodino waiting period. For accounting purposes, the acquisition of New River will be accounted for as a purchase business combination in accordance with SFAS No. 141.

The total consideration for the acquisition of New River amounts to approximately $2.6 billion in cash. Shire has entered into new bank facilities of $2.3 billion to provide part of the financing for the acquisition. This new facility is conditional upon, amongst other things, approval being given by Shire plc's shareholders at an Extraordinary General Meeting for Shire plc to exceed the limit on its aggregate borrowings set out in Shire plc's Articles of Association.

Shire plc has also raised approximately $900 million through the private placement of 42,883,721 new ordinary shares to certain institutional investors worldwide at a price of 1075 pence per share. The newly issued shares represent approximately 8.4 per cent of Shire plc's issued ordinary share capital prior to the placing.

For further information see Exhibit 99.2 to the 8-K filed on February 23, 2007.

VYVANSE (previously known as NRP104)

On February 23, 2007, the US Food and Drug Administration (FDA) approved VYVANSE, indicated for the treatment of ADHD. The FDA has proposed that VYVANSE be classified as a Schedule II controlled substance. This proposal was submitted to and accepted by the US Drug Enforcement Administration (DEA). A final scheduling decision is expected from the DEA following a 30-day period for public comment. Pending final scheduling designation, product launch is anticipated in Q2 2007.

ELAPRASE

On January 8, 2007 the EMEA granted marketing authorization for the use of ELAPRASE for the long-term treatment of patients with Hunter syndrome. Pricing and reimbursement procedures are already underway for ELAPRASE in many European countries and it will be launched across the majority of European countries in 2007.

LIALDA/MEZAVANT

On January 16, 2007 the FDA approved LIALDA, indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis. LIALDA is the first and only FDA-approved once-daily oral formulation of mesalamine. Once-daily LIALDA contains the highest mesalamine dose per tablet (1.2g), so patients can take as few as two tablets once daily. The Company anticipates launching LIALDA in the US during the first quarter of 2007.

In Europe, Shire has received core labelling information approval for MEZAVANT in 15 EU countries (including UK, Germany, France and Spain) following the decentralised procedures. Associated national approvals should follow in the first quarter of 2007 and have been received in Austria, Denmark and the UK.

SPD754

Shire licensed the US and Canadian rights for the investigational HIV compound, SPD754 (also known as apricitabine), to the Australian biotechnology company Avexa on January 23, 2007. Shire received an up-front cash payment of $10 million, 8 million additional Avexa shares (taking its shareholding in Avexa to just over 8%) and may receive further milestones and royalties.

ADDERALL XR

Health Canada granted a marketing license application for the adult indication in February 2007.

FOSRENOL

Shire launched FOSRENOL in the UK in February 2007 following the product's authorisation.

REPLAGAL

Dainippon Sumitomo Pharma Co., Ltd. launched REPLAGAL in Japan on February 15, 2007.

2006 Pipeline highlights

Shire focuses its development resources on projects within its core therapeutic areas of CNS, GI, HGT and GP.

- ELAPRASE: The US Food and Drug Administration (FDA) approved ELAPRASE in the US on July 24, 2006 and it was launched in the US in August 2006 and by December 31, 2006 over 110 patients in the US had received treatment.

- SPD465: On July 21, 2006 the Company submitted a NDA to the FDA for SPD465 for the treatment of ADHD in the adult population. The PDUFA date for the FDA to issue a formal response to this application is May 21, 2007.

- SPD503: The Company filed a NDA with the FDA on August 24, 2006 for the use of SPD503 as a treatment of ADHD in children and adolescents. The PDUFA date for the FDA to issue a formal response to this application is June 24, 2007.

- GA-GCB: The Phase 3 clinical program was initiated in January 2007.

- Enzyme Replacement Therapies: The Company has completed proof of concept studies and has advanced into pre-clinical development three projects for the treatment of lysosomal storage disorders; namely enzyme replacement therapies for Sanfilippo syndrome (Mucopolysaccharidosis IIIA), metachromatic leukodystrophy and intrathecal delivery of ELAPRASE for Hunter syndrome patients with significant central nervous system symptoms (Hunter CNS)

- SPD491 - A once-a-day, non opiate, transdermal analgesic being developed with the goal of non-scheduled labeling to treat moderate to severe pain, will enter Phase 1 testing in Q1 2007.

- SPD535 - Pre-clinical evaluation for development of a novel platelet-lowering agent.

In addition Shire in-licensed:

- Rights to the transvaginal ring technology of Duramed in a number of markets outside of North America including the larger European markets, in August 2006 together with a license in the same countries to Duramed's oral contraceptive, SEASONIQUE (levonorgestrel/ethinyl estradiol).

- Global rights to SPD500 (Tissue Protective Cytokine technology), from Warren Pharmaceuticals, Inc. (Warren) in September 2006. SPD500 is being developed pre-clinically in non-nervous system indications, including renal and genetic disease areas.

- Global rights to SPD493 (Valrocemide) and other related compounds, from Yissum Research and Development Company in July 2006. SPD493 is being developed at Phase 1 for the treatment of a number of central nervous system disorders.

Results of operations for the years to December 31, 2006 and 2005

For the year to December 31, 2006 the Company's total revenues increased by 12% to $1,796.5 million, compared to $1,599.3 million in 2005. Net income for the year to December 31, 2006 was $278.2 million compared to a net loss of $578.4 million (restated) in 2005. The Company's net loss for 2005 was primarily attributable to the IPR&D write-off of $815 million (restated) following the acquisition of TKT.

Total revenues

The following table provides an analysis of the Company's total revenues by source:

Year to December 31,	**2006**	**2005**	**Change**

	$M	$M	%
Product sales	1,535.8	1,327.7	+16
Royalties	242.9	242.9	+0
Other revenues	17.8	28.7	-38
Total	1,796.5	1,599.3	+12

All product sales are reported in the Pharmaceutical Products segment, all royalties are reported in the Royalty segment.

Product sales

Year to December 31,

	2006 $'M	2005 $M	Product sales growth %	US prescription growth %
CNS				
ADDERALL XR	863.6	730.8	+18	+8
ADDERALL	23.6	43.1	-45	-20
DAYTRANA	25.1	-	n/a	n/a
CARBATROL	68.3	72.1	-5	-9
GI				
PENTASA	137.8	136.1	+1	+2
COLAZIDE	9.2	8.6	+7	n/a
GP				
AGRYLIN and XAGRID				
RoW	53.3	46.8	+14	n/a
North America (US & Canada)	7.5	46.0	-84	-91
FOSRENOL	44.8	53.5	-16	+34
CALCICHEW	45.5	38.7	+18	n/a
REMINYL/REMINYL XL	21.5	13.5	+59	n/a
SOLARAZE	13.2	12.5	+6	n/a
VANIQA	7.9	6.3	+25	n/a
LODINE	12.6	12.6	-	n/a
HGT				
REPLAGAL*	117.7	41.3	n/a	n/a
ELAPRASE	23.6	-	n/a	n/a
Other	60.6	65.8	-8	
Total	1,535.8	1,327.7	+16	

* In 2005 this represents REPLAGAL sales for the five-month period since the acquisition of TKT. Total sales including pre-acquisition sales of $53.3 million were $94.6 million for the year ending December 31, 2005.

The following discussion includes references to US prescription and US market share data for key products. The source of this data is IMS, December 2006.

ADDERALL XR

ADDERALL XR is the leading brand in the US ADHD market with an average market share of 26% in 2006 (2005: 25%). US ADHD market growth of 4% and the 1% increase in average market share contributed to an 8% increase in US prescriptions for ADDERALL XR for year to December 31, 2006 compared to the same period in 2005.

Sales of ADDERALL XR for the year to December 31, 2006 were $863.6 million, an increase of 18% compared to the same period in 2005 (200 5: $730.8 million). Product sales growth was significantly higher than prescription growth due primarily to price increases in August 2005 and April 2006.

During October 2005 Shire filed a Citizen Petition with the FDA requesting that the FDA require more rigorous bioequivalence testing or additional clinical testing for generic or follow-on drug products that reference ADDERALL XR before they can be approved. Shire received correspondence from the FDA in April 2006 stating that, due to the complex issues raised requiring extensive review and analysis by the FDA's officials, a decision cannot yet be reached by the FDA. The FDA did not provide any guidance as to when that decision may be reached.

On August 14, 2006 Shire and Barr announced that all pending litigation in connection with Barr's ANDA and its attempt to market generic versions of Shire's ADDERALL XR had been settled. As part of the settlement, Barr entered into consent judgments and agreed to permanent injunctions confirming the validity and enforceability of Shire's US Patents Nos. 6,322,819 (the "'819 Patent"), 6,601,300 (the "'300 Patent") and 6,913,768 (the "'768

Patent"). Barr has also admitted that any generic product made under its ANDA would infringe the '768 patent. Under the terms of the settlement, Barr will not be permitted to market a generic version of ADDERALL XR in the US until April 1, 2009, except in certain limited circumstances, such as the launch of another party's generic version of ADDERALL XR. No payments to Barr are involved in the settlement agreement.

In January 2006, Shire settled its ADDERALL XR patent infringement lawsuits with Impax. Under the terms of the settlement, Impax will be permitted to market generic versions of ADDERALL XR in the US no later than January 1, 2010 and will pay the Company a royalty from those sales. In certain situations, such as the launch of another generic version of ADDERALL XR, Impax may be permitted to enter the market as the Company's authorized generic. No payments to Impax are involved in the settlement agreement.

Patent litigation proceedings relating to ADDERALL XR are in-progress. For further information see ITEM 3: Legal Proceedings.

ADDERALL

In September 2006, the Company sold to Duramed the product rights to ADDERALL for $63.0 million. The sales in the year of $23.6 million occurred prior to the sale of the product rights.

For further information see ITEM 3: Legal Proceedings.

DAYTRANA

Following its launch in June 2006, DAYTRANA achieved a 2% share of the US ADHD market by December 31, 2006. Sales for the year to December 31, 2006 were $25.1 million, a level of sales which triggered the first of three potential $25.0 million sales milestone payments to Noven. This milestone, which was paid on February 14, 2007, has been capitalized and will be amortized over 10 years. Net sales for 2006 were impacted by the redemption of $14 million of coupons issued to support the product launch.

The addition of DAYTRANA, combined with growth in ADDERALL XR's market share has helped Shire grow its total share of the US ADHD market to 28% at December 31, 2006 compared to 26% (which included a 1% share relating to ADDERALL) at December 31, 2005.

Shire has received reports concerning difficulty removing the release liner from a small percentage of Daytrana patches. Although the product meets specifications, during the first quarter of 2007 Noven implemented manufacturing enhancements intended to make Daytrana easier to use.

CARBATROL

US prescriptions for the year ending December 31, 2006 were down 9% compared to the same period in 2005. This was primarily due to a 6% decline in the US extended release carbamazepine prescription market. CARBATROL's US market share remained at 42%.

Sales of CARBATROL for the year ending December 31, 2006 were $68.3 million, a decrease of 5% compared to the same period in 2005 (2005: $72.1 million). The fall in sales is due to the decrease in the extended release carbamezapine market and a reduction of pipeline inventory in 2006 compared to stocking in 2005, offset by price increases in October 2005 and July 2006.

In July 2006 Impax deployed a sales force to begin promotion of CARBATROL under a promotional services agreement for the US market signed in January 2006.

Patent litigation proceedings with Nostrum and Corepharma relating to CARBATROL are in-progress. For further information see ITEM 3: Legal Proceedings.

PENTASA

US prescriptions for the year ending December 31, 2006 were up 2% compared to the same period in 2005 primarily due to a 4% increase in the US oral mesalamine prescription market. PENTASA's US market share remained at 18%.

Sales of PENTASA for the year ending December 31, 2006 were $137.8 million, an increase of 1% compared to the same period in 2005 (2005: $136.1 million). Sales growth is marginally lower than prescription growth due to the lower levels of pipeline stocking in 2006, partly offset by the impact of price increases in January 2006 and November 2006.

XAGRID

Sales for the year ended December 31, 2006 were $53.3 million, an increase of 14% compared to the same period in 2005 (2005: $46.8 million). Expressed in transaction currencies (XAGRID is primarily sold in Euros), sales increased by 13% due mainly to strong growth in France and Spain. In addition there was a benefit of 1% from favorable exchange rate movements against the US dollar.

AGRYLIN sales in North America (US and Canada) were $7.5 million for the year ended December 31, 2006 (2005: $46.0 million). This reduction was expected following the approval of generic versions of AGRYLIN in the US market in April 2005.

FOSRENOL

US prescriptions for the year ending December 31, 2006 were up 34% compared to 2005 due to FOSRENOL increasing its average share of the total US phosphate binding market to 9% (2005: 7%) and market growth of 9% over the same period. FOSRENOL was launched in the US in January 2005.

US sales of FOSRENOL for the year ending December 31, 2006 were $40.2 million (2005: $53.0 million). The decrease in net sales of 16% compared to prescription growth of 34% is primarily due to destocking in 2006 compared to significant stocking of higher strength formulations at the end of 2005.

An agreement with Abbott was signed in December 2006 for the co-promotion of FOSRENOL in the US. Abbott's US renal care sales team will co-promote FOSRENOL with its own renal product ZEMPLAR. Shire's US sales force will also continue to promote FOSRENOL. This agreement began in Q1 2007 and will continue for a term of five years.

European sales of FOSRENOL for the year ending December 31, 2006 were $4.6 million (2005: $0.5 million), giving total FOSRENOL sales worldwide of $44.8 million (2005: $53.5 million).

FOSRENOL has now been launched in Germany, France and a number of other European countries, including the UK which launched in February 2007. Launches will continue throughout 2007 in the EU including Italy and Spain, subject to finalization of national licensing and conclusion of pricing and re-imbursement negotiations.

On October 18, 2006 Health Canada granted a marketing license application for FOSRENOL. The Canadian launch is planned for Q2 2007.

REPLAGAL

Sales for the year ending December 31, 2006 were $117.7 million, of which 88% were in Europe and 12% in the rest of the world. Sales for REPLAGAL for the year ending December 31, 2005 were $94.6 million, including pre-acquisition sales of $53.3 million. This represents a like-for-like increase in sales of 24% which was due to greater European coverage by an increased number of sales representatives and strong growth in the rest of the world market (excluding the US).

ELAPRASE

ELAPRASE was launched in the US in August 2006 and has had a strong start with over 110 patients receiving treatment by the end of December 2006. In addition, through the pre-approval process, over 100 patients were receiving treatment in Europe by the end of the year. Sales reached $23.6 million by December 31, 2006.

Foreign exchange effect

As many of the Company's sales revenues are earned in currencies other than US dollars (primarily Canadian dollars, Pounds Sterling, Swedish Krona and Euros), revenue growth reported in US dollars includes the impact of translating the sales made in the transaction currency into US dollars. With the US dollar weakening against these currencies over the last 12 months, the translation of sales made in these currencies into US dollars has benefited reported growth rates. The table below shows the effect of foreign exchange translations on the revenue growth of the key affected products as well as the underlying performance of key products in their transaction currencies:

Year to December 31,	2006 sales in US dollars $M	2006 sales growth in transaction currency	Impact of translation to US dollars	2006 sales growth in US dollars
XAGRID sales in Euros	32.5	12 %	+1 %	13 %
XAGRID sales in Pounds Sterling	20.8	14 %	+2 %	16 %
CALCICHEW sales in Pounds Sterling	41.0	15 %	+2 %	17 %
REMINYL and REMINYL XL sales in Pounds Sterling	19.8	64 %	+3 %	67 %

Notes
Revenue growth analysis does not include REPLAGAL sales of $104.3 million in Euros and Swedish Krona. There is no comparative data for REPLAGAL as it was acquired with TKT in July 2005.

Royalties

Royalty revenue remained constant at $242.9 million for the year to December 31, 2006, (2005: $242.9 million).

Year to December 31,	2006 $M	2005 $M	Change %
3TC	150.9	159.8	-6
ZEFFIX	34.8	30.5	+14
Others	57.2	52.6	+9
Total			

242.9	242.9	+0

3TC

Royalties from sales of 3TC for the year to December 31, 2006 were $150.9 million, a decrease of 6% compared to the prior year (2005: $159.8 million).

Shire receives royalties from GSK on worldwide 3TC sales. GSK's worldwide sales of 3TC for the year to December 31, 2006 were $1,138 million, a decrease of 6% compared to prior year (2005: $1,211 million). The nucleoside analogue market for HIV has continued to grow, however competitive pressures within the market have increased, leading to a decline in 3TC sales.

ZEFFIX

Royalties from sales of ZEFFIX for the year to December 31, 2006 were $34.8 million, an increase of 14% compared to the prior year (2005: $30.5 million).

Shire receives royalties from GSK on worldwide ZEFFIX sales. GSK's worldwide sales of ZEFFIX for the year to December 31, 2006 were $301 million, an increase of 13% compared to prior year (2005: $266 million). This increase was mainly due to strong growth in the Korean, Japanese and Chinese markets.

OTHER

Other royalties are primarily in respect of REMINYL and REMINYL ER (known as RAZADYNE and RAZADYNE ER in the US), a product marketed worldwide (excluding the UK and the Republic of Ireland) by Janssen Pharmaceutical N.V. (Janssen), an affiliate of Johnson & Johnson. Shire has the exclusive marketing rights in the UK and the Republic of Ireland.

Sales of the REMINYL/ RAZADYNE range, for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type, continue to grow.

In June 2006 Janssen and Synaptech filed a law suit against Barr for infringement of their patent rights relating to RAZADYNE ER as a result of Barr filing an ANDA with the FDA for a generic version of RAZADYNE ER . No court date has been set.

Barr and other companies have filed ANDAs with the FDA for generic versions of RAZADYNE and Janssen and Synaptech have filed law suits against some of those ANDA filers. The court date for the first of these proceedings is May 2007.

Cost of product sales

For the year to December 31, 2006 the cost of product sales was 16% of product sales (2005: 16%). For the year to December 31, 2006 the cost of product sales for REPLAGAL included a $47.0 million adjustment in respect of acquired inventories (2005: $41.9 million). This fair value adjustment increased Shire's cost of product sales as a percentage of sales for the year ended December 31, 2006 by 3% (2005: 3%).

For the year to December 31, 2006 cost of product sales included a charge of $3.2 million for stock based compensation under SFAS 123(R) (2005: $1.5 million).

Research and development (R&D)

R&D expenditure increased from $339.1 million in the year to December 31, 2005 to $386.9 million in the year to December 31, 2006, an increase of 14%. The increase was primarily due to:

- The addition of two significant R&D projects following the acquisition of TKT (ELAPRASE and GA-GCB); and
- Upfront payments made to Duramed and Warren of $25.0 million and $5.5 million, respectively.

Expressed as a percentage of total revenues, R&D expenditure was 22% for the year to December 31, 2006 (2005: 21%). In both

periods payments were made to New River of $50 million for in-licensing VYVANSE. These payments have both been expensed in accordance with Shire's accounting policy. The payments to New River, Duramed and Warren in the year to December 31, 2006 totalled $80.5 million, equivalent to 5% of total revenues. In the year to December 31, 2005 the $50.0 million payment to New River was equivalent to 3% of total revenues.

For the year to December 31, 2006 R&D included a charge of $5.4 million for stock based compensation under SFAS123(R) (2005: $2.9 million).

Selling, general and administrative (SG&A) expenses

Total SG&A costs increased from $729.9 million in the year to December 31, 2005, to $935.0 million in the year to December 31, 2006, an increase of 28%. As a percentage of product sales, total SG&A costs were 61% (2005: 55%).

Year to December 31,	**2006**	**Adjusted 2005**	**Change**
	$'M	**$M**	**%**
Sales costs	244.3	190.3	+28
Marketing costs	343.4	255.3	+35
Other SG&A costs	247.7	209.9	+18
	835.4	655.5	+27
Depreciation and amortization [(1)]	99.6	74.4	+35
Total SG&A costs	935.0	729.9	+28

(1) Excludes depreciation from manufacturing plants of $4.8 million (2005: $3.5 million) which is included in cost of product sales.

SG&A expenses increased from $655.5 million in the year to December 31, 2005 to $835.4 million in the year to December 31, 2006, an increase of 27%. As a percentage of product sales, SG&A expenses were 54% (2005: 49%).

The increase in SG&A expenses was expected, with additional expenditure required for:

- The promotion and launch of DAYTRANA (including an increase in the ADHD sales force);
- The recruitment of a new GI sales force in the US;
- The recruitment of new US and European sales forces to launch ELAPRASE ; and
- Pre-launch activities relating to the 2007 launches of DYNEPO, LIALDA and VYVANSE.

For the year to December 31, 2006 SG&A included a charge of $34.4 million for stock based compensation under SFAS123(R) (2005: $24.8 million), representing 2% of total revenue (2005: 1%).

The depreciation charge for the year to December 31, 2006 was $43.3 million (2005: $29.2 million, including $6.5 million for impairments of property, plant and equipment). The amortization charge for the year to December 31, 2006 was $56.3 million (2005: $45.2 million). The increase in both depreciation and amortization is primarily due to the inclusion of a full year's amortisation and depreciation charge in respect of assets acquired through the TKT acquisition, together with the amortization of capitalized milestone payments for DAYTRANA following its launch in June 2006.

Intangible asset impairments

The charge for intangible asset impairments for the year to December 31, 2006 was $1.1 million (2005: $5.6 million). The

impairment charge for the year to December 31, 2006 resulted from the decision to stop selling a non-core product.

The impairment charge for the year to December 31, 2005 resulted from the approval of generic versions of AGRYLIN and the decision not to support and promote certain non-core products.

Reorganization costs

In 2005, the Company recorded reorganization costs of $9.4 million as a result of a consolidation of its North American sites. No reorganization costs were incurred in 2006.

Integration costs

For the year to December 31, 2006 the Company incurred $5.6 million of costs associated with the integration of the TKT business into the Shire group (2005: $9.7 million). This included retention payments for key staff of $3.0 million, IT costs of $1.2 million and other costs of $1.4 million.

Gain on sale of product rights

For the year to December 31, 2006 the Company recognized a pre-tax gain of $63.0 million (2005: $nil) on the disposal of ADDERALL to Duramed for $63.0 million in cash.

In-Process Research and Development

During the year to December 31, 2005 the Company wrote off the portion of the TKT purchase price allocated to IPR&D of $815 million (restated). This amount represents the value ascribed to those intangible assets acquired as part of the TKT acquisition, which at the time of acquisition had not been approved by the FDA or other regulatory authorities, including ELAPRASE and GA-GCB.

Interest income

For the year to December 31, 2006 the Company received interest income of $50.5 million (2005: $35.3 million). This income primarily related to interest received on Shire's cash balances. Interest income for the year ending December 31, 2006 is higher than for the year ending December 31, 2005 primarily as a result of increases in US dollar interest rates.

Interest expense

For the year to December 31, 2006 the Company incurred interest expense of $26.4 million (2005: $12.0 million).

In both years this expense primarily relates to a provision for interest, which may be awarded by the Court in respect of amounts due to those ex-TKT shareholders who have requested appraisal of the acquisition consideration payable for their TKT shares. The trial date for the appraisal rights litigation has been set for April 23, 2007 (see ITEM 3: Legal Proceedings and Note 1 to the Company's consolidated financial statements contained in Part IV of this Annual Report).

Other income, net

Year to December 31,	**2006**	**2005**
	$'M	**$'M**
Impairment of long-term investments (see Note 11)	(2.1)	(2.0)
GeneChem Funds management fee	4.6	4.3
Gain on sale of available-for-sale security (see Note 11)	-	3.9
Gain on sale of drug formulation business	-	3.6
Foreign exchange	3.2	(1.4)

Other	3.8	1.5
	9.5	9.9

The write-down of non-current asset investments in 2006 and 2005 resulted from events and circumstances that indicated there was an other-than-temporary impairment of investments and, accordingly, management recorded an impairment based on its assessment of fair value.

For further details see Note 26, Note 11 and Note 6 to the Company's consolidated financial statements contained in Part IV of this Annual Report.

Income taxes

The effective rate of tax for the year to December 31, 2006 was 26.8% (2005: 27.5%, after excluding the impact of the $815 million (restated) write-off of IPR&D in respect of the TKT acquisition). The effective rate has fallen by 0.7% as a result of an increase in deferred tax assets, offset by an increase in current tax liabilities. The increase in deferred tax assets was primarily due to the reversal of valuation allowances following changes in estimates as to realisation, and by the crystallisation of additional losses. The increase in current tax liabilities was primarily a result of additional tax contingencies of $187 million recognised in relation to ongoing tax audits. Following this reversal of valuation allowances, the net deferred tax asset has increased to $261.0 million at December 31, 2006 (2005: $116.2 million). Realization of deferred tax assets is dependent upon generating sufficient taxable income to utilize such assets. Although realization of these assets is not assured, it is more likely than not that the amount recognized will be realized. See Note 29 to the Company's consolidated financial statements contained in Part IV of this Annual Report for expiry dates of these tax losses.

Equity in earnings/(losses) of equity method investees

Net earnings of equity method investees of $5.7 million were recorded for the year to December 31, 2006 (2005: net losses of $1.0 million). This comprised earnings of $6.2 million from the 50% share of the antiviral commercialization partnership with GSK in Canada (2005: $5.3 million), offset by losses of $0.5 million being the Company's share of losses in the GeneChem and EGS Healthcare Funds (2005: losses of $6.3 million).

Discontinued operations

During the year to December 31, 2006 the gains on disposition of discontinued operations totaled $40.6 million (2005: $3.1 million). During 2006, IDB repaid $70.6 million, being the injectable flu development tranche of the $100.0 million development loan facility provided to IDB as part of their acquisition of Shire's vaccine business. The repayment followed GSK's acquisition of IDB, after which IDB was provided with resources by GSK to fund the early repayment of the injectable flu tranche. The $29.4 million pipeline development tranche of the loan facility is still outstanding.

At the time of the disposal, a provision of $70.0 million was charged to discontinued operations on the basis that there was no certainty of recovery of this amount. The $70.0 million provision was allocated against all of the pipeline development tranche ($29.4 million) and against $40.6 million of the $70.6 million injectable flu development tranche. Accordingly, a gain on disposition of discontinued operations of $40.6 million (2005: $3.1 million) was recognized on repayment of the loan by IDB.

The repayment of the $70.6 million injectable flu tranche had no tax effect.

Results of operations for the years to December 31, 2005 and 2004

For the year to December 31, 2005, the Company's total revenues increased by 17% to $1,599.3 million, compared to $1,363.2 million in 2004. Net loss for the year to December 31, 2005 was $578.4 million (restated) compared to net income of $236.3 million in 2004. The Company's net loss for 2005 was primarily attributable to the IPR&D write-off of $815.0 million (restated) following the

acquisition of TKT.

Total revenues

The following table provides an analysis of the Company's total revenues by source:

Year to December 31,	**2005**	**2004**	**Change**
	$M	**$M**	**%**
Product sales	1,327.7	1,112.5	+19
Royalties	242.9	230.4	+5
Licensing and development	15.0	13.4	+11
Other revenues	13.7	6.9	n/a
Total	1,599.3	1,363.2	+17

All product sales are reported in the Pharmaceutical Products segment, all royalties are reported in the Royalty segment.

Product sales

Year to December 31,	**2005 $'M**	**2004 $'M**	**Product sales growth %**	**US prescription growth %**
CNS				
ADDERALL XR	730.8	606.7	+20	+12
ADDERALL	43.1	34.5	+25	N/A
CARBATROL	72.1	54.3	+33	-8
GI				
PENTASA	136.1	115.0	+18	+6
COLAZIDE	8.6	8.2	+5	N/A
GP				
AGRYLIN and XAGRID				
North America (US & Canada)	46.0	119.1	-61	-48
RoW	46.8	33.4	+40	N/A
FOSRENOL	53.5	-	N/A	N/A
CALCICHEW	38.7	38.3	+1	N/A
SOLARAZE	12.5	9.5	+32	N/A
REMINYL/REMINYL XL	13.5	10.8	+25	N/A
LODINE	12.6	7.6	+66	N/A
HGT				
REPLAGAL*	41.3	-	N/A	N/A
Other	72.1	75.1	-4	N/A
Total	1,327.7	1,112.5	+19	

* This represents REPLAGAL sales for the five-month period since the acquisition of TKT.

The following discussion includes references to prescription and market share data for key products. The source of this data is IMS, December 2005.

During 2005, the Company concluded new ‘fee for service’ agreements with two of its three significant wholesale customers. These agreements, which are commonplace in the pharmaceutical industry, change the way wholesalers are compensated. Under the agreements, the wholesalers receive a distribution fee from pharmaceutical suppliers. These ‘fee for service’ agreements eliminate wholesalers' incentives to acquire and hold excess inventories. The Company believes this will reduce the significant impact of wholesaler stocking and de-stocking on its product sales. Further, the wholesalers will provide data regarding their inventories of the Company's products it has on hand. The Company is negotiating a ‘fee for service’ agreement with its remaining significant wholesale customer. ‘Fees for service’ are treated as a sales deduction, thus affecting revenues rather than cost of sales.

ADDERALL XR

US prescriptions for ADDERALL XR for the year to December 31, 2005, were up 12%. ADDERALL XR further strengthened its position as the leading brand in the US ADHD market with a 1% increase in market share to an all time high of 26% in December 2005 (December 2004: 25%). In addition, the US ADHD market grew 5% overall compared to the same period in 2004.

Product sales growth was higher than prescription growth for the year due mainly to the impact of price increases in December 2004 and August 2005, partially offset by a decrease in pipeline inventory and higher sales deductions.

FDA approval of the adolescent indication for ADDERALL XR was received on July 22, 2005.

On February 12, 2005, Shire announced that it had suspended sales of ADDERALL XR in Canada at the request of Health Canada. On August 24, 2005, Shire announced that Health Canada would reinstate the marketing authorization of ADDERALL XR in Canada effective August 26, 2005. This reinstatement follows the acceptance by Health Canada of the recommendations from the New Drug Committee, which was appointed by Health Canada at Shire’s request to review the suspension of ADDERALL XR in Canada.

During October 2005, Shire filed a Citizen Petition with the FDA requesting that the FDA require more rigorous bioequivalence testing or additional clinical testing for generic or follow-on drug products that reference ADDERALL XR before they can be approved. Shire believes that these requested criteria will ensure that generic formulations of ADDERALL XR or follow-on drug products will be clinically effective and safe. In January 2006, Shire chose to file a supplemental amendment to its original Citizen Petition, which included additional clinical data in support of the original filing. The FDA has six months to respond to Shire’s petition and while this petition is under review it will not grant final approval of generic or follow-on drug products referencing ADDERALL XR.

On February 9, 2006, an FDA Advisory Committee recommended to the FDA that risk information about cardiovascular events be included in a "black box warning" for all stimulant medicines used to treat ADHD. In making its recommendation, the Advisory Committee recognized that the reported incidence rates of the rare serious cardiovascular adverse events that were discussed by the Committee are generally within the rates that would be expected from the untreated general population. ADDERALL XR and ADDERALL already include a "black box warning" in their labels for safety concerns related to amphetamine abuse or misuse and also warn of the risk of sudden death in patients with structural cardiac abnormalities. Shire stands behind the current labeling and believes that further action is unwarranted. It is too early to tell at the time of filing of this Annual Report on Form 10-K what impact the actions of the FDA will have on consumer sentiment in the US ADHD market or on ADDERALL XR’s US market share.

In January 2006, Shire settled its ADDERALL XR patent infringement lawsuits with Impax. The litigations involved Shire US patents, Nos. 6,322,819 (the ‘819 Patent), 6,605,300 (the ‘300 Patent) and 6,913,768 (the ‘768 Patent). As part of the settlement, Impax has confirmed that its proposed generic ADDERALL XR product infringes Shire’s ‘819, ‘300 and ‘768 Patents and that the three patents are valid and enforceable. Under the terms of the settlement, Impax will be permitted to market generic versions of ADDERALL XR in the US no later than January 1, 2010, and will pay Shire a royalty from those sales. In certain situations, such as the launch of another generic version of ADDERALL XR, Impax may be permitted to enter the market as Shire’s authorized generic.

Shire’s ADDERALL XR patent infringement lawsuits with Barr continue. Shire is seeking a ruling that Barr’s ANDA seeking permission to market its generic versions of ADDERALL XR infringes the ‘819, ‘300 and ‘768 Patents. Barr’s 30-month stay under the Hatch-Waxman Act expired on February 18, 2006. Following the expiry of the 30 month stay, the FDA may approve Barr’s ANDA. A final pre-trial conference in the ‘819 and ‘300 Patent cases is set for March 10, 2006. No trial date has been set. Shire is

continuing its discussions with Barr in connection with these lawsuits and the discussions are progressing. For further information see ITEM 3: Legal Proceedings. If the Company does not prevail in the lawsuits, the Company's sales of ADDERALL XR will decrease. Any decrease in the sales of ADDERALL XR would significantly reduce revenues and earnings.

CARBATROL

US prescriptions for the year to December 31, 2005, were down 8% compared to the previous year. This was due primarily to supply constraints, a 4% decrease in Shire's market share of the total US extended release carbamazepine prescription market to 42% in December 2005 (December 2004: 46%) and a 5% decrease in that market as a whole. The supply constraints have now been resolved.

Product sales for the year to December 31, 2005 were up 33% compared to the previous year. The difference between sales growth and the lower level of prescriptions is due to price increases in August 2004 and October 2005 and to lower sales deductions than in 2004.

Patent litigation proceedings with Nostrum relating to CARBATROL are in-progress. For further information see ITEM 3: Legal Proceedings.

PENTASA

US prescriptions for the year to December 31, 2005 were up 6% compared to the previous year. The increase was due to the success of the co-promotional agreement with Solvay Pharmaceuticals Inc., the impact of the 500mg dosage form launched in the third quarter of 2004 and a 2% increase in the total US oral mesalamine prescription market.

Product sales for the year to December 31, 2005 were up 18%, compared to the previous year. The difference between sales growth and prescription growth is due to the impact of the September 2004 price increase and a normalization of pipeline inventories compared to lower levels in 2004.

PENTASA had an 18% share of the total US oral mesalamine prescription market in December 2005 (December 2004: 18%).

AGRYLIN/XAGRID

AGRYLIN/XAGRID sales worldwide for the year to December 31, 2005 were $92.8 million, down 39% compared to the previous year (2004: $152.5 million).

North American sales were $46.0 million, down 61% compared to the previous year (2004: $119.1 million). This reduction was expected following the approval of generic versions of AGRYLIN in the US market in April 2005.

Rest of the World sales (all sales outside North America) were $46.8 million, up 40%, compared to the previous year (2004: $33.4 million). This was primarily due to the successful launch of XAGRID in the UK, Germany and France in the first quarter of 2005 and Spain in the third quarter of 2005. In accordance with current orphan drug legislation in the EU, XAGRID will have up to 10 years of marketing exclusivity in the EU.

FOSRENOL

FOSRENOL was launched in the US in January 2005. Product sales for the year to December 31, 2005 were $53.5 million, with US prescriptions for the year totaling 137,000.

FOSRENOL had an 8% share of the total US phosphate binding market in December 2005.

On November 28, 2005 the FDA approved new, higher dose formulations of FOSRENOL. New, higher dose strengths of 750 milligrams and 1000 milligrams were shipped to wholesalers in the US in December 2005. Higher dose strengths should help to reduce the number of pills that end-stage renal disease patients need to take to achieve target phosphorus levels.

Product sales in Q4 2005 were $29.0 million compared with $9.7 million in Q3 2005. The variance relates primarily to increased pipeline inventory sales to wholesalers of the new higher dose formulation during December.

FOSRENOL was launched in Austria in December 2005. Shire continues its discussions relating to FOSRENOL with regulatory authorities and reimbursement agencies across Europe and other regions and further launches are expected in European markets over the next few months, subject to obtaining national approvals and concluding pricing and reimbursement negotiations.

REPLAGAL

REPLAGAL was acquired by Shire as part of the TKT acquisition, which completed on July 27, 2005. Product sales for the period since acquisition were $41.3 million. The majority of REPLAGAL sales are in Europe. Total sales for the full year, including pre-acquisition sales, were $94.6 million (2004: $77.4 million). The increase in sales (including pre-acquisition sales) is primarily due to greater European coverage by an increased number of sales representatives.

Foreign exchange effect

As many of the Company's sales revenues are earned in currencies other than US dollars (primarily Canadian dollars, Pounds Sterling, Swedish Krona and Euros), revenue growth reported in US dollars includes the impact of translating the sales made in a local currency, into US dollars. With the US dollar strengthening against these currencies over the last 12 months, the translation of sales made in these currencies into US dollars has impacted on the reported growth rates. The table below shows the effect of foreign exchange translations on the revenue growth of the key affected products as well as the underlying performance of key products in their transaction currency:

Year to December 31,	2005 sales in US dollars $M	2005 sales growth in transaction currency	Impact of translation to US dollars	2005 sales growth in US dollars
AGRYLIN sales in Canadian dollars	5.3	-49 %	+4%	-45%
AGRYLIN/XAGRID sales in Euros	28.3	+41%	-	+41%
AGRYLIN/XAGRID sales in Pounds sterling	18.9	+11%	-1%	+10%
CALCICHEW sales in Pounds sterling	35.0	+1%	-1%	-
REMINYL and REMINYL XL sales in Pounds sterling	11.8	+27%	-1%	+26%

Notes

Revenue growth analysis does not include sales of:

- ADDERALL XR in Canadian Dollars due to the fact that sales of ADDERALL XR in Canada were suspended for most of 2005; and
- REPLAGAL sales of $41.3 million in Euros and Swedish Krona. There is no comparative data for REPLAGAL as it was acquired with TKT in July 2005.

Royalties

Royalty revenue increased 5% to $242.9 million for the year to December 31, 2005, (2004: $230.4 million) primarily as a result of strong sales growth.

Year to December 31,	2005 $'M	2004 $'M	Change %
3TC	159.8	155.8	+3

ZEFFIX	30.5	27.4	+11
Others	52.6	47.2	+11
Total	242.9	230.4	+5

3TC

Royalties from sales of 3TC for the year to December 31, 2005, were $159.8 million, an increase of 3% compared to 2004 ($155.8 million). This was due to the continued growth in the nucleoside analog market for HIV and a small positive impact of foreign exchange movements.

Shire receives royalties from GSK on worldwide 3TC sales. GSK's worldwide sales of 3TC for the year to December 31, 2005, were $1,211 million, an increase of 2% compared to prior year (2004: $1,184 million).

ZEFFIX

Royalties from sales of ZEFFIX for the year to December 31, 2005, were $30.5 million, an increase of 11% compared to 2004 ($27.4 million), due to strong growth in the Japanese market and a small positive impact of foreign exchange movements.

Shire receives royalties from GSK on worldwide ZEFFIX sales. GSK's worldwide sales of ZEFFIX for the year to December 31, 2005, were $266 million, an increase of 11% compared to prior year (2004: $240 million).

OTHER

Other royalties are primarily in respect of REMINYL and REMINYL XL (now marketed as RAZADYNE and RAZADYNE ER in the US), a product marketed worldwide by Janssen Pharmaceutica N.V. (Janssen), an affiliate of

Johnson and Johnson, with the exception of the UK and the Republic of Ireland where Shire acquired the exclusive marketing rights from May 2004.

Sales of the REMINYL/RAZADYNE range, for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type, are growing well in the Alzheimer's market.

On April 11, 2005, Ortho-McNeil Neurologics Inc. (Janssen's US affiliate company) announced that REMINYL would be marketed in the US under the new product name of RAZADYNE. Subsequently, in the US, REMINYL XL was launched as RAZADYNE ER. Ortho-McNeil Neurologics Inc. worked closely with the FDA on a name change following dispensing errors in the US between REMINYL and the Type 2 diabetes mellitus drug known as AMARYL. Shire is only aware of one similar dispensing error outside the US.

On March 1, 2005, the National Institute for Health and Clinical Excellence (NICE) in England and Wales issued an Appraisal Consultation Document (ACD). This document included a recommendation that all existing approved products for the symptomatic treatment of mild to moderate Alzheimer's disease in England and Wales should no longer be reimbursed by the NHS when used in the treatment of new patients. The recommendation potentially affected sales of REMINYL and of REMINYL XL in England and Wales. An amended ACD was issued by NICE on January 23, 2006. The new ACD recommends that REMINYL and REMINYL XL, together with other drugs in the same class, be reimbursed by the NHS when used for the treatment of either (i) patients with existing Alzheimer's disease already being treated with one of these drugs; or (ii) newly diagnosed patients once their disease has progressed to a moderate stage. Therefore the current recommendation excludes the reimbursement of treatment for patients presenting with mild symptoms of Alzheimer's disease for which REMINYL and REMINYL XL are approved. A final appraisal document is expected from NICE in July 2006.

Cost of product sales

For the year to December 31, 2005, the cost of product sales amounted to 16% of product sales (2004: 13%). The decrease in gross margin is primarily due to the addition of REPLAGAL to Shire's product portfolio following the acquisition of TKT.

REPLAGAL's cost of product sales relates entirely to the acquired inventories, which in accordance with US generally accepted accounting principles (GAAP), have been accounted for at fair value, estimated to be 97% of the expected sales price of REPLAGAL. Accordingly, little or no margin will be reflected for REPLAGAL sales until all acquired finished goods have been sold (anticipated Q3 2006). For the year to December 31, 2005 the cost of product sales for REPLAGAL includes a $41.9 million adjustment in respect of the acquired inventory of which $39.8 million related to sales of acquired finished goods and $2.1 million was a write-off of damaged work-in-process. In 2005, this fair value adjustment increased Shire's cost of product sales by 3%.

Research and development (R&D)

R&D expenditure increased from $199.6 million in the year to December 31, 2004, to $339.1 million in 2005. Expressed as a percentage of total revenues, R&D expenditure was 21% for the year to December 31, 2005 (2004: 15%). The increase was primarily due to:

- The initial payment to New River of $50 million for in-licensing VYVANSE, which has been expensed in accordance with the Company's accounting policy; and
- The addition of two significant R&D projects following the acquisition of TKT (ELAPRASE and GA-GCB).

The New River payment and the R&D expenditure on ELAPRASE and GA-GCB represented 5% of R&D expenditure as a percentage of revenues.

Shire's pipeline is now well advanced with seven projects in late stage development or registration.

Selling, general and administrative (SG&A) expenses

Total SG&A costs increased from $545.4 million in the year to December 31, 2004, to $730.0 million in the year to December 31, 2005, an increase of 34%. As a percentage of product sales, SG&A costs were 55% (2004: 49%).

Year to December 31,	Adjusted 2005 $'M	Adjusted 2004 $'M	Change %
Sales costs	190.3	153.6	+24
Marketing costs	255.3	176.0	+45
Other SG&A costs	209.9	157.3	+33
	655.5	486.9	+35
Depreciation and amortization (1)	74.4	58.5	+27
Total SG&A costs	729.9	545.4	+34

(1) Excludes depreciation from manufacturing plants of $3.5 million (2004: $2.7 million) which is included in cost of product sales.

SG&A expenses increased from $486.9 million in the year to December 31, 2004, to $655.6 million in 2005, an increase of 35%. As a percentage of product sales, these expenses were 49% (2004: 44%).

This increase was expected, with additional costs attributable to four product launches during 2005, together with incremental costs in 2005 associated with the new FOSRENOL and EQUETRO sales forces, patent litigation and infrastructure, $24.5 million of SG&A costs related to the acquired TKT business and $4.5 million related to the set up of the new listed holding company for the Shire Company.

The depreciation charge for the year to December 31, 2005, was $29.2 million (2004: $19.8 million), which in 2005 included property, plant and equipment write-downs of $6.5 million (2004: $1.6 million). Amortization charges, including the amortization on acquired products, were $45.2 million for the year to December 31, 2005 (2004: $38.7 million).

Intangible asset impairments

The charge for intangible asset impairments for the year to December 31, 2005 was $5.6 million (2004: $13.5 million).

The approval of generic versions of AGRYLIN in April 2005 and the decision not to support and promote certain non-core products going forward resulted in changes to the estimate of the Company's future cash flows and, as a result, impairments were required in both 2005 and 2004.

Reorganization costs

Year to December 31,	2005 $'M	2004 $'M
Employee severance	1.6	20.0
Relocation costs	-	13.8
Write-off of property, plant and equipment	-	1.2
Consultancy costs	0.5	2.9
Duplicate facilities	7.3	5.1
Information technology costs	-	2.1
Other costs	-	3.4
	9.4	48.5

As previously disclosed, the Company began a consolidation of its North American sites in 2004, with the aim of decreasing the number of sites from 16 to four, including the opening of a new US headquarters office in Wayne, Pennsylvania. The Company recorded costs of $9.4 million in 2005 and $48.5 million in 2004 primarily associated with:

- severance costs relating to 137 employees;
- retention payments to key employees;
- relocation costs relating to 85 employees who relocated to Wayne, Pennsylvania;
- costs of duplicate facilities (including lease exit costs); and

- other incremental costs associated with the site closures, such as legal, consultancy, the write-down of property, plant and equipment and information technology costs.

Following the closure of the Newport site in July 2005, the site consolidation is now complete and no further reorganization costs are expected.

Integration costs

For the year to December 31, 2005, the Company incurred $9.7 million of costs associated with the integration of the TKT business into the Shire Company (2004: $nil). This included retention payments for key staff of $7.0 million, information technology costs of $1.0 million and other costs of $1.7 million.

In-process R&D write-off

During the year to December 31, 2005, as required by Financial Accounting Standards Board Interpretation No 4, "Applicability of FASB Statement No 2 to Business Combinations Accounted for by the Purchase Method" (FIN 4), the Company wrote off the portion of the TKT purchase price allocated to IPR&D of $815.0 million (restated). This amount represents the value of those intangible assets acquired as part of the TKT acquisition, which at the time of acquisition had not been approved by the FDA or other regulatory authorities, including ELAPRASE and GA-GCB. For the determination of the fair value of IPR&D see Critical Accounting Estimates below.

Interest income

For the year to December 31, 2005 the Company received interest income of $35.3 million (2004: $21.9 million). The increase compared to 2004 is due to higher interest rates on the Company's US cash deposits which were partially offset by the interest foregone by the Company on the net payments of $1.1 billion made to date in respect of the acquisition of TKT.

Interest expense

For the year to December 31, 2005 the Company incurred interest expense of $12.0 million (2004: $12.3 million).

In 2005, this expense included a $7.7 million provision for interest, which may be awarded by the court in respect of amounts due to former holders of approximately 11.3 million shares of TKT common stock who have submitted written demands for appraisal of these shares (see ITEM 3: Legal Proceedings and Note 1 to the Company's consolidated financial statements contained in Part IV of this Annual Report). In addition, interest expense includes $1.2 million, relating to the costs of a bridging loan to finance the TKT acquisition and other interest related expenses of $3.1 million.

In 2004, interest expense included the write-off of $7.4 million of deferred debt acquisition costs arising on the issue of convertible loan notes in August 2001. The write-off was required as a significant portion of the convertible loan notes were redeemed. The $7.4 million represented the balance of these fees at the date of redemption in August 2004. In addition, interest expense included a $4.2 million interest charge incurred prior to the redemption and $0.1 million of other interest related expenses.

Other income/(expense), net

Year to December 31,	2005 $'M	2004 $'M
Investment income	8.3	18.9
Write-down of non-current asset investments	(2.0)	(15.4)
Gain on sale of drug formulation business	3.6	-
Foreign exchange and other	-	0.3
Total	9.9	3.8

For further details see Note 26 and Note 6 to the Company's consolidated financial statements contained in Part IV of this Annual Report.

The write-down in investments in 2005 and 2004 resulted from events and circumstances that indicated there was an other-than-temporary impairment of investments and, accordingly, management recorded an impairment based on its assessment of fair value. Further details are disclosed in Note 11 to the Company's consolidated financial statements contained in Part IV of this Annual Report.

Investment income for 2005 included a $3.9 million realized gain on the sale of a portfolio investment (2004: $14.8 million).

Income taxes

The Company's effective tax rate for 2005 was 18.1% (restated) (a tax charge of $88.8 million on losses from continuing operations before income taxes and equity method investees of $491.7 million (restated)). The significant difference from the prior year effective tax rate of 28% is due to the IPR&D write-off of $815 million (restated), which is not tax deductible.

As at December 31, 2005, the Company had deferred tax assets net of valuation allowances of $116.2 million (2004: $78.1 million). The increase in deferred tax is primarily attributable to the acquisition of TKT that resulted in a net deferred tax asset of $60.4 million being recorded in the opening day balance sheet, although part of the asset was subsequently realized in the post acquisition period. Realization of deferred tax assets is dependent upon generating sufficient taxable income to utilize such assets.

Although realization of these assets is not assured, it is more likely than not that the amount recognized will be realized. See Note 29 to the Company's consolidated financial statements contained in Part IV of this Annual Report for expiry dates of these tax losses.

Equity in earnings/(losses) of equity method investees

Net losses of $1.0 million were recorded for the year to December 31, 2005 (2004: net earnings of $2.5 million). This comprised earnings of $5.3 million from the 50% share of the antiviral commercialization partnership with GSK in Canada (2004: $4.4 million), offset by the Company's share of losses in the GeneChem and EGS Healthcare Funds of $6.3 million (2004: $1.9 million).

Discontinued operations

During the year to December 31, 2005 gains on disposition of the discontinued operations totaled $3.1 million. This resulted from the finalization of the working capital agreement with IDB, which was part of the sale of Shire's vaccines business to IDB in 2004. As a result, a disputed amount, which had previously been provided for, was received and the corresponding provision was released.

Liquidity and capital resources

General

The Company's funding requirements depend on a number of factors, including its development programs; corporate, business and product acquisitions; the level of resources required for the expansion of manufacturing and marketing capabilities as the product base expands; increases in accounts receivable and inventory which may arise as sales levels increase; competitive and technological developments; the timing and cost of obtaining required regulatory approvals for new products; the timing and quantum of milestone payments on collaborative projects; the timing of and quantum of tax and dividend payments; the timing and quantum of purchases of Shire shares in the market to satisfy option exercises and the continuing cash generated from sales of Shire's key products.

An important part of Shire's business strategy is to protect its products and technologies through the use of patents, proprietary technologies and trademarks, to the extent available. The Company intends to defend its intellectual property and as a result may need cash for funding litigation expenses incurred.

The Company ordinarily finances its activities through cash generated from operating activities, credit facilities, private and public offerings of equity and debt securities and the proceeds of asset or investment disposals.

Credit Facilities

In connection with the acquisition of TKT, Shire plc and certain subsidiary companies entered into a Multicurrency Revolving Facilities Agreement (the "Facilities Agreement") with ABN AMRO Bank N.V., Barclays Capital, Citigroup Global Markets Limited, HSBC Bank plc and The Royal Bank of Scotland plc (the "Lenders") on June 15, 2005. The Facilities Agreement comprises two credit facilities: (i) a committed multicurrency three year revolving loan facility in an aggregate amount of $500 million ("Facility A") and (ii) a committed 364 day revolving loan facility in an aggregate amount of $300 million ("Facility B" and, together with Facility A, the "Facilities"). Shire plc has agreed to act as guarantor for any of its subsidiaries that borrow under the Facilities Agreement. In June 2006 Facility B was extended for a further 364 days to June 13, 2007. In October 2006, Facility B was reduced to $200 million.

As at December 31, 2006 and 2005, the Company had not drawn down on these Facilities. The Facilities Agreement was cancelled in full with effect from February 27, 2007.

In connection with the acquisition of New River, Shire plc entered into a Multicurrency Term and Revolving Facilities Agreement (the "New Facilities Agreement") with ABN AMRO Bank N.V., Barclays Capital, Citigroup Global Markets Limited and The Royal Bank of Scotland plc (the "Arrangers") on February 20, 2007. The New Facilities Agreement comprises three credit facilities: (i) a committed multicurrency five year term loan facility in an aggregate amount of $1,000 million ("Term Loan A"), (ii) a committed

multicurrency 364 day term (with a further 364 day extension option) loan facility in an aggregate amount of $300 million ("Term Loan B") and (iii) a committed five year revolving loan facility in an aggregate amount of $1,000 million (the "RCF" and, together with Term Loan A and Term Loan B, the "New Facilities"). Shire plc has agreed to act as guarantor for any of its subsidiaries that borrow under the New Facilities Agreement.

The RCF, which includes a $250 million swingline facility, may be used for general corporate purposes. Term Loan A and Term Loan B may be used only for financing the acquisition of New River (including related fees and transaction costs) and refinancing any existing indebtedness of New River or its subsidiaries.

The RCF and Term Loan A mature on February 20, 2012. Term Loan A is repaid in annual installments on the anniversary of the New Facilities Agreement in the following amounts: $150 million in 2008, $150 million in 2009, $200 million in 2010, $200 million in 2011 and the balance on maturity. Term Loan B matures on February 19, 2008. As noted above, at Shire's request, the maturity date of Term Loan B may be extended for a further 364 days.

The availability of loans under the New Facilities is subject to customary conditions, including the absence of any defaults thereunder and the accuracy (in all material respects) of Shire's representations and warranties contained therein.

The New Facilities include representations and warranties, covenants and events of default, including (i) requirements that Shire's ratio of Net Debt to EBITDA (as defined in the New Facilities Agreement) does not exceed 3.50:1 for the 12 month period ending December 31, 2007; 3.25:1 for the 12 month period ending 30 June 2008; and 3.00:1 for each 12 month period ending 31 December and 30 June thereafter and (ii) that the ratio of EBITDA to Net Interest (as defined in the New Facilities Agreement) must not be less than 4.0 to 1, for each 12 month period ending 31 December or 30 June, and additional limitations on the creation of liens, disposal of assets, incurrence of indebtedness, making of loans and giving of guarantees.

Interest on loans under the New Facilities will be payable on the last day of each interest period, which period may be one week or one, two, three or six months at the election of Shire (or as otherwise agreed with the Lenders). The interest rate on each loan drawn under the RCF or Term Loan A for each interest period is the percentage rate per annum which is the aggregate of the applicable margin (initially set at 0.80 per cent. per annum until delivery of the

compliance certificate for the year ending 31 December, 2007 and thereafter ranging from 0.40 to 0.80 per cent per annum, depending on the ratio of Net Debt to EBITDA), LIBOR, and mandatory cost, if any (as calculated in accordance with Schedule 5 of the New Facilities Agreement). The interest rate on each loan drawn under Term Loan B for each interest period is the percentage rate per annum which is the aggregate of the applicable margin (being from 0.50 per cent for the first six months from the date of the New Facilities Agreement, 0.75 per cent for the second six months and 1.00 per cent per annum thereafter), LIBOR, and mandatory cost, if any (as calculated in accordance with Schedule 5 of the New Facilities Agreement).

Shire shall also pay fees equal to 35 per cent per annum of the applicable margin on available commitments under the RCF for the availability period applicable to the RCF and 20 per cent per annum of the applicable margin on available commitments under Term Loan A and Term Loan B for the availability period applicable to Term Loan A and Term Loan B. Interest on overdue amounts under the New Facilities will accrue at a rate, which is one percentage point higher than the rates otherwise applicable to the loans under the New Facilities.

The New Facilities Agreement restricts (subject to certain carve-outs) Shire's ability to incur additional financial indebtedness, grant security over its assets or provide or guarantee loans. Further any lender may require mandatory prepayment of its participation if there is a change in control of Shire. In addition, in certain circumstances, the net proceeds of certain asset disposals by Shire must be applied towards mandatory prepayment of the facilities, subject to certain exceptions.

Upon a change of control of Shire or upon the occurrence of an event of default and the expiration of any applicable cure period, the total commitments under the New Facilities may be cancelled, all or part of the loans, (together with accrued interest and all other amounts accrued or outstanding) may become immediately due and payable. Events of default under the New Facilities Agreement include: (i) non-payment of any amounts due under the New Facilities; (ii) failure to satisfy any financial covenants; (iii) material misrepresentation in any of the finance documents; (iv) failure to pay, or certain other defaults under other financial indebtedness; (v) certain insolvency events or proceedings; (vi) material adverse changes in the business, operations, assets or financial condition of the group; (vii) certain ERISA breaches which would have a material adverse effect; (viii) if it becomes illegal for Shire or any of its subsidiaries that are parties to the New Facilities Agreement to perform their obligations or (ix) if Shire or any

subsidiary of Shire which is party to the New Facilities Agreement repudiates the New Facilities Agreement or any Finance Document (as defined in the New Facilities Agreement). The New Facilities Agreement is governed by English law.

Equity financing

Shire also raised approximately $900 million through the private placement of 42,883,721 new ordinary shares to certain institutional investors at a price of 1075 pence per share. The newly issued shares represent approximately 8.4 per cent of Shire plc's issued ordinary share capital prior to the placing.

Shire anticipates that its operating cash flow together with available cash, cash equivalents and short-term investments and the above mentioned New Facilities will be sufficient to meet its anticipated future operating expenses, any costs arising as a result of the acquisition of New River, outstanding costs related to the acquisition of TKT, capital expenditures, dividends, tax payments, share repurchases and debt service and lease obligations as they become due over the next twelve months.

If the Company decides to acquire other businesses, it expects to fund these acquisitions from existing cash resources, the New Facilities Agreement discussed above and possibly through new borrowings and/or the issue of new equity if necessary.

Sources and uses of cash

The following table provides an analysis of the Company's gross and net cash funds (excluding restricted cash) as at December 31, 2006 and 2005:

December 31,	2006 $'M	2005 $'M	Change %
Cash and cash equivalents	1,126.9	656.5	+72
Short term investments	-	6.9	n/a
Gross cash funds	1,126.9	663.4	+70
Total debt	-	(0.1)	n/a
Net cash funds	1,126.9	663.3	+70

Cash flow activity

Net cash provided by operating activities for the year to December 31, 2006, was $531.9 million, an increase of $147.6 million compared to the previous year. The increase in cash generation is primarily due to favorable

movements in working capital, in particular the timing of sales within the final quarter of 2006 coupled with a reduction in the net tax paid of $48.5 million due to the utilization of tax losses acquired as part of the TKT acquisition.

Net cash used in investing activities was $26.9 million in the year to December 31, 2006. This included purchases of property, plant and equipment of $100.3 million, intangibles of $58.8 million and long-term investments of $9.8 million respectively, offset by proceeds from the sale of the ADDERALL product rights for $63.0 million and proceeds from the loan repaid by IDB of $70.6 million (see Note 6 to the Company's consolidated financial statements contained in Part IV of this Annual Report). Capital expenditure on property, plant and equipment included $32.2 million on IT projects at the Wayne, Pennsylvania US headquarters; $8.0 million on building improvements and $12.5 million on IT at the Basingstoke, UK, headquarters; $9.9 million on construction work at Shire's manufacturing facility at Owings Mills, Maryland; and $8.8 million and $13.1 on leasehold improvements and IT equipment, respectively at Shire's site in Cambridge, Massachusetts. Capital expenditure on intangible assets included $50.0 million paid to Noven on the approval of DAYTRANA.

Net cash used in financing activities was $42.6 million for the year to December 31, 2006. This was primarily due to the cost to purchase treasury stock of $92.0 million and dividend payments of $32.4 million, offset by inflows of $81.9 million from the exercise of employee stock options.

Outstanding Letters of credit

As at December 31, 2006, the Company had irrevocable standby letters of credit with Barclays Bank plc in the amount of $14.2 million providing security on the recoverability of insurance claims, and with Bank of America in the amount of $7.8 million, providing security on the payment of lease obligations.

Cash Requirements

Aggregate Contractual Obligations

As at December 31, 2006, the Company's contractual obligations were as follows:

	Payments due by period				
Contractual obligations	**Total $'M**	**Less than 1 year $'M**	**1 - 3 years $'M**	**3 - 5 years $'M**	**More than 5 years $'M**
Operating leases [(i)]	157.4	28.8	51.2	39.1	38.3
Purchase obligations [(ii)]	155.1	117.8	27.7	8.3	1.3
Other long-term liabilities reflected on the Balance Sheet [(iii)]	500.7	481.6	10.9	1.8	6.4
Total	813.2	628.2	89.8	49.2	46.0

(i) The Company leases certain properties, motor vehicles and equipment under operating leases expiring through 2025.

(ii) Purchase obligations include agreements to purchase goods or services that are enforceable and legally binding and that specify all significant terms, including open purchase orders. Shire expects to fund these commitments with cash flows from operations.

(iii) Other long-term liabilities include the liability to dissenting shareholders. As at December 31, 2006, appraisal rights had been asserted in respect of approximately 11.3 million shares of TKT common stock. For further information see ITEM 3: Legal proceedings. As at December 31, 2006 the Company recorded a liability of $419.9 million based on the merger consideration of $37 per share for the 11.3 million shares outstanding at that time plus a provision for interest of $32.4 million that may be awarded by the Court (see Note 1). Until such time as the appraisal process is complete the Company is unable to determine the extent of its liability. For every $1 increase/decrease in the merger consideration applicable to those TKT shareholders who have asserted appraisal rights, the total estimated purchase price would increase/decrease by approximately $11.3 million.

The contractual obligations table above does not include payments yet to fall due upon the occurrence of certain milestones and other contractual commitments. The most significant payments are as follows:

(i) DAYTRANA

In connection with the Company's acquisition in 2003 from Noven of the worldwide sales and marketing rights to DAYTRANA, as at December 31, 2006 Shire has a remaining obligation to pay Noven up to $50 million, contingent on future sales performance.

DAYTRANA received final regulatory approval from the FDA on April 6, 2006 and as a result Shire paid a $50 million milestone to Noven. During the year, the Company also reached a sales milestone for DAYTRANA and as a result, Shire made a payment to Noven of $25 million in February 2007. Both amounts have been capitalized during the year to December 31, 2006 and amortization of these amounts, together with the upfront milestone payment of $25 million made in 2003, will continue over the estimated life of the product of approximately 10 years.

(ii) VYVANSE

In January 2005, Shire entered into an agreement with New River to collaborate in developing, manufacturing, marketing and selling VYVANSE in the US. In the rest of the world, Shire acquired the license to develop and commercialize VYVANSE, in consideration of a low double-digit royalty.

Under the terms of the agreement, the parties will collaborate on VYVANSE development, manufacturing, marketing and sales in the US. New River will be financially and operationally responsible for clinical and manufacturing development. Shire will book the product sales and New River will supply up to 25% of the sales effort under a co-promotion right. Shire is obligated to give VYVANSE marketing and promotional priority over its other oral ADHD stimulants should VYVANSE's label contain a claim that it has decreased potential for abuse or increased overdose protection. Shire paid an initial sum of $50 million on signing and a further $50 million was paid to New River following acceptance of the filing of a NDA by the FDA in January 2006.

If VYVANSE is approved with a Schedule III, IV or V classification or is unscheduled ("favorable scheduling"), Shire will pay New River a $300 million milestone payment. US operating profit will be divided as follows: Shire will retain 75% of profits for the first two years following launch, and the parties will share the profits equally thereafter.

In the event that VYVANSE receives a final Schedule II classification, no milestone payment will be payable by Shire to New River upon approval. Division of profits will be calculated under an alternative profit sharing scheme. New River's share of U.S. product profits for the first two years will be at least 25%, though it may increase to a value determined by a preset sales based formula; for following years, it will be at least 50%, though it may increase to a value determined by a preset sales based formula thereafter. These formulas, which include yearly threshold sales, were included in an 8-K filed with the SEC on October 10, 2006. If VYVANSE is classified as Schedule II on approval and then gets favorable scheduling within one year of the first commercial sale, Shire will pay New River a $200 million milestone payment; if favorable scheduling occurs by the third anniversary, the milestone payment will be $100 million. Upon favorable scheduling being achieved under each of these scenarios, the profit sharing formula reverts to that applicable to favorable scheduling. In addition, New River will be entitled to a $100 million milestone payment at the end of the first calendar year in which cumulative worldwide net sales of all collaboration products during that calendar year exceed $1 billion. A $5 million milestone payment is payable following the first commercial sale in specified European countries. Shire intends to capitalize and amortize any milestone payments over the life of the product.

Shire is entitled to terminate the agreement until 30 days following approval of VYVANSE. If Shire terminates before regulatory approval, no payment would be due to Shire. If Shire terminates after approval and VYVANSE has received a favorable scheduling assignment, no payment would be due to Shire. If the approved VYVANSE has received a Schedule II classification, Shire would be entitled to a $50 million termination payment, payable in cash, New River common stock, or an unsecured, 5-year promissory note, as will be agreed upon by Shire and New River.

On February 20, 2007 the Company announced that it had agreed to acquire New River for $2.6 billion in cash. On completion of the acquisition of New River, Shire will terminate these commitments. For further information see note 32 .

(iii) Women's Health Products

Shire and Duramed entered into an agreement related to Duramed's transvaginal ring technology that will be applied to at least five women's health products, as well as a license in a number of markets outside of North America, including the larger European markets to Duramed's oral contraceptive, SEASONIQUE. This agreement became effective on September 6, 2006.

Under this agreement, Shire will reimburse Duramed for US development expenses incurred going forward up to a maximum of $140 million over eight years. US development expenditure reimbursement for the year ended December 31, 2006, totalled $2.5 million, with $2.0 million due for reimbursement at December 31, 2006. At

December 31, 2006, the maximum future reimbursement for Duramed incurred US development expenditure is therefore $137.5 million. Shire will separately be responsible for development costs in its licensed territories.

(iv) Tissue Protective Cytokine (TPC) development rights

In connection with the Company's licence of TPC rights in non-nervous system indications from Warren, the Company is committed to making payments on achievement of certain milestones. The Company is not required to make any payments to Warren upon regulatory approval of the first product for the first indication. However, it is obligated to make milestone payments to Warren of $25 million upon regulatory approval in up to five subsequent major indications.

(v) Other R&D and sales milestones

In addition to the commitments set out in (i) to (iv) above, at December 31, 2006 the Company had commitments payable on achievement of specified milestones and fees payable for products under development in-licensed from third parties of $75.6 million (December 31, 2005: $18.0 million), of which $12.9 million could be paid in 2007.

Off-balance sheet arrangements

There are no off-balance sheet arrangements that have, or are reasonably likely to have, a current or future effect on the Company's financial condition, revenues or expenses, results of operations, liquidity, capital expenditures or capital resources that are material to investors.

Foreign currency fluctuations

A number of operating units in the Company have functional currencies other than the US Dollar. As such, the consolidated financial results are subject to fluctuations in exchange rates, particularly those between the US Dollar, Canadian Dollar, Pound Sterling, Euro and Swedish Krona. The accumulated foreign currency translation differences of $80.4 million are reported within accumulated other comprehensive income in the consolidated balance sheet and a $3.2 million gain is reported in other income on the consolidated income statement.

As at December 31, 2006, the Company had 18 outstanding forward foreign exchange contracts with a total principal amount equivalent to $98.3 million to manage the currency risk associated with certain inter-company loans. As at December 31, 2006 there were net unrealized losses of $8.1 million on these contracts.

Concentration of credit risk

The Company's revenues from product sales are mainly derived from agreements with major pharmaceutical companies and relationships with pharmaceutical wholesale distributors and retail pharmacy chains. For the year to December 31, 2006 there were three customers in the US who accounted for 71% of the Company's total revenues. However, such clients typically have significant cash resources and as such the risk from concentration of credit is considered minimal. The Company has taken positive steps to manage any credit risk associated with these transactions and operates clearly defined credit evaluation procedures.

Financial instruments that potentially expose Shire to concentrations of credit risk consist primarily of short-term cash investments and trade accounts receivable. Excess cash is invested in short-term money market instruments, including bank term deposits, money market and liquidity funds and other debt securities from a variety of financial institutions with strong credit ratings. These investments typically bear minimal risk.

Inflation

Although at reduced levels in recent years, inflation continues to apply upward pressure on the cost of goods and services which are used in the business. However, the Company believes that the net effect of inflation on its operations has been minimal during the past three years.

Critical accounting estimates

The preparation of consolidated financial statements, in conformity with US GAAP and SEC regulations, requires management to

make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the consolidated financial statements and reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates. Estimates and assumptions are primarily made in relation to provisions for litigation, valuation of intangible assets (including those acquired through the acquisition of TKT), inventory acquired through the acquisition of TKT, the valuation of IPR&D, the valuation of equity investments, sales deductions, income taxes and share-based payments. and the amount payable to former holders of TKT common stock of approximately 11.3 million shares who have submitted written demands for appraisal of these shares in relation to the Company's acquisition of TKT on July 27, 2005.

(i) Litigation

The Company has a number of lawsuits pending that relate to product liability claims. Shire accounts for litigation losses in accordance with SFAS No. 5 "Accounting for Contingencies" (SFAS No 5). Under SFAS No. 5, loss contingency provisions are recorded for probable losses when management is able to reasonably estimate the loss. Where the estimated loss lies within a range and no particular amount within that range is a better estimate than any other amount the minimum amount is recorded. In other cases management's best estimate of the loss is recorded. These estimates are developed substantially earlier than the ultimate loss is known, and the estimates are refined each accounting period, as additional information becomes known. Best estimates are reviewed quarterly and estimates are changed when expectations are revised. Any outcome upon settlement that deviates from Shire's best estimate may result in an additional or lesser expense in a future accounting period. There were no significant changes in estimates in respect of product liability claim provisions in 2006.

(ii) Valuation of intangible assets

(a) General

The Company has acquired and continues to acquire significant intangible assets, recorded at acquisition cost. As at December 31, 2006, the carrying value of such intangibles was $762.4 million, which primarily related to the Company's DAYTRANA, DYNEPO, FOSRENOL, PENTASA, REMINYL, REPLAGAL, SOLARAZE and XAGRID products. Those assets which do not yet have a defined revenue stream and for which there are no alternative uses are expensed upon acquisition, and those that do have a defined revenue stream (namely commercial products or rights to products awaiting final regulatory approval) are capitalized and amortized over their estimated useful life. Management's estimate of the useful life considers, inter alia, the following factors: the expected use of the asset by the Company; any legal, regulatory, or contractual provisions that may limit the useful life and the effects of demand; competition; and other economic factors (such as the stability of the industry, known technological advances, legislative action that results in an uncertain or changing regulatory environment, and expected changes in distribution channels).

A prolonged general economic downturn, sustained government pressure on prices and, specifically, competitive pricing, could create an imbalance of industry supply and demand, or otherwise diminish volumes or profits. Such events, combined with changes in interest rates, could adversely affect Shire's valuation of the estimated future net cash flows generated by its long-lived assets. As a result, future operating results could be materially and adversely affected by impairment charges related to the recoverability of long-lived assets.

In the year to December 31, 2006, changes to the estimated future net cash flows from certain products resulted in a $1.1 million impairment of intangible assets (2005: $5.6 million, 2004: $13.5 million). In the year to December 31, 2005, the Company decreased the estimated life of a product, which resulted in an additional amortization charge of $1.7 million in the year to December 31, 2005 and $5.9 million in the year to December 2006.

The Company reviews intangible assets subject to amortization for impairment periodically using an undiscounted net cash flow approach whenever events or circumstances suggest that the carrying value of the intangible asset is not recoverable. If the undiscounted cash flows of an intangible asset are less than its carrying value, the intangible asset is written down to its fair value, based on estimated discounted cash flows. When cash flows cannot be identified for an individual asset, the review is applied at the lowest group level for which cash flows are identifiable.

(b) Intangible assets acquired through the acquisition of TKT

The fair values of all of the identifiable intangible assets acquired through the acquisition of TKT have been determined using an income approach on a project-by-project basis, by independent valuation specialists. This method starts with a forecast of all of the expected future net cash flows either generated or saved as a result of ownership of the intellectual property, the customer relationships and the other intangible assets. These cash flows are then adjusted to present value by applying an appropriate discount rate that reflects the risk factors associated with the cash flow streams.

The forecast of future cash flows requires various assumptions to be made, including:

- revenue that is reasonably likely to result from the sale of products including the estimated number of units to be sold, estimated selling prices, estimated market penetration and estimated market share and year-over-year growth rates over the product life cycles
- royalty or license fees saved by owning the intellectual property associated with the products
- cost of sales for the products using historical data, industry data or other sources of market data
- sales and marketing expense using historical data, industry data or other sources of market data
- general and administrative expenses
- research and development expenses
- the estimated life of the products
- the tax amortisation benefit available to a market participant purchasing the assets piecemeal

The valuations are based on information at the time of the acquisition and the expectations and assumptions that have been deemed reasonable by the Company's management. No assurance can be given, however, that the underlying assumptions or events associated with such assets will occur as projected. For these reasons, among others, the actual cash flows may vary from forecasts of future cash flows.

The Company reviews intangible assets for impairment periodically using an undiscounted net cash flow approach whenever events or circumstances suggest that the carrying value of the intangible asset is not recoverable. If the discounted cash flows of an intangible asset are less than its carrying value, the intangible asset is written down to its fair value, based on estimated discounted cash flows. When cash flows cannot be identified for an individual asset, the review is applied at the lowest group level for which cash flows are identifiable.

(iii) Inventory acquired through the acquisition of TKT

Inventory acquired through the acquisition of TKT has been fair valued in accordance with SFAS No. 141 as follows:

- Finished goods and merchandise at estimated selling prices less the sum of (a) costs of disposal and (b) a reasonable profit allowance for the selling effort of the acquiring entity
- Work in process at estimated selling prices of finished goods less the sum of (a) costs to complete, (b) costs of disposal, and (c) a reasonable profit allowance for the completing and selling effort of the acquiring entity based on profit for similar finished goods

The Company's management assumed that a "reasonable profit allowance for the selling effort of the acquiring entity" would be 3% of sales proceeds (expected at the acquisition date). This is due to the minimal sales effort required by Shire as acquiror to realize sales of the acquired inventory, given the small size of the existing prescription population to whom specialized physicians prescribe REPLAGAL, the frequency and duration of treatment required, and low levels of patient switching, together with the low cost and complexity of distribution. The relevance of this assumption is that it has an impact on the recorded cost of product sales for acquired REPLAGAL inventory. For every one percentage point increase in the profit allowance percentage for the selling effort, our cost of product sales in the year to December 31, 2006 would have reduced by approximately $0.6 million. All REPLAGAL inventories acquired as part of the TKT acquisition had been consumed by December 31, 2006.

The valuation of acquired work in process required the Company's management to estimate the level of completion reached at the acquisition date. This required the exercise of judgment in ascribing value creation to different phases of a complex biological

manufacturing process. The relevance of this estimate is that it has an impact on the recorded cost of product sales for acquired REPLAGAL inventory. For every one percentage point increase in the assumed percentage level of completion, our cost of product sales in the year to December 31, 2006 would have increased by $0.5 million. All REPLAGAL work in process acquired as part of the TKT acquisition had been consumed by December 31, 2006.

The fair value of inventory is based on information at the date of acquisition and the expectations and assumptions that have been deemed reasonable by the Company's management. No assurance can be given, however, that the underlying assumptions or events associated with inventory will occur as projected. For these reasons, among others, the actual completion costs, disposal costs and proceeds associated with acquired inventory may vary from those forecasted. As each estimate was made in the context of the conditions that existed at the TKT acquisition date, they are not expected to change from period to period.

(iv) In-process R&D write-off

IPR&D is defined by FIN 4 as being a development project that has been initiated and achieved material progress but has not yet resulted in a commercially viable product.

As required by FIN 4, the portion of the purchase price allocated to IPR&D of $815 million (restated), acquired as part of the TKT transaction, was immediately expensed in the year to December 31, 2005. During the year to December 31, 2006 the Company determined that the value ascribed to IPR&D acquired as a result of the TKT

acquisition did not include the benefit of tax amortization as required by the American Institute of Certified Public Accountants (AICPA) Practice Aid, *Assets Acquired in a Business Combination to Be Used in Research and Development Activities: A Focus on Software, Electronic Devices, and Pharmaceutical Industries* . Consequently the financial statements for the year to December 31, 2005 have been restated in respect of the value ascribed to IPR&D, acquired as part of the TKT acquisition and subsequently written off as required under US GAAP in the quarter ended September 30, 2005. S ee note 3(a) to the Company's consolidated financial statements contained in Part IV of this Annual Report.

In the identification of intangible assets, consideration is given to whether any technology that is identified is developed or in-process. The American Institute of Certified Public Accountants Practice Aid "Assets Acquired in a Business Combination to Be Used in Research and Development Activities: A Focus on Software, Electronic Devices and Pharmaceutical Industries" gives guidance on the factors that should be considered when identifying IPR&D.

The fair value of IPR&D acquired with TKT was determined using the income approach on a project-by-project basis. This method is based on the present value of earnings attributable to the asset or costs avoided as a result of owning the assets. This method includes risk factors, which include applying an appropriate discount rate that reflects the project's stage of completion, the nature of the product, the scientific data associated with the technology, the current patent situation and market competition.

The forecast of future cash flows required the following assumptions to be made:

- Revenue that is likely to result from specific IPR&D projects, including the likelihood of approval of the product, estimated number of units to be sold, estimated selling prices, estimated market penetration, estimated market share and year-over-year growth rates over the product life cycles
- Cost of sales related to the potential products using historical data, industry data or other sources of market data
- Sales and marketing expense using historical data, industry data or other market data
- General and administrative expenses
- R&D expenses
- The tax amortisation benefit available to a market participant purchasing the assets piecemeal

The valuations are based on information at the time of the acquisition and the expectations and assumptions that have been deemed reasonable by the Company's management. No assurance can be given, however, that the underlying assumptions or events associated with such assets will occur as projected. For these reasons, among others, the actual cash flows may vary from forecasts of future cash flows.

(v) Valuation of Equity Investments

The Company has investments in certain public and private pharmaceutical and biotechnology companies. The carrying values of these investments are periodically reviewed for other-than-temporary impairments whenever certain events or circumstances suggest that the carrying value of an investment exceeds the fair market value of the investment. Indicators of other-than-temporary impairments include:

- the market value of a quoted investment being below the carrying value of the investment for an extended period
- adverse news on a private company's progress in scientific technology/development of compounds
- recent stock issuances at a price below the investment price

If the fair value appears to be below the carrying value the Company considers all available evidence in assessing whether there is an other-than-temporary impairment. This evidence would include:

- the level of progress in the investee's scientific technology/ development of compounds
- ongoing activity in collaborations with the investee
- whether or not other substantial investee-specific adverse events have occurred which may cause a decline in value
- analysis and valuation of comparable companies
- the overall financial condition of the investee

In instances when the review indicates that there is an other-than-temporary impairment, the Company writes down the investment to the fair value of the investment, recording an impairment charge in the consolidated statements of operations. During 2006, Shire recorded a charge for an other than temporary impairment of $0.3 million (2005: $0.4 million) to an investment in a public company. The determination of the fair value of private company investments and the determination of whether an unrealized loss on a publicly quoted investment is permanent requires

significant judgment and can have a material impact on the reported results. During 2006, Shire recorded impairments on long-term investments of $2.1 million (2005: $2.0 million, 2004: $15.4 million).

(vi) Sales Deductions

Sales deductions consist of statutory rebates to state Medicaid and other government agencies, contractual rebates with health-maintenance organizations (HMOs), product returns, sales discounts (including trade discounts and distribution service fees), wholesaler chargebacks, and allowances for the coupon sampling program. These deductions are recorded as reductions to revenue in the same period as the related sales with estimates of future utilization derived from historical experience adjusted to reflect known changes in the factors that impact such reserves.

The Company accounts for these sales deductions in accordance with EITF Issue No. 01-9, *Accounting for Consideration Given by a Vendor to a Customer (Including a Reseller of the Vendor's Products)* , and SFAS No. 48, *Revenue Recognition When Right of*

Return Exists, as applicable.

The Company has the following significant categories of sales deductions, all of which involve estimates and judgments which the Company considers to be critical accounting estimates, and require the Company to use information from external sources:

Medicaid and HMO Rebates

Statutory rebates to state Medicaid agencies and contractual rebates to HMOs under managed care programs are based on statutory or negotiated discounts to the selling price. Medicaid rebates generally increase as a percentage of the selling price over the life of the product (if prices increase faster than inflation).

As it can take up to six months for information to reach the Company on actual usage of the Company's products in managed care and Medicaid programs and on the total discounts to be reimbursed, the Company maintains reserves for amounts payable under these programs relating to sold products.

The amount of the reserve is based on historical experience of rebates, the timing of payments, the level of reimbursement claims, changes in prices (both normal selling prices and statutory or negotiated prices), changes in prescription demand patterns, and the levels of inventory in the distribution channel.

Shire's estimates of the level of inventory in the distribution channel are based on product-by-product inventory data provided by wholesalers (including data provided by wholesalers as part of the new 'fee for service' agreements -- see Item 1: Business - Manufacturing and Distribution - Material Customers for further information) and third-party prescription data (such as IMS Health National Prescription Audit data).

Revisions or clarification of guidelines from Centers for Medicare and Medicaid Services (CMS) related to state Medicaid and other government program reimbursement practices with retroactive application can result in changes to management's estimates of the rebates reported in prior periods. However, since the prices of the Company's products are fixed at the time of sale and the quantum of rebates is therefore reasonably determinable at the outset of each transaction, these factors would not impact the recording of revenues in accordance with generally accepted accounting principles.

The accrual estimation process for Medicaid and HMO rebates involves in each case a number of interrelating assumptions, which vary for each combination of product and Medicaid agency or HMO. Accordingly, it would not be meaningful to quantify the sensitivity to change for any individual assumption or uncertainty. However, Shire does not believe that the effect of uncertainties, as a whole, significantly impacts the Company's financial condition or results of operations.

As at the balance sheet date, accruals for Medicaid and HMO rebates were $126.4 million in 2006, $105.4 million in 2005 and $99.4 million in 2004, or 8%, 8%, and 9%, respectively, of net product sales.

Product Returns

The Company typically accepts customer product returns in the following circumstances: a) expiration of shelf life, b) product damaged while in the possession of Shire, or c) under sales terms that allow for unconditional return (guaranteed sales).

Shire estimates the proportion of recorded revenue that will result in a return by considering relevant factors, including:

- past product returns activity
- the duration of time taken for products to be returned
- the estimated level of inventory in the distribution channel
- product recalls and discontinuances
- the shelf life of products

- the launch of new drugs or new formulations

- the loss of patent protection or new competition

Shire's estimate of the level of inventory in the distribution channel is based on product-by-product inventory data provided by wholesalers, third-party prescription data and, for some product return provisions, market research of retail pharmacies.

Returns for new products are more difficult for the Company to estimate than for established products. For shipments made to support the commercial launch of a new product (which are typically guaranteed sales), the Company cannot reliably estimate expected returns, and the Company's policy is therefore to defer recognition of the sales revenue until there is evidence of end-patient acceptance (primarily third-party prescription data), in accordance with SAB No. 104, *Revenue Recognition* . For shipments after launch under standard terms (ie not guaranteed sales), the Company's initial estimates of sales return accruals are primarily based on the historical sales returns experience of similar products shortly after launch. Once sufficient historical data on actual returns of the product are available, the returns provision is based on this data and any other relevant factors as noted above.

The accrual estimation process for product returns involves in each case a number of interrelating assumptions, which vary for each combination of product and customer. Accordingly, it would not be meaningful to quantify the sensitivity to change for any individual assumption or uncertainty. However, Shire does not believe that the effect of uncertainties, as a whole, significantly impacts the Company's financial condition or results of operations.

As at the balance sheet date, provisions for product returns were $36.5 million in 2006, $31.8 million in 2005 and $22.5 million in 2004, or 2%, 2% and 2%, respectively, of net product sales.

Sales Coupon accrual

For certain products, primarily ADDERALL XR and DAYTRANA, the Company uses coupons as a form of sales incentive. These coupons reimburse part or all of the cost of the first prescription. Each coupon can only be used once and coupons typically expire three to 15 months after the date of issuance. The Company's management calculates an accrual for the estimated value of coupons that will be redeemed against sold products, based on the rebate value per coupon, the timing and volume of coupon distributions, the estimated level of inventory in the distribution channel and expected coupon redemption rates, using historical trends and experience.

Shire's estimate of the level of inventory in the distribution channel is based on product-by-product inventory data provided by wholesalers and third-party prescription data.

Shire believes that historical redemption rates, adjusted for known changes in coupon programs (such as length of coupon life and redemption conditions) are an appropriate basis for predicting future redemption rates. For coupon programs open at December 31, 2006 the redemption rates assumed by Shire range between 15% and 35% of coupons distributed (depending on the life of the coupons). A one percentage point increase in estimated coupon redemption rates would increase the provision at December 31, 2006 by $0.2 million.

At December 31, 2006 the accrual for coupon redemptions was $13.0 million (2005: $5.2 million, 2004: $15.9 million). The accrual levels in each year fluctuate according to the timing and volume of coupon distributions, in addition to changes in estimated redemption rates.

For rebates, returns and sales coupons the actual experience and the level of these deductions to revenue may deviate from the estimate. Shire reviews its estimates every quarter and may be required to adjust the estimate in a subsequent period. Historically, actual payments have not varied significantly from the reserves provided.

(vii) Income Taxes

Shire operates in numerous countries where its income tax returns are subject to audit and adjustment by local tax authorities. Because Shire operates globally, the nature of the audit items is often very complex and subject to change and the amounts at

issue can be substantial. The Company uses internal expertise and professional advisors to minimize audit adjustments where possible.

Shire develops best estimates of income taxes payable for probable liabilities using experience, judgment and assistance from professional advisors. Estimates are refined as additional information becomes known. Any outcome upon settlement that differs from Shire's best estimate may result in additional or lower tax expense in future periods. Income taxes payable increased from $93.6 million in 2005 to $294.5 million in 2006 primarily as a result of additional tax contingencies recognized in relation to ongoing tax audits.

The Company has significant deferred tax assets due to net operating losses (NOLs) in the United States, UK and other countries. The realization of these assets is not assured and is dependent on the generation of sufficient taxable income in the future. Management has exercised judgment in determining the extent of the realization of these losses based upon estimates of future taxable income in the various jurisdictions in which these NOLs exist. Where there is an expectation that on the balance of probabilities there will not be sufficient taxable profits to utilize these NOLs a valuation allowance is held against these deferred tax assets. If actual events differ from

management's estimates, or to the extent that these estimates are adjusted in the future, any changes to the valuation allowance could materially impact the Company's financial position and results.

At December 31, 2006, the Company had gross deferred tax assets of $568 million and had recorded a valuation allowance of $110 million against this amount.

At December 31, 2005, the Company had gross deferred tax assets of $579 million and had recorded a valuation allowance of $235 million against this amount.

At December 31, 2004, the Company had gross deferred tax assets of $268 million and had recorded a valuation allowance of $153 million against this amount.

(viii) Share based payments

Shire plc has historically granted options to the Company's directors and employees over ordinary shares under six stock option plans. On November 28, 2005 the ordinary shareholders of Shire plc approved the adoption of the Shire Plc Portfolio Share Plan (Parts A and B), a new share-based compensation plan, which provides for stock settled share appreciation rights and performance share awards to be made to the directors and employees over ordinary shares and American Depositary Shares. Further details on these plans can be found in note 31 to the consolidated financial statements contained in the Part IV of this Annual Report.

Effective January 1, 2006 the Company adopted the provisions of SFAS 123(R) which establishes accounting for share based compensation for employees.

The Company measures share-based compensation cost for awards classified as equity at the grant date, based on the estimated fair value of the award, and recognizes the cost as an expense on a straight-line basis (net of estimated forfeitures) over the employee requisite service period. The Company measures share-based compensation cost for awards classified as liabilities at fair value, which is re-measured at the end of each reporting period. The Company estimates the fair value of share-based awards without market-based performance conditions using a Black-Scholes valuation model and awards with market-based performance conditions are valued using a binomial valuation model.

Several critical assumptions are made in the determination of the Company's share based compensation cost. The Company believes that the most critical assumptions are the expected life of the award and the weighted average volatility of the Company's stock. Other assumptions made by the Company in respect of the determination of share based compensation cost include the risk free rate, the expected dividend yield and the expected forfeiture rate.

The Company's estimate of the expected life of the award is based on historical trends of employee exercise behaviour. The Company reviews these trends at the time of each new grant for equity classified awards, and at the end of each reporting period for liability classified awards, to ensure that the estimated life of the award is consistent with historical exercise behaviour. The

weighted average volatility is based upon historical share price data of the Company's stock for the requisite expected life of the awards. Given the related nature of each of the assumptions underlying the valuation of share-based payment awards, it would not be meaningful to quantify the sensitivity to change for each individual assumption.

The Company believes that the valuation technique and the approach utilized to develop the underlying assumptions are appropriate in estimating the fair values of Shire's stock-based awards. Estimates of fair value are not intended to predict actual future events or the value ultimately realized by employees who receive equity awards, and subsequent events are not indicative of the reasonableness of the original estimates of fair value made by the Company under SFAS 123(R).

Recent accounting pronouncements update

See note 2(y) to the consolidated financial statements contained in the Part IV of this Annual Report for a full description of recent accounting pronouncements, including the expected dates of adoption and effects on financial condition, results of operations and cash flows.

ITEM 7A : Quantitative and qualitative disclosures about market risk

Treasury policies and organization

The Company's principal treasury operations are coordinated by its corporate treasury function, which is based in the UK. All treasury operations are conducted within a framework of policies and procedures approved by the Board. As a matter of policy, the Company does not undertake speculative transactions that would increase its currency or interest rate exposure.

The Board reviews and agrees policies for managing the risks in the following areas:

Interest rate risk

As at December 31, 2006 the Company had no material debt outstanding. Therefore, the Company's interest charge on its debt obligations is low and consequently the Company's interest expense charge has limited exposure to interest rate movements. The Company is exposed to movements in interest rates affecting interest income. This exposure is primarily to US Dollar interest rates. As the Company maintains all of its investments on a short term basis for liquidity purposes this risk is not actively managed.

In the year to December 31, 2006 the average interest rate received on cash and liquid investments was approximately 4.7% per annum. The largest proportion of investments was in US Dollar money market and liquidity funds.

The acquisition of New River will change the financial profile of the Company and will increase interest rate exposure, still primarily to US Dollar interest rates. The Company's Treasury Committee will review the impact of the change and implement an appropriate policy to manage this risk.

Foreign exchange risk

The Company is exposed to movements in foreign exchange rates against the US Dollar for trading transactions and the translation of net assets, liabilities and earnings of non-US subsidiaries. The main trading currencies of the Company are the US Dollar, the Canadian Dollar, Pounds Sterling, the Euro and Swedish Krona. The consolidated financial statements of foreign entities are translated using the accounting policies described in Note 3 (a) to the Company's consolidated financial statements contained in Part IV of this Annual Report.

The exposure to foreign exchange risk is managed and monitored by the treasury function. Exposures are generally managed through natural hedging via the currency denomination of cash balances. As at December 31, 2006 the Company had 18 outstanding forward foreign exchange contracts with a total principal amount of $98.3 million equivalent to manage the currency risk associated with certain inter-company loans. As at December 31, 2006 there were net unrealized losses of $8.1 million on these contracts.

Market risk of investments

As at December 31, 2006 the Company has $55.8 million of investments comprising equity investment funds ($24.2 million), private companies ($15.1 million) and publicly quoted equities ($16.5 million). The investment in public quoted companies and equity investment funds are exposed to market risk. No financial instruments or derivatives have been employed to hedge this risk.

ITEM 8 : Financial statements and supplementary data

The consolidated financial statements and supplementary data called for by this item are submitted as a separate section of this report.

ITEM 9 : Changes in and disagreements with accountants on accounting and financial disclosure

Not applicable.

ITEM 9A: Controls and procedures

Disclosure Controls and Procedures

The Company, under the supervision and with the participation of the Company's management, including the Chief Executive Officer and the Chief Financial Officer, has performed an evaluation of the effectiveness of the Company's disclosure controls and procedures, as at December 31, 2006. The Company's management necessarily applied its judgment in assessing the costs and benefits of such controls and procedures, which by their nature can provide only reasonable assurance regarding management's control objectives. Based on this evaluation, the Company's Chief Executive Officer and Chief Financial Officer concluded that the Company's disclosure controls and procedures are effective at a reasonable level of assurance for gathering, analyzing and disclosing the information that the Company is required to disclose in the reports it files under the Securities Exchange Act of 1934, within the time periods specified in the SEC's rules and forms.

Management's Report on Internal Control Over Financial Reporting

The Company's management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rule 13a-15(f) or 15d-15(f) promulgated under the Securities Exchange Act of 1934.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

The Company's management assessed the effectiveness of the Company's internal control over financial reporting as at December 31, 2006. In making this assessment, the Company's management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control-Integrated Framework.

Based on its assessment, management believes that, as at December 31, 2006, the Company's internal control over financial reporting is effective based on those criteria.

Deloitte & Touche LLP, an independent registered public accounting firm, has issued an audit report on management's assessment of the Company's internal control over financial reporting. This report appears on page F-2 of the Company's consolidated financial statements contained in Part IV of this Annual Report.

Changes in Internal Control Over Financial Reporting

In 2004, the Company commenced the implementation of a new integrated information system covering financial processes, production, logistics and quality management. Further implementations were made in 2005 and 2006 and more are planned for

2007. The implementations have involved changes in the Company's information systems that included aspects of the Company's internal control over financial reporting and therefore changes to the Company's internal control over financial reporting. The Company has reviewed each system as it is being implemented and the controls affected by the implementation of the new systems and made appropriate changes to affected internal controls as it implemented the new systems. Management believes that the controls as modified are appropriate and functioning effectively.

In connection with the restatement of the Company's consolidated financial statements for the year ended December 31, 2005 contained in this report and as discussed under Item 7: "Management's Discussion and Analysis of Financial Condition and Results of Operations", the Company, under the supervision and with the participation of the Company's management, including the Chief Executive Officer and the Chief Financial Officer, reconsidered the adequacy of its assertions concerning the effectiveness of its disclosure controls and procedures in its Annual Report on Form 10-K for the year ended December 31, 2005 and in its Quarterly Reports for the periods ended September 30, 2005 and March 31, June 30 and September 30, 2006.

The Company, and its independent registered public accounting firm Deloitte & Touche LLP, had concluded that the Company's accounting treatment in respect of the value ascribed to IPR&D acquired as part of the TKT acquisition was in accordance with generally accepted accounting principles. However, following the identification by the Company's staff of the omission that resulted in the 2005 restatement, the Company's management has concluded that the Company did not identify and apply correctly generally accepted accounting principles as they related to the original accounting for IPR&D because it did not have adequate specialist internal accounting resources at the time of the original accounting for IPR&D.

Recognizing the inherent limitations of a retrospective evaluation, the Company's management further concluded that, as a result of this resource inadequacy, a material weakness had existed in its internal control over financial reporting with respect to the identification and application of generally accepted accounting principles as they related to the accounting for IPR&D acquired in a business combination at the time of the original accounting for the IPR&D and, as a result, its disclosure controls and procedures for the identification and application of generally accepted accounting principles as they related to the accounting for IPR&D acquired in a business combination were not effective in the periods covered by, and as asserted in, its reports for the year ended December 31, 2005 and the periods ended September 30, 2005 and March 31, June 30 and September 30, 2006.

During 2006, as part of the Company's ongoing improvement of its internal control over financial reporting, the Company recruited additional staff with appropriate expertise, whose full time responsibility was to focus on selection and application of generally accepted accounting principles and related financial reporting matters. As a result of the improved controls implemented during 2006, the omission that resulted in the 2005 restatement was identified and resolved. Therefore, as of December 31, 2006, the Company's management determined that the inadequacy in its disclosure controls and procedures for the identification and application of generally accepted accounting principles as they related to the accounting for IPR&D acquired in a business combination had been remedied.

ITEM 9B: Other Information

None

PART III

ITEM 10 : Directors and executive officers of the registrant

Directors of the Company

Name	Age	Position
Dr James Cavanaugh	69	Non-executive Chairman
Matthew Emmens	55	Chief Executive Officer
Angus Russell	51	Chief Financial Officer
Dr Barry Price	63	Senior Non-executive Director
Ronald Nordmann [1]	65	Non-executive Director
The Hon. James Grant	69	Non-executive Director

Robin Buchanan	54	Non-executive Director
David Kappler	59	Non-executive Director
Patrick Langlois	61	Non-executive Director
Kate Nealon [2]	53	Non-executive Director
Dr Jeffrey Leiden [3]	51	Non-executive Director

[1] Retired from the Board December 22, 2006
[2] Appointed with effect from July 27, 2006
[3] Appointed with effect from January 1, 2007

Executive Officers of the Company

Name	Age	Position
Matthew Emmens	55	Chief Executive Officer
Angus Russell	51	Chief Financial Officer
Mike Cola	47	President Specialty Pharmaceuticals
Dr David Pendergast	58	President Shire Human Genetic Therapies
Tatjana May	41	General Counsel and Executive Vice President Global Legal Affairs
Dr Eliseo Salinas	51	Chief Scientific Officer and Executive Vice President of Global R&D
John Lee	56	Executive Vice President Global Supply Chain & Quality
Joseph Rus	61	Executive Vice Alliance Management & New Market Development
Anita Graham	35	Executive Vice President Global Human Resources
Barbara Deptula	52	Executive Vice President of Business Development
Caroline West	49	Senior Vice President, Chief Compliance and Risk Officer

For the purposes of the NASDAQ corporate governance rules, the independent directors are Dr James Cavanaugh, Dr Barry Price, the Hon. James Grant, Robin Buchanan, David Kappler, Patrick Langlois, Kate Nealon and Dr Jeffrey Leiden and Ronald Nordmann prior to his retirement in December 2006.

There is no family relationship between or among any of the directors or executive officers.

The Company's directors, including non-executive directors (NEDs), are subject to the "retirement by rotation" provisions of the Company's Articles of Association. These are designed to ensure that all directors are re-elected by shareholders at least every three years, a common practice for UK public companies.

In addition to the requirements of the Articles of Association, the non-executive directors are appointed to office pursuant to individual letters of appointment for a term of two years (with the exception of Dr Barry Price who has a one year term and Ronald Nordmann who had a one-year term), subject to invitation to serve further terms at the discretion of the Board. At the expiration of the two-year term, the NEDs are not required to be re-elected by shareholders (unless the expiration of the term coincides with a particular NEDs turn to retire by rotation), but may be re-appointed by the Board. NEDs who have served on the Board for nine or more years are appointed to office for a term of one year, subject to annual re-election by shareholders, and by invitation to serve further terms at the discretion of the Board. The current terms of the NEDs are as set out below:

Name	Date of Term Expiration
Dr James Cavanaugh	March 23, 2007
Dr Barry Price	January 24, 2008
The Hon. James Grant	May 10, 2007
Robin Buchanan	July 29, 2007
David Kappler	April 4, 2008
Patrick Langlois	November 10, 2007
Kate Nealon	July 26, 2008
Dr Jeffrey Leiden	December 31, 2008

Executive officers are appointed pursuant to service agreements, which are not limited in term.

Biographical details of directors and executive officers of the Company

Dr. James Cavanaugh
Chairman

Dr. Cavanaugh has been a member of Shire's Board since March 24, 1997 and Chairman since May 11, 1999. He is a General Partner of HealthCare Partners, a Managing Director of HealthCare Ventures, a venture capital fund devoted to healthcare, Non-Executive Chairman of Diversa Corporation and Xanodyne Pharmaceuticals Inc. up to February 2007 after which he remained a Board member, and a Non-Executive Director of MedImmune Inc. and Advancis Pharmaceutical Corporation. He is a former President of SmithKline & French Laboratories, SmithKline Beecham Corporation's clinical laboratory business, and Allergan International, and served as Deputy Assistant to the US President on the White House Staff. Dr. Cavanaugh is also Chairman of Shire's Nomination Committee.

Matthew Emmens
Chief Executive Officer

Mr. Emmens has been Shire's Chief Executive Officer and a member of the Board since March 12, 2003. He also serves as a non-executive director of Vertex Pharmaceuticals Inc and Incyte Corporation. He began his career in international pharmaceuticals with Merck & Co, Inc. in 1974, where he held a wide range of sales, marketing and administrative positions. In 1992, he helped to establish Astra Merck, a joint venture between Merck and Astra AB of Sweden, becoming President and Chief Executive Officer. In 1999, he joined Merck KGaA and established EMD Pharmaceuticals, the company's US prescription pharmaceutical business. He was later promoted to President of Merck KGaA's global prescription business, based in Germany. Mr. Emmens holds a degree in Business Management from Fairleigh Dickinson University. He is also Chairman of Shire's Management and Senior Staff Committees.

Angus Russell
Chief Financial Officer and Executive Vice President of Global Finance

Mr. Russell has been Shire's Chief Financial Officer and a member of the Board since December 13, 1999. He also serves as a Non-Executive Director of the City of London Investment Trust plc. Between 1980 and 1999, Mr. Russell held a number of positions of increasing responsibility at ICI, Zeneca and AstraZeneca plc, including Vice President-Corporate Finance at AstraZeneca and Group Treasurer at Zeneca. Mr. Russell is a chartered accountant, having qualified with Coopers & Lybrand, and a fellow of the Association of Corporate Treasurers. He is also a member of Shire's Management and Senior Staff Committees and is Chairman of Shire's Corporate Responsibility Committee.

Dr. Barry Price
Non-Executive Director

Dr. Price has been a member of Shire's Board since January 16, 1996 and is the Company's Senior Non-Executive Director. He also serves as Chairman of Antisoma plc, Biowisdom Ltd and VASTox plc. Dr. Price worked for Glaxo for 28 years, where he held positions of increasing responsibility with the company's research group. Dr. Price is also Chairman of Shire's Remuneration Committee and a member of Shire's Audit, Compliance and Risk Committee and Nomination Committee.

Ronald Nordmann
Non-Executive Director

Mr. Nordmann was a member of Shire's Board from December 23, 1999 until his retirement from the Board and its Committees on December 22, 2006 and he previously served as a Non-Executive Director of Roberts Pharmaceutical Corporation. He is also a Director of Par Pharmaceuticals Companies Inc. Mr. Nordmann is Co-President of Global Health Associates. He has been a financial analyst in healthcare equities since 1971, holding senior positions with Deerfield Management, PaineWebber, Oppenheimer & Co., F Eberstadt & Co., and Warner-Chilcott Laboratories. He holds a bachelor's degree from Johns Hopkins University and an MBA from Fairleigh Dickinson University. During 2006, Mr. Nordmann was a member of Shire's Audit, Compliance and Risk, Nomination and Remuneration Committees.

The Hon. James Grant, P.C., C.M., Q.C.
Non-Executive Director

Mr. Grant has been a member of Shire's Board since May 11, 2001 and previously served as a Director of BioChem Pharma Inc. since 1986. He also sits on the boards of two Canadian public corporations and the boards of a number of other private corporations and not-for-profit foundations and councils. He is a partner and Chair Emeritus with the law firm Stikeman Elliott in Montreal. Mr. Grant holds degrees in Arts and Law from McGill University. He is also a member of Shire's Nomination Committee.

Robin Buchanan
Non-Executive Director

Mr. Buchanan has been a member of Shire's Board since July 30, 2003. He also serves as a Non-Executive Director of Liberty International plc. Mr. Buchanan is the Senior Partner of the UK operations and Director of the global business consultancy, Bain & Company Inc. He has also recently been appointed Dean of the London Business School and will commence his appointment no later than 1 July 2007. He is a member of the Trilateral Commission. He previously worked for American Express International Banking Corporation in New York, McKinsey & Company, and Deloitte & Touche, where he qualified as a chartered accountant (FCA). Mr. Buchanan holds an MBA with High Distinction (Baker Scholar) from Harvard Business School. He is also a member of Shire's Remuneration Committee.

David Kappler
Non-Executive Director

Mr. Kappler has been a member of Shire's Board since April 5, 2004. He also serves as the Non-Executive Chairman of Premier Foods plc and as a Non-Executive Director of Intercontinental Hotels Group plc. In addition, he was a Director of Camelot Group plc from 1996-2002, and of HMV Group plc from 2002-2006. Mr. Kappler retired from Cadbury Schweppes plc in April 2004 after serving as Chief Financial Officer since 1995. He worked for the Cadbury Schweppes group between 1965 and 1984 and rejoined the company in 1989 following its acquisition of Trebor Group, where he was Financial Director. Mr. Kappler is a fellow of the Chartered Institute of Management Accountants. He is also Chairman of Shire's Audit, Compliance and Risk Committee and a member of the Nomination Committee.

Patrick Langlois
Non-Executive Director

Mr. Langlois has been a member of Shire's Board since November 11, 2005. He is also a Non-Executive Director of Coley Pharmaceuticals Group, Inc. and Exonhit S.A.. Mr. Langlois previously served as Vice Chairman of the Management Board of Aventis S.A., Strasbourg, having been Group Executive Vice President and Chief Financial Officer for several years. He also spent many years in senior financial roles with the Rhone-Poulenc Group, including three years as a member of the Executive Committee and Chief Financial Officer. Mr. Langlois holds a PhD in Economics and a diploma in banking studies. He is also a member of Shire's Audit, Compliance and Risk Committee and Remuneration Committee.

Ms Kate Nealon
Non-executive Director

Ms Nealon was appointed to Shire's Board on July 27, 2006. She also holds Non Executive Director positions with HBOS plc and Cable & Wireless plc. She is also a Senior Associate at the Judge Business School at Cambridge University. Ms Nealon was previously Group Head of Legal & Compliance at Standard Chartered plc until 2004. She is a US qualified lawyer and spent several years in her early career practising law in New York. She is also a member of Shire's Remuneration Committee and Audit, Compliance and Risk Committee.

Dr Jeffrey Leiden
Non-executive Director

Dr Leiden was appointed to Shire's Board on January 1, 2007. He served as President and Chief Operating Officer, Pharmaceutical Products Group and Chief Scientific Officer at Abbott Laboratories from 2001-2006; during this time he was also a member of the Boards of Directors of Abbott and TAP Pharmaceutical Products, Inc. Prior to joining Abbott, Dr Leiden served as the Elkan R. Blout Professor of Biological Sciences, Harvard School of Public Health and Professor of Medicine, Harvard Medical School. Prior to that, he was the Frederick H. Rawson Professor of Medicine and Pathology and Chief of the Section of Cardiology at the University of Chicago. His extensive business and consulting experience includes both the pharmaceutical and medical device areas. Dr Leiden was a founder of Cardiogene, Inc., a biotechnology company specializing in cardiovascular gene therapy. Dr. Leiden earned a bachelor's degree in biological sciences, a doctorate in virology and a medical degree, all from the University of Chicago. He is a fellow of the American Academy of Arts and Sciences and an elected member of the Institute of Medicine of the National Academy of Sciences. Dr Leiden is currently a Partner at Clarus Ventures LLC.

Mike Cola has been with Shire since July 2005. He was previously President of the life sciences division of Safeguard Scientifics, Inc. Mr. Cola also worked for AstraMerck/AstraZeneca and was responsible for developing AstraMerck's product development, medical affairs, business research, licensing and pharmaceutical business units. He is also a member of Shire's Management and Senior Staff Committees.

Dr David D Pendergast has been with Shire since July 2005 and was previously Chief Executive Officer of TKT until its acquisition by Shire. He also worked as Vice President of Product Development and Quality at Biogen, Inc., and held senior positions at Fisons Ltd.'s Pharmaceutical Division and The Upjohn Company. He has over 30 years of pharmaceutical and biotechnology experience. He is also a member of Shire's Management and Senior Staff Committees.

Tatjana May has been with Shire since May 2001. She was previously Assistant General Counsel at the corporate headquarters of AstraZeneca plc and prior to that she worked at the law firm Slaughter and May.

Dr Eliseo Salinas has been with Shire since June 2004. Dr. Salinas joined from Wyeth Research where he spent 11 years, most recently as Head of Global Central Nervous Systems (CNS) and Vice President for Regional Clinical Research & Development. Prior to that, he was International Project Leader (CNS) with Synthélabo Recherche. He obtained his Medical Degree from the University of Buenos Aires and performed his Residency in Psychiatry and gained a Masters in Pharmacology in Paris.

John Lee has been with Shire since April 2000. He was previously Vice President, Operations at Schwarz Pharma, and also worked at Central Pharmaceuticals, The Vitarine Company (now Eon), and Glenwood Laboratories. He has over 34 years of experience in the pharmaceutical industry.

Joseph Rus has been with Shire since 1999. Following the merger of Shire Pharmaceuticals and BioChem Pharma in May 2001, he was appointed President and CEO of Shire BioChem Inc. He has more than 25 years of experience in the international pharmaceutical industry including European country management with both Warner Lambert and Hoffmann La Roche.

Anita Graham has been with Shire since January 2004. She was previously Vice President of Human Resources at Cytyc Corporation. She also held senior HR positions at Serono, Inc. and Scudder Kemper Investments, Inc. (now part of Deutsche Bank) and has extensive experience in all aspects of HR, both in Europe and the US.

Barbara Deptula has been with Shire since September 2004. She was previously President of the biotechnology division of Sicor Inc. and Senior Vice President for commercial and product development at Coley Pharmaceutical Group. She also held senior management positions focused on licensing and business development at US Bioscience, Schering-Plough, American Cyanamid, and Genetics Institute.

Caroline H. West has been with Shire since May of 2005. She was previously Vice President, Global Legal Compliance at Aventis. She also worked at Rhone-Poulenc Rorer in compliance, commercial law and litigation capacities and prior to joining the pharmaceutical industry practised law at Pepper Hamilton LLP.

Audit, Compliance and Risk Committee Financial Expert

The members of the Audit, Compliance and Risk Committee as at December 31, 2006 were Mr David Kappler, Dr. Barry Price and Mr Patrick Langlois. Mr Nordman was a member of the Committee during 2006, until his retirement from the Board on December 22, 2006. Ms Nealon was elected to the committee on February 22, 2007.

The Board of Directors has determined that David Kappler is the serving member of the Audit Committee who is an Audit Committee financial expert and that he is independent as defined under applicable SEC rules. A description of Mr Kappler's relevant experience is provided above.

Code of Ethics

Shire's Board of Directors has adopted a Code of Ethics that applies to all its directors, officers and employees, including its Chief Executive Officer, Chief Financial Officer and Group Financial Controller. The Code of Ethics is posted on Shire's internet website at www.shire.com.

ITEM 11 : Executive compensation

In respect of the financial year to December 31, 2006, the total compensation paid to the Company's directors and executive officers as a group for the periods during which they served in any capacity was $14.9 million. The total amounts set aside or accrued by the Company to provide pension, retirement or similar benefits for this group was $1.3 million. During 2006, members of the group were granted options over ordinary shares of the Company. All such holdings were issued pursuant to the various executive share option plans described in note 31 to the Company's consolidated financial statements contained in Part IV of this Annual Report.

The Company provides information on the individual compensation of its directors in the Directors Remuneration Report included within its financial statements filed in the UK in accordance with the requirements of the UK Companies Act 1985. As the remuneration report is made publicly available, it is reproduced in full below. As at the time of filing this Form 10-K, the Directors Remuneration Report is subject to the conclusion of certain audit procedures in relation to the audit of the Company's statutory financial statements to be filed in the UK and to approval of Shire plc's shareholders at the Annual General Meeting.

Directors' Remuneration Report

Introduction

This report has been prepared in accordance with Schedule 7A to the Companies Act 1985 ('the Act') and complies with the Combined Code on Corporate Governance. The report also meets the relevant requirements of the Listing Rules of the Financial Services Authority and describes how the Board has applied the principles relating to Directors' remuneration under the Directors' Remuneration Report Regulations 2002. As required by the Act, a resolution to approve the report will be proposed at the Annual General Meeting of Shire plc at which the financial statements will be approved. The Act requires the auditors to report to Shire plc's members on certain parts of the Director's Remuneration Report and to state whether in their opinion these parts of the report have been properly prepared in accordance with the Companies Act 1985.

Dear Shareholder,

Directors' remuneration

During the year ended December 31, 2006 the Remuneration Committee continued its work, on behalf of the Board, on Directors' remuneration.

In 2006, the Company continued to implement a focused business strategy for identifying, developing and marketing pharmaceuticals in targeted therapeutic areas for diseases treated by specialist physicians. The Company focused its business on ADHD, HGT, GI and renal diseases. Each of these businesses achieved significant successes in the development, approval and promotion of new and existing products in 2006.

The Company operates in a competitive multi-national environment. In 2006, approximately 90% of the Company's revenues were generated, and 85% of its employees were based, outside the UK. Indeed most of the Company's revenues are generated in the US and the majority of its employees and most of its senior executives are based in the US. Over the past two years, the Committee has been in dialogue and consultation with shareholders regarding the challenges it faces with key elements of the remuneration package. In the fall of 2005, Shire plc replaced older equity schemes with a new share plan and made amendments

to the annual incentive plan.

During 2006 the Remuneration Committee conducted a regular review of executive remuneration levels relative to competitive data and is satisfied that the elements of the remuneration package as well as remuneration values are well positioned relative to the competitive market and that awards are commensurate with corporate performance.

The Remuneration Committee is committed to a continuing dialogue with shareholders and we take account of your views. We hope that this report provides helpful context and explanation about the policies and practical considerations that influence our decisions.

Dr. Barry Price
Chairman of the Remuneration Committee

The Remuneration Committee

The Remuneration Committee is responsible for all elements of the Executive Directors' remuneration, as well as the management of their performance.

The constitution of the Committee was reviewed in 2004 and changes were made to ensure compliance with the Combined Code. The Company considers all members of the Remuneration Committee to be independent. During 2006 the Committee also reviewed and updated its charter to effectively reflect its responsibilities.

The Chief Executive Officer and the Chief Financial Officer attend meetings of the Remuneration Committee at its invitation, but neither is involved in any decisions relating to their own remuneration.

The members of the Remuneration Committee during 2006 were:

- Dr. Barry Price, the Senior Independent Director of the Company and Chairman of the Committee;
- Mr Robin Buchanan, an Independent Non-Executive Director;
- Mr Ronald Nordmann, an Independent Non-Executive Director; and
- Ms Kate Nealon, an Independent Non-Executive Director.

Mr Nordmann retired as a Non-Executive Director of the Company effective December 22, 2006 and stepped down as a member of the Remuneration Committee as of the same date. In addition, Mr Patrick Langlois was appointed to the Remuneration Committee effective December 12, 2006.

The Remuneration Committee was materially assisted in 2006 by Mrs Anita Graham, EVP Global Human Resources. The following external advisers were appointed by and materially assisted the Remuneration Committee:

- Towers Perrin, who provided data in relation to Executive Directors' remuneration;
- Deloitte & Touche LLP (who also provided audit and tax services to the Company), who provided data and advice on general issues around the design and operation of the Company's incentive schemes; and
- Slaughter and May, who provided general legal advice to the Company.

Executive remuneration policy

The Remuneration Committee considers that an effective remuneration policy, aligned to the Company's business needs, is important to the Company's success. It directly impacts the Company's ability to recruit, retain and motivate high calibre executives who deliver sustained value to shareholders and build the Company for long-term success.

The Remuneration Committee is responsible for developing, reviewing and overseeing the implementation of the Company's compensation and benefits policy. The Remuneration Committee regularly monitors the effectiveness of the policy and reviews this policy based on independent analysis and advice, an understanding of the business drivers and competitive environment in which the Company operates and on-going dialogue with shareholders.

The Company's executive compensation and benefits policy is based on the following principles:

- Base pay is market and performance driven, with reference to a blended US/UK market comparison. It is targeted at or around the median relative to the comparison, based on individual performance.
- The Annual Incentive Plan is performance-based and is linked to the achievement of an appropriate mix of corporate and individual performance targets. The Annual Incentive Plan allows the Company to measure and reward progress against its strategic goals and is closely tied to delivery of sustained shareholder value.
- Share-based compensation is a key element of the Company's remuneration policy as it aligns the interests of the Company's executives with the interests of its shareholders. This element of compensation also utilises a blended US/UK market comparison to determine the face value of awards to Executive Directors.
- Benefits programs are locally competitive and provide for the welfare and well-being of the Company's employees and their families.
- The Remuneration Committee currently aims for variable compensation to represent over 2/3rds of total remuneration.
- The Remuneration Committee believes that Executive Directors should be encouraged to own shares in the Company in order to ensure the alignment of their interests with those of the Company's shareholders. Share ownership guidelines became effective in 2006.

The remuneration package

The main elements of the remuneration package for Executive Directors and senior management are:

- Salary
- Annual Incentive Plan
  - (a) Cash Component
  - (b) Share Component
- Long Term Incentives
  - (a) Portfolio Share Plan
  - (b) Share Options
  - (c) Long Term Incentive Plan
- Pension and other benefits

1) Salary

The Remuneration Committee reviews salaries annually. In late 2004 and early 2005 the Remuneration Committee undertook a competitive review of the Company's executive remuneration programs and practices, including base salary benchmarks and levels. Based on the competitive analysis the Remuneration Committee determined that the correct comparator group is a blend of US and UK companies with sector, size, complexity and international characteristics similar to those of the Company. Where appropriate, the competitive review included a detailed analysis to align these characteristics to best represent the

Company's operating position.

As part of its normal annual salary review process, the Remuneration Committee conducts a review of a range of factors such as competitive market data provided by independent external consultants, US and UK market conditions, performance-related pay increases across the Company and individual skills, performance and results achieved. The Remuneration Committee's policy is for salary to be targeted at or around the median of the blend of US/UK comparators, with appropriate differentiation based upon skills and experience as well as individual performance. Based on this review, and on corporate and individual performance results, salaries for the CEO and CFO were increased 5% each effective January 1, 2007, respectively, to $1,158,167 (denominated in $) and £390,726 ($722,843 equivalent based on the average exchange rates prevailing in 2006). These increases are in line with increases provided to the Company's employees.

2) Annual Incentive Plan

Shire operates an Annual Incentive Plan which rewards Executive Director performance based on achievement of pre-defined, Board-approved corporate objectives and Committee-approved individual objectives. The Company implemented the Balanced Scorecard in 2005 and utilized it to set corporate objectives in 2006. The Scorecard organises corporate objectives into all areas that drive the success of the business: financial, products and markets, people and capabilities, and operational effectiveness.

At the start of the year corporate objectives are set by the Board for each area of the Scorecard. These objectives apply to all employees participating in the Company's Annual Incentive Plan and include a description of the objective and key performance indicators (KPI), including targets and deadlines. Awards under the Plan are made only when exacting levels of performance specified by the KPI have been achieved. Objectives measured by the Company's financial performance are assessed on the Company's results, as reported in the Company's Form 10-K under US GAAP.

The detailed objectives and performance standards contain commercially sensitive information and therefore are not detailed here. However, some of the objectives are summarised below according to the four Scorecard areas for 2006:

- Financial
  - Growth in revenue;
  - Revenue growth tied to key products, including Adderall XR;
  - Revenue generation related to new product launches; and
  - Business Development targets.
- Products/Markets
  - Successful product launches;
  - Key R&D milestones such as submissions and approvals; and
  - Product pipeline growth - progression and in-licensing/acquisition.

- People and Capabilities
  - Development of capabilities to support the operating model and the businesses; and

- Talent acquisition and leadership development of Shire's people.

- Operational Effectiveness
  - Systems implementation;
  - Supply chain integrity; and
  - Risk management, compliance initiatives and operational excellence targets.

Personal objectives are also set at the beginning of the year and are aligned with individual accountabilities for the development and execution of plans to achieve corporate objectives in the current year and build for the future success of the Company.

The Remuneration Committee assesses performance against objectives in the first quarter of the following year. The target incentive is paid where Executive Directors have fully achieved their individual objectives and the corporate objectives have been met in full. The maximum incentive is paid when the Remuneration Committee determines that individual and/or corporate performance has been exceptional. Maximum incentive payments for 2006 were capped at 115% of salary in cash and 65% of salary in deferred shares for the Chief Executive Officer and 100% of salary in cash and 55% of salary in deferred shares for the Chief Financial Officer.

	Target incentive (as a % of salary)	Maximum incentive (as a % of salary)	Weighting of target incentive objectives	
			Corporate	Individual
Mr Matthew Emmens Chief Executive Officer	65% cash / 20% shares	115% cash / 65% shares	80%	20%
Mr Angus Russell Chief Financial Officer	55% cash / 15% shares	100% cash / 55% shares	70%	30%

The incentive payments awarded to each Executive Director for 2006 reflect the corporate and individual achievements and amounted to 115% of salary in cash and 65% in deferred shares for Mr Emmens and 76% of salary in cash and 51% in deferred shares for Mr Russell.

These incentive awards are consistent with the overall performance of the Company in 2006, which included:

- Total revenue growth of 12%;
- Product sales up 16%;
- Settlements with Impax and Barr regarding ADDERALL XR.;
- The in-licensing/acquisition of four new products (SEASONIQUE, Transvaginal Ring technology, Valrocemide, Tissue Protective Cytokine technology);
- The successful launch of three new products (ELAPRASE, FOSRENOL in the EU, DAYTRANA);
- Highly successful achievement of R&D milestones including the filing and approvable status for LIALDA and the subsequent US approval in January 2007; the approvable status of VYVANSE, the submissions of SPD465 and SPD503, both for treatment for ADHD, and advancement of the HGT pipeline with GA-GCB and three pre-clinical candidates, Hunter Syndrome CNS, Sanfilippo Syndrome and Metachromatic Leukodystrophy; and
- The highly successful implementation of other Scorecard objectives focused on the continuing growth of the Company.

3) Long term incentives

(a) The Portfolio Share Plan

The Portfolio Share Plan (the Plan), was adopted by Shire plc's shareholders on October 28, 2005. This plan replaced the 2000 Executive Share Option Scheme and the Long Term Incentive Plan. Shire plc has made no awards in 2006 and will make no further awards to Executive Directors or any other employee under the previous plans.

The purpose of the Plan is to enable the Company to motivate and reward its workforce by reference to share price performance, and to link the interests of participants with those of the Company's shareholders. The Plan is designed to align the interests of selected employees of the Company with long-term value creation for shareholders. Participation in the Plan is discretionary. Under the Plan, awards granted to Executive Directors will be subject to a performance target, which must, in normal circumstances, be met before the award vests. Performance targets will normally be measured over a period of not less than three years. Special rules apply in the event of the participant's employment terminating early or on a change of control of the Company.

The Plan is split into two parts, which can be operated separately.

Under Part A of the Plan, Stock Appreciation Right (SAR) Awards can be granted. A SAR Award is the right to receive shares (or ADSs) in Shire plc linked to the increase in value of a specified number of shares over a period between three and five years from the date of grant and, in the case of Executive Directors, subject to the satisfaction of performance targets. SAR Awards will normally vest three years after the date of grant, subject to the satisfaction of performance targets in the case of Executive Directors, and can be exercised up until the fifth anniversary of the date of grant.

Under Part B of the Plan, Performance Share (PSP) Awards can be granted. A PSP Award is the right to receive a specified number of shares (or ADSs) three years from the date of grant. In the case of Executive Directors, performance targets must be satisfied before a PSP Award vests. Upon vesting of the PSP Award, shares will be released to the participant automatically without any action on the part of the participant.

The Plan contains individual grant limits set at six times base salary for SAR awards in any one year and four times base salary for PSP awards in any one year. It is the Company's intention for awards granted under the Plan to Executive Directors to be comprised of either or both a SAR Award and a PSP Award. Ordinarily, it is the Company's intention to provide annual grants to the CEO and CFO with face values (calculated by reference to the average share price over the prior twelve month calendar period) as follows:

- For the CEO, equivalent to approximately 4 times base salary in SARs and 3 times base salary in PSPs; and
- For the CFO, equivalent to approximately 2.2 times base salary in SARs and 1.6 times base salary in PSPs.

Performance criteria

Awards under the Plan normally vest on the third anniversary of the date of grant. In the case of Executive Directors, awards will only vest if the Remuneration Committee determines that the performance conditions have been satisfied and that, in the opinion of the Remuneration Committee, the underlying performance of the Company is sufficient to justify the vesting of the award.

Performance criteria are based on relative Total Shareholder Return (TSR) measured against two comparator groups. Vesting of one-third of an Award will depend upon the Company's performance relative to the TSR performance of FTSE 100 constituents, excluding financial institutions. The vesting of the remaining two-thirds of an Award will depend upon the Company's performance relative to the TSR performance of a group of international companies from the pharmaceutical sector (see below). Vesting will be as follows:

- Performance below the median versus the comparator companies and the FTSE 100 - 0% vesting;
- Performance at median versus the comparator companies and the FTSE 100 - 33 and 1/3% vesting; and
- Performance between median and upper quartile versus the comparator companies and the FTSE 100 - straight-

line vesting from 33 and 1/3% to 100% for at or above upper quartile performance.

The comparator group of international companies from the pharmaceutical sector currently includes the following companies: Novo Nordisk, Schering AG, Serono, Altana, UCB, Lundbeck, Forest Labs, Allergan, Sepracor, Cephalon, Watson, Biovail, King, Valeant, Medicis, Kos.

The Remuneration Committee has the discretion to amend this group of companies to ensure that the group stays both relevant and representative; however, the change must not have the effect of making the performance criteria either materially easier or materially more difficult to achieve, in the opinion of the Remuneration Committee, than it was or they were immediately before the circumstance in question.

TSR performance will be measured using an averaging period of three months. In addition, the Remuneration Committee will have regard to the same calculation using an averaging period of six months as part of a fairness review to ensure that vesting properly reflects underlying performance.

If the performance conditions are not met, awards will lapse.

Awards made under the Plan in 2006 are set out below.

(b) Share options

No awards were made under the Company's 2000 Executive Share Option Scheme in 2006.

In 2005, discretionary grants of share options under this scheme were made to Executive Directors to align their interests with those of shareholders and to promote sustained long-term Company performance. The face value of annual option grants under the Scheme was capped at three times salary. In order for options to vest, stretching performance targets must be met. For 2005 grants, the performance target is based on real growth in diluted earnings per share (EPS) as reported under US GAAP adjusted to ensure a consistent basis of measurement, as approved by the Remuneration Committee, including the add back of significant one time items.

The minimum performance required in order for Executive Directors' options to vest is that Shire's EPS grows by 22.9% in the three years following the date of grant. In the case of an annual grant of options worth three times salary, Shire's EPS must grow by 28.4% in the three years following the date of grant for all the options to vest.

Options with a value on grant as a % of salary	Three-year EPS growth
Up to 100%	22.9% (for Executive Directors) (16.9% for all other employees)
101% to 200%	22.9%
201% to 300%	28.4%
Over 301% of salary	34.9%

The 2000 Executive Share Option Scheme, which was approved by shareholders in 2000, contained an unlimited retesting feature from the date of grant. The Remuneration Committee decided, after consultation with some of Shire plc's major institutional shareholders in 2003, that for options granted under the scheme from 2004 onwards, the performance condition should be retested once only, five years after the grant and then only where Shire's EPS growth has not met the minimum level of performance over the first three years. The level of EPS growth over the five-year period needs to be commensurately higher to meet the retest.

The new Portfolio Share Plan, which has replaced the 2000 Executive Share Option Scheme, does not allow re-testing.

Details of the Company's share option schemes are set out in Note 31 to the Company's consolidated financial statements contained in Part IV of this Annual Report.

(c) Long Term Incentive Plan

No awards were made under Shire plc's Long Term Incentive Plan (LTIP) in 2006.

The LTIP was adopted at Shire plc's 1998 Annual General Meeting and amended in 2000. Under the LTIP, the Remuneration Committee has discretion to make awards of shares subject to a maximum of 100% of salary a year.

The performance condition attached to the vesting of awards under the LTIP is Shire's TSR relative to the FTSE 100 Index over a three-year period. The Remuneration Committee considers that this measure is a reliable and appropriate measure of the Company's performance and that the FTSE 100 is an appropriate benchmark given that Shire plc is a member of the Index.

Under the LTIP:

- all shares vest if Shire's TSR is in the top 10% of the FTSE 100;
- 20% of the shares vest if Shire's TSR is at the median of the FTSE 100, with vesting between these points on a linear basis; and
- no shares vest if Shire's TSR is below the median of the FTSE 100.

The Remuneration Committee determines whether and to what extent the performance condition has been met on the basis of data provided by an independent third party. To date, all awards made under the LTIP have been made as a "conditional allocation", thereby allowing, at the Remuneration Committee's discretion, for a cash equivalent to be paid on maturity of the award. Whilst the performance period is measured over three years, an award is normally transferred after the fourth anniversary of grant, to the extent the performance condition has been met.

4) The implementation of share ownership guidelines

The Remuneration Committee believes that Executive Directors and certain other members of senior management should be encouraged to own shares in Shire plc in order to ensure the alignment of their interests with those of the Shire plc's shareholders. The Remuneration Committee discussed this matter with shareholders during its consultation process in 2005, and has developed share ownership guidelines which came into effect in 2006.

The Executive Share Ownership Guidelines are administered by the Remuneration Committee and are based on the following principles:

- The Remuneration Committee believes that share ownership is an important element of an executive's role in running the Company and represents both a commitment by the executive as well as an alignment of the executive's interests with those of shareholders.
- The Remuneration Committee believes that share ownership by executives should be strongly encouraged, but not mandated.
- The Remuneration Committee understands that, depending on personal and other circumstances, an executive may not be able to achieve the desired level of share ownership.
- The Remuneration Committee believes that executives should understand the importance of share ownership in the stewardship of the Company, and both appropriate time and latitude will be provided to executives to achieve desired share ownership levels, where possible.
- Share ownership levels will be reviewed annually for each executive.

Executives are encouraged, within a five-year period following the later of either the initiation of these guidelines, or their appointment or election, to attain and hold an investment position no less than the multiples of base salary set forth below.

The following are the guideline share ownership levels for the Executive Directors:

- Chief Executive Officer: 2 x Base Salary
- Chief Financial Officer: 1.5 x Base Salary

All shares beneficially owned by an executive (excluding unexercised vested Stock Options or SARs) count towards achieving these guidelines.

The Remuneration Committee will review share ownership levels for each executive on an annual basis. The Committee will discuss with each Executive Director their plans for share ownership on a regular basis; the CEO will discuss with each of the remaining executives their plans for share ownership on a regular basis.

5) Pension and other benefits

The Company's policy is to ensure that pension benefits are competitive in the markets in which Shire operates. Shire contributes 30% of the CEO's annual salary to a Supplemental Employee Retirement Plan (SERP) and 401(k) Plan in the US. The SERP is an unfunded defined benefit scheme; the benefits are payable to certain senior US employees as lump sums on leaving the Group's employment or earlier due to death, disability or termination. The amount of benefit is based on the value of notional contributions adjusted for "earned" investment returns as if they were invested in investments of the employees' choice.

In the UK, Shire operates a defined contribution scheme. The Company contributes 25% of salary towards pension benefits for the CFO. In addition to salary, the Executive Directors receive certain benefits in kind, principally a car or car allowance, life insurance, private medical insurance and dental cover. These benefits are not pensionable.

Service contracts

The Remuneration Committee continues to believe that Executive Directors' service contracts should be for a rolling term and, for UK contracts, incorporate notice periods of twelve months. The Remuneration Committee also believes that the Company should retain the right to make a payment in lieu of notice to a Director. The contracts contain obligations on the Executive Directors in respect of intellectual property, together with post-termination restrictions. The Remuneration Committee's view is that, in the event of early termination, Executive Directors should be treated fairly but paid no more than is necessary. Moreover, there should be no element of reward for failure.

The Executive Directors' contracts of employment, which were revised following consultation with some of the Company's major shareholders in 2003, are dated March 10, 2004 in the case of Mr Russell and March 12, 2004 in the case of Mr Emmens. Both agreements were revised on November 21, 2005 to provide for Shire plc being established as the new holding company for the Shire group. Mr Russell's contract requires him to give the

Company twelve months' notice and expires on him reaching 65. Mr Emmens' contract requires him to give the Company, in certain circumstances, six months' notice and no age is specified for retirement. The Company is required to give Mr Russell twelve months' notice of termination, other than if termination is for cause, whereas it is not obliged to give Mr Emmens any notice. If Mr Emmens' contract is terminated without cause the Company is required to pay him one year's salary and the cash equivalent of one year's pension, car and other contractual benefits.

In the event of termination of employment within twelve months of a change of control, the amount payable in respect of each of Mr Emmens and Mr Russell is one year's salary and the cash equivalent of one year's pension, car and other contractual benefits. Any incentive payable is at the discretion of the Remuneration Committee and is capped at the contractual maximum incentive.

The amount of incentive payable upon termination of employment in any other circumstances, other than for cause, is at the discretion of the Remuneration Committee and is capped at the contractual target incentive.

Non-Executive Directors and the Chairman

Each Non-Executive Director is paid a fee for serving as a Director and additional fees are paid for membership or chairmanship of the Audit, Remuneration and Nomination Committees. The Chairman of the Company receives an inclusive fee. Fees are determined by the Board, with the exception of the Chairman's fee which is determined by the Remuneration Committee and confirmed by the Board. Fees are benchmarked against Non-Executive Director fees of comparable companies. The fees paid to Non-Executive Directors are not performance-related. Details of fees paid to the Chairman and Non-Executive Directors in 2006 are set out in the table below.

The Non-Executive Directors are not eligible to join the Company's pension scheme.

Non-Executive Directors do not participate in any of the Company share schemes or other employee benefit schemes and no options have been granted to Non-Executive Directors in their capacity as Non-Executive Directors of Shire plc. On the merger of the Company with BioChem Pharma Inc in 2001, options were granted to The Hon James Grant in replacement for Mr Grant's BioChem Pharma options. The grant of these replacement options and the original BioChem Pharma option grant were made on the same terms as applied to other employees at the time, including that these options are not subject to any performance conditions.

Non-Executive Directors are appointed ordinarily for a term of two years, subject to shareholder approval. Non-Executive Directors who have served on the Board for nine years or more are appointed for one year terms and, in accordance with the Combined Code on Corporate Governance, are subject to annual re-election by shareholders. Re-appointment of Non-Executive Directors following the expiry of their term of appointment is subject to Board approval. Non-Executive Directors are not entitled to compensation for loss of office.

Details of the unexpired terms of the letters of appointment and notice periods are as follows:

Director	Date of appointment	Date of term expiry	Notice period
Dr. James Cavanaugh	March 24, 2005	March 23, 2007	3 months
Dr. Barry Price	January 25, 2007	January 24, 2008	3 months
The Hon. James Grant	May 11, 2005	May 10, 2007	3 months
Mr Robin Buchanan	July 30, 2005	July 29, 2007	3 months
Mr David Kappler	April 5, 2006	April 4, 2008	3 months
Mr Patrick Langlois	November 11, 2005	November 10, 2007	3 months
Ms Kate Nealon	July 27, 2006	July 26, 2008	3 months
Dr Jeff Leiden	January 1, 2007	December 31, 2008	3 months

The fee policy structure for Non-Executive Directors, effective January 1, 2007, is presented in the table below.

2007 Board membership annual basic fees [1]		
Chairman of the Board (inclusive of all committees)	$	488,051
Senior Non-Executive Director (inclusive of NED fee)	$	96,689
Non-Executive Director	$	86,560
Committee Membership Fees		
Audit, Compliance and Risk Committee Chair	$	36,834
Remuneration Committee Chair	$	23,021
Nomination Committee Chair	$	23,021
Audit, Compliance and Risk Committee member	$	18,417
Remuneration Committee member	$	13,813
Nomination Committee member	$	9,209

(1) Denominated in £ sterling and translated into $ at the average exchange rate prevailing in 2006.

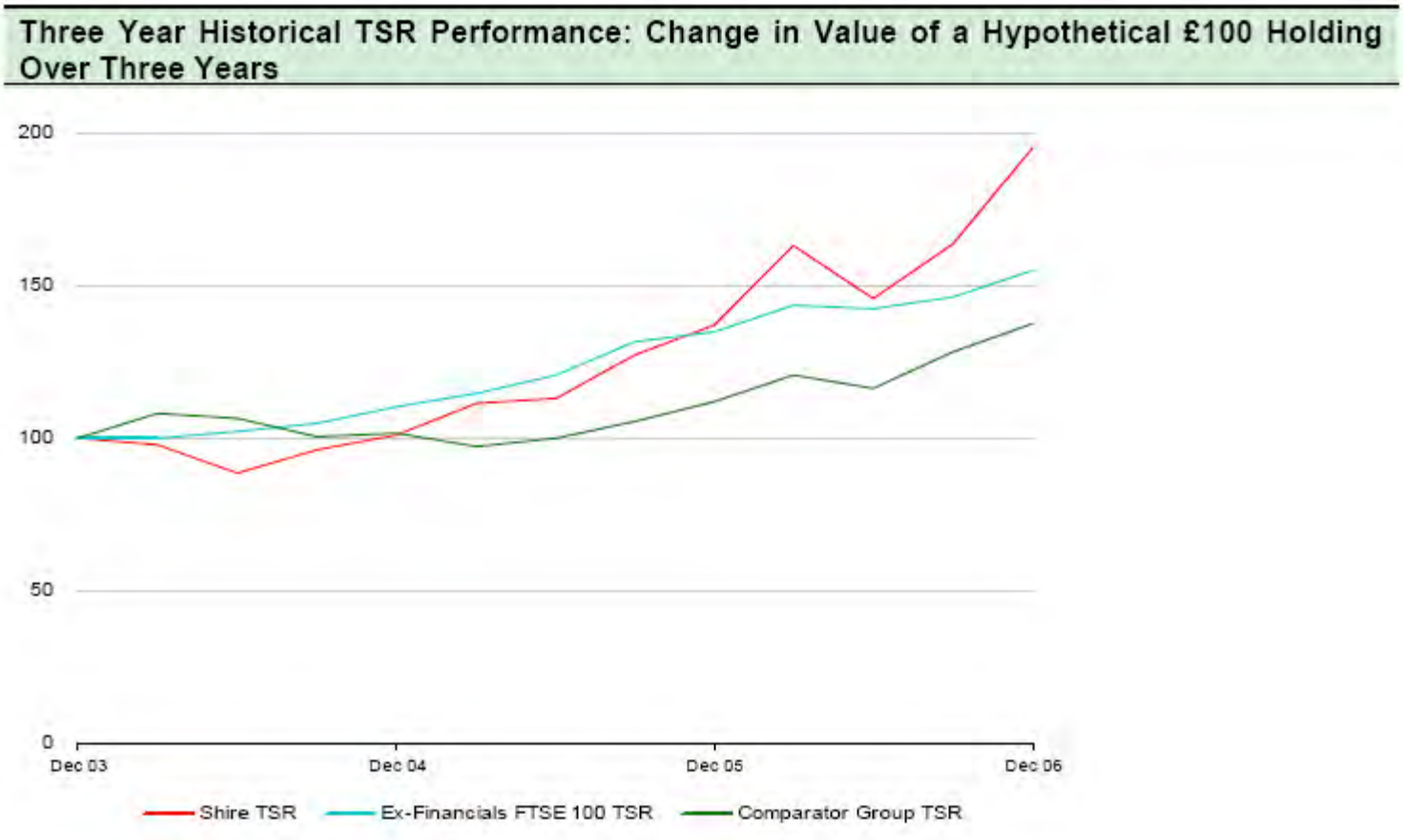
Related party transactions

Details of transactions relating to Dr. James Cavanaugh, The Hon. James Grant, who is a partner of a Canadian law firm with which the Company incurred professional fees during the year and with Dr. Francesco Bellini, a former Non-Executive Director, are given in Item 13: Certain relationships and related transactions.

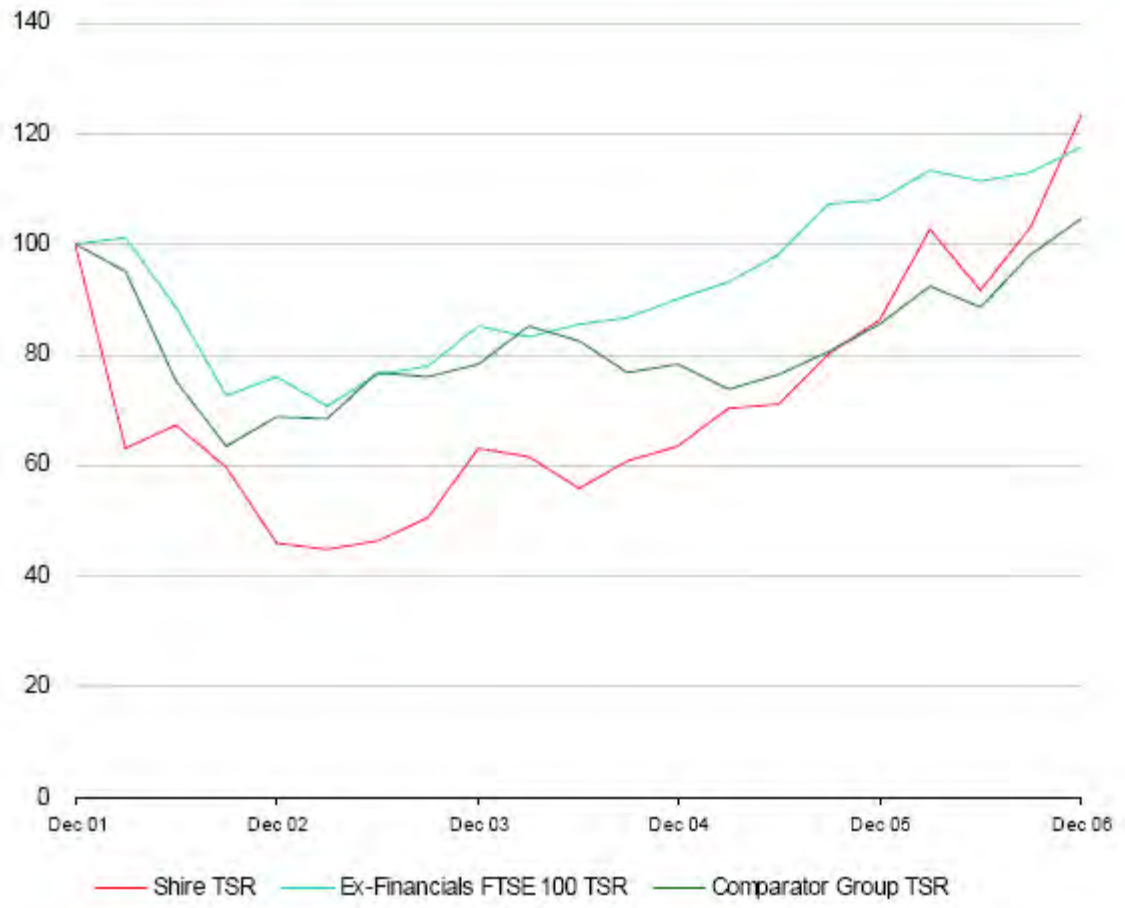
Performance graph

The graphs below set out the TSR for the three and five years ending December 31, 2006. The graphs compare the performance of a hypothetical £100 holding of Shire plc's shares with that of a holding of shares in the FTSE 100 index (excluding financial institutions) and with a holding in a group comprised of the following pharma companies: Novo Nordisk, Schering AG, Serono, Altana, UCB, Lundbeck, Forest Labs, Allergan, Sepracor, Cephalon, Watson, Biovail, King, Valeant, Medicis and Kos. This comparator group is a blend of US and UK companies with sector, size, complexity and international characteristics similar to those of the Company. The Company is a member of the FTSE 100 Index and consequently, for the purpose of the graphs which are set out below, we have selected the FTSE 100 Index (excluding financial institutions) as the appropriate index. These comparisons will also be used to determine achievement of performance conditions relating to the Annual Incentive Plan and the Portfolio Share Plan.

The three year graph has been included as it tracks the TSR performance since the Company started to implement its new strategic plan under new management.



Five Year Historical TSR Performance: Change in Value of a Hypothetical £100 Holding Over Five Years



Other remuneration

The Company believes there are benefits to Executive Directors' participation at the Board level at other companies, including cross-industry and cross-company exposure and the added perspective of outside views. It is therefore the Company's policy to allow Executive Directors to take up Non-Executive positions at other companies and retain associated earnings as long as such appointments are expressly permitted by the Board of Directors.

Mr Emmens was appointed as a Non-Executive Director of Vertex Pharmaceuticals Inc during 2004 and was appointed a Director of Incyte Corporation in 2006. In this capacity he was paid $42,000 and $16,107 respectively in 2006, which he will retain.

Mr Russell is a Non-Executive Director of The City of London Investment Trust plc (and its associated companies, The City of London European Trust Limited, The City of London Investments Limited and The City of London Finance Company Limited). In this capacity, he was paid £17,500 ($32,230 equivalent) in 2006, which he will retain.

Aggregate Directors' remuneration

The total amounts for Directors' remuneration were as follows:

	2006 $'000	2005 $'000
Emoluments	**5,969**	4,289
Money purchase pension contributions	**532**	488
Gains on exercise of share options	**390**	194
	6,891	4,971

Directors' emoluments

	Salary $'000	Incentive $'000	Fees $'000	Cash benefits in kind $'000	Non-cash benefits in kind $'000	Total 2006 $'000	Total 2005 $'000
Executive							
Mr Matthew Emmens [vi]	**1,105**	**1,985**		**87**	**-**	**3,177**	2,286
Mr Angus Russell [vii]	**701**	**971**		**20**	**12**	**1,704**	1,103
Total Executive	**1,806**	**2,956**		**107**	**12**	**4,881**	3,389
Non-executive							
Dr. James Cavanaugh [i]	**-**	**-**	**423**	**-**	**-**	**423**	364
Dr. Barry Price [iii]	**-**	**-**	**134**	**-**	**-**	**134**	132
The Hon. James Grant [i]	**-**	**-**	**85**	**-**	**-**	**85**	82
Mr Ronald Nordmann [i]	**-**	**-**	**118**	**-**	**-**	**118**	114
Mr Robin Buchanan [iii]	**-**	**-**	**87**	**-**	**-**	**87**	87
Mr David Kappler [iii]	**-**	**-**	**111**	**-**	**-**	**111**	109
Mr Patrick Langlois [iv]	**-**	**-**	**94**	**-**	**-**	**94**	12
Ms Kate Nealon [iii] [v]	**-**	**-**	**36**	**-**	**-**	**36**	-
Total Non-Executive	**-**	**-**	**1,088**	**-**	**-**	**1,088**	900
Total	**1,806**	**2,956**	**1,088**	**107**	**12**	**5,969**	4,289

Notes

(i) Paid in US$.

(ii) Salary and benefits in kind paid in £ Sterling and translated into $ at the average exchange rates for the year. Incentive payable in £ Sterling and translated at the exchange rate at the end of February 2007.

(iii) Fees paid in £ Sterling and translated into $ at the average exchange rates for the year.

(iv) Paid in Euros and translated into $ at the average exchange rate for the service period.

(v) Ms Nealon was appointed a Non-Executive Director on July 27, 2006.

(vi) Mr Emmen's incentive was split 64% receivable in cash, 36% receivable in deferred shares.

(vii) Mr Russell's incentive was split 61% receivable in cash, 39% receivable in deferred shares.

Cash benefits in kind represent expense allowances (including dental costs). Non-cash benefits in kind consist of private medical insurance, life insurance and fuel allowance.

Details of the exercise of share options are disclosed below. Non-Executive Director remuneration is to/from the date of resignation/appointment.

Directors' pension entitlements
The following Directors are members of money purchase schemes. Contributions made by the Company (not included in emoluments above) in respect of 2006 were as follows:

Name of Director	**2006 $'000**	2005 $'000
Mr Matthew Emmens	**361**	323
Mr Angus Russell [(i)]	**171**	165
	532	488

(i) At Mr Russell's request the Company deferred pension contributions of $59,000 earned in 2005, which were paid in 2006.

Directors' shareholdings
Directors who held office at the end of the year had interests in the share capital of the Company as follows (all interests are beneficial):

Name of Director	**2006: number of ordinary shares**	2005: number of ordinary shares
Dr. James Cavanaugh	**412,849**	412,849
Mr Matthew Emmens	**18,938**	18,938
Mr Angus Russell	**1,882**	1,882
Dr. Barry Price	**31,350**	31,350
The Hon. James Grant	**100,128**	68,269
Mr Robin Buchanan	**7,500**	7,500
Mr David Kappler	**10,000**	5,000
Mr Patrick Langlois	**Nil**	Nil
Ms Kate Nealon	**2,251**	Nil

Directors' share options
Aggregate emoluments disclosed above do not include any amounts for the value of options to acquire ordinary shares in the Company granted to or held by the Directors.

Directors and employees have been granted options over ordinary shares under the Shire Pharmaceuticals Group plc 2000 Executive Share Option Scheme (Parts A and B) (2000 Executive Scheme), the Shire Holdings Limited Share Option Scheme (SHL Scheme), the Pharmavene 1991 Stock Option Plan (SLI Plan), the Shire Pharmaceuticals Executive Share Option Scheme (Parts A and B) (Executive Scheme), the Shire plc Sharesave Scheme (Sharesave Scheme), the Shire Pharmaceuticals Group plc Employee Stock Purchase Plan (Stock Purchase Plan), the Roberts Stock Option Plan (Roberts Plan) and the BioChem Stock Option Plan (BioChem Plan).

Details of options exercised during the year are as follows:

Director	Scheme	Number of options	Exercise price £	Market price at exercise date £	Gains on exercise 2006 $'000
The Hon. James Grant	BioChem Plan	31,859	6.26	7.85	**94**
Mr Angus Russell	Executive Scheme B	45,819	7.175	10.56	**296**

Details of the options of Directors who served during the year are as follows:

		Number of ordinary shares						Exercise dates	
Director	Scheme	At 1 January 2006	Granted	Exercised	Lapsed	At 31 December 2006	Exercise price £	Earliest	Latest
Mr Matthew Emmens									
2000 Executive Scheme B [iii]		945,010	-	-	-	**945,010**	3.68	18.03.06	17.03.13
		315,777	-	-	-	**315,777**	5.26	25.03.07	24.03.14
		295,000	-	-	-	**295,000**	5.59	11.05.08	10.05.15
Stock Purchase Plan [v]		-	713	-	-	**713**	7.48	21.11.08	21.11.08
		1,555,787	713	-	-	**1,556,500**			
Mr Angus Russell									
Executive Scheme A [i]		4,181	-	-	-	**4,181**	7.175	13.12.02	12.12.09
Executive Scheme B [i]		45,819	-	45,819	-	**-**	7.175	13.12.02	12.12.06
		6,422	-	-	-	**6,422**	10.275	01.03.03	28.02.07
2000 Executive Scheme B [iii]		69,213	-	-	-	**69,213**	12.57	05.06.04	04.06.11
		114,474	-	-	-	**114,474**	5.065	04.03.05	03.03.12
		284,024	-	-	-	**284,024**	3.38	04.03.06	03.03.13
		195,285	-	-	-	**195,285**	5.26	25.03.07	24.03.14
		195,000	-	-	-	**195,000**	5.585	11.05.08	10.05.15
Sharesave [ii]		-	2,342	-	-	**2,342**	6.99	01.12.11	31.05.12
		914,418	2,342	45,819	-	**870,941**			
The Hon James Grant									
BioChem [iv]		31,859	-	31,859	-	**-**	6.26	14.05.01	04.06.06
		2,275	-	-	-	**2,275**	6.20	14.05.01	05.05.07
		2,275	-	-	-	**2,275**	6.94	14.05.01	20.04.08
		7,964	-	-	-	**7,964**	5.70	14.05.01	10.06.09
		13,653	-	-	-	**13,653**	6.58	14.05.01	23.05.10
		58,026	-	31,859	-	**26,167**			

For those options which remain unexercised during the year, no payment was made by any Director in consideration of the grant award.

Details of the SARs of Directors who served during the year are as follows:

Director	Scheme	At 1 January 2006	Granted	Exercised	Lapsed	At 31 December 2006*	Market Price at the date of the award	Exercise dates Earliest	Latest
Number of SARs - ADSs*									
Mr Matthew Emmens									
	PSP part A (vi)	-	126,831	-	-	**126,831**	$ 49.36	17.08.09	17.08.11
	PSP part B (vi)	-	92,671	-	-	**92,671**	$ 49.36	17.08.09	17.08.09
		-	219,502	-	-	**219,502**			
Number of SARs - Ordinary shares									
Mr Angus Russell									
	PSP part A (vi)	-	128,542	-	-	**128,542**	£8.65	17.08.09	17.08.11
	PSP part B (vi)	-	96,406	-	-	**96,406**	£8.65	17.08.09	17.08.09
		-	224,948	-	-	**224,948**			

* 1 ADS is equal to 3 ordinary shares.

Notes

(i) Options granted under this scheme are subject to performance criteria and cannot be exercised in full, unless Shire plc's ordinary share price increases at a compound rate of at least 20.5% per annum over a minimum three-year measurement period. If Shire plc's share price increases at a compound rate of 14.5% per annum over a minimum three-year measurement period, 60% of the options may be exercised. If these conditions are not met after the initial three years, they are thereafter tested quarterly by reference to share price growth over the extended period. If the share price does not meet these conditions at any time, none of the options granted become exercisable.

On February 28, 2000, the Remuneration Committee of the Board exercised its powers to amend the terms of Part B of the Executive Share Option Scheme so as to include a cliff vesting provision. It is intended that no further options will be granted under the Executive Scheme.

(ii) Options granted under the Sharesave Scheme are granted with an exercise price equal to 80% of the mid-market price on the day before invitations are issued to employees. Employees may enter into three or five-year savings contracts.

(iii) Options granted under the 2000 Executive Scheme are exercisable subject to certain performance criteria. In respect of any option granted prior to August 2002, if Shire plc's ordinary share price increases at a compound rate of at least 20.5% per annum over a minimum three-year measurement period, the option becomes exercisable in full. If it increases by at least 14.5% per annum over the same three-year period, 60% of the options granted become exercisable. If these conditions are not met after the initial three-year measurement period, they will thereafter be tested quarterly by reference to compound annual share price growth over an extended period.

The performance criteria were reviewed in 2002 to ensure the criteria reflected the market in which Shire operates. Given Shire's development, it was considered appropriate that an earnings per share based measure should be adopted in place of share price growth targets. The performance criteria are based on real growth in the diluted earnings per share reported in the Company's Form 10-K under US GAAP, adjusted to ensure a consistent basis of measurement, as approved by the Remuneration Committee, including the add back of significant one time items (option EPS) . Therefore, the performance criteria were amended so that an option would become exercisable in full if Shire plc's option EPS growth over a three year period from the date of award exceed the UK Retail Prices Index (RPI) for the following tranches of grants:

Options with a grant value of up to 100% of salary	RPI plus 9% (Directors, RPI plus 15%)

Between 101% and 200% of salary	RPI plus 15%
Between 201% and 300% of salary	RPI plus 21%
Over 301% of salary	RPI plus 27%

The RPI based earnings per share performance criteria applied to options granted under the 2000 Executive Scheme from August 2002. After consultation with certain of its institutional shareholders, the Company decided that, for options granted under the scheme from 2004 onwards, the retest of the performance condition, if Shire plc's option EPS growth falls short of the minimum annual average percentage increase over the three year period from grant, would be changed. The performance condition will be retested once only, therefore, at five years after the grant. Hence the level of option EPS growth in the next two years needs to be consequentially higher to meet the test.

In December 2006 the Remuneration Committee exercised its powers to amend the performance conditions for options granted under the 2000 Executive Scheme which had not vested. The RPI based growth rate was replaced with an equivalent fixed growth rate based on historical and forecast inflation.

Under Part B of the scheme, six weeks prior to the expiration date, any options that have not become exercisable at an earlier date, automatically vest without reference to the performance criteria.

It is intended that no further options will be granted under the 2000 Executive Scheme.

(iv) Following the acquisition of BioChem Pharma Inc. on May 11, 2001, the BioChem Stock Option Plan was amended such that options over BioChem Pharma Inc.'s common stock became options over ordinary shares of Shire plc. All BioChem Pharma Inc. options, which were not already exercisable, vested and became exercisable as a result of the acquisition. It is intended that no further options will be granted under the BioChem Stock Option Plan.

(v) Under the Stock Purchase Plan, options are granted with an exercise price equal to 85% of the fair market value of a share on the enrolment date (the first day of the offering period) or the exercise date (the last day of the offering period), whichever is the lower. The offering period is for 27 months.

(vi) Details of the Portfolio Share Plan and vesting criteria are set out in Note 31 to the consolidated financial statements included within Part IV of this Annual Report.

The market price of the ordinary shares at December 31, 2006 was £10.59 and the range during the year was £7.00 to £10.80. The market price of the ADSs at December 31, 2006 was $61.76 and the range during the year was $38.54 to $64.10.

Long Term Incentive Plan

The following award, granted under the Long Term Incentive Plan lapsed during the year 2006 and no payment was made under it as the performance criteria were not met at the maturity date:

Director	Date of award	Initial award made	Actual performance-related award	Date of maturity
Mr Angus Russell [(i)]	March 4, 2002	19,078	Nil	March 4, 2006

Notes

(i) The performance criteria attaching to awards made under the Long Term Incentive Plan are detailed above.

Details of current and outstanding awards under the Long Term Incentive Plan for Directors who served during the year are as follows:

	Ordinary shares at January 1	Date of	Ordinary shares at December 31	Value of award at grant date	Earliest date on which an award

Name of Director	2006	award	2006	$'000	can be transferred
Mr Matthew Emmens	80,960	March 20, 2003	**80,960**	458	March 20,2007
	105,259	March 25, 2004	**105,259**	1,032	March 25, 2008
	97,468	May 11, 2005	**97,468**	1,025	May 11, 2009
	283,687		**283,687**	2,515	
Mr Angus Russell	19,078	March 4, 2002	**Nil**	180	Lapsed
	44,667	March 20,2003	**44,667**	252	March 20,2007
	65,059	March 25, 2004	**65,059**	638	March 25, 2008
	63,217	May 11, 2005	**63,217**	664	May 11, 2009
	192,021		**172,943**	1,734	

Notes

(i) The performance criteria attaching to awards made under the Long Term Incentive Plan are detailed above.

Approval

This report was approved by the Board of Directors on February 22, 2007 and signed on its behalf by:

Dr. Barry Price
Chairman of the Remuneration Committee

ITEM 12 : Security ownership of certain beneficial owners and management and related stockholder matters

Set forth in the following table is the beneficial ownership of ordinary shares as at February 16, 2007 for (i) each person (or group of affiliated persons) known to the Company to be the beneficial owner of more than 5% of ordinary shares, (ii) all current directors, (iii) certain of the Company's named executive officers in 2006, where applicable, and (iv) all other current directors and executive officers as a group. Except as indicated by the notes to the following table, the holders listed below have sole voting power and investment power over the shares beneficially held by them. The address of each of Shire plc's directors and executive officers is that of Shire plc's.

Name	Number of ordinary shares beneficially owned as at February 21, 2007	Percent of ordinary shares (1)
Beneficial owner		
Fidelity International Limited and its direct and indirect subsidiaries (Pembrooke Hall, 42 Crow Lane, Pembroke, HN19 Bermuda) (2)	26,759,374	5 %
Management		
Dr James Cavanaugh	412,849	*
Matthew Emmens (3)	1,279,725	*
Angus Russell (4)	675,481	*
Dr Barry Price	31,350	*
Robin Buchanan	7,500	*

The Hon James Grant [5]	126,295	*
David Kappler	10,000	*
Patrick Langlois	-	-
Jeffrey Leiden	-	-
Kate Nealon	2,251	-
Michael Cola	-	-
David Pendergast	-	-
Tatjana May [6]	407,693	*
Greg Flexter [7]	57,500	*
All Directors and Executive Officers of the Company (19 persons) [8]	3,368,095	*

* Less than 1%

(1) For the purposes of this table, a person or a group of persons is deemed to have "beneficial ownership" as at a given date of any shares, which that person has the right to acquire within 60 days after that date. For purposes of computing the percentage of outstanding shares held by each person or a group of persons named above on a given date, any shares which that person or persons has the right to acquire within 60 days after that date are deemed to be outstanding.
(2) Based solely on information provided to the Company by Fidelity International Limited (and its direct and indirect subsidiaries) on February 27, 2006.
(3) Includes 1,260,787 ordinary shares issuable upon exercise of options.
(4) Includes 673,599 ordinary shares issuable upon exercise of options.
(5) Includes 26,167 ordinary shares issuable upon exercise of options.
(6) Includes 405, 087 ordinary shares issuable upon exercise of options.
(7) Mr Flexter resigned in 2006. All of Mr Flexter's ordinary shares are issuable upon exercise of options.
(8) Includes 2,814,908 ordinary shares issuable upon exercise of options.

Equity Compensation Plan Information

Set forth in the following table are the details, for the year to December 31, 2006, in respect of compensation plans (including individual compensation arrangements) under which equity securities of the Company are authorized for issuance.

Plan category	Number of securities to be issued upon exercise of outstanding equity awards	Weighted-average price of outstanding equity awards	Number of securities remaining available for future issuance under equity compensation plans
Equity compensation plans approved by security holders	32,032,919	$ 12.87	8,870,700
Equity compensation plans not approved by security holders	-	-	-

ITEM 13 : Certain relationships and related transactions

The Company incurred professional fees with Stikeman Elliott, a law firm in which the Hon. James Grant is a partner, totaling $0.6 million for the year to December 31, 2006 (2005: $0.5 million; 2004: $2.1 million).

In April 2004, the Company contributed cash of $3.7 million (CAN$5.0 million) and equipment and intellectual property to the start-up of a new Canadian-based pharmaceutical research and development organization, ViroChem Pharma Inc. (ViroChem), in return for an equity interest and royalties on the sale of certain products subsequently launched by ViroChem. In April 2006 and April 2005, the Company contributed cash of $8.0 million (CAN$9 million) and $4.1 million (CAN$5 million) respectively to ViroChem in return for an additional equity interest. Dr Bellini, a non-executive director of BioChem and, until May 10, 2003, a non-executive director of Shire, had, at the time of the transaction, an indirect substantial interest in a company, which is a co-investor of

ViroChem. The Company has undertaken to invest an additional $5.0 million (CAN$6.0 million) in ViroChem.

In October 2005, the Company sub-leased its office premises in Newport to Xanodyne Pharmaceuticals Inc. Dr James Cavanaugh, the non-executive Chairman of the Company, was the Chairman of the Board of Directors of Xanodyne Pharmaceuticals, Inc. up to February 9, 2007 and he remains a Board Director. As a result of the transaction the Company will receive $7.8 million (net of inducements) in lease income over the sub-lease period from Xanodyne Pharmaceuticals Inc.

In April 2004 Shire BioChem Inc. (BioChem), a subsidiary of Shire, sold a Canadian property to NeuroChem Inc. for $7.8 million (CAN$10.5 million). At the time of the transaction, Dr Bellini, a non-executive director of Biochem and, until May 10, 2003 a non-executive director of Shire, and Mr Nordmann, a non-executive director of Shire until December 2006, were both directors of NeuroChem Inc. and Dr Bellini had an indirect substantial interest in the issued share capital of Neurochem Inc. at the time of the transaction. Mr Nordmann stepped down as a director of Neurochem Inc. in August 2006.

ITEM 14 : Principal accountant fees and services

The Audit Committee reviews the scope and results of the audit and non-audit services, including tax advisory and compliance services, provided by the Company's Independent Registered Public Accountants, Deloitte & Touche LLP, the cost effectiveness and the independence and objectivity of the Registered Public Accountants. In recognition of the importance of maintaining the independence of Deloitte & Touche LLP, a process for pre-approval has been in place since July 1, 2002 and has continued through to the end of the period covered by this Report.

The following table provides an analysis of the amount paid to the Company's Independent Registered Public Accountants, Deloitte & Touche LLP, all fees having been pre-approved by the Audit Committee.

Year to December 31,	**2006**	**2005**
	$'000	**$'000**
Audit fees (1)	2,624	2,731
Audit-related fees (2)	319	2,390
Tax fees (3)	1,077	2,066
All other fees (4)	505	708
Total fees	4,525	7,895

(1) Audit fees consisted of audit work only the Independent Registered Public Accountant can reasonably be expected to perform, such as statutory audits and included the audit of management's assessment that the Company maintained effective internal control over financial reporting and the audit of the effectiveness of the Company's internal control over financial reporting.
(2) Audit related fees consist of work generally only the Independent Registered Public Accountant can reasonably be expected to perform, such as procedures relating to regulatory filings.
(3) Tax fees consisted principally of assistance with matters related to compliance, planning and advice in various tax jurisdictions.
(4) All other fees relate to assisting the remuneration committee and corporate responsibility.

Policy on Audit Committee pre-approval of audit and permissable non-audit services of Independent Registered Public Accountant

Consistent with SEC policies regarding auditor independence, the Audit Committee has responsibility for appointing, setting compensation and overseeing the work of the Independent Registered Public Accountant. In recognition of this responsibility, the Audit Committee pre-approves all audit and permissible non-audit services provided by the Independent Registered Public Accountant.

Certain services have been pre-approved by the Audit Committee as part of its pre-approval policy, including:

- audit services, such as audit work performed in the preparation of financial statements, as well as work that generally only the Independent Registered Public Accountant can reasonably be expected to provide, including comfort letters,

statutory audits and consultation regarding financial accounting and/or reporting standards;

- audit-related services, such as the audit of employee benefit plans, and special procedures required to meet certain regulatory requirements; and

- tax services, such as tax compliance services and tax advice on employee remuneration strategies.

Where it is necessary to engage the Independent Registered Public Accountant for services not contemplated in the pre-approval policy, the Audit Committee must pre-approve the proposed service before engaging the Independent Registered Public Accountant. For this purpose, the Audit Committee has delegated pre-approval authority to the Chairman of the Audit Committee. The pre-approval policy is reviewed and updated periodically and was last updated on February 21, 2006. The Chairman must report any pre-approval decisions to the Audit Committee at its next scheduled meeting.

PART IV

ITEM 15 : Exhibits, financial statement schedules

The following documents are included as part of this Annual Report on Form 10-K

Index to the consolidated financial statements

Report of Independent Registered Public Accountants

Consolidated Balance Sheets as at December 31, 2006 and 2005

Consolidated Statements of Operations for each of the three years in the period ended December 31, 2006

Consolidated Statements of Changes in Shareholders' Equity for each of the three years in the period ended December 31, 2006

Consolidated Statements of Comprehensive Income for each of the three years in the period ended December 31, 2006

Consolidated Statements of Cash Flows for each of the three years in the period ended December 31, 2006

Notes to the Consolidated Financial Statements

Financial statement schedule

The following schedule is filed as part of this Form 10-K:

Schedule II - Valuation and Qualifying Accounts for each of the three years in the period ended December 31, 2006.

All other schedules are omitted as the information required is inapplicable or the information is presented in the consolidated financial statements or the related notes.

Exhibits

Exhibit number	Description
3.1	Articles of Association of Shire plc as adopted by special resolution on September 19, 2005 (1) .
10.1*	Settlement Agreement, dated August 14, 2006 by and between Shire Laboratories Inc. and Barr Laboratories, Inc. (2)
10.2*	Product Development and License Agreement, dated August 14, 2006 by and between Shire LLC and Duramed Pharmaceuticals, Inc. (2)
10.3*	Product Acquisition and License Agreement, dated August 14, 2006 by and among Shire LLC, Shire plc and Duramed Pharmaceuticals, Inc. (2)
21	List of Subsidiaries.
23.1	Consent of Deloitte & Touche LLP.
31.1	Certification of Matthew Emmens pursuant to Rule 13a - 14 under The Exchange Act.
31.2	Certification of Angus Russell pursuant to Rule 13a - 14 under The Exchange Act.
32	Certification of Matthew Emmens and Angus Russell pursuant to Section 906 of the Sarbanes - Oxley Act of 2002

* Certain portions of this exhibit have been omitted intentionally, subject to a confidential treatment request. A complete version of this agreement has been filed separately with the Securities and Exchange Commission.

(1) Incorporated by reference to Exhibit 3.01 to Shire's Form 8-K filed on November 25, 2005.
(2) Incorporated by reference to Shire ' s Form 10-Q filed on November 7, 2006.

INDEX TO THE CONSOLIDATED FINANCIAL STATEMENTS AND SUPPLEMENTARY SCHEDULE

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the Board of Directors and Stockholders of Shire plc , Basingstoke, England

We have audited the accompanying consolidated balance sheets of Shire plc and subsidiaries (the Company) as at December 31, 2006 and 2005, and the related consolidated statements of operations, stockholders' equity, comprehensive income/(loss), and cash flows for each of the three years in the period ended December 31, 2006. Our audits also included the financial statement schedule listed in the Index at ITEM 15. We also have audited management's assessment, included in the accompanying Management Report on Internal Controls Over Financial Reporting, that the Company maintained effective internal control over financial reporting as of December 31, 2006, based on criteria established in *Internal Control—Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission. The Company's management is responsible for these financial statements and the financial statement schedule, for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting. Our responsibility is to express an opinion on these financial statements and the financial statement schedule, an opinion on management's assessment, and an opinion on the effectiveness of the Company's internal control over financial reporting based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement and whether effective internal control over financial reporting was maintained in all material respects. Our audit of financial statements included examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. Our audit of internal control over financial reporting included obtaining an understanding of internal control over financial reporting, evaluating management's assessment, testing and evaluating the design and operating effectiveness of internal control, and performing such other procedures as we considered necessary in the circumstances. We believe that our audits provide a reasonable basis for our opinions.

A company's internal control over financial reporting is a process designed by, or under the supervision of, the company's principal executive and principal financial officers, or persons performing similar functions, and effected by the company's board of directors, management, and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of the inherent limitations of internal control over financial reporting, including the possibility of collusion or improper management override of controls, material misstatements due to error or fraud may not be prevented or detected on a timely basis. Also, projections of any evaluation of the effectiveness of the internal control over financial reporting to future periods are subject to the risk that the controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, the consolidated financial statements referred to above present fairly, in all material respects, the financial position of the Company as of December 31, 2006 and 2005, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2006, in conformity with accounting principles generally accepted in the United States of America. Also, in our opinion, such financial statement schedule, when considered in relation to the basic consolidated financial statements taken as a whole, presents fairly, in all material respects, the information set forth therein. Also, in our opinion, management's assessment that the Company maintained effective internal control over financial reporting as of December 31, 2006, is fairly stated, in all material respects, based on the criteria established in *Internal Control—Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission. Furthermore, in our opinion, the Company maintained, in all material respects, effective internal control over financial reporting as of December 31, 2006, based on the criteria established in *Internal Control—Integrated Framework* issued by the Committee of Sponsoring Organizations of the Treadway Commission .

As discussed in Note 3(a) to the financial statements, the accompanying 2005 financial statements have been restated.

As discussed in Notes 3 and 31 to the financial statements, in 2006 the Company changed its method of accounting for share based compensation plans to conform to FASB Statement No. 123(R), Share Based Payment and, retrospectively, adjusted the 2005 and 2004 financial statements for the change.

DELOITTE & TOUCHE LLP

Reading, United Kingdom
March 1, 2007

CONSOLIDATED BALANCE SHEETS
(In millions of US dollars, except share data)

	Notes	December 31, 2006 $'M	[1][2] Adjusted and Restated December 31, 2005 $'M
ASSETS			
Current assets:			
Cash and cash equivalents		1,126.9	656.5
Restricted cash		29.8	30.6
Short-term investments		-	6.9
Accounts receivable, net	8	310.8	329.9
Inventories	9	131.1	136.0
Deferred tax asset	29	105.7	54.2
Prepaid expenses and other current assets	10	106.0	98.1
Total current assets		1,810.3	1,312.2
Non current assets:			
Investments	11	55.8	50.2
Property, plant and equipment, net	12	292.8	234.0
Goodwill	13	237.4	225.6
Other intangible assets, net	14	762.4	729.3
Deferred tax asset	29	155.3	62.0
Other non-current assets	15	12.4	42.9
Total assets		3,326.4	2,656.2
LIABILITIES AND SHAREHOLDERS' EQUITY			
Current liabilities:			
Accounts payable and accrued expenses	16	566.1	431.8
Liability to dissenting shareholders	4	452.3	427.6
Other current liabilities	17	313.6	106.0
Total current liabilities		1,332.0	965.4
Non-current liabilities	19	52.1	43.5
Total liabilities		1,384.1	1,008.9
Commitments and contingencies	21		

(1) Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.
(2) Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

CONSOLIDATED BALANCE SHEETS (continued)
(In millions of US dollars, except share data)

	Notes	December 31, 2006 $'M	(1)(2) Adjusted and Restated December 31, 2005 $'M
Shareholders' equity:			
Common stock of 5p par value; 750.0 million shares authorized; and 506.7 million shares issued and outstanding (2005: 750.0 million shares authorized; and 495.7 million shares issued and outstanding)	2 , 22	43.7	42.7
Exchangeable shares: 1.3 million shares issued and outstanding (2005: 2.2 million)		59.4	101.2
Treasury stock	22	(94.8)	(2.8)
Additional paid-in capital		1,493.2	1,327.5
Accumulated other comprehensive income		87.8	71.5
Retained earnings		353.0	107.2
Total shareholders' equity		1,942.3	1,647.3
Total liabilities and shareholders' equity		3,326.4	2,656.2

(1) Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.
(2) Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

The accompanying notes are an integral part of these consolidated financial statements.

CONSOLIDATED STATEMENTS OF OPERATIONS
(In millions of US dollars, except share and per share data)

Year to December 31,	Notes	2006 $'M	(1) (2) Adjusted and Restated 2005 $'M	(1) Adjusted 2004 $'M
Revenues:				
Product sales		1,535.8	1,327.7	1,112.5
Royalties		242.9	242.9	230.4
Other revenues		17.8	28.7	20.3
Total revenues		1,796.5	1,599.3	1,363.2
Costs and expenses:				
Cost of product sales		247.7	215.5	143.3
Research and development		386.9	339.1	199.6

Selling, general and administrative		935.0	729.9	545.4
Intangible asset impairment	14	1.1	5.6	13.5
Reorganization costs	6	-	9.4	48.5
Integration costs	5	5.6	9.7	-
In-process R&D write-off	4	-	815.0	-
Gain on sale of product rights	7	(63.0)	-	-
Total operating expenses		1,513.3	2,124.2	950.3
Operating income/(loss)		283.2	(524.9)	412.9
Interest income		50.5	35.3	21.9
Interest expense	26	(26.4)	(12.0)	(12.3)
Other income, net	27	9.5	9.9	3.9
Total other income, net		33.6	33.2	13.5
Income/(loss) from continuing operations before income taxes, equity in earnings/(losses) of equity method investees and discontinued operations		316.8	(491.7)	426.4
Income taxes	29	(84.9)	(88.8)	(128.3)
Equity in earnings/(losses) of equity method investees	30	5.7	(1.0)	2.5
Income/(loss) from continuing operations		237.6	(581.5)	300.6
Loss from discontinued operations (net of income tax expense of $nil, $nil and $nil respectively)	6	-	-	(20.1)
Gain/(loss) on disposition of discontinued operations (net of income tax expense of $nil, $nil and $nil respectively)	6	40.6	3.1	(44.2)
Net income/(loss)		278.2	(578.4)	236.3

(1) Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.
(2) Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

CONSOLIDATED STATEMENTS OF OPERATIONS (continued)
(In millions of US dollars, except share and per share data)

Year to December 31,	**Notes**	**2006**	**(1) (2) Adjusted and Restated 2005**	**(1) Adjusted 2004**
Earnings per share - basic	24			
Income/(loss) from continuing operations		47.2c	(116.2c)	60.6c
Loss from discontinued operations		-	-	(4.1c)
Gain/(loss) on disposition of discontinued operations		8.1c	0.6c	(8.9c)
		55.3c	(115.6c)	47.6c
Earnings per share - diluted	24			
Income/(loss) from continuing operations		46.6c	(116.2c)	59.4c
Loss from discontinued operations		-	-	(3.9c)
Gain/(loss) on disposition of discontinued operations		8.0c	0.6c	(8.6c)
		54.6c	(115.6c)	46.9c
Weighted average number of shares (millions):				
Basic		503.4	500.2	496.3

Diluted	509.3	500.2	511.3

(1) Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.
(2) Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

T he accompanying notes are an integral part of these consolidated financial statements.

CONSOLIDATED STATEMENTS OF CHANGES IN SHAREHOLDERS' EQUITY
(In millions of US dollars except share data)

	Common stock	Common stock number shares	Exchange-able shares	Exchange-able shares number shares	Treasury stock	(1) Adjusted Additional paid-in capital	Accumu-lated other compre-hensive income	(1) Adjusted Retained earnings	(1) Adjusted Total share-holders' equity
	$'M	M's	$'M	M's	$'M	$'M	$'M	$'M	$'M
As at December 31, 2003	41.2	477.9	270.6	5.8	-	1,045.5	79.1	486.7	1,923.1
Net income	-	-	-	-	-	-	-	236.3	236.3
Foreign currency translation	-	-	-	-	-	-	46.8	-	46.8
Exchange of exchangeable shares	0.4	4.8	(74.8)	(1.6)	-	74.4	-	-	-
Options exercised	0.2	2.1	-	-	-	13.2	-	-	13.4
Stock option compensation and warrants	-	-	-	-	-	33.8	-	-	33.8
Tax benefit associated with exercise of stock options	-	-	-	-	-	(0.4)	-	-	(0.4)
New shares issued	-	0.1	-	-	-	0.8	-	-	0.8
Treasury stock (51,286 shares)	-	-	-	-	(0.3)	-	-	-	(0.3)
Unrealized holding gain on available-for-sale securities	-	-	-	-	-	-	27.0	-	27.0
Realized gain on available-for-sale securities	-	-	-	-	-	-	(20.9)	-	(20.9)
Dividends	-	-	-	-	-	-	-	(8.9)	(8.9)
As at December 31, 2004	41.8	484.9	195.8	4.2	(0.3)	1,167.3	132.0	714.1	2,250.7

(1) Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.

Dividends per share

During the year to December 31, 2004 the Company declared dividends totaling 1.82 US cents per ordinary share equivalent to

5.47 US cents per American Depositary Share, and 7.27 Canadian cents per exchangeable share.

CONSOLIDATED STATEMENTS OF CHANGES IN SHAREHOLDERS' EQUITY (continued)
(In millions of US dollars except share data)

	Common stock $'M	Common stock number shares M's	Exchangeable shares $'M	Exchangeable shares number shares M's	Treasury stock $'M	(1) Adjusted Additional paid-in capital $'M	Accumulated other comprehensive income $'M	(1)(2) Adjusted and Restated Retained earnings $'M	(1) Adjusted Total shareholders' equity $'M
As at December 31, 2004	41.8	484.9	195.8	4.2	(0.3)	1,167.3	132.0	714.1	2,250.7
Net loss	-	-	-	-	-	-	-	(578.4)	(578.4)
Foreign currency translation	-	-	-	-	-	-	(56.0)	-	(56.0)
Exchange of exchangeable shares	0.5	6.1	(94.6)	(2.0)	-	94.1	-	-	-
Options exercised	0.4	4.7	-	-	-	36.7	-	-	37.1
Stock option compensation and warrants	-	-	-	-	-	29.2	-	-	29.2
Tax benefit associated with exercise of stock options	-	-	-	-	-	0.2	-	-	0.2
Treasury stock (242,302 shares)	-	-	-	-	(2.5)	-	-	-	(2.5)
Unrealized holding loss on available-for-sale securities	-	-	-	-	-	-	(1.0)	-	(1.0)
Realized gain on available-for-sale securities	-	-	-	-	-	-	(3.5)	-	(3.5)
Dividends	-	-	-	-	-	-	-	(28.5)	(28.5)
As at December 31, 2005	42.7	495.7	101.2	2.2	(2.8)	1,327.5	71.5	107.2	1,647.3

(1) Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.
(2) Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

The accompanying notes are an integral part of these consolidated financial statements.

Dividends per share

During the year to December 31, 2005 the Company declared dividends totaling 5.67 cents per ordinary share, equivalent to 17.02 cents per American Depositary Share, and 21.09 Canadian cents per exchangeable share.

CONSOLIDATED STATEMENTS OF CHANGES IN SHAREHOLDERS' EQUITY (continued)
(In millions of US dollars except share data)

	Common stock	Common stock number shares	Exchange-able shares	Exchange-able shares number shares	Treasury stock	[1] Additional paid-in capital	Accumulated other compre-hensive income	[1] [2] Retained earnings	Total share-holders' equity
	$'M	M's	$'M	M's	$'M	$'M	$'M	$'M	$'M
As at December 31, 2005	42.7	495.7	101.2	2.2	(2.8)	1,327.5	71.5	107.2	1,647.3
Net income	-	-	-	-	-	-	-	278.2	278.2
Foreign currency translation	-	-	-	-	-	-	18.1	-	18.1
Exchange of exchangeable shares	0.2	2.7	(41.8)	(0.9)	-	41.6	-	-	-
Options exercised	0.8	8.3	-	-	-	81.1	-	-	81.9
Stock option compensation and warrants	-	-	-	-	-	43.0	-	-	43.0
Treasury stock (5.8 million shares)	-	-	-	-	(92.0)	-	-	-	(92.0)
Unrealized holding loss on available-for-sale securities	-	-	-	-	-	-	(1.8)	-	(1.8)
Dividends								(32.4)	(32.4)
As at December 31, 2006	43.7	506.7	59.4	1.3	(94.8)	1,493.2	87.8	353.0	1,942.3

[1] Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.
[2] Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

The accompanying notes are an integral part of these consolidated financial statements.

Dividends per share

During the year to December 31, 2006 the Company declared dividends totaling 6.35 US cents per ordinary share, equivalent to 19.06 US cents per American Depositary Share, and 21.81 Canadian cents per exchangeable share.

C ONSOLIDATED STATEMENTS OF COMPREHENSIVE INCOME/(LOSS)
(In millions of US dollars)

Year to December 31,	2006	[1] [2] Adjusted and Restated 2005	[1] Adjusted 2004
	$'M	$'M	$'M

Net income/(loss)	278.2	(578.4)	236.3
Other comprehensive income/(loss):			
Foreign currency translation	18.1	(56.0)	46.8
Unrealized holding (loss)/gain on available-for-sale securities	(1.8)	(1.0)	27.0
Realized gain on available-for-sale securities	-	(3.5)	(20.9)
Comprehensive income/(loss)	294.5	(638.9)	289.2

The components of accumulated other comprehensive income as at December 31, 2006 and 2005 are as follows:

	December 31, 2006 $'M	December 31, 2005 $'M
Foreign currency translation	80.4	62.3
Unrealized holding gains on available-for-sale securities	7.4	9.2
Accumulated other comprehensive income	87.8	71.5

(1) Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.

(2) Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

There are no material tax effects related to the items included above.

The accompanying notes are an integral part of these consolidated financial statements.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In millions of US dollars)

Year to December 31,	2006 $'M	(1) (2) Adjusted and Restated 2005 $'M	(1) Adjusted 2004 $'M
CASH FLOWS FROM OPERATING ACTIVITIES:			
Net income/(loss)	278.2	(578.4)	236.3
Adjustments to reconcile net income to net cash provided by operating activities:			
Depreciation and amortization:			
Cost of product sales	4.8	3.5	2.7
Selling, general and administrative expense	99.1	68.0	58.5
Stock option compensation	43.0	29.2	33.9
In-process R&D write-off	-	815.0	-
Write-down of long-term assets	3.8	14.1	29.3
Gain on sale of long-term assets	(0.3)	(3.9)	(15.3)
Gain on sale of drug formulation business	-	(3.6)	-
Equity in (earnings)/ losses of equity method investees	(5.7)	1.0	(2.5)
Gain on sale of product rights	(63.0)	-	-

Loss from discontinued operations	-		20.1
(Gain)/loss on disposition of discontinued operations	(40.6)	(3.1)	44.2
Changes in operating assets and liabilities, net of acquisitions:			
Decrease/(increase) in accounts receivable	27.6	(79.9)	(28.1)
Increase in sales deduction accrual	24.8	18.6	50.7
Decrease in inventory	7.2	8.6	2.2
(Increase)/decrease in prepayments and other current assets	(6.2)	(40.1)	2.5
Decrease/(increase) in other assets	0.7	(0.7)	13.5
Movement in deferred taxes	(142.4)	22.3	(15.0)
Increase in accounts and notes payable and other liabilities	297.0	122.9	76.8
(Decrease)/increase in deferred revenue	(1.9)	(13.5)	6.2
Returns on investments from joint ventures	5.8	4.7	4.0
Cash flows used in discontinued operations	-	(0.4)	(30.5)
Net cash provided by operating activities [A]	531.9	384.3	489.5

CONSOLIDATED STATEMENTS OF CASH FLOWS (continued)
(In millions of US dollars)

Year to December 31,	**2006 $'M**	**[1] Adjusted 2005 $'M**	**[1] Adjusted 2004 $'M**
CASH FLOWS FROM INVESTING ACTIVITIES:			
Movement in short-term investments	6.9	366.7	(20.3)
Movements in restricted cash	0.7	(0.8)	24.8
Purchase of subsidiary undertaking, net of cash acquired	(0.8)	(1,114.0)	-
Expenses of acquisition	-	(37.5)	-
Purchase of long-term investments	(9.8)	(7.7)	(6.1)
Purchase of property, plant and equipment	(100.3)	(86.2)	(57.6)
Purchase of intangible assets	(58.8)	(20.5)	(30.2)
Proceeds from sale of long-term investments	-	10.1	26.7
Proceeds from sale of property, plant and equipment	0.9	0.1	3.5
Proceeds from sale of intangible assets	0.4	-	3.7
Proceeds from sale of assets held for sale	-	-	11.3
Proceeds from sale of drug formulation business	-	0.6	-
Proceeds from sale of product rights	63.0	-	-
Returns of equity investments	0.3	3.8	1.5
Loan made to ID Biomedical Corporation (IDB)	-	(43.2)	(56.8)
Proceeds from loan repaid by IDB	70.6	-	-
Proceeds from sale of the vaccines business	-	92.2	34.9
Cash flows used in discontinued operations	-	-	(12.7)
Net cash used in investing activities [B]	(26.9)	(836.4)	(77.3)
CASH FLOWS FROM FINANCING ACTVITIES:			
Redemption of 2% convertible loan notes	(0.1)	-	(370.1)
Repayment of long-term debt, capital leases and notes	-	-	(6.1)
Proceeds from exercise of options	81.9	37.1	13.4
Proceeds from issue of common stock, net	-	-	0.8

Tax benefit of stock option compensation, charged directly to reserves	-	0.2	(0.4)
Payments to acquire treasury stock	(92.0)	(2.5)	(0.3)
Payment of dividend	(32.4)	(28.5)	(8.9)
Cash flows used in discontinued operations	-	-	-
Net cash (used in)/provided by financing activities [C]	(42.6)	6.3	(371.6)
Effect of foreign exchange rate changes on cash and cash equivalents	8.0	(9.2)	7.5
Effect of foreign exchange rate changes on discontinued operations	-	-	-
Net effect of foreign exchange rate changes [D]	8.0	(9.2)	7.5
Net increase/(decrease) in cash and cash equivalents [A+B+C+D]	470.4	(455.0)	48.1
Cash flows used in discontinued operations	-	-	-
Cash and cash equivalents at beginning of year	656.5	1,111.5	1,063.4
Cash and cash equivalents at end of year	1,126.9	656.5	1,111.5

CONSOLIDATED STATEMENTS OF CASH FLOWS (continued)
(In millions of US dollars)

Supplemental information associated with continuing operations:

Year to December 31,	**2006**	**2005**	**2004**
	$'M	**$'M**	**$'M**
Interest paid	1.8	4.3	4.8
Income taxes paid	5.6	54.1	123.5
Non cash activities:			
Proceeds from our product outlicensing:			
Equity in Avexa Ltd	-	1.7	-
Proceeds from sale of drug formulation business:			
Equity in Supernus Pharmaceuticals Inc.	-	3.9	-
Proceeds from sale of a business:			
4,931,864 shares of IDB	-	-	60.0
Escrow funds	-	-	30.0

[1] Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.

[2] Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

The accompanying notes are an integral part of these consolidated financial statements.

NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS
(In millions of US dollars, except where indicated)

1. Description of operations

Shire plc and its subsidiaries' (collectively referred to as “Shire” or the “Company”) strategic goal is to become the leading specialty pharmaceutical company that focuses on meeting the needs of the specialist physician. The Company focuses its business on attention deficit and hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire believes that a carefully selected portfolio of products with strategically aligned and relatively small-scale sales forces will deliver strong results.

The Company’s focused strategy is to develop and market products for specialty physicians. The Company’s in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe.

In accordance with this strategy the Company completed the acquisition of Transkaryotic Therapies Inc. (TKT) on July 27, 2005. This acquisition added HGT to the Company’s existing business, which is complementary to, and consistent with, the Company’s stated strategy of meeting the needs of the specialist physician using small-scale sales forces. TKT was renamed Shire Human Genetic Therapies, Inc. with effect from January 17, 2006.

On February 20, 2007, consistent with its stated focus on the growing ADHD market, Shire announced that it had agreed to acquire New River Pharmaceuticals Inc. allowing Shire to progress and benefit from its successful strategy of acquiring, developing and marketing specialty pharmaceutical products.

2. Change in reporting entity

On November 25, 2005, Shire plc, a public limited company incorporated in England and Wales, became the holding company of Shire Pharmaceuticals Group plc (SPG) pursuant to a Scheme of Arrangement under Section 425 of the UK Companies Act 1985 that was approved by the High Court of Justice in England and Wales and the shareholders of SPG (the Scheme of Arrangement). Pursuant to the Scheme of Arrangement, ordinary shares, each having a nominal value of £3.50, of Shire plc (Shire Ordinary Shares) were exchanged for ordinary shares, each having a nominal value of £0.05 of SPG (SPG Ordinary Shares), on a one-for-one basis. As a result of the Scheme of Arrangement, SPG is now a wholly-owned subsidiary of Shire plc and was re-registered as a private company under the name Shire Pharmaceuticals Group Limited. The Shire plc Ordinary Shares carry substantially the same rights as did the SPG Ordinary Shares. The Scheme of Arrangement did not involve any payment for the new Shire plc Ordinary Shares.

Shire plc’s Board of Directors, management and corporate governance arrangements immediately following the Scheme of Arrangement were the same as SPG immediately before the Scheme of Arrangement became effective. The consolidated assets and liabilities of Shire immediately after the Scheme of Arrangement were the same as the consolidated assets and liabilities of SPG immediately prior thereto.

The SPG Ordinary Shares underlying the SPG American Depositary Shares (the SPG ADSs), each representing three SPG Ordinary Shares, participated in the Scheme of Arrangement like all other SPG Ordinary Shares. The Scheme of Arrangement did not involve any payment for the new Shire ADSs, which represent three ordinary shares of Shire.

Shire plc was incorporated on June 27, 2005. Prior to November 25, 2005 Shire had not commenced trading or made any profits or trading losses.

On November 28, 2005, the High Court of Justice in England and Wales approved a reduction of Shire plc share capital to take effect on November 29, 2005, when the nominal value of each Shire plc ordinary share was reduced from £3.50 pence to £0.05 pence. This reduction increased the distributable reserves potentially available to Shire plc by approximately $2.95 billion, which the directors of Shire plc can utilize for future dividend payments at their discretion.

In accordance with Statement of Financial Accounting Standards (SFAS) No. 141 “Accounting for Business Combinations” (SFAS No. 141), the corporate restructuring is accounted for as a reorganization of entities under common control. Accordingly, the historical financial statements prior to the reorganization are labeled as those of Shire, but continue to represent the operations of SPG. For periods prior to the corporate restructuring, the equity of Shire represents the historical equity of SPG, restated to reflect the nominal value of shares received in the Scheme of Arrangement as adjusted by the reduction of capital. The difference in the nominal value of shares before and after the restatement relates to the effect of foreign exchange movements and the offset is recorded in additional paid-in capital.

Earnings per share were unaffected by the reorganization.

All SPG stock options granted to directors and employees under stock option plans that were in existence immediately prior to the Scheme of Arrangement were exchangeable for stock options in Shire on a one-for-one basis with no change in any of the terms or conditions. The number of stock options for which this exchange did not take place was not material.

For periods presented prior to the 2005 corporate restructuring, the equity of Shire represents the historical equity of SPG, restated to reflect the change in nominal value of shares resulting from the corporate restructuring.

3. Summary of significant accounting policies

(a) Restatement of the financial statements for the year to December 31, 2005

Subsequent to the issuance of the Company's' 2005 financial statements the Company discovered an error in its valuation of in-process research and development (IPR&D). Consequently the financial statements for the year to December 31, 2005 have been restated in respect of the value ascribed to IPR&D, acquired as part of the TKT acquisition and subsequently written off as required under US GAAP in the quarter ended September 30, 2005. IPR&D represented those assets which, at the time of the acquisition, had not been approved by the FDA or other regulatory authorities, including I2S (now known as ELAPRASE) and GA-GCB. The Company has determined that the value ascribed to IPR&D acquired as a result of the TKT acquisition did not include the benefit of tax amortization as required by the American Institute of Certified Public Accountants (AICPA) Practice Aid, *Assets Acquired in a Business Combination to Be Used in Research and Development Activities: A Focus on Software, Electronic Devices, and Pharmaceutical Industries* . The effect of this omission was to understate the value of IPR&D expensed in the year to December 31, 2005 by $142 million, with a corresponding overstatement of goodwill as at December 31, 2005.

As a result of the restatement, certain amounts for the year to December 31, 2005 presented in this Form 10-K have been restated. The impact of the restatement is as follows:

Consolidated Statement of Operations

	As restated 2005 $'M	As previously reported 2005 $'M
In-process R&D write-off	815.0	673.0
Total operating expenses	2,124.2	1,982.2
Loss from continuing operations before income taxes, equity in losses of equity method investees	(491.7)	(349.7)
Net loss	(578.4)	(436.4)
Per share amounts:		
Loss from continuing operations per common share - basic and diluted	(116.2c)	(87.8c)
Net loss - basic and diluted	(115.6c)	(87.2c)

Consolidated Balance Sheet

	As restated 2005 $'M	As previously reported 2005 $'M
Goodwill	225.6	367.6
Total assets	2,656.2	2,798.2

Retained earnings	107.2	249.2
Total shareholders' equity	1,647.3	1,789.3
Total liabilities and shareholders' equity	2,656.2	2,798.2

Consolidated Statement of Cashflows

	As restated 2005 $'M	As previously reported 2005 $'M
Net loss	(578.4)	(436.4)
Adjustments to reconcile net income to net cash provided by operating activities:		
In-process R&D write off	815.0	673.0
Net cash provided by operating activities	384.3	384.3

There have been no changes to any line-items or totals for cash flows from financing or investing activities.

(b) Basis of preparation

The accompanying consolidated financial statements include the accounts of Shire and all of its subsidiary undertakings after elimination of inter-company accounts and transactions.

(c) Use of estimates in consolidated financial statements

The preparation of consolidated financial statements, in conformity with US generally accepted accounting principles (GAAP) and Securities Exchange Commission (SEC) regulations, requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities at the date of the consolidated financial statements and reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates. Estimates and assumptions are primarily made in relation to provisions for litigation, valuation of intangible assets (including those acquired through the acquisition of TKT), inventory acquired through the acquisition of TKT, valuation of IPR&D, the valuation of equity investments, sales deductions, income taxes and share-based payments and the amount payable to former holders of TKT common stock of approximately 11.3 million shares who have submitted written demands for appraisal of these shares in relation to the Company's acquisition of TKT on July 27, 2005.

(d) Revenue recognition

The Company recognizes revenue when:

- there is persuasive evidence of an agreement or arrangement;
- delivery of products has occurred or services have been rendered;
- the seller's price to the buyer is fixed or determinable; and
- collectability is reasonably assured.

Where applicable, all revenues are stated net of value added tax and similar taxes, and trade discounts.

No revenue is recognized for consideration, the value or receipt of which is dependent on future events, future performance, or refund obligations.

The Company's principal revenue streams and their respective accounting treatments are discussed below:

Product sales

Revenue for the sales of products is recognized upon shipment to customers or at the time of delivery depending on the terms of sale. Provisions for rebates, product returns and discounts to customers are provided for as reductions to revenue in the same period as the related sales are recorded. The Company monitors and tracks the amount of sales deductions based on historical experience to estimate the amount of reduction to revenue.

Licensing and development fees

Licensing and development fees represent revenues derived from product out-licensing agreements and from contract research and development agreements.

Initial license fees received in connection with product out-licensing agreements, even where such fees are non-refundable and not creditable against future royalty payments, are deferred and recognized over the period of the license term, or the period of the associated collaborative assistance if that period is reasonably estimable. In circumstances where initial license fees are not for a defined period, revenues are deferred until the period of associated collaborative assistance is either reasonably estimable or any performance obligations are inconsequential: thereafter revenues are deferred and recognized over the period to the expiration of the relevant patent to which the license relates.

Revenue from contract research and development agreements is recognized as the services are performed.

Royalty income

Royalty income relating to licensed technology is recognized when the licensee sells the underlying product. The Company receives sales information from the licensee on a monthly basis. For any period that the information is not available, the Company estimates sales amounts based on the historical product information.

Milestones

During the term of certain research and development agreements and licensing agreements, the Company receives non-refundable milestones as certain technical targets are achieved. Revenues are recognized on achievement of such milestones.

The Company also receives non-refundable clinical milestones when certain targets are achieved during the clinical phases of development, such as the submission of clinical data to a regulatory authority. These clinical milestones are recognized when receivable (i.e. on completion of the relevant phase). If milestone payments are creditable against future royalty payments, the milestones are deferred and released over the period in which the royalties are anticipated to be paid.

(e) Sales deductions

(i) Rebates

Rebates primarily consist of statutory rebates to state Medicaid agencies and contractual rebates with health-maintenance organizations. These rebates are based on price differentials between a base price and the selling price. As a result, rebates generally increase as a percentage of the selling price over the life of the product (as prices increase). Provisions for rebates are recorded as reductions to revenue in the same period as the related sales, with estimates of future utilization derived from historical trends.

(ii) Returns

The Company estimates the proportion of recorded revenue that will result in a return, based on historical trends and when applicable, specific factors affecting certain products at the balance sheet date. The accrual is recorded as a reduction to revenue in the same period as the related sales are recorded.

(iii) Coupons

The Company uses coupons as a form of sales incentive. An accrual is established based on the Company's expectation of the level of coupon redemption, using historical trends. The accrual is recorded as a reduction to revenue in the same period as the related sales are recorded.

(iv) Discounts

The Company offers cash discounts to customers for the early payment of receivables. Those discounts are recorded as reductions to revenue and accounts receivable in the same period that the related sale is recorded.

(v) Wholesaler chargebacks

The Company has contractual agreements whereby it supplies certain products to third parties at predetermined prices. Wholesalers acting as intermediaries in these transactions are reimbursed by the Company if the predetermined prices are less than the prices paid by the wholesaler to the Company. Accruals for wholesaler chargebacks, which are based on historical trends, are recorded as reductions to revenue in the same period as the related sales are recorded.

(f) Cost of product sales

Cost of sales includes the cost of purchasing finished product for sale, the cost of raw materials and manufacturing for those products that are manufactured by the Company and shipping and handling costs. Royalties that are payable on those products that the Company does not own the rights to are also included in cost of sales.

(g) Leased assets

The costs of operating leases are charged to operations on a straight-line basis over the lease term, even if rental payments are not made on such a basis.

Assets acquired under capital leases are included in the balance sheet as property, plant and equipment and are depreciated over the shorter of the period of the lease or their useful lives. The capital elements of future lease payments are recorded as liabilities, while the interest element is charged to operations over the period of the lease to produce a level yield on the balance of the capital lease obligation.

(h) Advertising expense

The Company expenses the cost of advertising as incurred. Advertising costs amounted to $91.6 million, $62.3 million, and $47.6 million for the years to December 31, 2006, 2005 and 2004 respectively and were included within selling, general and administrative expenses.

(i) Research and development expense

Research and development costs are expensed as incurred. Upfront and milestone payments made to third parties for products that have not yet received marketing approval and for which no alternative future use has been identified, are also expensed as incurred.

Milestone payments made to third parties subsequent to regulatory approval are capitalized as intangible assets, and amortized over the remaining useful life of the related product.

(j) Valuation and impairment of long-lived assets other than goodwill and investments

The Company evaluates the carrying value of long-lived assets other than goodwill and investments for impairment annually or

whenever events or changes in circumstances indicate that the carrying amounts of the assets may not be recoverable. When such a determination is made, management's estimate of undiscounted cash flows to be generated by the assets is compared to the carrying value of the assets to determine whether an impairment is indicated. If an impairment is indicated, the amount of the impairment recognized in the consolidated financial statements is determined by estimating the fair value of the assets and recording a loss for the amount that the carrying value exceeds the estimated fair value. This fair value is usually determined based on estimated discounted cash flows.

(k) Finance costs of debt

Finance costs of debt are recorded as a deferred asset and amortized to the statement of operations over the term of the debt, using the effective interest rate method. Deferred financing costs relating to debt extinguishments are written off and reflected in interest expense in the consolidated statements of operations.

(l) Foreign currency

Monetary assets and liabilities in foreign currencies are translated into the relevant functional currency at the rate of exchange ruling at the balance sheet date. Transactions in foreign currencies are translated into the relevant functional currency at the rate of exchange ruling at the date of the transaction. Transaction gains and losses are recognized in arriving at operating net (loss)/income.

The results of overseas operations, whose functional currency is not US Dollars, are translated at the average rates of exchange during the period and their balance sheets at the rates ruling at the balance sheet date. The cumulative effect of exchange rate movements is included in a separate component of other comprehensive income.

Foreign currency exchange transaction gains and losses on an after-tax basis included in consolidated net income in the years to December 31, 2006, 2005, and 2004, amounted to a $3.2 million gain, $1.4 million loss and $2.5 million loss, respectively.

(m) Income taxes

The Company provides for income taxes in accordance with SFAS No.109, "Accounting for Income Taxes". Deferred tax assets and liabilities are provided for differences between the carrying amounts of assets and liabilities in the consolidated financial statements and the tax bases of assets and liabilities that will result in future taxable or deductible amounts. The deferred tax assets and liabilities are measured using the enacted tax laws and rates applicable to the periods in which the differences are expected to affect taxable income. Income tax expense is computed as the tax payable or refundable for the period, plus or minus the change during the period in deferred tax assets and liabilities.

Deferred tax assets are reduced by a valuation allowance when, in the opinion of management, it is more likely than not that some portion or all of the deferred tax assets will not be realized.

(n) Earnings per share

Earnings per share is computed in accordance with SFAS No. 128, "Earnings per Share". Basic earnings per share is based upon net income/(loss) available to ordinary shareholders divided by the weighted average number of ordinary shares outstanding during the period. Diluted earnings per share is based upon net income/(loss) available to ordinary shareholders divided by the weighted average number of ordinary share equivalents outstanding during the period, adjusted for the effect of all dilutive potential ordinary shares that were outstanding during the year. Such potentially dilutive shares are excluded when the effect would be to increase earnings per share or reduce a loss per share.

(o) Share-based compensation

Share-based compensation represents the cost of share-based awards granted to employees. The Company measures share-based compensation cost for awards classified as equity at the grant date, based on the estimated fair value of the award, and

recognizes the cost as expense on a straight-line basis (net of estimated forfeitures) over the employee requisite service period. The Company measures share based compensation cost for awards classified as liabilities at fair value, which is re-measured at the end of each reporting period. Changes in the fair value that occur during the requisite service period are recognized as compensation cost over the requisite service period. The Company estimates the fair value of share-based awards without market-based performance conditions using a Black-Scholes valuation model and awards with market-based performance conditions are valued using a binomial valuation model. The following assumptions were used to value share based awards:

- Risk-free interest rate - For awards granted over ADSs, the US Federal Reserve treasury constant maturities rate with a term consistent with the expected life of the award is used. For awards granted over ordinary shares, the yield on UK government bonds with a term consistent with the expected life of the award is used;

- Expected dividend yield - measured as the average annualised dividend estimated to be paid by the Company over the expected life of the award as a percentage of the share price at the grant date;

- Expected life - the average of the vesting period and the expiration period from the date of issue of the award; and

- Weighted average expected volatility - measured using historical daily price changes of the Company's share price over the respective expected life of the share-based awards at the date of the award.

The forfeiture rate is estimated using historical trends of the number of awards forfeited prior to vesting.

The expense is recorded in cost of product sales; research and development; and selling, general and administrative in the statement of operations based on the employees' respective functions.

The Company records deferred tax assets for awards that result in deductions on the Company's income tax returns, based on the amount of compensation cost recognized and the Company's statutory tax rate in the jurisdiction in which it will receive a deduction. Differences between the deferred tax assets recognized for financial reporting purposes and the actual tax deduction reported on the Company's income tax return are recorded in additional paid-in capital (if the tax deduction exceeds the deferred tax asset) or in the statement of operations (if the deferred tax asset exceeds the tax deduction and no additional paid-in capital exists from previous awards).

As at December 31, 2006 the Company had seven share-based employee compensation plans, which are described more fully in Note 31 .

(p) Cash and cash equivalents

Cash and cash equivalents are defined as short-term highly liquid investments with original maturities of ninety days or less.

(q) Short-term investments

Short-term investments consist of commercial paper and institutional and managed cash funds. In accordance with SFAS No. 115 "Accounting for Certain Investments in Debt and Equity Securities" (SFAS No. 115), and based on the Company's intentions regarding these instruments, the Company has classified all short-term investments held at December 31, 2006 as available-for-sale. Accordingly, the Company records these investments at their fair values with unrealized gains and losses included in the consolidated statements of comprehensive income, net of any related tax effect. Realized gains and losses and declines in value judged to be other-than-temporary on available-for-sale securities are included in other income, net (see Note 27).

Institutional and managed cash funds are short-term money market instruments, including bank and building society term deposits and other debt securities from a variety of companies with strong credit ratings.

(r) Financial instruments - derivatives

The Company uses derivative financial instruments to manage its exposure to foreign exchange risk associated with inter-company loan arrangements. These instruments consist of forward foreign exchange contracts and foreign exchange swaps. The Company does not adopt hedge accounting treatment for these instruments and movements in their fair values are recognized in the statement of operations. The fair values of these instruments are included on the balance sheet in current assets/liabilities.

(s) Inventories

Inventories are stated at the lower of cost (including manufacturing overheads, where appropriate) or net realizable value. Cost incurred in bringing each product to its present location and condition is based on purchase costs calculated on a first-in, first-out basis, including transport. Net realizable value is based on estimated normal selling price less further costs expected to be incurred to completion and disposal.

(t) Assets held for sale

An asset is classified as held for sale when, amongst other things, the Company has committed to a plan of disposition, the asset is available for immediate sale, and the plan is not expected to change significantly.

(u) Investments

The Company has certain investments in pharmaceutical and biotechnology companies.

Investments are accounted for using the equity method of accounting if the investment gives the Company the ability to exercise significant influence, but not control over, the investee. Significant influence is generally deemed to exist if the Company has an ownership interest in the voting stock of the investee between 20% and 50%, although other factors, such as representation on the investee's Board of Directors and the impact of commercial arrangements, are considered in determining whether the equity method of accounting is appropriate. Under the equity method of accounting, the Company records its investments in equity-method investees in the consolidated balance sheet as investments and its share of the investees' earnings or losses together with other-than-temporary impairments in value as equity in earnings/(losses) of equity method investees in the consolidated statement of operations.

All other equity investments, which consist of investments for which the Company does not have the ability to exercise significant influence, are accounted for under the cost method or at fair value. Investments in private companies are carried at cost, less provisions for other-than-temporary impairment in value. For public companies that have readily determinable fair values, the Company classifies its equity investments as available-for-sale and, accordingly, records these investments at their fair values with unrealized gains and losses included in the consolidated statements of comprehensive income, net of any related tax effect. Realized gains and losses and declines in value judged to be other-than-temporary on available-for-sale securities are included in other income, net (see Note 26). The cost of securities sold is based on the specific identification method. Interest and dividends on securities classified as available-for-sale are included as interest income.

(v) Property, plant and equipment

Property, plant and equipment is shown at cost, less accumulated depreciation and any impairment. The cost of significant assets includes capitalized interest incurred during the construction period. Depreciation is provided on a straight-line basis at rates calculated to write off the cost less estimated residual value of each asset over its estimated useful life as follows:

Buildings	20 to 50 years
Office furniture, fittings and equipment	3 to 10 years
Warehouse, laboratory and manufacturing equipment	3 to 10 years

The cost of land is not depreciated.

Expenditures for maintenance and repairs are charged to operations as incurred. The costs of major renewals and improvements are capitalized. At the time property, plant and equipment is retired or otherwise disposed of, the cost and accumulated

depreciation are eliminated from the asset and accumulated depreciation accounts. The profit or loss on such disposition is reflected in operating (loss)/income.

(w) Goodwill and other intangible assets

(i) Goodwill

In a business combination, goodwill represents the excess of the fair value of the consideration given over the fair value of the identifiable assets and liabilities acquired.

Goodwill is not amortized to operations, but instead is reviewed for impairment, at least annually or whenever events or changes in circumstances indicate that the carrying value may not be recoverable. Some factors the Company considers important which could trigger an impairment review include the following: (i) significant underperformance of a reporting unit relative to expected historical or projected future operating results; (ii) significant changes in the manner of the Company's use of acquired assets or the strategy for the overall business; and (iii) significant negative industry or economic trends.

In accordance with SFAS No. 142 "Goodwill and Other Intangible Assets" (SFAS No. 142), goodwill is reviewed for impairment by comparing the carrying value of each reporting unit's net assets (including allocated goodwill) to the fair value of those net assets. If the reporting unit's carrying amount is greater than its fair value, then a second step is performed whereby the portion of the fair value that relates to the reporting unit's goodwill is compared to the carrying value of that goodwill. The Company recognizes a goodwill impairment charge for the amount the carrying value of goodwill exceeds the fair value. The Company has determined that there are no impairment losses for any of the reporting periods covered by these financial statements.

(ii) Other intangible assets

Other intangible assets, which comprise intellectual property including trademarks for products with a defined revenue stream (namely commercial products or rights to products awaiting final regulatory approval), are recorded at cost and amortized over the estimated useful life of the related product, which ranges from 5 to 35 years (weighted average 13 years). Intellectual property with no defined revenue stream, where the related product has not yet completed the necessary approval process, is written off to operations on acquisition.

The following factors are considered in estimating useful lives. Where an intangible asset is a composite of a number of factors, the period of amortization is determined from considering these factors together:

- expected use of the asset;
- regulatory, legal or contractual provisions, including the regulatory approval and review process, patent issues and actions by government agencies;
- the effects of obsolescence, changes in demand, competing products and other economic factors, including the stability of the market, known technological advances, development of competing drugs that are more effective clinically or economically; and
- actions of competitors, suppliers, regulatory agencies or others that may eliminate current competitive advantages.

(x) Non-monetary transactions

The Company enters into certain non-monetary transactions that involve either the granting of a license over the Company’s patents or the disposal of an asset or group of assets in exchange for a non-monetary asset, usually equity. The Company accounts for these transactions at fair value if the Company is able to determine the fair value within reasonable limits. To the extent that the Company concludes that it is unable to determine the fair value of a transaction, that transaction is accounted for at the recorded amounts of the assets exchanged. Management is required to exercise its judgment in determining whether or not the fair value of the asset received or that given up can be determined.

(y) New accounting pronouncements

Adopted in the current year

SFAS 123(R)

On January 1, 2006 the Company adopted SFAS No. 123(R) which requires that the cost resulting from all share-based payment transactions be recognized in the financial statements at fair value and that excess tax benefits be reported as a financing cash inflow rather than as a reduction of taxes paid.

The Company has elected to adopt the modified-retrospective method which permits companies to retrospectively adjust, based on the amounts previously recognized under SFAS No. 123 for pro forma disclosure purposes, all prior periods presented. The following table shows the total share-based compensation expense included in the Company's statements of operations as a result of adopting SFAS No. 123(R):

	2006 $'M	2005 $'M	2004 $'M
Cost of product sales	3.2	1.5	1.4
Research and development	5.4	2.9	3.5
Selling, general and administrative	34.4	24.8	28.9
Total operating expenses	43.0	29.2	33.8
Income tax credit	(6.5)	(3.2)	(0.8)
Total charge to net income	36.5	26.0	33.0

As previously discussed, the Company elected to adopt SFAS No. 123(R) under the modified retrospective application method. As a result, the financial statement amounts for the period to December 31, 2005 presented in this Form 10-K have been retrospectively adjusted to reflect the fair value method of expensing prescribed by SFAS No. 123(R). The impact of this retrospective application is as follows:

	2005		2004	
	Restated Post adoption of SFAS 123(R) $'M	Restated Pre adoption of SFAS 123(R) $'M	Post adoption of SFAS 123(R) $'M	Pre adoption of SFAS 123(R) $'M
(Loss)/Income from continuing operations before income taxes, equity in losses of equity method investees	(491.7)	(462.9)	426.4	459.9
(Loss)/Income from continuing operations	(581.5)	(555.9)	300.6	333.3
Net (loss)/income	(578.4)	(552.8)	236.3	269.0
Per share amounts:				
Net (losses)/earnings per common share - basic	(115.6c)	(110.5c)	47.6	54.2
Net (losses)/earnings per common share - diluted	(115.6c)	(110.5c)	46.9	53.3

At December 31, 2005	Restated Post adoption of SFAS 123(R) $'M	Restated Pre adoption of SFAS 123(R) $'M
Additional paid-in capital	1,327.5	1,205.3
Retained earnings	107.2	229.4

The cumulative effect of the change arising from the adoption of SFAS No. 123(R) on shareholder's equity as at January 1, 2005 increased additional paid in capital to $1,167.3 million from $1,070.7 million as previously reported, and decreased retained earnings to $714.1 million from $810.7 million pre adoption of SFAS No. 123(R).

FSP SFAS 123(R)-2

In October 2005, the Financial Accounting Standards Board (FASB) issued a FASB Staff Position (FSP) SFAS No. 123(R)-2, "Practical Accommodation of Grant Date as Defined in FASB Statement No. 123(R)" (FSP SFAS No. 123(R)-2). FSP SFAS No. 123(R)-2 is in response to recent enquiries from constituents to provide guidance on the application of grant date as defined in SFAS No. 123(R). One of the criteria in defining the grant date in SFAS No. 123(R) is a mutual understanding by the employer and the employee of the key terms and conditions of a share-based payment award. Practice has developed such that the grant date of an award is generally the date the award is approved in accordance with an entity's corporate governance provisions, so long as the approved grant is communicated to employees within a relatively short period of time from the date of approval. For many companies, the number and geographic dispersion of employees receiving share-based awards limit the ability to communicate with each employee immediately after the awards have been approved. As a practical accommodation, a mutual understanding of the key terms and conditions of an award to an individual employee shall be presumed to exist at the date the award is approved if the award is a unilateral grant and the key terms and conditions of the award are expected to be communicated to an individual recipient within a relatively short time period from the date of approval. FSP SFAS No. 123(R)-2 is effective for the Company from January 1, 2006. The adoption of FSP SFAS No. 123(R)-2 has had no material impact on the consolidated financial position, results of operations or cash flows of the Company.

FSP SFAS 123(R)-3

In November 2005, the FASB issued a staff position FSP SFAS No. 123(R)-3, "Transition Election Related to Accounting for the Tax Effects of Share-Based Payment Awards." This FSP provides a practical exception when a company transitions to the accounting requirements in SFAS No. 123(R), which requires a company to calculate the pool of excess tax benefits available to absorb tax deficiencies recognized subsequent to adopting SFAS No. 123(R) (termed the "APIC Pool"), assuming the company has been following the recognition provisions prescribed by SFAS No. 123. The FASB learned that several companies do not have the necessary historical information to calculate the APIC pool as envisioned by SFAS No. 123(R) and accordingly, the FASB decided to allow a practical exception as documented in this FSP. FSP SFAS No. 123(R)-3 is effective for the Company from January 2006. The Company has used the practical exception of this FSP and has calculated its APIC Pool at transition.

FSP SFAS 123(R)-4

In February 2006, the FASB issued a staff position FSP SFAS No. 123(R)-4 "Classification of Options and Similar Instruments Issued as Employee Compensation that Allow for Cash Settlement upon Occurrence of a Contingent Event." This position amends SFAS No. 123(R) to incorporate that a cash settlement feature that can be exercised only upon the occurrence of a contingent event that is outside the employee's control does not meet certain conditions in Statement 123(R) until it becomes probable that the event will occur. The guidance in this position shall be applied upon initial adoption of SFAS No. 123(R). The adoption of FSP SFAS No. 123(R)-4 did not have a material impact on the Company's consolidated financial position, results of operations or cash flows.

SFAS 151

In November 2004, the FASB issued SFAS No. 151, "Inventory Costs - an amendment of ARB No. 43, Chapter 4" (SFAS No. 151). SFAS No. 151 clarifies that abnormal amounts of idle facility expense, freight, handling costs, and wasted materials (spoilage) should be recognized as current-period charges and requires the allocation of fixed production overheads to inventory based on the normal capacity of the production facilities. SFAS No. 151 is effective for fiscal years beginning after June 15, 2005. The adoption of SFAS No. 151 has had no material impact on the consolidated financial position, results of operations or cash flows of the Company.

SFAS 154

In May 2005, SFAS No. 154, "Accounting Changes and Error Corrections - replacement of APB Opinion No. 20 and FASB Statement No. 3," (SFAS No. 154) was issued. SFAS No. 154 changes the accounting for and reporting of a change in accounting

principle by requiring retrospective application to prior periods' financial statements of changes in accounting principle unless impracticable. SFAS No. 154 is effective for accounting changes made in fiscal years beginning after December 15, 2005. The adoption of SFAS No. 154 required no adjustment or restatement of the consolidated financial position, results of operations or cash flows of the Company as there were no material misstatements which had not been corrected.

FSP SFAS 115-1 and SFAS No. 124-1

In November 2005, the FASB issued FSP FAS 115-1 and 124-1, "The Meaning of Other-Than-Temporary Impairment and Its Application to Certain Investments." The guidance in this FSP addresses the determination of when an investment is considered impaired, whether that impairment is other than temporary, and the measurement

of an impairment loss. The FSP also includes accounting considerations subsequent to the recognition of an other-than-temporary impairment and requires certain disclosures about unrealized losses that have not been recognized as other-than-temporary impairments. FSP SFAS No. 115-1 and SFAS 124-1 are effective for the Company in the first quarter of fiscal year 2006. The adoption of FSP SFAS No. 115-1 and SFAS 124-1 has had no material impact on the Company's consolidated financial position, results of operations or cash flows.

EITF 04-5

In June 2005, the Emerging Issues Task Force (EITF) reached a consensus regarding the issue, "Investor's Accounting for an Investment in a Limited Partnership when the Investor is the Sole General Partner and the Limited Partners have Certain Rights" (Issue), on how to evaluate whether a partnership should be consolidated by one of its partners. The scope of this Issue is limited to limited partnerships or similar entities (such as limited liability companies that have governing provisions that are the functional equivalent of a limited partnership) that are not variable interest entities under FASB Interpretation 46(R). The EITF concluded that a general partner or a group of general partners of a limited partnership is presumed to control the limited partnership, unless either the limited partners have the substantive ability to dissolve the limited partnership or otherwise remove the general partner without cause or the limited partners have substantive participating rights. The guidance in this Issue is effective after June 29, 2005 for general partners of all new limited partnerships formed and for existing limited partnerships for which the partnership agreements are modified. For general partners in all other pre-existing limited partnerships, the guidance in this Issue is effective no later than the beginning of the first reporting period in fiscal years beginning after December 15, 2005. The adoption of EITF 04-5 has had no material impact on the Company's consolidated financial position, results of operations or cash flows.

FSP EITF 00-19-2

In December 2006, the FASB issued a staff position FSP EITF 00-19 - 2, "Accounting for Registration Payment Arrangements". The FSP clarifies that a registration payment arrangement and the financial instrument(s) subject to that arrangement should be separately measured and recognized. Specifically, the contingent obligation to make future payments or otherwise transfer consideration under a registration payment arrangement shall be recognized and measured separately in accordance with Statement 5 and FASB Interpretation No. 14, *Reasonable Estimation of the Amount of a Loss* .This FSP's guidance is effective immediately for registration payment arrangements and the financial instruments subject to those arrangements that are entered into or modified after December 21, 2006. Otherwise, the guidance is effective for financial statements issued for fiscal years beginning after December 15, 2006, and interim periods within those fiscal years. The adoption of this FSP did not and is not expected to have a material impact on the Company's consolidated financial position, results of operations or cash flows.

SFAS 158

In September 2006 the FASB issued SFAS 158, "Employer's Accounting for Defined Benefit Pension and Other Post-Retirement Plans - an amendment of FASB Statements No. 87, 88, 106 and 132R". SFAS 158 requires that the over funded or under funded status of defined benefit pension plans and other post-retirement benefit plans be measured in the balance sheet, with any changes in the funded status recognized through other comprehensive income in the year that they occur. SFAS 158 does not change the computation of benefit expense recognized in the income statement.

SFAS 158 is effective for fiscal years ending after December 15, 2006, therefore SFAS 158 is effective for the Company in its current fiscal year ending December 31, 2006. The adoption of SFAS 158 has had no material impact on the Company's

consolidated financial position, results of operations or cash flows.

SAB 108

In September 2006, the SEC staff issued the Staff Accounting Bulletin (SAB) Topic 1N, "Financial Statements - Considering the Effects of Prior Year Misstatements when Quantifying Misstatements in Current Year Financial Statements" (SAB 108). This bulletin provides guidance on how prior year misstatements should be taken into consideration when quantifying misstatements in current year financial statements for purposes of determining whether the current year's financial statements are materially misstated. In providing this guidance, the SEC staff references requires use of both the "iron curtain" and "rollover" approaches. The iron curtain approach focuses on how the current year's balance sheet would be affected in correcting a misstatement without considering the year(s) in which the misstatement originated. The rollover approach focuses on the amount of the misstatement that originated in the current year's income statement. If a registrant has historically been using either the iron curtain approach or the rollover approach and, upon application of the guidance in SAB 108, determines that there is a material misstatement in its financial statements, the SEC staff will not require the registrant to restate its prior year financial statements provided that: (a) management properly applied the approach it previously used as its accounting policy and (b) management considered all relevant qualitative factors in its materiality assessment using the cumulative effect of applying SAB 108 in the current year beginning balances of the affected assets and liabilities with a corresponding adjustment to the current year opening balance in retained earnings. SAB 108 is effective for fiscal years ending after November 15, 2006. The adoption of SAB 108 required no adjustment or

restatement of the consolidated financial position, results of operations or cash flows of the Company as there were no material misstatements which had not been corrected.

To be adopted in future periods

FIN 48

In July 2006, the FASB issued FASB Interpretation No. 48, “Accounting for Uncertainty in Income Taxes—an interpretation of FASB Statement No. 109” (‘FIN 48’), which clarifies the accounting for uncertainty in tax positions. The evaluation of a tax position under FIN 48 is a two-step process. The first step is recognition: tax positions taken or expected to be taken in a tax return should be recognized only if those positions are more likely than not of being sustained upon examination, based on the technical merits of the position. In evaluating whether a tax position has met the more likely than not recognition threshold, it should be presumed that the position will be examined by the relevant taxing authority that would have full knowledge of all relevant information. The second step is measurement: tax positions that meet the recognition criteria are measured at the largest amount of benefit that is greater than 50 percent likely of being recognized upon ultimate settlement.

FIN 48 also provides guidance on derecognition, classification, interest and penalties, accounting in interim periods, disclosure and transition. FIN 48 is effective for fiscal years beginning after December 15, 2006 and is effective for the Company in the first quarter of the year beginning January 1, 2007. The Company’s analysis of FIN 48 is not yet complete, although it is not anticipated that there will be a material impact on the Company's consolidated financial position, results of operations or cash flows at the date from adoption.

EITF 06-3

In September 2006, the EITF reached a consensus regarding the issue “How Sales Taxes Collected from Customers and Remitted to Governmental Authorities should be presented in the Income Statement (That Is, Gross versus Net Presentation)”. The scope of the issue includes any tax assessed by a governmental authority that is directly imposed on a revenue producing transaction between a seller and a customer and may include, but is not limited to, sales, use, value added, and some excise taxes. The EITF concluded that the presentation of taxes within the scope of EITF 06-3 as either gross (included within revenues and costs) or net (excluded from revenues) is an accounting policy decision that should be disclosed. In addition, for any such taxes that are reported on a gross basis, a company should disclose the amounts of those taxes in interim and annual financial statements for each period for which an income statement is presented if those amounts are significant. The disclosure of those taxes can be done on an aggregate basis. The guidance in this Issue should be applied to financial reports for interim and annual reporting periods beginning after December 15, 2006. The adoption of EITF 06-03 will have no material impact on the Company's consolidated financial position, results of operations or cash flows or financial statement disclosure.

SFAS 157

In September 2006 the FASB issued SFAS 157, “Fair Value Measurements”, which provides a single definition of fair value, establishes a framework for the measurement of fair value and expands disclosure about the use of fair value to measure assets and liabilities. SFAS 157 is effective for fiscal years beginning after November 15, 2007, and for interim periods within those fiscal years; SFAS 157 will therefore be applicable for the Company’s fiscal year commencing January 1, 2008. The Company is currently reviewing the impact of the adoption of SFAS 157 on its financial statements.

EITF 06-6

In November 2006, the EITF reached a consensus on “Debtor's Accounting for a Modification (or Exchange) of Convertible Debt Instruments.” The EITF concluded that the change in the fair value of an embedded conversion option resulting from an exchange of debt instruments or a modification in the terms of an existing debt instrument should not be included in the cash flow test of whether the terms of the new debt instrument are substantially different from the terms of the original debt instrument under Issue 96-19. However, a separate analysis must be performed if the cash flow test under Issue 96-19 does not result in a conclusion that a substantial modification or exchange has occurred. The EITF also reached a consensus that when a convertible debt instrument is modified or exchanged in a transaction that is not accounted for as an extinguishment, an increase in the fair value of the embedded conversion option should reduce the carrying amount of the debt instrument with a corresponding increase in additional paid-in capital. However, a decrease in the fair value of an embedded conversion option resulting from a modification or exchange should not be recognized.

The guidance in this Issue will be applicable to modifications or exchanges occurring in the first interim or annual reporting period beginning after November 29, 2006. The adoption of EIFT 06-6 is not expected to have a material impact on the Company’s consolidated financial position, results of operations or cash flows.

(z) Statutory accounts

The consolidated financial statements as at December 31, 2006 and 2005, and for each of the three years in the period to December 31, 2006, do not comprise statutory accounts within the meaning of Section 240 of the UK Companies Act 1985.

Statutory accounts prepared in accordance with International Financial Reporting Standards, as adopted for use in the EU for the year ended 31 December 2005 and statutory accounts prepared in accordance with generally accepted accounting principles in the UK for the years to December 31, 2004, have been delivered to the Registrar of Companies for England and Wales. The auditors’ reports on those accounts was unqualified.

4. Business combinations : TKT acquisition

On July 27, 2005 Shire completed its acquisition of TKT in an all-cash transaction. The acquisition was effected by merging a wholly owned subsidiary of Shire with and into TKT, with TKT continuing as the surviving corporation. As consideration, Shire paid to TKT’s stockholders $37 in cash for each share of TKT common stock outstanding at the time of the acquisition, less any applicable withholding taxes.

The total cash consideration for the acquisition of TKT is expected to be approximately $1.6 billion, subject to change as may be required by the appraisal rights process.

As at December 31, 2006, shareholders owning approximately 24.8 million TKT shares (being 69% of the 36.2 million TKT shares outstanding at the acquisition date) had accepted the offer and $917.9 million has been paid to them; $83.9 million was paid in connection with TKT stock options; and $170.1 million in connection with convertible notes outstanding at the date of acquisition. These amounts were paid in the year to December 31, 2005.

In connection with the acquisition, as at December 31, 2006, the former holders of approximately 11.3 million shares of TKT common stock submitted written demands for appraisal of these shares and elected not to accept the $37 per share merger consideration. To the extent that these demands were validly asserted in accordance with the applicable requirements of Delaware law and these holders perfect their rights thereunder, such holders will be entitled to receive the fair value of their shares as determined by the Delaware Court of Chancery. The determination of fair value of the TKT shares will be made excluding any element of value arising from the transaction, such as cost savings or business synergies. The Delaware Court of Chancery may ascribe a valuation to the shares that is greater than, less than or equal to $37 per share and may award interest on the amount determined in the appraisal process. Shire has recognized a liability in respect of the fair value of the consideration in respect of those TKT shareholders who have asserted appraisal rights based on $37 per share. As at December 31, 2006, the liability in respect of those TKT shareholders who have asserted appraisal rights was $452.3 million, (including accrued interest of $32.4 million). See note 21 (d) for further information.

For accounting purposes, the acquisition of TKT has been accounted for as a purchase business combination in accordance with SFAS No. 141. Under the purchase method of accounting, the assets acquired and the liabilities assumed from TKT are recorded at the date of acquisition at their respective fair values. Financial statements and reported results of operations of Shire reflect these values, with the results of TKT included from July 27, 2005 in the statement of operations.

The purchase price for TKT is as follows:

			$'M
Common stock			
Number of shares of TKT common stock - non-dissenting (Millions)		24.8	
Price per TKT share ($)	$	37.0	917.9
Number of shares of TKT common stock - dissenting (Millions)		11.3	
Price per TKT share ($)	$	37.0	419.9
Total number of shares of TKT common stock outstanding as at July 27, 2005 (Millions)		36.2	1,337.8
Stock options			
Cash cost of settling TKT stock options			83.9
Convertible notes			
Nominal value of convertible loan notes as at July 27, 2005 (Millions)		85.0	
Conversion ratio into TKT common stock		18.49	
Total shares payable upon conversion (Millions)		4.6	
Price per TKT share ($)	$	37.0	
Cost of settling convertible notes			170.1
Direct costs of acquisition			37.5
Total purchase price			1,629.3

The purchase price stated above has been allocated according to Shire's estimate of the fair value of assets acquired and liabilities assumed.

The allocation of the purchase price was completed in 2006, and has been allocated to assets and liabilities acquired as outlined below. Goodwill in respect of the TKT acquisition increased by $5.9 million in 2006 from $24.4 million (restated) as provisionally determined as at December 31, 2005, to $30.3 million following the recognition of certain assets and liabilities, net of related deferred tax, as the fair values of these assets and liabilities became reasonably estimable during the allocation period.

As of the end of the allocation period, the fair value of the pre-acquisition contingency relating to the Purported Class Action Shareholder Suit had not been determined. The fair value of this contingency continues to be subject to the expected outcome of the Purported Class Action Shareholder Suit. As the allocation period has ended, the contingency will be recorded as a liability in

accordance with the criteria in SFAS 5, *Accounting for Contingencies* , with any loss arising recognized in the statement of operations. See note 21 (d) for further information.

The final allocation of the purchase price to assets and liabilities acquired is as follows:

	Notes	Book value $'M	Restated Adjustments $'M	Restated Fair value $'M
ASSETS				
Current assets:				
Cash and cash equivalents		56.8	-	56.8
Restricted cash		8.2	-	8.2
Short-term investments		46.9	-	46.9
Accounts receivable, net		28.4	-	28.4
Inventories	(a)	12.9	88.9	101.8
Prepaid expenses and other current assets		7.9	4.9	12.8
Total current assets		161.1	93.8	254.9
Property, plant and equipment, net		57.3	-	57.3
Goodwill		39.0	(39.0)	-
- on TKT acquisition	(c)	-	30.3	30.3
Other intangible assets, net	(d)	20.2	460.8	481.0
In-process research and development	(e)	-	815.0	815.0
Deferred tax asset	(b)	-	99.8	99.8
Other non-current assets		3.4	-	3.4
Total assets		281.0	1,460.7	1,741.7
LIABILITIES				
Current liabilities:				
Accounts payable and accrued expenses	(f)	35.4	0.4	35.8
Deferred tax liability	(b)	-	36.4	36.4
Other current liabilities		24.5	13.9	38.4
Total current liabilities		59.9	50.7	110.6
Other long-term liabilities		1.8	-	1.8
Total liabilities		61.7	50.7	112.4
Estimated fair value of identifiable assets acquired and liabilities assumed		219.3	1,410.0	1,629.3

(a) Inventory

Components of the increase in fair value for acquired inventory are as follows:

	Book value	Fair value adjustment	Fair value
	$'M	$'M	$'M
Finished goods	3.4	66.8	70.2
Work-in-process	7.0	22.1	29.1
Raw materials	2.5	-	2.5
	12.9	88.9	101.8

Finished goods were fair valued at estimated selling price less the sum of costs of disposal and a reasonable profit allowance for the selling effort of the Company. Work in-process was fair valued on the same basis less costs to complete.

(b) Deferred taxes

The estimated tax effects of the acquisition, including TKT trading losses and the effect of the fair value adjustments for inventory and other intangible assets are as follows:

	$'M
Deferred tax asset on TKT losses carried forward and short term timing differences (net of valuation allowance of $60.3 million)	288.7
Deferred tax liability on other intangible assets	(188.9)
Deferred tax asset, net	99.8
Deferred tax liability on inventory - current	(36.4)
Deferred tax, net	63.4

The following estimates relating to deferred tax were adjusted for:

- The deferred tax rate has been adjusted to reflect the US federal rate and state tax combined 41% rate that should apply to measure the deferred tax liability.
- The deferred tax asset on TKT losses, which increased as a result of the identification of further tax deductible expenses in prior years.

(c) Goodwill

In accordance with the requirements of SFAS No. 142, "Goodwill and Other Intangible Assets" (SFAS No. 142), the goodwill associated with the TKT acquisition will not be amortized but will be subject to the Company's impairment review. Goodwill resulting from this acquisition has been allocated to the Pharmaceutical Products segment.

(d) Other intangible assets

The acquired identifiable intangible assets are attributable to the following categories:

	Book value	Fair value adjustment	Fair value	Asset life
	$'M	$'M	$'M	years
Intellectual property [(1)]	-	335.0	335.0	14 to 20
Customer relationships [(2)]	14.9	104.1	119.0	15
Other (survey data) [(2)]	5.3	21.7	27.0	7
	20.2	460.8	481.0	

(1) Relates to REPLAGAL (excluding US and Japan) and DYNEPO (for the treatment of anemia associated with kidney disease).

(2) Relates to REPLAGAL (excluding US and Japan).

Acquired identifiable intangible assets have been allocated to the Pharmaceutical Products reporting segment.

Acquired identifiable intangible assets represent the value associated with developed technology to which the Company has all associated rights. These rights can include the right to develop, use, market, sell and/or offer for sale the technical processes, intellectual property and institutional understanding (including the way in which compounds react in the body, an understanding of the mechanisms of action which allow the compound to work and the knowledge related to the associated clinical and marketing studies performed for these compounds) that were acquired as part of the transaction with respect to products and/or processes that have been developed.

The fair value of all of the identifiable intangible assets has been determined using an income approach on a project-by-project basis. This method starts with a forecast of all of the expected future net cash flows either generated or saved as a result of ownership of the intellectual property, the customer relationships and the other intangible assets. These cash flows are then adjusted to present value by applying an appropriate discount rate that reflects the risk factors associated with the cash flow streams.

The forecast of future cash flows requires various assumptions to be made, including:

- revenue that is reasonably likely to result from the sale of products including the estimated number of units to be sold, estimated selling prices, estimated market penetration and estimated market share and year-over-year growth rates over the product life cycles;
- royalty or license fees saved by owning the intellectual property associated with the products;
- cost of sales for the products using historical data, industry data or other sources of market data;
- sales and marketing expense using historical data, industry data or other sources of market data;
- general and administrative expenses;
- research and development expenses;
- the estimated life of the products; and
- the tax amortisation benefit available to a market participant purchasing assets piecemeal.

The valuations are based on information at the time of the acquisition and the expectations and assumptions that have been deemed reasonable by the Company's management. No assurance can be given, however, that the underlying assumptions or events associated with such assets will occur as projected. For these reasons, among others, the actual cash flows may vary from the forecast future cash flows.

(e) In-process research and development

As required by FASB Interpretation No. 4, "Applicability of FASB Statement No. 2 to Business Combinations Accounted for by the Purchase Method", the portion of the purchase price allocated to IPR&D of $815 million (restated) was immediately expensed.

During the year to December 31, 2006 the Company determined that the value ascribed to IPR&D acquired as a result of the TKT acquisition did not include the benefit of tax amortization as required by the American Institute of Certified Public Accountants (AICPA) Practice Aid, *Assets Acquired in a Business Combination to Be Used in Research and Development Activities: A Focus on Software, Electronic Devices, and Pharmaceutical Industries* . The financial statements for the year ended December 31, 2005 and

this note have been restated to correct this omission. See note 3(a) for further information.

A project-by-project valuation using the guidance in SFAS No. 141 and the American Institute of Certified Public Accountants (AICPA) Practice Aid *"Assets Acquired in a Business Combination to Be Used In Research and Development Activities: A Focus on Software, Electronic Devices and Pharmaceutical Industries"* has been performed by independent valuation specialists to determine the fair value of research and development projects of TKT which were in-process, but not yet completed.

The fair value was determined using the income approach on a project-by-project basis. This method starts with a forecast of the expected future net cash flows. These cash flows are then adjusted to present value by applying an appropriate discount rate that reflects the project's stage of completion and other risk factors. These other risk factors can include the nature of the product, the scientific data associated with the technology, the current patent situation and market competition.

The forecast of future cash flows required various assumptions to be made including:

- revenue that is likely to result from specific IPR&D projects, including estimated number of units to be sold, estimated selling prices, estimated market penetration and estimated market share and year-over-year growth rates over the product life cycles;

- cost of sales related to the potential products using historical data, industry data or other sources of market data;
- sales and marketing expense using historical data, industry data or other market data;
- general and administrative expenses;
- research and development expenses; and
- the tax amortisation benefit available to a market participant purchasing assets piecemeal.

In addition the Company considered:

- the project’s stage of completion;
- the costs incurred to date;
- the projected costs to complete;
- the contribution, if any, of the acquired identifiable intangible assets;
- the projected launch date of the potential product; and
- the estimated life of the potential product.

To the extent that the IPR&D project is expected to utilize the acquired identified intangible assets, the value of the IPR&D project has been reduced to reflect this utilization. The acquired identified intangible assets include the technical processes, intellectual property, and institutional understanding with respect to products and processes that have been completed and that may aid in the development of future products or processes.

(f) Accounts payable and accrued expenses

Included in “Accounts payable and accrued expenses” are the following fair value adjustments:

(i) *Restructuring costs*

An estimate of restructuring costs that impact goodwill, pursuant to EITF Issue No. 95-3, “Recognition of Liabilities in Connection with Purchase Business Combinations”. Such costs total $2.0 million and are associated with the involuntary termination of 15 TKT employees all of whom had left the Company by December 31, 2005. As at December 31, 2005, $1.5 million had been paid and $0.5 million was paid in the period to December 31, 2006; and

(ii) Deferred revenue

A fair value adjustment of $1.6 million in respect of a deferred revenue stream relating to pre-acquisition activities of TKT.

Pro forma financial information

The following unaudited pro forma financial information presents the combined results of the operations of Shire and TKT as if the acquisition had occurred at the beginning of the periods presented. The unaudited pro forma financial information is not necessarily indicative of what the consolidated results of operations actually would have been had the acquisition been completed at the dates indicated. In addition, the unaudited pro forma financial information does not purport to project the future results of operations of the combined Company.

Year to December 31,	**2005**	**2004**
	$’M	**$’M**
Revenues	1,652.9	1,441.3
Income before extraordinary items and cumulative effect of change in accounting principles	220.0	188.0
Net income	220.0	188.0
Per share amounts:		
Net income per common share - basic	44.0c	37.9c
Net income per common share - diluted	43.5c	37.4c

The unaudited pro forma financial information above reflects the following pro forma adjustments applied using the principles of Article 11 of Regulation S-X under the Securities Exchange Act of 1934:

(i) elimination of historical amortization expense recorded by legacy TKT for definite-lived intangible assets;

(ii) elimination of interest expense recorded by legacy TKT on convertible loan notes;

(iii) an adjustment to increase interest expense by $6.0 million in the year to December 31, 2005, and $8.1 million in the year to December 31, 2004, to reflect the interest payable to dissenting shareholders;

(iv) an adjustment to decrease interest income by $15.0 million in the year to December 31, 2005, and $17.4 million in the year to December 31, 2004, to reflect the cash consideration paid to TKT shareholders, option holders and convertible note holders; and

(v) an adjustment to increase amortization expense based on the estimated fair value of identifiable intangible assets from the purchase price allocation, which are being amortized over their estimated useful lives over a range of 7 to 20 years, of approximately $13.7 million in the year to December 31, 2005, and $23.4 million in the year to December 31, 2004.

In addition, the unaudited pro forma financial information above excludes the following material, non-recurring purchase accounting

adjustments in the year to December 31, 2005, as follows:

- an IPR&D charge of $815 million (restated);
- a $41.9 million charge relating to the use or sale of purchased inventory that was written up to fair value reported in cost of product sales; and
- a $17.2 million credit relating to the current deferred tax liability with regard to the purchased inventory charge in cost of product sales above.

5. Integration costs

In connection with the acquisition of TKT, the Company's management approved and initiated plans to restructure the operations of the enlarged Company to eliminate duplicate facilities and reduce costs.

Integration costs represent incremental costs incurred by the Company directly related to the absorption of the TKT business into the Company, including expenditures for consulting and systems integration. The charges have been presented as integration costs in the statement of operations and are accounted for solely within the Pharmaceutical Products reporting segment.

Integration costs expensed in the year to December 31, 2006:

	Opening liability $'M	Costs recorded in year to December 31, 2006 $'M	Paid in year to December 31, 2006 $'M	Closing liability $'M
Employee severance and retention payments for key TKT employees	5.9	3.0	(6.2)	2.7
Information technology costs	-	1.2	(1.1)	0.1
Other	0.2	1.4	(1.6)	-
	6.1	5.6	(8.9)	2.8
Included within:				
Current liabilities	5.3	5.6	(8.1)	2.8
Other long-term liabilities	0.8	-	(0.8)	-
	6.1	5.6	(8.9)	2.8

Integration costs expensed in the year to December 31, 2005:

	Costs recorded in year to December 31, 2005 $'M	Paid in year to December 31, 2005 $'M	Closing liability $'M
Employee severance and retention payments for key TKT employees	7.0	(1.1)	5.9
Information technology costs	1.1	(1.1)	-
Other	1.6	(1.4)	0.2
	9.7	(3.6)	6.1
Included within:			

Current liabilities	8.9	(3.6)	5.3
Other long-term liabilities	0.8	-	0.8
	9.7	(3.6)	6.1

6. Reorganizations

Actions commenced in 2005

Sale of the drug formulation business

On December 22, 2005, Shire sold its drug formulation business to Supernus Pharmaceuticals, Inc. (Supernus), a newly formed specialty pharmaceutical company funded by two venture capital companies.

The sale resulted in:

- a profit on sale of $3.6 million. Proceeds from the sale included an equity interest (of less than 10%) in Supernus, which has been included in investments in private companies (see Note 11) at its fair value of $3.9 million. The fair value was determined by reference to the cash invested in Supernus by the venture capital companies;
- the transfer of the lease on the East Gude Drive, Rockville premises to Supernus, with Shire being released from all obligations under the lease by the landlord;
- an ongoing projects agreement relating to services that Supernus provided to Shire for a transitional period (ending in March 2006), on certain Shire projects until the projects were moved to third party suppliers; and
- the severance of 28 employees. As at December 31, 2005, 16 had left the Company, and the remaining employees had left by March 31, 2006. Severance payments were made to the former employees over a 42 week period, as required by local regulations.

The sale has been reflected in the statement of operations in the period ended December 31, 2005 as follows:

	Other income, net	Research and development expense
	$'M	$'M
Gain on disposition	3.6	-
Employee severance	-	(1.2)
Other costs	-	(0.2)
	3.6	(1.4)

All items are recorded in the Pharmaceutical Products segment.

Actions commenced in 2004

North American site consolidation

As previously disclosed, the Company began a consolidation of its North American sites in 2004, with the aim of decreasing the number of sites from 16 to four, including the opening of a new US headquarters office in Wayne, Pennsylvania. The Company recorded reorganization costs of $9.4 million and $48.5 million in the year to December 31, 2005 and 2004 respectively. Following the closure of the Newport site in July 2005, the site consolidation was completed and no further reorganization costs have been incurred in the year ended December 31, 2006.

The primary costs associated with the site consolidation included:

- severance costs relating to 137 employees;
- retention payments to key employees;
- relocation costs relating to 85 employees who were moved to Wayne, Pennsylvania;
- costs of duplicate facilities (including lease exit costs); and
- other incremental costs associated with the site closures, such as legal, consultancy, the write-down of property, plant and equipment and information technology costs.

As at December 31, 2005 all 137 employees had left the Company. The cost of the employee severance was ratably recognized over the period from the communication date to the termination date. In addition, all 85 of those employees who had agreed to relocate had relocated. The cost of relocation was recorded as it was incurred.

The following table presents the cost of the reorganization recorded to date and the total costs of the reorganization.

	Total costs recorded in year to December 31, 2005	Total costs recorded in year to December 31, 2004	Total costs of reorganization
	$'M	$'M	$'M
Employee severance and relocation costs	1.6	33.8	35.4
Write-off of property, plant and equipment	-	1.2	1.2
Consultancy costs	0.5	2.9	3.4
Duplicate facilities	7.3	5.1	12.4
Information technology costs	-	2.1	2.1
Other costs	-	3.4	3.4
	9.4	48.5	57.9

These charges have been reflected within reorganization costs in the statement of operations and are accounted for solely within the Pharmaceutical Products reporting segment.

As noted above, the duplicate facilities costs will be paid over the remaining life of the relevant leases, which all expire before October 31, 2012.

The following provides a reconciliation of the liability as at December 31, 2006:

	Opening liability	Utilization in year to December 31, 2006	Closing liability
	$m	$m	$m
Employee severance and relocation costs	0.6	(0.6)	-
Duplicate facilities	7.2	(2.2)	5.0
	7.8	(2.8)	5.0

Current liabilities (Note 17)	3.4	(1.0)	2.4
Other long-term liabilities (Note 19)	4.4	(1.8)	2.6
	7.8	(2.8)	5.0

The following provides a reconciliation of the liability as at December 31, 2005:

	Opening liability	Costs recorded in year to December 31, 2005	Utilization in year to December 31, 2005	Closing liability
	$'M	$'M	$'M	$'M
Employee severance and relocation costs	1.7	1.6	(2.7)	0.6
Consultancy costs	-	0.5	(0.5)	-
Duplicate facilities	2.5	7.3	(2.6)	7.2
	4.2	9.4	(5.8)	7.8
Current liabilities (Note 17)	1.7	7.5	(5.8)	3.4
Other long-term liabilities (Note 19)	2.5	1.9	-	4.4
	4.2	9.4	(5.8)	7.8

Disposition of the vaccines business

On September 9, 2004 the Company completed the disposition of its vaccines business to IDB. The total consideration for the sale was $120 million comprising $30 million of cash received at completion, $30 million of cash held in escrow and due on the first anniversary of completion and $60 million received at completion in the form of 4,931,864 subscription receipts of IDB. If, prior to January 10, 2005, IDB were to raise up to $60 million from equity related issuances, then it was required under the terms of the sale agreement to redeem the subscription receipts from Shire for $60 million. Accordingly, following the completion of such a fund raising on January 7, 2005, IDB redeemed the subscription receipts from Shire for $60 million in cash. On the first anniversary of completion, Shire received the $30 million of cash held in escrow.

As part of the transaction, Shire entered into an agreement to provide IDB with a loan facility of up to $100 million, which could be drawn down over the four years following completion. As at December 31, 2005, IDB had drawn down the entire $100 million loan. It was required that this facility be used by IDB to fund the development of injectable flu and pipeline products within the vaccines business acquired from Shire. Drawings under the loan facility were segregated into two components:

(i) Drawings for injectable flu development of $70.6 million repayable out of income generated by IDB on future non-Canadian injectable flu products, subject to minimum annual repayments in respect of the first $30 million of the drawing, to be made between 2007 and 2017; and

(ii) Drawings for pipeline development of $29.4 million repayable out of income generated by IDB on future pipeline products and have no fixed repayment schedule.

The transaction gave rise to an overall loss on disposition of the vaccines business of $41.1 million, recorded as a loss on disposition at completion in 2004 of $44.2 million and a subsequent provision release of $3.1 million being recognized during the year to December 31, 2005. This net loss on disposition of $41.1 million comprised a gain on disposition of net assets of $28.9 million together with a provision for a loss of $70 million out of the $100 million loan facility available to IDB. This provision was made on the basis that those loan repayments based solely on future sales of flu and pipeline products in development provided no certainty of recovery.

The historical consolidated financial statements reflect the vaccines business as a discontinued operation for all periods presented. The results of the discontinued operation have been removed from all periods on a line-by-line basis from product sales revenue to income from continuing operations. The net loss from the discontinued operation, together with the loss on disposition, are shown as separate line items.

Operating results of the discontinued operations are summarized below.

Year to December 31,	**2004**
	$'M
Revenues:	
Product sales	3.6
Total revenues	3.6
Costs and expenses:	
Cost of product sales	8.3
Research and development	9.2
Selling, general and administrative	5.6
Total operating expenses	23.1
Operating loss	(19.5)
Other (expense)/income, net	(0.6)
Loss from discontinued operations	(20.1)
Loss on disposition	(44.2)
	(64.3)

At December 31, 2004, the assets and liabilities of the discontinued vaccines operation were $nil.

On February 14, 2006 the Company received $78.7 million from IDB, being the full repayment of the $70.6 million injectable flu development drawings, together with accrued interest of $8.1 million. The repayment followed GSK's acquisition of IDB, after which IDB was provided with resources by GSK to fund the early repayment of the injectable flu tranche. The $29.4 million pipeline development tranche of the loan facility is still outstanding and is fully provided against.

At the time of the disposal, a provision of $70.0 million was charged to discontinued operations on the basis that there was no certainty of recovery of this amount. The $70.0 million provision was allocated against all of the pipeline development tranche ($29.4 million) and against $40.6 million of the $70.6 million injectable flu development tranche.

Accordingly, the $78.7 million received was recorded as follows:

- a gain on disposition of discontinued operations of $40.6 million (being the amount previously provided against the injectable flu development tranche);
- settlement of the loan receivable balance of $31.6 million (being the unprovided component of the injectable flu development loan, plus recognised and accrued interest); and
- interest income of $6.5 million (being interest earned in the year of $1.0 million and $5.5 million of interest earned but provided for in previous periods).

The repayment of the $70.6 million injectable flu tranche had no tax effect. There were no further developments in respect of the $29.4 million outstanding tranche of the IDB loan.

7. Gain on sale of product rights

During the year, the Company disposed of its ADDERALL (immediate-release mixed amphetamine salts) product to Duramed Pharmaceuticals Inc, (Duramed) a subsidiary of Barr Pharmaceuticals, Inc., (Barr) for $63 million in cash. The sale completed on September 29, 2006. As a result the Company has recognised a pre-tax gain of $63 million within income from continuing operations.

8. Accounts receivable, net

Trade receivables at December 31, 2006 of $310.8 million (December 31, 2005: $329.9 million), are stated net of a provision for doubtful accounts and sales discounts of $8.8 million (December 31, 2005: $9.7 million).

The movement in the provision for doubtful accounts and sales discounts is as follows:

	2006 $'M	2005 $'M	2004 $'M
As at January 1,	9.7	4.3	7.9
Charged to operations	47.1	51.1	38.2
Released to income	-	-	(3.4)
Utilization	(48.0)	(45.6)	(38.4)
As at December 31,	8.8	9.7	4.3

Revenues are mainly derived in the US (71% of total revenues) from agreements with major pharmaceutical companies and relationships with pharmaceutical wholesale distributors and retail pharmacy chains. Material customers are disclosed in Note 25 . Such clients have significant cash resources and therefore any credit risk associated with these transactions is considered minimal.

9. Inventories

	December 31, 2006 $'M	December 31, 2005 $'M
Finished goods	50.1	63.3
Work-in-process	59.2	53.9
Raw materials	21.8	18.8
	131.1	136.0

10. Prepaid expenses and other current assets

	December 31, 2006 $'M	December 31, 2005 $'M
Prepaid expenses	39.0	30.2
Income tax receivable	20.7	40.8
Value added taxes receivable	16.0	10.2
Supplemental Executive Retirement Plan (SERP) investment (see Note 28)	1.3	1.3
Other current assets	29.0	15.6
	106.0	98.1

The increase in other current assets is due to an increase in accrued income in relation to out-licensing and research and development arrangements.

11. Investments

	December 31, 2006 $'M	December 31, 2005 $'M
Investments in private companies	15.1	9.1
Available-for-sale securities	16.5	18.1
Equity method investments	24.2	23.0
	55.8	50.2

The Company recorded impairments of $2.1 million on its investments during the year to December 31, 2006 (2005: $2.0 million; 2004 $15.4 million). See Note 26. All impairments in the three years presented were recorded in the Pharmaceutical Products segment.

(i) Investments in private companies

During the year to December 31, 2006 additions to investments in private companies included $8.0 million (2005: $4.1 million) to ViroChem Pharma Inc. in return for an additional equity interest.

During the year to December 31, 2005 additions to investments in private companies included a $3.9 million investment in Supernus (less than 10% of total equity), as part consideration for the sale of the drug formulation business. The fair value of the investment was determined by reference to cash invested in Supernus by the other investors.

During the year to December 31, 2006 the Company recorded impairments of $1.8 million (2005: $1.6 million) against its investments in private companies based on a decline in the estimates of their fair value that the Company believes are other-than-temporary.

During the year to December 31, 2004 the Company recorded impairments of $9.8 million against these investments based on changes in the estimates of their fair value. This amount includes $4.2 million to reduce the value of an investment in a private company that gained a listing on March 24, 2004; the initial listing price was below the anticipated flotation price used to value the investment at December 31, 2003 and the Company believed the decline in value was other-than-temporary. After the date of the listing the investment was reclassified to available-for-sale securities and so any changes since the initial listing date have been recorded in other comprehensive income.

The changes in fair market value, which resulted in the write-downs referred to above, were based on the Company's estimates of fair value. These estimates were derived from financial and other publicly available information such as press releases and recent capital raising activities.

(ii) Available-for-sale securities

During 2006, there were no sales of available-for-sale securities. During the year to December 31, 2005 the Company sold an investment in an available-for-sale security, valued at $6.0 million (2004: $11.9 million), realizing a gain on the sale of $3.9 million (2004: $14.8 million). See Note 26 .

The Company recorded other-than-temporary impairments of $0.3 million, $0.4 million and $1.6 million against its available for sale securities in the years to December 31, 2006, 2005 and 2004 respectively. At December 31, 2006 the Company had no available-for-sale investments in a significant unrealized loss position for which other-than-temporary impairments have not been recognized.

Equity method investments

	December 31, 2006 $'M	December 31, 2005 $'M
GSK Partnership	6.5	6.0
GeneChem Funds	11.2	12.7
Other	6.5	4.3
	24.2	23.0

(a) GSK Partnership

The Company has accounted for its commercialization partnership with GSK (through which the products 3TC and ZEFFIX are marketed in Canada), using the equity method of accounting. The Company's 50% share of the partnership is included within "Equity in earnings/(losses) of equity method investees".

(b) GeneChem Funds

The GeneChem Technologies Venture Fund and the GeneChem Therapeutics Venture Fund ("The Funds") are Canadian limited partnerships investing in healthcare research and development companies, in which the Company owns 30% and 11% of the issued shares respectively. At December 31, 2006, the Funds' net assets totaled approximately $72.0 million (2005: $71 million). The Company is involved as a limited partner and the general partner of the Funds; involvement in the Funds dates from between 1997 and 2000. The Company's exposure to loss as a result of its involvement with the Funds is limited to the carrying value of the investment, $11.2 million at December 31, 2006 and its commitment to further investment of $1.7 million.

During the year to December 31, 2004 the Company recorded an impairment of $4.0 million against the investment in the Funds following reviews of the Funds' investment portfolios that identified other-than-temporary declines in the value of certain private and publicly quoted securities held by the Funds.

12. Property, plant and equipment, net

	December 31, 2006 $'M	December 31, 2005 $'M
Land and buildings	188.6	157.2
Office furniture, fittings and equipment	136.4	91.1
Warehouse, laboratory and manufacturing equipment	39.3	44.1
Assets under construction	35.0	18.4
	399.3	310.8
Less: Accumulated depreciation	(106.5)	(76.8)
	292.8	234.0

Depreciation expense for the years to December 31, 2006, 2005 and 2004 was $48.1 million, $32.7 million, and $22.5 million respectively. The expense included a $0.5 million (2005: $6.5 million) impairment loss. In 2005, the impairment related to the plant and equipment of the drug formulation business. At the time of the impairment loss, the Company was expecting to close the business and, because the carrying value of the assets exceeded the expected future cash flows resulting from the closure, the assets were considered impaired.

13. Goodwill, net

Restated

	December 31, 2006 $'M	December 31, 2005 $'M
Goodwill arising on businesses acquired	237.4	225.6

The increase in the net book value of goodwill for the year to December 31, 2006 and 2005 is shown in the table below:

	2006 $'M	Restated 2005 $'M
As at January 1,	225.6	235.4
Acquisitions	0.6	24.4
Adjustments relating to prior year acquisitions	7.6	-
Foreign currency translation	3.6	(34.2)
As at December 31,	237.4	225.6

During the period to December 31, 2006, the Company finalized the allocation of the purchase price in respect of the acquisition of TKT and as a result, goodwill in respect of the TKT acquisition increased by $5.9 million following the recognition of certain assets and liabilities, net of related deferred tax, as the fair values of these assets and liabilities are now reasonably estimable.

In accordance with FASB Statement 109, "Accounting for Income Taxes ", the Company is required to adjust goodwill for all changes in estimates related to tax contingencies regardless of the time elapsed since the date of

acquisition. In the period to December 31, 2006, the goodwill in respect of the TKT acquisition increased by $1.7 million due to a change in estimate of pre-acquisition income tax contingencies.

As a result of these adjustments goodwill in respect of the TKT acquisition increased to $32.0 million (restated).

During the year to December 31, 2006 the Company acquired a company for $0.8 million which resulted in goodwill of $0.6 million. This goodwill is recorded in the Pharmaceutical Products segment.

During the period to December 31, 2005 the Company recognized $24.4 million (restated) as goodwill on acquisition of TKT (see Note 4), in accordance with SFAS No. 141. This goodwill is recorded in the Pharmaceutical Products segment.

Goodwill by operating segment

Shire's internal management reporting structures show two operating segments: Pharmaceutical Products and Royalties. The Pharmaceutical Products segment comprises four therapeutic areas: CNS, GI, HGT and GP. The net book value of goodwill as at December 31, 2006 is all held in the Pharmaceutical Products segment.

14. Other intangible assets, net

	December 31, 2006 $'M	December 31, 2005 $'M
Other intangible assets:		
Intellectual property rights acquired	1,069.3	978.9
Less: accumulated amortization	(306.9)	(249.6)
	762.4	729.3

The increase in the net book value of other intangible assets for the year to December 31, 2006 is shown in the table below:

	Other intangible assets
	$'M
As at January 1, 2006	729.3
Acquisitions	82.3
Amortization charged	(56.3)
Asset impairments	(1.1)
Foreign currency translation	8.2
As at December 31, 2006	762.4

In 2006, the Company acquired $82.3 million of identifiable intangible assets. The weighted average amortization period of these assets is 10.1 years. These acquisitions relate to milestone payments made to third parties subsequent to regulatory approval which are capitalized as intangible assets, and amortized over the remaining useful life of the related product.

Amortization charged for the three years to December 31, 2006, 2005 and 2004 was $56.3 million, $45.3 million and $38.7 million, respectively.

The estimated lives of all intangible assets that continue to be amortized under SFAS No. 142 are reviewed periodically by management. Management estimates that the annual amortization charges in respect of intangible fixed assets held as at December 31, 2006 will average approximately $51.6 million for each of the five years to December 31, 2011. Estimated amortization expense can be affected by various factors including future acquisitions (including the agreed acquisition of New River, see note 32), disposals of product rights and the technological advancement and regulatory approval of competitor products.

During 2006, the Company recorded impairments of $1.1 million. This impairment resulted from the decision not to support and promote certain non-core products going forward.

During 2005, the Company recorded impairments of $5.6 million. These impairments resulted from the approval of generic versions of AGRYLIN and the decision not to support and promote certain non-core products going forward.

During 2004, the Company recorded impairments of $13.5 million. These impairments resulted from a change of operational management and their views of the economic value and strategic worth of the products concerned, which decreased estimated future cash flows.

All impairments in the three years presented were recorded in the Pharmaceutical Products segment.

15. Other non-current assets

	December 31, 2006	December 31, 2005
	$'M	$'M
SERP investment (see Note 28)	7.0	7.6
IDB loan (see Note 6)	-	31.5
Other assets	5.4	3.8
	12.4	42.9

Further details of the SERP investment are provided in Note 28 . The amount shown above is the cash surrender value of life insurance policies, which is backed by short-term investments. A liability of $4.7 million is included within Notes 17 and 19 (2005: $4.6 million).

16. Accounts payable and accrued expenses

	December 31, 2006 $'M	December 31, 2005 $'M
Trade accounts payable	54.5	71.0
Accrued rebates - Medicaid	94.7	83.6
Accrued rebates - managed care	31.7	21.8
Sales return reserve	36.5	31.8
Accrued bonuses	47.5	39.4
Accrued employee compensation and benefits payable	29.7	20.9
Accrued coupons	13.0	5.2
Research and development accruals	52.9	22.1
Marketing accrual	32.1	17.4
Accrued royalties	4.3	4.7
Deferred revenue	7.1	11.8
Accrued settlement costs	22.0	13.0
Other accrued expenses	140.1	89.1
	566.1	431.8

17. Other current liabilities

	December 31, 2006 $'M	December 31, 2005 $'M
Income taxes payable	294.5	93.6
Value added taxes	4.8	3.8
SERP (see Note 28)	1.0	1.3
Other accrued liabilities	13.3	7.3
	313.6	106.0

18. Long-term debt

Credit Facilities

In connection with the acquisition of TKT, Shire plc and certain subsidiary companies entered into a Multicurrency Revolving Facilities Agreement (the "Facilities Agreement") with ABN AMRO Bank N.V., Barclays Capital, Citigroup Global Markets Limited, HSBC Bank plc and The Royal Bank of Scotland plc (the "Lenders") on June 15, 2005. The Facilities Agreement comprises two credit facilities: (i) a committed multicurrency three year revolving loan facility in an aggregate amount of $500 million ("Facility A") and (ii) a committed 364 day revolving loan facility in an aggregate amount of $300 million ("Facility B" and, together with Facility A, the "Facilities"). Shire plc has agreed to act as guarantor for any of its subsidiaries that borrow under the Facilities Agreement. In June 2006 Facility B was extended for a further 364 days to June 13, 2007. In October 2006, Facility B was reduced to $200 million.

As at December 31, 2006 and 2005, the Company had not drawn down on these Facilities. The Facilities Agreement was cancelled in full with effect from February 27, 2007.

In connection with the acquisition of New River, Shire plc entered into a Multicurrency Term and Revolving Facilities Agreement

(the “New Facilities Agreement”) with ABN AMRO Bank N.V., Barclays Capital, Citigroup Global Markets Limited and The Royal Bank of Scotland plc (the “Arrangers”) on February 20, 2007. The New Facilities Agreement comprises three credit facilities: (i) a committed multicurrency five year term loan facility in an aggregate amount of $1,000 million (“Term Loan A”), (ii) a committed multicurrency 364 day term (with a further 364 day extension option) loan facility in an aggregate amount of $300 million (“Term Loan B”) and (iii) a committed five year revolving loan facility in an aggregate amount of $1,000 million (the “RCF” and, together with Term Loan A and Term Loan B, the “Facilities”). Shire plc has agreed to act as guarantor for any of its subsidiaries that borrow under the New Facilities Agreement.

The RCF, which includes a $250 million swingline facility, may be used for general corporate purposes. Term Loan A and Term Loan B may be used only for financing the acquisition of New River (including related fees and transaction costs) and refinancing any existing indebtedness of New River or its subsidiaries.

The RCF and Term Loan A mature on February 20, 2012. Term Loan A is repaid in annual installments on the anniversary of the New Facilities Agreement in the following amounts: $150 million in 2008, $150 million in 2009, $200 million in 2010, $200 million in 2011 and the balance on maturity. Term Loan B matures on February 19, 2008. As noted above, at Shire’s request, the maturity date of Term Loan B may be extended for a further 364 days.

The availability of loans under each of the Facilities is subject to customary conditions, including the absence of any defaults thereunder and the accuracy (in all material respects) of Shire’s representations and warranties contained therein.

The Facilities include representations and warranties, covenants and events of default, including (i) requirements that Shire’s ratio of Net Debt to EBITDA (as defined in the Facilities Agreement) does not exceed 3.50:1 for the 12 month period ending 31 December, 2007; 3.25:1 for the 12 month period ending 30 June 2008; and 3.00:1 for each 12 month period ending 31 December and 30 June thereafter, and (ii) that the ratio of EBITDA to Net Interest (as defined in the New Facilities Agreement) must not be less than 4.0 to 1, for each 12 month period ending 31 December or 30 June, and (iii) additional limitations on the creation of liens, disposal of assets, incurrence of indebtedness, making of loans and giving of guarantees.

Interest on loans under the Facilities will be payable on the last day of each interest period, which period may be one week or one, two, three or six months at the election of Shire (or as otherwise agreed with the Lenders). The interest rate on each loan drawn under the RCF or Term Loan A for each interest period is the percentage rate per annum which is the aggregate of the applicable margin (initially set at 0.80 per cent per annum until delivery of the

compliance certificate for the year ending 31 December, 2007 and thereafter ranging from 0.40 to 0.80 per cent per annum, depending on the ratio of Net Debt to EBITDA), LIBOR, and mandatory cost, if any (as calculated in accordance with Schedule 5 of the New Facilities Agreement). The interest rate on each loan drawn under Term Loan B for each interest period is the percentage rate per annum which is the aggregate of the applicable margin (being from 0.50 per cent for the first six months from the date of the New Facilities Agreement, 0.75 per cent for the second six months and 1.00 per cent per annum thereafter), LIBOR, and mandatory cost, if any (as calculated in accordance with Schedule 5 of the Facilities Agreement).

Shire shall also pay fees equal to 35 per cent per annum of the applicable margin on available commitments under the RCF for the availability period applicable to the RCF and 20 per cent per annum of the applicable margin on available commitments under Term Loan A and Term Loan B for the availability period applicable to Term Loan A and Term Loan B. Interest on overdue amounts under the Facilities will accrue at a rate, which is one percentage point higher than the rates otherwise applicable to the loans under the Facilities.

The Facilities Agreement restricts (subject to certain carve-outs) Shire’s ability to incur additional financial indebtedness, grant security over its assets or provide or guarantee loans. Further, any lender may require mandatory prepayment of its participation if there is a change in control of Shire.

Upon a change of control of Shire or upon the occurrence of an event of default and the expiration of any applicable cure period, the total commitments under the Facilities may be cancelled, all or part of the loans, (together with accrued interest and all other amounts accrued or outstanding) may become immediately due and payable. Events of default under the New Facilities Agreement include: (i) non-payment of any amounts due under the Facilities; (ii) failure to satisfy any financial covenants; (iii) material misrepresentation in any of the finance documents; (iv) failure to pay, or certain other defaults under other financial indebtedness; (v) certain insolvency events or proceedings; (vi) material adverse changes in the business, operations, assets or financial

condition of the group; (vii) certain US Employee Retirement Income Security Act (ERISA) breaches which would have a material adverse effect; (viii) if it becomes illegal for Shire or any of its subsidiaries that are parties to the New Facilities Agreement to perform their obligations or (ix) if Shire or any subsidiary of Shire which is party to the New Facilities Agreement repudiates the New Facilities Agreement or any Finance Document (as defined in the Facilities Agreement). The New Facilities Agreement is governed by English law.

Shire anticipates that its operating cash flow together with available cash, cash equivalents and short-term investments and the above mentioned debt facilities will be sufficient to meet its anticipated future operating expenses, any costs arising as a result of the acquisition of New River, outstanding costs related to the acquisition of TKT, capital expenditures, dividends, share repurchases and debt service and lease obligations as they become due over the next twelve months.

If the Company decides to acquire other businesses, it expects to fund these acquisitions from existing cash resources, the Facilities Agreement discussed above and possibly through new borrowings and/or the issue of new equity if necessary.

TKT convertible loan notes

As at December 31, 2005 all of TKT's 1.25% 2011 Convertible Notes had been converted and redeemed.

19. Other non-current liabilities

	December 31, 2006 $'M	December 31, 2005 $'M
SERP (see Note 28)	3.7	3.3
Long-term bonuses	6.9	4.8
Deferred revenue	9.0	5.9
Insurance provisions	13.7	11.3
Onerous lease provisions	6.9	7.7
Other accrued liabilities	11.9	10.5
	52.1	43.5

Deferred revenue relates to amounts received from the out-licensing of AGRYLIN, FOSRENOL, ELAPRASE and REPLAGAL in Japan and the global out-licensing of TROXATYL.

The onerous lease provisions at December 31, 2006 include $2.6 million in respect of the North American site consolidation (2005: $4.4 million).

20. Financial instruments

The estimated fair values of the Company's financial instruments as at December 31, 2006 and 2005 are summarized below. Certain estimates and judgments were required to develop the fair value amounts. The fair value amounts shown below are not necessarily indicative of the amounts that the Company would realize upon disposition, nor do they indicate the Company's intent or ability to dispose of the financial instrument.

The following methods and assumptions were used to estimate the fair value of each material class of financial instrument:

- Short-term investments (commercial paper and institutional and managed cash funds) - the carrying value approximates fair value because of the short-term nature of these instruments.

- Restricted cash - the carrying value either approximates fair value because of the short-term nature of the instruments or equals the fair value as such instruments are marked to market.

- Investments (available-for-sale securities) - the carrying value of non-current investments with readily determinable market values equals the fair value as such instruments are marked to market.

- Long-term debt - the fair value of long-term debt is estimated based on the discounted future cash flows using currently available interest rates or, where the debt instrument is traded, by reference to the market price.

- Derivatives - derivative instruments comprise forward foreign exchange contracts. As at December 31, 2006 the Company had 18 outstanding forward foreign exchange contracts with a total principal amount of $98.3 million equivalent to manage the currency risk associated with certain inter-company loans. The Company does not seek hedge accounting treatment for these hedges and therefore changes in the fair value of these derivatives are accounted for in the statement of operations. As at December 31, 2006 there were net unrealized losses of $8.1 million on these contracts.

The carrying amounts and corresponding fair values of financial instruments are as follows:

December 31, 2006	**Carrying amount**	**Fair value**
	$'M	**$'M**
Financial assets:		
Restricted cash	29.8	29.8
Investments (available-for-sale securities) (Note 11)	16.5	16.5
Financial liabilities:		
Derivatives	(8.1)	(8.1)

December 31, 2005	**Carrying amount**	**Fair value**
	$'M	**$'M**
Financial assets:		
Short-term investments (institutional and managed cash funds)	6.9	6.9
Restricted cash	30.6	30.6
Investments (available-for-sale securities) (Note 11)	18.1	18.1
Derivatives	2.5	2.5
Financial liabilities:		
Long-term debt	(0.1)	(0.1)

The carrying amounts of cash and cash equivalents, accounts receivable, accounts payable and accrued liabilities approximate fair value because of the short-term maturity of these amounts.

21. Commitments and contingencies

(a) Operating Leases

Future minimum operating lease payments presented below include lease payments and other fixed executory fees under lease arrangements as at December 31, 2006

Operating

	leases $'M
2007	28.8
2008	27.5
2009	23.7
2010	23.1
2011	16.0
Thereafter	38.3
	157.4

(i) Operating leases

The Company leases facilities, motor vehicles and certain equipment under operating leases expiring through 2025. Lease and rental expense included in selling, general and administrative expenses in the accompanying statements of operations amounted to $23.7 million, $20.6 million and $15.3 million for the years to December 31, 2006, 2005 and 2004 respectively.

During the year to December 31, 2004, Shire Inc., a wholly owned subsidiary of Shire, signed two eleven-year operating leases on properties in Wayne, Pennsylvania. Shire US, Inc., another wholly owned subsidiary, acts as guarantor in respect of these leases. The future minimum lease payments under the lease agreements are $52.6 million in aggregate.

(ii) Restricted cash in respect of leases

At December 31, 2006 the Company had $6.7 million of restricted cash held as collateral for certain equipment leases (2005: $5.5 million).

(b) Letters of credit and guarantees

As at December 31, 2006 the Company had the following letters of credit:

(i) an irrevocable standby letter of credit with Barclays Bank plc, in the amount of $14.2 million, providing security on the recoverability of insurance claims. The Company has restricted cash of $15.3 million, as required by this letter of credit; and

(ii) an irrevocable standby letter of credit with Bank of America in the amount of $7.8 million, providing security on the payment of lease obligations. The Company has restricted cash of $7.8 million, as required by this letter of credit.

(c) Commitments

(i) DAYTRANA

In connection with the Company's acquisition in 2003 from Noven Pharmaceuticals, Inc. (Noven) of the worldwide sales and marketing rights to DAYTRANA, Shire has a remaining obligation to pay Noven up to $50 million, contingent on future sales performance.

DAYTRANA received final regulatory approval from the US Food and Drug Administration (FDA) on April 6, 2006 and as a result Shire paid a $50 million milestone to Noven. During the year, the Company also reached a sales milestone for DAYTRANA, and, as a result, Shire will make a payment to Noven of $25 million in 2007. Both amounts have been capitalized and amortization of these amounts, together with the upfront milestone payment of $25 million made in 2003, will continue over the estimated life of the product of approximately 10 years.

(ii) VYVANSE

In January 2005, Shire entered into an agreement with New River to collaborate in developing, manufacturing, marketing and selling VYVANSE in the US. In the rest of the world, Shire acquired the license to develop and commercialize VYVANSE, in consideration of a low double-digit royalty.

Under the terms of the agreement, the parties will collaborate on VYVANSE development, manufacturing, marketing and sales in the US. New River will be financially and operationally responsible for clinical and manufacturing development. Shire will book the product sales and New River will supply up to 25% of the sales effort under a co-promotion right. Shire is obligated to give VYVANSE marketing and promotional priority over its other oral ADHD stimulants should VYVANSE's label contain a claim that it has decreased potential for abuse or overdose protection. Shire paid an initial sum of $50 million on signing and a further $50 million was paid to New River following acceptance of the filing of a New Drug Application (NDA) by the FDA in January 2006.

If VYVANSE is approved with a Schedule III, IV or V classification or is unscheduled ("favorable scheduling"), Shire will pay New River a $300 million milestone payment. US operating profit will be divided as follows: Shire will retain 75% of profits for the first two years following launch, and the parties will share the profits equally thereafter.

In the event that VYVANSE receives a final Schedule II classification, no milestone payment will be payable by Shire to New River upon approval. Division of profits will be calculated under an alternative profit sharing scheme. New River's share of U.S. product profits for the first two years will be at least 25%, though it may increase to a value determined by a preset sales based formula; for following years, it will be at least 50%, though it may increase to a value determined by a preset sales based formula thereafter. These formulas, which include yearly threshold sales, are set out in Exhibit 99.02 to the Company's Form 8-K filed on October 10, 2006. If VYVANSE is classified as Schedule II on approval and then gets favorable scheduling within one year of the first commercial sale, Shire will pay New River a $200 million milestone payment; if favorable scheduling occurs by the third anniversary, the milestone payment will be $100 million. Upon favorable scheduling being achieved under each of these scenarios, the profit sharing formula reverts to that applicable to favorable scheduling.

In addition, New River will be entitled to a $100 million milestone payment at the end of the first calendar year in which cumulative worldwide net sales of all collaboration products during that calendar year exceed $1 billion. A $5 million milestone payment is payable following the first commercial sale in specified European countries. Shire intends to capitalize and amortize any milestone payments over the life of the product.

Shire is entitled to terminate the agreement until 30 days following approval of VYVANSE. If Shire terminates before regulatory approval, no payment would be due to Shire. If Shire terminates after approval and VYVANSE has received a favorable scheduling assignment, no payment would be due to Shire. If the approved VYVANSE has received a Schedule II classification, Shire would be entitled to a $50 million termination payment, payable in cash, New River common stock, or an unsecured, 5-year promissory note, as will be agreed upon by Shire and New River.

On February 20, 2007 the Company announced that it had agreed to acquire New River for $2.6 billion in cash. On completion of the acquisition of New River, Shire will terminate these commitments. For further information see note 32 .

(iii) Women's Health Products

Shire and Duramed entered into an agreement related to Duramed's transvaginal ring technology that will be applied to at least five women's health products, as well as a license in a number of markets outside of North America, including the larger European markets to Duramed's oral contraceptive, SEASONIQUE. This agreement became effective on September 6, 2006.

Under this agreement, Shire will reimburse Duramed for US development expenses incurred going forward up to a maximum of $140 million over eight years. US Development expenditure reimbursement for the year ended December 31, 2006 totalled $2.5 million, with $2.0 million due for reimbursement at December 31, 2006. At December 31, 2006, the maximum future reimbursement for Duramed incurred US development expenditure is therefore $137.5 million. Shire will separately be responsible for development costs in its licensed territories.

(iv) Tissue Protective Cytokine (TPC) technology development rights

In connection with the Company's licence of TPC rights in non-nervous system indications from Warren, the Company is committed to making payments on achievement of certain milestones. The Company is not required to make any payments to Warren upon regulatory approval of the first product for the first indication. However, it is obligated to make milestone payments to Warren of $25 million upon regulatory approval in up to five subsequent major indications.

(iv) Other R&D and sales milestones

In addition to the commitments set out in (i) to (iv) at December 31, 2006 the Company had commitments payable on achievement of specified milestones and fees payable for products under development in-licensed from third parties of $75.6 million (December 31, 2005: $18.0 million), of which $12.9 million could be paid in 2007.

(v) TKT shareholders seeking appraisal rights

As at December 31, 2006, appraisal rights had been asserted in respect of approximately 11.3 million shares of TKT common stock. For further information see section (d) below. At December 31, 2006 the Company recorded a liability of $419.9 million based on the merger consideration of $37 per share for the 11.3 million shares outstanding at that time plus a provision for interest of $32.4 million that may be awarded by the Court (see Note 4). Until such time as the appraisal process is complete the Company is unable to determine the extent of its liability. For every $1 increase/decrease in the merger consideration applicable to those TKT shareholders who have asserted appraisal rights, the total estimated purchase price would increase/decrease by approximately $11.3 million.

(vi) Clinical testing

As at December 31, 2006, the Company had committed to pay approximately $55.0 million to contract vendors for administering and executing clinical trials. The Company expects to pay $36.1 million for these commitments throughout 2007. However, the timing of payments is not reasonably certain as payments are dependent upon actual services performed by the organizations as determined by patient enrollment levels and related activities.

(vii) Contract manufacturing

As at December 31, 2006 the Company had committed to pay approximately $83.4 million in respect of contract manufacturing, of which $64.5 million will be payable in 2007 and a further $18.9 million will be payable in 2008.

(viii) Investment commitments

As at December 31, 2006 the Company had outstanding commitments to subscribe for interests in companies and partnerships for amounts totaling $15.9 million (2005: $25.2 million) which could be payable in 2007, depending on the timing of capital calls.

(ix) Capital commitments

At December 31, 2006, the Company has committed to spend $0.8 million in 2006 in respect of capital commitments. This relates to the expansion and modification of its manufacturing facilities at Owings Mills, Maryland.

(d) Legal proceedings

General

The Company accounts for litigation losses and insurance claims and provisions in accordance with SFAS No. 5, "Accounting for Contingencies" (SFAS No. 5). Under SFAS No. 5, loss contingency provisions are recorded for probable losses when management is able to reasonably estimate the loss. Where the estimated loss lies within a range and no particular amount within that range is a better estimate than any other amount, the minimum amount is recorded. In other cases management's best estimate of the loss is recorded. These estimates are developed substantially before the ultimate loss is known and the estimates are refined in each accounting period in light of additional information becoming known. In instances where the Company is unable to develop a reasonable estimate of loss, no litigation loss is recorded at that time. As information becomes known a loss provision is set up when a reasonable estimate can be made. The estimates are reviewed quarterly and the estimates are changed when expectations are revised. Any outcome upon settlement that deviates from the Company’s estimate may result in an additional expense in a future accounting period.

As at December 31, 2005 provisions for litigation losses, insurance claims and other disputes totaled $35.7 million (2005: $27.8 million).

ADDERALL XR

(i) Barr Laboratories, Inc.

Shire's extended release "once daily" version of ADDERALL, ADDERALL XR, is covered by US Patent No. 6,322,819 (the '819 Patent) and US Patent No. 6,605,300 (the '300 Patent). In January 2003 the Company was notified that Barr had submitted an Abbreviated New Drug Application (ANDA) under the Hatch-Waxman Act seeking permission to market its generic versions of the 5mg, 10mg, 15mg, 20mg, 25mg and 30mg strengths of ADDERALL XR (Barr's ANDA products) prior to the expiration date of the Company's '819 Patent, and alleging that the '819 Patent is not infringed by Barr's ANDA products. In August 2003 Shire was notified that Barr also was seeking permission to market its ANDA products prior to the expiration date of the '300 Patent and alleging that the '300 Patent is invalid. Shire Laboratories, Inc, (Shire Laboratories) filed suit against Barr for infringement of the '819 Patent in February 2003 and for infringement of the '300 Patent in September 2003. The schedules for the lawsuits against Barr with respect to the '819 and '300 Patents were consolidated in December 2003. The Company sought a ruling that Barr's ANDA and ANDA products infringe the '819 and '300 Patents and that its ANDA should not be approved before the expiration date of the patents. The Company also sought injunctions to prevent Barr from commercializing its ANDA products before the expiration of the '819 and '300 Patents, damages in the event that Barr should engage in such commercialization, and its attorneys' fees and costs. On September 27, 2004 Barr filed an amended Answer, Affirmative Defense and Counterclaim in which Barr added the following counterclaims: invalidity of the '819 patent, non-infringement of the '300 Patent and unenforceability of the '819 and '300 Patents due to inequitable conduct. Shire asserted affirmative defenses, alleging, among other things, that Barr has waived its right to assert the counterclaims set forth in its September 27, 2004 amended Answer. Under the Court's schedule summary judgment motions were to be filed and fully briefed by October 14, 2005. Neither Shire nor Barr filed summary judgment motions. On December 9, 2005, the Court continued the final pre-trial conference to March 10, 2006.

Shire's lawsuits triggered stays of final FDA approval of Barr's ANDA of up to 30 months from the date of the Company's receipt of Barr's notice letters. The second and final 30 month stay related to the lawsuit regarding the '300 Patent expired on February 18, 2006. As the stay has expired, the FDA may approve Barr's ANDA, subject to satisfaction by Barr of the FDA's requirements. The FDA has not approved Barr's ANDA at this time.

On October 19, 2005 Shire brought another lawsuit against Barr in the Southern District of New York alleging infringement of US Patent No. 6,913,768 (the '768 Patent), which issued on July 5, 2005. The Company sought an injunction to prevent Barr from infringing the '768 Patent, damages in the event that Barr should commercialize its ANDA products, attorneys' fees and costs. Barr moved to dismiss this action asserting that there was no subject matter jurisdiction. A hearing on this motion was held on February 17, 2006. The Court never ruled on this motion.

During October 2005 Shire filed a Citizen Petition with the FDA requesting that the FDA require more rigorous bioequivalence testing or additional clinical testing for generic or follow-on drug products that reference ADDERALL XR before they can be approved. Shire believes that these requested criteria will ensure that generic formulations of ADDERALL XR or follow-on drug products will be clinically effective and safe. In January 2006 Shire filed a supplemental amendment to its original Citizen Petition, which included additional clinical data in support of the original filing. On April 20, 2006 Shire received correspondence from the FDA informing Shire that the FDA has not yet resolved the issues raised in Shire's pending ADDERALL XR Citizen Petition. The correspondence states that, due to the complex issues raised requiring extensive review and analysis by the FDA's officials, a decision cannot be reached at this time. The FDA's interim response is in accordance with FDA regulations concerning Citizen Petitions.

On August 14, 2006, Shire and Barr announced that all pending litigation in connection with Barr's ANDA and its attempt to market generic versions of Shire's ADDERALL XR had been settled. As part of the settlement agreement, Barr entered into consent judgments and agreed to permanent injunctions confirming the validity and enforceability of Shire's '819, '300 and '768 Patents. Barr has also admitted that any generic product made under its ANDA would infringe the '768 patent. Under the terms of the settlement, Barr will not be permitted to market a generic version of ADDERALL XR in the United States until April 1, 2009, except for certain limited circumstances, such as the launch of another party's generic version of ADDERALL XR. No payments to Barr are involved in the settlement agreement.

Shire and Duramed, a subsidiary of Barr, entered into an agreement related to Duramed's transvaginal ring technology that will be applied to at least five women's health products, as well as a license to Duramed's currently marketed oral contraceptive, SEASONIQUE (levonorgestrel/ethinyl estradiol tablets 0.15 mg/0.03 mg and ethinyl estradiol tablets 0.01 mg) (the product development and license agreement). Shire was granted exclusive rights to market these products on a royalty-free basis in a number of markets outside of North America, including the larger European markets. Duramed will market these products in North America. SEASONIQUE is already marketed in the United States by Duramed but Shire will need to obtain appropriate regulatory authorisations to commence marketing this product in Europe. Under this agreement, Shire made an initial payment of $25 million to Duramed on September 13, 2006 for previously incurred product development expenses, and will reimburse Duramed for

development expenses incurred going forward up to a maximum of $140 million over eight years, with the amount capped at $30 million per annum.

The settlement agreement and the product development and license agreement became effective upon the Courts signing the last of the consent judgments for the litigations on September 6, 2006.

Duramed agreed to purchase Shire's ADDERALL (immediate-release mixed amphetamine salts) product for $63 million. Shire reported the transaction to the FTC and the DOJ under the Hart Scott Rodino (HSR) Act on August 28, 2006. The HSR Act's 30-day waiting period expired on September 27, 2006 and the transaction closed on September 29, 2006.

As required by law, Shire submitted to the FTC and the DOJ all of the agreements with Barr and its subsidiaries that were entered into on August 14, 2006. On October 3, 2006, the FTC notified Shire that it is reviewing the settlement agreement with Barr. While the Company has not received any requests for information regarding the settlement agreement, Shire intends on cooperating with the FTC should it receive any such requests. The FTC's review should not be considered to be an indication that Shire or any other company violated any law, and Shire believes that the settlement agreement is in compliance with all applicable laws.

(ii) Impax Laboratories, Inc.

In November 2003, Shire was notified that Impax had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic version of the 30mg strength of ADDERALL XR (Impax's ANDA product) prior to the expiration date of the '819 and '300 Patents. In December 2003, Shire Laboratories filed suit against Impax for infringement of the '819 and '300 Patents.

In December 2004, Shire received an additional notification from Impax advising of the filing of an amendment to its ANDA for a generic version of the 5mg, 10mg, 15mg, 20mg and 25mg strengths of ADDERALL XR in addition to the 30mg strength, the subject of Impax's initial ANDA submission. In January 2005, Shire Laboratories filed suit against Impax for infringement of the '819 and '300 Patents by these lower strength dosage forms; this suit was consolidated with the earlier case against Impax.

As part of the October 19, 2005 lawsuit against Barr, Shire also brought suit in the Southern District of New York against Impax for infringing the '768 Patent. Impax filed a declaratory judgment action in Delaware alleging that the '768 Patent was invalid and that its ANDA did not infringe the '768 Patent.

On January 19, 2006, Shire and Impax announced that all pending litigation in connection with Impax's ANDA had been settled. As part of the settlement, Impax confirmed that its proposed generic products infringe Shire's '819, '300 and '768 Patents and that the three patents are valid and enforceable.

Under the terms of the settlement agreement, Impax will be permitted to market generic versions of ADDERALL XR in the United States no later than January 1, 2010 and will pay Shire a royalty from those sales. In certain situations, such as the launch of another generic version of ADDERALL XR, Impax may be permitted to enter the market as Shire's authorized generic. No payments to Impax are involved in the settlement agreement. The settlement agreement, which was effective immediately, has been submitted to the United States Federal Trade Commission for its review, as required by law.

(iii) Colony Pharmaceuticals, Inc.

In December 2004, Shire was notified that Colony Pharmaceuticals, Inc. (Colony) had submitted an ANDA under the Hatch-

Waxman Act seeking permission to market its generic versions of the 5mg, 10mg, 15mg, 20mg, 25mg and 30mg strengths of ADDERALL XR prior to the expiration date of the Company's '819 and '300 Patents. Shire has chosen not to sue Colony.

(iv) Teva Pharmaceuticals USA, Inc.

In February 2005, Shire was notified that Teva Pharmaceuticals, Inc. (Teva Pharmaceuticals) had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic versions of the 10mg and 30mg strengths of ADDERALL XR prior to the expiration date of the Company's '819 and '300 Patents. In June 2005, Shire was notified that Teva Pharmaceuticals had amended its ANDA to seek permission to market additional strengths of 5mg, 15mg and 20mg of its generic ADDERALL XR prior to the expiration of the '819 and '300 Patents. In January 2006, Shire received a third notice letter that Teva Pharmaceuticals had further amended its ANDA to seek permission to market the 25mg strength generic version of ADDERALL XR prior to the expiration of the '819 and '300 Patents. On March 2, 2006 Shire filed a lawsuit in the Eastern District of Pennsylvania against Teva Pharmaceuticals Industries Ltd. (Teva Israel) and Teva Pharmaceuticals USA, Inc. (Teva USA) (collectively Teva) alleging that all of Teva's ANDA products infringe both the '819 and the '300 Patents. The lawsuit triggered a stay of FDA approval of Teva's 25 mg strength product for 30 months from the date of the Company's receipt of Teva's third notice letter. There is no such stay with respect to Teva's 5mg, 10mg, 15mg, 20mg and 30 mg strengths versions of ADDERALL XR. On January 30, 2007, the case was transferred to the civil suspense docket with an

Order requiring the parties to notify the Court of the status of the case on the first business day of every month. No trial date has been set.

(v) Andrx Pharmaceuticals, LLC

In September 2006, Shire was notified that Andrx Pharmaceuticals, LLC (Andrx) had submitted a ANDA under the Hatch-Waxman Act seeking permission to market its generic versions of the 5mg, 10mg, 15mg, 20mg, 25mg and 30mg strengths of ADDERALL XR prior to the expiration date of the Company's '819 and '300 patents. Shire Laboratories and Shire LLC. have filed lawsuits in the US District Court for the District of New Jersey and the Southern District of Florida against Andrx Pharmaceuticals, LLC. and Andrx Corporation (collectively "Andrx") for infringement of the Company's '819 and '300 Patents. Watson Pharmaceuticals, Inc., the recent acquiror of Andrx, is also named in the lawsuits. The lawsuits allege that all of Andrx's generic strengths infringe the patents in suit. Pursuant to Hatch-Waxman legislation, there will be a 30-month stay with respect to Andrx's proposed generic products.

(vi) Sandoz Inc.

In December 2006, Shire was notified that Sandoz Inc. ("Sandoz") had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic versions of the 5mg, 10mg, 15mg, 20mg, 25mg, 30mg strengths of ADDERALL XR prior to the expiration of the Company's '819 and '300 patents. On January 26, 2007, Shire filed suit in the US District Court for the District of Colorado for infringement of the '819 and '300 patents. The lawsuit triggers a stay of FDA approval of up to 30 months from the Company's receipt of Sandoz's notice. The court has ordered a scheduling and planning conference for March 21, 2007. No trial date has been set.

None of Colony, Andrx, Teva or Sandoz may launch their generic versions of ADDERALL XR before they receive final FDA approval of their respective ANDAs and before the expiration of the first to file's exclusivity rights.

CARBATROL

(i) Nostrum Pharmaceuticals, Inc.

In August 2003, the Company was notified that Nostrum Pharmaceuticals, Inc. (Nostrum) had submitted an ANDA under the Hatch-Waxman Act seeking permission to market its generic version of the 300mg strength of CARBATROL (Nostrum's ANDA product) prior to the expiration date of the Company's US patents for CARBATROL, US patent No. 5,912,013 (the '013 Patent) and US patent No. 5,326,570 (the '570 Patent). The notification alleges that the '013 and '570 Patents are not infringed by Nostrum's ANDA product. On September 18, 2003, Shire filed suit against Nostrum in the United States District Court for the District of New

Jersey alleging infringement of these two patents by Nostrum's ANDA and ANDA product. The Company was seeking a ruling that Nostrum's ANDA infringes the '013 and '570 Patents and should not be approved before the expiration date of the '013 and '570 Patents. The Company was also seeking an injunction to prevent Nostrum from commercializing its ANDA product before the expiration of the '013 and '570 Patents, damages in the event that Nostrum should engage in such commercialization, as well as its attorneys' fees and costs. On January 23, 2004, the Company amended the complaint to drop the allegations with respect to the '013 Patent while maintaining the suit with respect to the '570 Patent. By way of counterclaims Nostrum is seeking a declaration that the '570 and '013 Patents are not infringed by Nostrum's ANDA product. Nostrum also was seeking actual and punitive damages for alleged abuse of process by Shire. On July 12, 2004, the Court dismissed Nostrum's abuse of process counterclaim for failure to state a claim upon which relief can be granted. On December 10, 2004, Nostrum filed a summary judgment motion seeking a declaration of non-infringement of the '570 Patent, which Shire opposed. The Court heard arguments with respect to Nostrum's motion on July 15, 2005. At the conclusion of the hearing the Court denied Nostrum's motion for summary judgment of non-infringement. On July 17, 2006 the Court entered an order staying discovery in this case until and through September 15, 2006. The parties requested, and the Court granted, an extension of the stay of discovery until and through December 29, 2006. On the January 8, 2007 the parties requested a further stay discovery until March 30, 2007, which has not yet been granted by the Court. No trial date has been set.

Nostrum may not launch a generic version of CARBATROL before it receives final approval of its ANDA from the FDA. The lawsuit triggered a stay of FDA approval of up to 30 months from Shire's receipt of Nostrum's notice letter. The 30 month stay expired on February 6, 2006. Following expiry of the stay, Nostrum could be in a position to market its 300mg extended-release carbamazepine product upon FDA final approval of its ANDA.

(ii) Corepharma LLC

On March 30, 2006 the Company was notified that Corepharma LLC (Corepharma) had filed an ANDA under the Hatch-Waxman Act seeking permission to market its generic version of carbamazepine extended release products in 100mg, 200mg and 300mg strengths prior to the expiration date of the '013 and the '570 Patents. On May 17,

2006, Shire filed suit against Corepharma in the United States District Court for the District of New Jersey alleging infringement of these two patents by Corepharma's ANDA and ANDA products. The Company was seeking a ruling that Corepharma's ANDA infringes the '013 and '570 Patents and should not be approved before their expiration dates. The Company was also seeking an injunction to prevent Corepharma from commercializing its ANDA products before the expiration of the '013 and '570 Patents, damages in the event that Corepharma should engage in such commercialization, as well as its attorneys' fees and costs. On September 1, 2006, the Company amended the complaint to drop the allegations with respect to the '013 Patent while maintaining the suit with respect to the '570 Patent. By way of counterclaims, Corepharma is alleging noninfringement and invalidity of the '570 Patent, noninfringement of the '013 Patent and federal and state antitrust violations. The parties have agreed to, and the court has accepted, a dismissal without prejudice of the antitrust counterclaims until a final judgment has been entered in the patent case. Corepharma has also filed a motion for a judgment on the pleadings of noninfringement of the '013 Patent, which Shire has opposed, including moving to dismiss the '013 Patent noninfringement counterclaim for lack of subject matter jurisdiction. The Court heard oral argument on these two motions on February 26, 2007, immediately after which the Court granted Shire's motion to dismiss for lack of subject matter jurisdiction, rendering moot Corepharma's motion for noninfringement of the '013 Patent.

The parties exchanged written discovery on January 26, 2007, and will appear before the Court for a status conference on March 13, 2007. No further discovery schedule or trial date has been set.

Corepharma may not launch a generic version of CARBATROL before it receives final approval of its ANDA from the FDA. The lawsuit triggered a stay of FDA approval of up to 30 months from Shire's receipt of Corepharma's notice letter.

GENE ACTIVATION

In 1996, Applied Research Systems Holding N.V., a wholly-owned subsidiary of Serono S.A. (Serono) and Cell Genesys became involved in a patent interference involving Serono's US Patent No. 5,272,071 (the '071 Patent), which purportedly covers certain methods of gene activation. In June 2004, the Board of Patent Appeals and Interferences of the US Patent and Trademark Office (PTO) held that both Serono and Cell Genesys were entitled to certain claims in their respective patent and patent application, and Serono and Cell Genesys each appealed the decision of the interference to the US District Court of Massachusetts and the US District Court of the District of Columbia, respectively. Shire HGT (formerly known as TKT) was not a party to this interference. The

District of Columbia action was subsequently transferred and consolidated with the District of Massachusetts action (the Appeal).

In August 2004, Serono served Shire HGT with an amended complaint in the Appeal. The amended complaint alleges that Shire HGT infringes Serono's '071 Patent. In August 2005, the US District Court of Massachusetts severed and stayed the infringement action pending resolution of the interference claim of the Appeal at the District Court level.

Pre-trial proceedings concerning the Appeal between Serono and Cell Genesys are ongoing and Serono's infringement action against the Company remains stayed pending resolution of those proceedings. In view of the stay, the Company has not yet answered Serono's complaint.

GA-GCB

In January 2005, Genzyme Corporation (Genzyme) filed suit against Shire HGT in the District Court of Tel Aviv-Jaffa, Israel, claiming that Shire HGT's Phase 1/2 clinical trial in Israel evaluating GA-GCB for the treatment of Gaucher disease infringes one or more claims of Genzyme's Israeli Patent No. 100,715. In addition, Genzyme filed a motion for preliminary injunction, including a request for an ex parte hearing and relief on the merits, to immediately seize and destroy all GA-GCB being used to treat patients and to prevent Shire HGT from submitting data generated from the clinical trial to regulatory agencies. In March 2005 the District Court refused to grant Genzyme's motion for a preliminary injunction. The lawsuit was dismissed in January 2006.

DYNEPO

Since 1997, Shire HGT and Sanofi-Aventis have been involved in ongoing patent litigation regarding Amgen's allegations that DYNEPO infringes claims of five of Amgen's patents. In 2001, the United States District Court of Massachusetts concluded that DYNEPO infringed certain claims of the patents that Amgen had asserted. This decision was appealed to the United States Court of Appeals for the Federal Circuit (the "Federal Circuit") which affirmed in part, reversed in part, and remanded the action to the United States District Court of Massachusetts for further proceedings.

In 2004, the United States District Court of Massachusetts issued a decision on the remanded issues, finding that certain claims related to four of the patents asserted by Amgen are infringed by Shire HGT and Sanofi-Aventis. This decision was subsequently appealed to the Federal Circuit which affirmed in part, reversed in part, and once again remanded certain issues to the District Court. Recently, Amgen has filed a request for an extension of time to file a petition for certiorari with the Supreme Court.

Under the most recent Federal Circuit decision, the Company and Sanofi-Aventis would be precluded from making, using and selling DYNEPO in the United States until the expiration of the relevant patents. The Company is required to reimburse Sanofi-Aventis, which controls the litigation and is paying the litigation expenses, for 50% of the expenses incurred in connection with the litigation from and after March 26, 2004. This litigation has no impact on Shire's ability to make, use and sell DYNEPO outside of the United States.

Appraisal Rights

In connection with Shire's merger with TKT, former holders of approximately 11.7 million shares of TKT common stock submitted written demands to the Delaware Court of Chancery for appraisal of these shares and, as a result, elected not to accept the $37 per share merger consideration. On October 10, 2005, at the request of one of the holders to tender 365,000 shares at the merger price of $37 per share, TKT filed a motion to dismiss the holder's demand. On October 12, 2005, the Delaware Court of Chancery granted this motion, and the holder tendered the shares at the merger consideration of $37 per share. Therefore, as at December 31, 2006, former holders of approximately 11.3 million shares of TKT common stock maintained written demands for appraisal of these shares and have elected not to accept the $37 merger consideration. In November 2005, the Delaware Court of Chancery approved a consolidation order filed by Shire HGT whereby actions brought by all petitioners have been consolidated as one case. In April 2006, Shire filed a motion for partial summary judgment in respect of approximately 8 million shares, claiming that the petitioners were not entitled to assert appraisal rights in connection with such shares.

To the extent that petitioners' demands were validly asserted in accordance with the applicable requirements of Delaware law and the former holders perfect their rights thereunder, such former holders will be entitled to receive the fair value of these shares as determined by the Delaware Court of Chancery. The determination of fair value will be made excluding any element of value arising

from the transaction, such as cost savings or business synergies. The Delaware Court of Chancery may ascribe a valuation to the shares that is greater than, less than or equal to $37 per share and may award interest on the amount determined in the appraisal process.

The total consideration for the acquisition of TKT, including amounts payable in respect of stock options and convertible securities, is approximately $1.6 billion at the merger price of $37 per share. This could change if Shire is required to pay a different amount of consideration in respect of the approximately 11.3 million shares for which holders have asserted appraisal rights. For every dollar increase/decrease in the merger consideration applicable to those TKT shareholders who have asserted appraisal rights, the total estimated purchase price would increase/decrease by approximately $11.3 million. Until such time as the appraisal process is complete, the Company is unable to determine the extent of its liability. The trial date has been set for April 23, 2007.

Class Action Shareholder Suit

In January and February 2003, various parties filed purported securities fraud class action lawsuits against TKT and Richard Selden, TKT's former Chief Executive Officer, in the United States District Court for the District of Massachusetts. In April 2003, the Court appointed a Lead Plaintiff and Lead Counsel and consolidated the various matters under one matter: In re Transkaryotic Therapies, Inc., Securities Litigation, C.A. No. 03-10165-RWZ.

In July 2003, the plaintiffs filed a Consolidated and Amended Class Action Complaint (the "Amended Complaint") against TKT; Dr Selden; Daniel Geffken, TKT's former Chief Financial Officer; Walter Gilbert, Jonathan S. Leff, Rodman W. Moorhead, III, and Wayne P. Yetter, then members of TKT's board of directors; William R. Miller and James E. Thomas, former members of TKT's board of directors; and SG Cowen Securities Corporation, Deutsche Bank Securities Inc., Pacific Growth Equities, Inc. and Leerink Swann & Company, underwriters of TKT’s common stock in prior public offerings.

The Amended Complaint alleges that the defendants made false and misleading statements and failed to disclose material information concerning the status and progress for obtaining United States marketing approval of REPLAGAL during the period between January 4, 2001 and January 10, 2003. The Amended Complaint asserts claims against Dr. Selden and TKT under Section 10(b) of the Securities Exchange Act of 1934 and Rule 10b-5 promulgated thereunder; and against Dr. Selden under Section 20(a) of the Exchange Act. The Amended Complaint also asserts claims based on TKT's public offerings of June 29, 2001, December 18, 2001 and December 26, 2001 against each of the defendants under Section 11 of the Securities Act of 1933 and against Dr. Selden under Section 15 of the Securities Act; and against SG Cowen Securities Corporation, Deutsche Bank Securities Inc., Pacific Growth Equities, Inc., and Leerink Swann & Company under Section 12(a)(2) of the Securities Act. The plaintiffs seek equitable and monetary relief, an unspecified amount of damages, with interest, and attorneys' fees and costs.

In May 2004, the Court granted in part and denied in part TKT's motion to dismiss. In particular, the Court dismissed allegations against TKT to the extent they arose out of certain forward-looking statements protected by the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995 and dismissed claims based on the public offerings of June 29, 2001 and December 18, 2001.The Court allowed all other allegations to remain. In July 2004, the plaintiffs voluntarily dismissed all claims based on the third public offering dated December 26, 2001.

In November 2005, the court granted the plaintiffs’ motion for class certification. On May 23, 2005, the court entered judgment on all claims alleged against SG Cowen Securities Corporation, Deutsche Bank Securities Inc., Pacific Growth Equities, Inc., and Leerink Swann & Company. On June 5, 2006, the court entered judgment on all claims alleged against Messrs. Gilbert, Leff, Moorhead, Yetter, Miller, and Thomas. On November 9, 2006, Mr. Geffken filed an Agreement for Judgment on all claims alleged against him. The Company is obligated to indemnify Dr Selden for his costs incurred in connection with the SEC Action.

22. **Shareholders’ equity**

(i) Authorised common stock

The authorized stock of Shire plc as at December 31, 2006 was 750,000,000 ordinary shares, 10,000,000 special voting shares and 2 deferred ordinary shares.

The special voting shares are held by a Voting Trustee, providing the holders of exchangeable shares in Shire Acquisition, Inc.,

with as nearly as practicable voting rights equivalent to those attached to Shire's ordinary shares. During 2006, 50,000 non-voting preference shares, which were authorized and issued for the purpose of the Scheme of Arrangement only, have been redeemed.

(ii) Dividends

Under English law, Shire can pay dividends only out of its distributable reserves, defined as the accumulated realized profits under UK generally accepted accounting principles (including reserves arising from a reduction of share capital), of the parent company, Shire plc (and not the consolidated Company), so far as not previously utilized by distribution or capitalization, less accumulated realized losses, so far as not previously written off in a reduction or reorganization of capital duly made. Shire plc can make a distribution only if the distribution does not reduce its net assets below the aggregate of the called up share capital and undistributable reserves. Any dividends will be at the discretion of the Board of Directors, will be declared in US dollars and will be paid in Pounds Sterling to Ordinary Shareholders, US Dollars to ADS holders and Canadian Dollars to Exchangeable Shareholders. At December 31, 2006 Shire plc's distributable reserves were $2,899 million.

(iii) Treasury stock

The Company records the purchase of its own shares as a reduction of shareholders' equity based on the price paid for the shares. During the period to December 31, 2006 a total of 5.3 million ordinary shares and 0.1 million American Depository Shares had been purchased for total consideration of $92.0 million, including stamp duty and broker commission.

Equity financing in 2007

On February 20, 2007 Shire also raised approximately $900 million through the private placement of 42,883,721 new ordinary shares to certain institutional investors at a price of 1075 pence per share. The newly issued shares represent approximately 8.4 per cent of Shire plc's issued ordinary share capital prior to the placing.

23. Related parties

(i) *Professional fees*

The Company incurred professional fees with Stikeman Elliott, a law firm in which the Hon. James Grant, a non-executive director of Shire, is a partner, totaling $0.6 million for the year to December 31, 2006 (2005: $0.5 million; 2004: $2.1 million).

(ii) *NeuroChem Inc.*

In April 2004 Shire BioChem Inc. (BioChem), a subsidiary of Shire, sold a Canadian property to NeuroChem Inc. for $7.8 million (CAN$10.5 million). At the time of the transaction, Dr Bellini, a non-executive director of Biochem and, until May 10, 2003 a non-executive director of Shire, and Mr Nordmann, a non-executive director of Shire were both directors of NeuroChem Inc. and Dr Bellini had an indirect substantial interest in the issued share capital of Neurochem Inc. at the time of the transaction. Mr Nordmann stepped down as a director of Neurochem Inc. in August 2006.

(iii) *ViroChem Pharma Inc.*

In April 2004, the Company contributed cash of $3.7 million (CAN$5.0 million) and equipment and intellectual property to the start-up of a new Canadian-based pharmaceutical research and development organization, ViroChem Pharma Inc. (ViroChem), in return for an equity interest and royalties on the sale of certain products subsequently launched by ViroChem. In April 2006 and April 2005, the Company contributed cash of $8.0 million (CAN$9 million) and $4.1 million (CAN$5 million) respectively to ViroChem in return for an additional equity interest.

Dr Bellini, a non-executive director of BioChem and, until May 10, 2003, a non-executive director of Shire, had, at the time of the transaction, an indirect substantial interest in a company, which is a co-investor of ViroChem. The Company has undertaken to invest an additional $5.0 million (CAN$6.0 million) in ViroChem.

(iv) *Xanodyne Pharmaceuticals Inc.*

In October 2005, the Company sub-leased its office premises in Newport to Xanodyne Pharmaceuticals Inc. Dr James Cavanaugh, the non-executive Chairman of the Company, was the Chairman of the Board of Directors of Xanodyne Pharmaceuticals, Inc. up to February 9, 2007 and remains a Board Director. As a result of the transaction the Company will receive $7.8 million (net of inducements) in lease income over the sub-lease period from Xanodyne Pharmaceuticals Inc.

24. Earnings per share

The following table reconciles income/(loss) from continuing operations and the weighted average ordinary shares outstanding for basic and diluted earnings per share for the periods presented:

Year to December 31,	**2006**	**Adjusted and restated 2005**	**Adjusted 2004**
	$'M	**$'M**	**$'M**
Income/(loss) from continuing operations	237.6	(581.5)	300.6
Loss from discontinued operations, net of tax	-	-	(20.1)
Gain/(loss) on disposition of discontinued operations, net of tax	40.6	3.1	(44.2)
Numerator for basic earnings/(loss) per share	278.2	(578.4)	236.3
Interest charged on convertible debt, net of tax	-	-	3.4
Numerator for diluted earnings/(loss) per share	278.2	(578.4)	239.7

Year to December 31, Weighted average number of shares outstanding	**2006 No. of shares Millions**	**2005 No. of shares Millions**	**2004 No. of shares Millions**
Basic	503.4	500.2	496.3
Effect of dilutive shares:			
Share options	5.3	-	3.0
Convertible debt	-	-	11.9
Warrants	0.6	-	0.1
	5.9	-	15.0
Diluted	509.3	500.2	511.3

	2006	**Adjusted and restated 2005**	**Adjusted 2004**
Basic earnings per share:			
Income/(loss) from continuing operations	47.2c	(116.2c)	60.6c
Loss from discontinued operations, net of tax	-	-	(4.1c)
Gain/(loss) on disposition of discontinued operations	8.1c	0.6c	(8.9c)
	55.3c	(115.6c)	47.6c
Diluted earnings per share:			
Income/(loss) from continuing operations	46.6c	(116.2c)	59.4c
Loss from discontinued operations, net of tax	-	-	(3.9c)
Gain/(loss) on disposition of discontinued operations	8.0c	0.6c	(8.6c)

	54.6c	(115.6c)	46.9c

The share options and warrants not included in the calculation of the diluted weighted average number of shares are shown below:

Year to December 31,	2006 No. of shares (1) Million	2005 No. of shares (2) Million	2004 No. of shares (1) Million
Share options	7.7	20.7	16.6
Warrants	-	1.3	-
	7.7	22.0	16.6

1. Not included as the exercise price exceeded the Company's average share price during the calculation period.

2. Not included as the Company made a loss during the reporting period.

During the year to December 31, 2004 the Company recorded a loss on redemption of the convertible loan notes of $7.4 million, which resulted from the write-off of unamortized debt issuance costs.

25. Segment reporting

SFAS No. 131 establishes standards for reporting information about operating segments and related disclosures, products and services, geographic areas and major customers. Operating segments are components of an enterprise about which separate financial information is available that is evaluated regularly by the chief operating decision-maker in deciding how to allocate resources and in assessing performance.

Shire sells a number of pharmaceutical products in multiple geographic markets across the world. The Company is continuously looking to develop and replenish the pharmaceutical product pipeline and has continued to focus on meeting the needs of the specialist physician in targeting therapeutic areas within its pool of expertise.

Shire's internal management reporting structures show two segments, Pharmaceutical Products and Royalties. The Pharmaceutical Products segment comprises four therapeutic areas, CNS, GI, HGT and GP and all products have been aggregated for reporting purposes within this segment.

The Company evaluates performance based on revenue and operating income. The Company does not have inter-segment transactions.

The Pharmaceutical Products segment represents the Company's commercial operations and costs in respect of products currently promoted and sold together with costs of developing projects for future commercialization. The Royalties segment represents royalties earned from the out-licensing of projects to third parties. These projects have been developed and commercialized by the third party and royalties are being received on the sale of the commercialized product. 'All Other' has been included in the table below in order to reconcile the segments to the

total consolidated figures. Costs have not been allocated to Royalties below as the magnitude of the costs incurred in respect of managing this segment is small and the internal reporting consequently does not allocate costs to this segment. Assets that are directly attributable to the Royalty segment have been separately disclosed from the Pharmaceutical Products segment.

Year to December 31, 2006	Pharmaceutical Products $'M	Royalties $'M	Segment Sub-total $'M	All Other $'M	Total $'M
Product sales	1,535.8	-	1,535.8	-	1,535.8

Royalties	-	242.9	242.9	-	242.9
Other revenues	-	-	-	17.8	17.8
Total revenues	1,535.8	242.9	1,778.7	17.8	1,796.5
Cost of product sales [2]	247.7	-	247.7	-	247.7
Research and development [2]	386.9	-	386.9	-	386.9
Selling, general and administrative [2]	835.4	-	835.4	-	835.4
Depreciation and amortization [1]	99.6	-	99.6	-	99.6
Intangible asset impairment	1.1	-	1.1	-	1.1
Integration costs	5.6	-	5.6	-	5.6
Gain on sale of product rights	(63.0)	-	(63.0)	-	(63.0)
Total operating expenses	1,513.3	-	1,513.3	-	1,513.3
Operating income	22.5	242.9	265.4	17.8	283.2
Total assets from continuing operations	3,265.9	60.5	3,326.4	-	3326.4
Long-lived assets	1,516.1	-	1,516.1	-	1,516.1
Capital expenditure on long-lived assets	168.9	-	168.9	-	168.9

1. Included in depreciation and amortization is the write-down of property, plant and equipment of 0.5 million. Depreciation from manufacturing plants of $4.8 million is included in cost of product sales.

2. Stock-based compensation of $43.0 million is included in: cost of product sales ($3.2 million), research and development ($5.4 million) and selling, general and administrative ($34.4 million).

Year to December 31, 2005	**Adjusted and restated Pharmaceutical Products**	**Royalties**	**Adjusted and restated Segment Sub-total**	**All Other**	**Adjusted and restated Total**
	$'M	**$'M**	**$'M**	**$'M**	**$'M**
Product sales	1,327.7	-	1,327.7	-	1,327.7
Royalties	-	242.9	242.9	-	242.9
Other revenues	-	-	-	28.7	28.7
Total revenues	1,327.7	242.9	1,570.6	28.7	1,599.3
Cost of product sales [2]	215.5	-	215.5	-	215.5
Research and development [2]	333.7	-	333.7	5.4	339.1
Selling, general and administrative [2]	655.5	-	655.5	-	655.5
Depreciation and amortization [1]	74.4	-	74.4	-	74.4
Intangible asset impairment	5.6	-	5.6	-	5.6
Reorganization costs	9.4	-	9.4	-	9.4
Integration costs	9.7	-	9.7	-	9.7
In-process research and development write-off	815.0	-	815.0	-	815.0
Total operating expenses	2,118.8	-	2,118.8	5.4	2,124.2
Operating (loss)/ income	(791.1)	242.9	(548.2)	23.3	(524.9)
Total assets from continuing operations	2,597.0	59.2	2,656.2	-	2,656.2
Long-lived assets	1,344.0	-	1,344.0	-	1,344.0

Capital expenditure on long-lived assets	114.4	-	114.4	-	114.4

1. Included in depreciation and amortization is the write-down of property, plant and equipment of $6.5 million. Depreciation from manufacturing plants ($3.5 million) is included in cost of product sales.

2. Stock-based compensation of $29.2 million is included in: cost of product sales ($1.5 million), research and development ($2.9 million) and selling, general and administrative ($24.8 million).

Year to December 31, 2004	**Adjusted Pharmaceutical Products $'M**	**Royalties $'M**	**Adjusted Segment Sub-total $'M**	**All Other $'M**	**Adjusted Total $'M**
Product sales	1,112.5	-	1,112.5	-	1,112.5
Royalties	-	230.4	230.4	-	230.4
Other revenues	-	-	-	20.3	20.3
Total revenues	1,112.5	230.4	1,342.9	20.3	1,363.2
Cost of product sales (2)	143.3	-	143.3	-	143.3
Research and development (2)	196.3	-	196.3	3.3	199.6
Selling, general and administrative (2)	486.9	-	486.9	-	486.9
Depreciation and amortization (1)	58.5	-	58.5	-	58.5
Intangible asset impairment	13.5	-	13.5	-	13.5
Reorganization costs	48.5	-	48.5	-	48.5
Total operating expenses	947.0	-	947.0	3.3	950.3
Operating income	165.5	230.4	395.9	17.0	412.9
Total assets from continuing operations	2,654.0	60.9	2,714.9	-	2,714.9
Long-lived assets	785.9	-	785.9	-	785.9
Capital expenditure on long-lived assets	93.9	-	93.9	-	93.9

(1) Depreciation from manufacturing plants ($2.7 million) is included in cost of product sales.

(2) Stock-based compensation of $33.8 million is included in: cost of product sales ($1.4 million), research and development ($3.5 million) and selling, general and administrative ($28.9 million).

Geographic Information

Revenues (based on the geographic location from which the sale originated):

Year to December 31,	**2006 $'M**	**2005 $'M**	**2004 $'M**
United Kingdom	187.5	184.6	84.9
North America	1,341.0	1,233.5	1,086.1
Rest of World	268.0	181.2	192.2
Total	1,796.5	1,599.3	1,363.2

Long-lived assets (all non-current assets, excluding deferred tax assets, investments and financial instruments based on the geographic location within which the economic benefits arise):

Year to December 31,	2006 $'M	Restated 2005 $'M
United Kingdom	136.1	124.4
North America	559.3	579.9
Rest of World	609.6	527.5
Total	1,305.0	1,231.8

Material customers

In the periods set out below, certain customers, all within the Pharmaceutical Products operating segment, accounted for greater than 10% of the Company's total revenues:

Year to December 31,	2006 $'M	2006 % revenue	2005 $'M	2005 % revenue	2004 $'M	2004 % revenue
Cardinal Health Inc.	665.0	37 %	599.5	37%	339.1	25%
McKesson Corp.	439.8	24%	345.7	22%	304.0	22%
Amerisource Bergen Corp.	172.5	10%	154.7	10%	168.0	12%
Walgreen Co.	n/a	n/a	n/a	n/a	156.6	11%

Amounts outstanding as at December 31, in respect of these material customers were as follows:

December 31,	2006 $'M	2005 $'M
Cardinal Health Inc.	57.6	94.1
McKesson Corp.	42.2	47.2
Amerisource Bergen Corp.	13.4	20.4

Revenues by product

In the periods set out below, revenues by major product were as follows:

	2006 $'M	2005 $'M	2004 $'M
ADDERALL XR	863.6	730.8	606.7
PENTASA	137.8	136.1	115.0
REPLAGAL	117.7	41.3	-
CARBATROL	68.3	72.1	54.3
AGRYLIN/XAGRID	60.8	92.8	152.5
FOSRENOL	44.8	53.5	-
CALCICHEW	45.5	38.7	38.3
DAYTRANA	25.1	-	-
ELAPRASE	23.6	-	-
ADDERALL	23.6	43.1	34.5
Other	125.0	119.3	111.2

	1,535.8	1,327.7	1,112.5

26. Interest expense

Interest expense for the year to December 31, 2006, 2005 and 2004 was $26.4 million, $12.0 million and $12.3 million respectively. Included in the amount for the year to December 31, 2006 was a $24.6 million (2005: $7.7 million) provision for interest, which may be awarded by the court in respect of amounts due to former holders of approximately 11.3 million shares of TKT common stock who have submitted written demands for appraisal of these shares. The provision was based on an estimate of Shire's average marginal cost of borrowing from the acquisition date.

In the year to December 31, 2005 Shire also incurred interest expense of $1.2 million relating to the costs of a bridging loan to finance the TKT acquisition.

In the year to December 31, 2004 interest expense included the write-off of $7.4 million of deferred financing costs following the redemption of $370.1 million of convertible loan notes during 2004 and the interest expense prior to the redemption of $4.2 million.

27. Other income, net

Year to December 31,	**2006**	**2005**	**2004**
	$'M	**$'M**	**$'M**
Impairment of long-term investments (see Note 11)	(2.1)	(2.0)	(15.4)
GeneChem Funds management fee	4.6	4.3	4.0
Gain on sale of available-for-sale security (see Note 11)	-	3.9	14.8
Gain on sale of drug formulation business	-	3.6	-
Foreign exchange	3.2	(1.4)	(2.5)
Other	3.8	1.5	3.0
	9.5	9.9	3.9

28. Retirement benefits

(a) Personal defined contribution pension plans

The Company makes contributions to defined contribution retirement plans that together cover substantially all employees. For the defined contribution retirement plans, the level of the Company's contribution is fixed at a set percentage of employee's pay.

Company contributions to personal defined contribution pension plans totaled $15.0 milllion, $14.1 million and $9.0 million for the years to December 31, 2006, 2005 and 2004, respectively, and were charged to operations as they became payable.

(b) Defined benefit pension plans

(i) The Roberts SERP

The Roberts SERP is for some US employees of Roberts Pharmaceutical Corporation (Roberts) who met certain age and service requirements. Shire acquired Roberts in 1999, and the plan was discontinued in 2000. There were no contributions payable by the Company in respect of 2006 and 2005. The Company paid a lump sum of $18.0 million into the Roberts SERP, which was accounted for as a fair value adjustment, on the acquisition of Roberts to make good the deficit on this scheme at the time of acquisition. This lump sum payment has led to the Company having no future liability under the SERP, which is closed to new members with contributions no longer payable by existing members. Assets are set aside to fund these benefits in a "Rabbi Trust". The legal form of the trust is such that the assets held to cover the pension liabilities are available to the general creditors of the Company on winding up. Accordingly, the assets held by the trust are not plan assets and are recorded on the balance sheet.

In accordance with EITF 97-14, “Accounting for Deferred Compensation Arrangements Where Amounts Earned Are Held in a Rabbi Trust and Invested” the assets and liabilities of $8.3 million and $4.7 million, respectively, are shown on the balance sheet within the categories “Other current assets”, “Other non-current assets”, “Other current liabilities” and “Other non-current liabilities”.

(ii) The Shire SERP

The Shire SERP defined benefit scheme is an unfunded arrangement; the benefits are payable to certain senior US employees as lump sums on leaving the Company’s employment or earlier due to death, disability or termination.

The amount of benefit is based on the value of notional contributions increased with “earned” investment returns as if they were invested in investments of the employees’ choice. The entire benefit liability has been recognised on the balance sheet.

29. Income taxes

The components of pre tax income/(loss) from continuing operations are as follows:

Year to December 31,	**2006 $’M**	**Adjusted and restated 2005 $’M**	**Adjusted 2004 $’M**
UK	20.5	61.6	(80.1)
US	(28.3)	44.5	248.7
In-process research and development	-	(815.0)	-
Other jurisdictions	324.6	217.2	257.8
	316.8	(491.7)	426.4

The provision/(benefit) for income taxes by location of the taxing jurisdiction for the years to December 31, consisted of the following:

Year to December 31,	**2006 $’M**	**Adjusted 2005 $’M**	**Adjusted 2004 $’M**
Current income taxes:			
UK corporation tax	7.0	7.4	0.7
US federal tax	6.1	13.5	97.9
US state and local taxes	3.8	7.3	5.1
Other	210.0	39.1	36.4
Total current taxes	226.9	67.3	140.1
Deferred taxes			
UK corporation tax	(81.0)	5.4	(0.5)
US federal tax	(57.8)	(8.2)	(12.1)
US state and local taxes	0.2	(3.3)	(0.1)
Other	(3.4)	27.6	0.9
Total deferred taxes	(142.0)	21.5	(11.8)
Total income taxes attributable to continuing operations	84.9	88.8	128.3
Total income taxes attributable to discontinued operations	-	-	-

Total income taxes	84.9	88.8	128.3

The reconciliation of income from continuing operations before income taxes and earnings/(losses) of equity method investees and discontinued operations to the provision for income taxes is shown in the table below:

Year to December 31,

	2006 $'M	Adjusted and restated 2005 $'M	Adjusted 2004 $'M
Income/(loss) from continuing operations before income taxes and earnings/(losses) of equity method investees and discontinued operations	316.8	(491.7)	426.4
UK Corporation tax rate	30.0 %	30.0%	30.0%
Adjustments to derive effective rate:			
Non-deductible items:			
Permanent differences	(18.8%)	6.2%	2.1%
In-process research and development	-	(49.7%)	-
Other items:			
Change in valuation allowance	(30.0%)	(4.3%)	3.6%
Difference in taxation rates	50.5%	(0.2%)	0.7%
Prior year adjustment	(6.5%)	0.7%	(4.8%)
Change in prior year tax rates	-	0.5%	-
Other	1.6%	(1.3%)	(1.5%)
Provision for income taxes on continuing operations	26.8%	(18.1%)	30.1%

The effective rate of tax for the year to December 31, 2006 was 26.8% (2005: 27.5%, after excluding the impact of the $815 million (restated) write-off of IPR&D in respect of the TKT acquisition). The effective rate has fallen by 0.7% as a result of an increase in deferred tax assets, offset by an increase in current tax liabilities. The increase in deferred tax assets was primarily due to the reversal of valuation allowances following changes in estimates as to realisation, and by the crystallisation of additional losses (included within prior year adjustments above). The increase in current tax liabilities was primarily a result of additional tax contingencies of $187 million recognised in relation to ongoing tax audits (included in difference in taxation rates above). Following this reversal of valuation allowances the net deferred tax asset has increased to $261.0 million at December 31, 2006 (2005: $116.2 million). Realization of deferred tax assets is dependent upon generating sufficient taxable income to utilize such assets. Although realization of these assets is not assured, it is more likely than not that the amount recognized will be realized.

The significant components of deferred income tax assets and liabilities and their balance sheet classifications, as at December 31, are as follows:

	December 31, 2006 $'M	December 31, 2005 $'M
Deferred tax assets:		
Deferred revenue	5.6	6.4
Inventory & warranty provisions	21.8	12.2
Losses carried forward (including tax credits)	369.0	417.9

Provisions for product returns and doubtful accounts	30.3	28.3
Restructuring	50.3	50.3
Intangibles	21.5	19.4
Other	69.3	44.8
Gross deferred tax assets	567.8	579.3
Less: valuation allowance	(109.6)	(235.1)
	458.2	344.2
Deferred tax liabilities:		
Excess of tax value over book value of assets	(197.2)	(228.0)
Net deferred tax assets	261.0	116.2
Balance sheet classifications:		
Deferred tax assets - current	105.7	54.2
Deferred tax assets - non-current	155.3	62.0
	261.0	116.2

The approximate operating loss and tax credit carry-forwards as at December 31, are as follows:

	2006	**2005**
	$'M	**$'M**
US federal tax NOLs	203.4	270.3
US state tax NOLs	66.6	99.4
UK NOLs	152.3	227.8
Canadian NOLs	84.7	153.2
Foreign tax jurisdictions	167.3	82.9
R&D tax credits	318.2	301.9

The operating loss and tax credit carry-forwards shown above have the following expiration dates:

	December 31 2006
	$'M
Within 1 year	13.1
Within 1 to 2 years	18.0
Within 2 to 3 years	22.6
Within 3 to 4 years	13.1
Within 4 to 5 years	17.3
Within 5 to 6 years	15.2
Within 6 to 7 years	16.5
After 7 years	518.3
Indefinitely	358.4

As at December 31, 2006, the Company had a valuation allowance of $109.6 million to reduce its deferred tax assets to estimated realizable value. The valuation allowance relates to the deferred tax assets arising from operating loss carry-forwards and capital loss carry-forwards. The utilization of operating loss carry-forwards is restricted to the taxable income of the subsidiary generating the losses. In addition, capital loss carry-forwards can only be offset against capital gains. As at December 31, 2006, based upon

the level of historical taxable income and projections for future taxable income over the periods in which the temporary differences are anticipated to reverse, and reasonable and feasible tax-planning strategies, management believes it is more likely than not that the Company will realize the benefits of these deductible differences, net of the valuation allowances. However, the amount of the deferred tax asset considered realizable could be adjusted in the future if estimates of taxable income are revised.

As at December 31, 2006, the Company had not made a tax provision on approximately $2.1 billion of unremitted earnings of the Company's international subsidiaries. As at December 31, 2006, these earnings are expected to be reinvested overseas. Because of complexity, it is not practical to compute the estimated deferred tax liability on these earnings.

30. Equity in earnings/(losses) of equity method investees

Year to December 31,	2006 $'M	2005 $'M	2004 $'M
GSK (see Note 11)	6.3	5.3	4.4
GeneChem Funds (see Note 11)	(1.3)	(4.0)	-
Other	0.7	(2.3)	(1.9)
	5.7	(1.0)	2.5

31. Share based compensation plans

Effective January 1, 2006 the Company adopted the provisions of SFAS No. 123(R), which establishes accounting for share-based compensation to employees. The Company measures share-based compensation cost at the grant date, based on the fair value of the award, and recognizes the expense over the employee requisite service period. The Company previously applied Accounting Principles Board (APB) Opinion No. 25, “Accounting for Stock Issued to Employees,” and related Interpretations and provided the required pro forma disclosures of SFAS No. 123, “Accounting for Stock-Based Compensation”. The Company has elected to adopt the modified retrospective application method as provided by SFAS No. 123(R) and accordingly, financial statement amounts for the prior period presented in this Form 10-K have been retrospectively adjusted to reflect the fair value method of expensing prescribed by SFAS No. 123(R).

The following table shows the total share-based compensation expense (see below for types of share-based awards) included in the statements of operations:

	2006 $'M	2005 $'M	2004 $'M
Cost of product sales	3.2	1.5	1.4
Research and development	5.4	2.9	3.4
Selling, general and administrative	34.4	24.8	28.9
Total operating expenses	43.0	29.2	33.7
Tax benefit	(6.5)	(3.2)	(0.8)
Total charge to net income	36.5	26.0	32.9

There were no capitalized share-based compensation costs at December 31, 2006 and 2005.

As at December 31, 2006 $80.6 million of total unrecognized compensation cost relating to non-vested awards, is expected to be recognized over a weighted average period of 4.2 years.

Share-based compensation plans

Historically the Company has granted options to directors and employees over ordinary shares under six stock option plans. On November 28, 2005 the ordinary shareholders of Shire approved the adoption of the Shire plc Portfolio Share Plan (Parts A and B), a new share based compensation plan, which provides for stock-settled share appreciation rights and performance share awards to

be made to directors and employees over ordinary shares and American depositary shares. No further awards will be made under the previous stock option plans.

The following awards were outstanding as at December 31, 2006:

	Compensation type	Number of awards	Expiration period from date of issue	Vesting period
Executive Scheme	Stock options	663,993	7 to 10 years	3-10 years, subject to performance criteria
2000 Executive Scheme	Stock options	16,955,079	10 years	3 -10 years, subject to performance criteria
Sharesave Scheme	Stock options	359,004	6 months after vesting	3 or 5 years
Stock Purchase Plan	Stock options	738,515	On vesting date	27 months
BioChem Plan	Stock options	843,282	10 years	Immediate on acquisition by Shire
Total stock option awards		19,559,873		
Portfolio Share Plan - Part A	Stock-settled share appreciation rights - ordinary shares	2,919,223	5 years	3 years, subject to performance criteria for executive directors only
Portfolio Share Plan - Part A	Stock-settled share appreciation rights - ADSs (1)	8,897,394	5 years	3 years, subject to performance criteria for executive directors only
Total Portfolio Share Plan - Part A		11,816,617		
Portfolio Share Plan - Part B	Performance share awards - ordinary shares	130,406	3 years	3 years, subject to performance criteria for executive directors only
Portfolio Share Plan - Part B	Performance share awards - ADSs(1)	526,023	3 years	3 years, subject to performance criteria for executive directors only
Total Portfolio Share Plan - Part B		656,429		

(1) For the purposes of this table ADSs have been converted into ordinary shares. One ADS is equivalent to three ordinary shares.

(a) Stock option plans

(i) Shire Pharmaceuticals Executive Share Option Scheme - Parts A and B (Executive Scheme)

Options granted under the Executive Scheme are subject to performance criteria and cannot be exercised in full, unless Shire's ordinary share price increases at a compound rate of at least 20.5% per annum over a minimum three-year measurement period. If Shire's ordinary share price increases at a compound rate of 14.5% per annum over a minimum three-year measurement period, 60% of the options may be exercised. If these conditions are not met after the initial three years, they are thereafter tested quarterly by reference to share price growth over the extended period. If the share price does not meet these conditions at any time, none of the options will become exercisable.

On February 28, 2000, the Remuneration Committee of the Board exercised its powers to amend the terms of the Executive Share Option Scheme so as to include a cliff vesting provision. It is intended that no further options will be granted under the Executive Scheme.

(ii) Shire plc 2000 Executive Share Option Scheme (2000 Executive Scheme)

Options granted under this scheme are exercisable subject to certain performance criteria. In respect of any option granted prior to August 2002, if Shire's ordinary share price increases at a compound rate of at least 20.5% per annum over a minimum three-year measurement period, the option becomes exercisable in full. If it increases by at least 14.5% per annum over the same three-year period, 60% of the options granted become exercisable. If these

conditions are not met after the initial three-year measurement period, they will thereafter be tested quarterly by reference to compound annual share price growth over an extended period.

The performance criteria were reviewed in 2002 to ensure the criteria reflected the market in which Shire operates. Given Shire's development, it was considered appropriate that an earnings per share based measure should be adopted. The performance criteria are based on real growth in the diluted earnings per share reported in the Company's Form 10-K under US GAAP, adjusted to ensure a consistent basis of measurement, as approved by the Remuneration Committee, including the add back of significant one time items (Option EPS) . Therefore, the performance criteria were amended so that an option would become exercisable in full if Shire's Option EPS growth over a three year period from the date of award exceeds the UK Retail Prices Index (RPI) for the following tranches of grants:

Options with a grant value of up to 100% of salary	RPI plus 9% (directors, RPI plus 15%)
Between 101% and 200% of salary	RPI plus 15%
Between 201% and 300% of salary	RPI plus 21%
Over 301% of salary	RPI plus 27%

The new earnings per share performance criteria apply to options granted under the 2000 Executive Scheme from August 2002. After consultation with certain of its institutional shareholders, the Company has decided that for options granted under the scheme from 2004 onwards, the retest of the performance condition if Shire's option EPS growth has fallen short of the minimum annual average percentage increase over the three year period from grant, should be changed. The revised performance condition will be retested once only, at five years after the grant. Hence the level of option EPS growth in the next two years needs to be consequentially higher to meet the test.

Six weeks prior to the expiration date, any options that have not become exercisable at an earlier date, automatically vest without reference to the performance criteria.

In December 2006, the Remuneration Committee exercised its powers to amend the performance criteria for options granted under the 2000 Executive Scheme which had not vested. The RPI based growth rate was replaced with an equivalent fixed growth rate based on historical and forecast inflation. The fair values of the awards were unaffected by this change and no additional employee compensation cost was recorded as a result of the modification.

It is intended that no further options will be granted under the 2000 Executive Scheme.

(iii) Shire Pharmaceuticals Sharesave Scheme (Sharesave Scheme)

Options granted under the Sharesave Scheme are granted with an exercise price equal to 80% of the mid-market price on the day before invitations are issued to employees. Employees may enter into three or five-year savings contracts.

(iv) Shire plc Employee Stock Purchase Plan (Stock Purchase Plan)

Under the Stock Purchase Plan, options are granted with an exercise price equal to 85% of the fair market value of a share on the enrolment date (the first day of the offering period) or the exercise date (the last day of the offering period), whichever is the lower. The offering period is for 27 months.

(v) Pharmavene 1991 Stock Option Plan (SLI Plan)

Options issued under the SLI Plan were originally granted over shares in SLI, formerly Pharmavene Inc., a company acquired by

the Company on March 23, 1997. Exercise of these options results in the option holder receiving ordinary shares in Shire. As a result of the acquisition of SLI, and in accordance with the terms of the original share option plan, all options granted under that plan became immediately capable of exercise. It is intended that no further options will be granted under the SLI Plan.

(vi) BioChem Stock Option Plan (BioChem Plan)

Following the acquisition of BioChem Pharma Inc. on May 11, 2001, the BioChem Stock Option Plan was amended such that options over BioChem Pharma Inc.'s common stock became options over ordinary shares of Shire. All BioChem Pharma Inc. options, which were not already exercisable, vested and became exercisable as a result of the acquisition. It is intended that no further options will be granted under the BioChem Stock Option Plan.

A summary of the status of the Company's stock option plans as at December 31, 2006, 2005 and 2004 and of the related transactions during the periods then ended is presented below:

Year to December 31, 2006

	Weighted average exercise price £	Number of shares	Aggregate Intrinsic Value £'M
Outstanding as at beginning of period	5.85	28,470,739	
Granted	7.33	386,159	
Exercised	5.21	(8,312,174)	
Forfeited	8.83	(984,851)	
Outstanding as at end of period	5.90	19,559,873	92.1
Exercisable as at end of period	6.77	5,742,106	24.2

0.1 million options were granted under the Sharesave Scheme at a price of £6.99. These options were granted with an exercise price equal to 80% of the mid-market price on the day before invitations were issued to employees. The weighted average fair value of options granted was £3.21.

0.3 million options were granted under the Stock Purchase Plan at a price of £7.48. These options were granted with an exercise price equal to 85% of the mid-market price on the day before invitations were issued to employees. The weighted average fair value of options granted was £3.71.

Year to December 31, 2005

	Weighted average exercise price £	Number of shares	Aggregate Intrinsic Value £'M
Outstanding as at beginning of period	5.85	27,343,625	
Granted	5.88	8,733,811	
Exercised	4.53	(4,701,699)	
Forfeited	8.17	(2,904,998)	
Outstanding as at end of period	5.85	28,470,739	55.8
Exercisable as at end of period	7.97	7,987,369	6.2

8.2 million options were granted under the 2000 Executive Scheme. These options were granted with exercise prices equivalent to the market value on the date of grant. The weighted average fair value of options granted was £3.08.

0.1 million options were granted under the Sharesave Scheme at a price of £5.13. These options were granted with an exercise

price equal to 80% of the mid-market price on the day before invitations were issued to employees. The weighted average fair value of options granted was £3.24.

0.04 million and 0.4 million options were granted under the Stock Purchase Plan at a price of £5.86 and £5.85, respectively. These options were granted with an exercise price equal to 85% of the mid-market price on the day before invitations were issued to employees. The weighted average fair value of options granted was £2.00.

Year to December 31, 2004	Weighted average exercise price £	Number of shares	Aggregate Intrinsic Value £'M
Outstanding as at beginning of period	6.10	25,995,543	
Granted	5.14	6,966,411	
Exercised	3.71	(2,097,716)	
Forfeited	7.58	(3,520,613)	
Outstanding as at end of period	5.85	27,343,625	19.2
Exercisable as at end of period	8.65	8,728,709	1.4

6.7 million options were granted under the 2000 Executive Scheme. These options were granted with exercise prices equivalent to the market value on the date of grant. The weighted average fair value of options granted was £2.78.

0.1 million options were granted under the Sharesave Scheme at a price of £3.74. These options were granted with an exercise price equal to 80% of the mid-market price on the day before invitations were issued to employees. The weighted average fair value of options granted was £2.31.

0.2 million options were granted under the Stock Purchase Plan at a price of £3.92. These options were granted with an exercise price equal to 85% of the mid-market price on the day before invitations were issued to employees. In relation to a grant under the Stock Purchase Plan at a price of £8.06 in 2001, an additional 32,793 options were granted at a price of £4.58 on the 2004 maturity date. The weighted average fair value of options granted was £1.28.

Options outstanding as at December 31, 2006 have the following characteristics:

Number of options outstanding	Exercise prices £	Weighted average remaining contractual term (years)	Weighted average exercise price of options outstanding £	Number of options exercisable	Weighted average exercise price of options exercisable £
2,518,812	0.01 - 4.00	6.0	3.51	2,387,588	3.50
11,981,596	4.01 - 6.00	7.4	5.39	773,918	4.45
3,323,340	6.01 - 10.00	5.7	7.02	920,110	7.39
1,736,125	10.01 - 13.00	3.0	11.82	1,660,490	11.87
19,559,873				5,742,106	

(b) Stock-settled share appreciation rights

Portfolio Share Plan - Part A

Stock-settled share appreciation rights granted under the Portfolio Share Plan - Part A are exercisable subject to certain performance criteria. In respect of any award made to executive directors performance conditions will be based on relative total

shareholder return. Vesting will depend on relative total shareholder return performance against two comparator groups. For one-third of the award, the comparator group will be the Financial Times Stock Exchange 100 constituents (excluding financial institutions) and for two-thirds of the award the comparator group will be a group of international companies from the pharmaceutical sector. In addition, before awards granted to executive directors will vest, the Committee must be satisfied that the underlying performance of the Company is sufficient to justify this. Where median performance is achieved, 33 1/3 per cent of stock-settled share appreciation rights will vest, rising on a straight-line basis to full vesting at upper quartile performance.

Awards granted to employees below executive director level will not be subject to performance conditions.

Once awards have vested, participants will have until the fifth anniversary of the date of grant to exercise their awards.

A summary of the status of the Company's stock-settled share appreciation rights as at December 31, 2006 and of the related transactions during the periods then ended is presented below:

Year to December 31, 2006 Ordinary shares	**Weighted average exercise price £**	**Number of shares**	**Intrinsic Value £' M**
Outstanding as at beginning of period	7.17	449,490	
Granted	8.74	2,561,292	
Exercised	-	-	
Forfeited	7.19	(91,559)	
Outstanding as at end of period	8.54	2,919,223	6.0
Exercisable as at end of period		-	-

2.6 million stock-settled share appreciation rights were granted over ordinary shares under the Portfolio Share Plan - Part A. These options were granted with exercise prices equivalent to the market value on the date of grant. The weighted average fair value of options granted in the year to December 31, 2006 is £2.58.

A summary of the status of the Company's stock-settled share appreciation rights as at December 31, 2005 and of the related transactions during the periods then ended is presented below:

Year to December 31, 2005 Ordinary shares	**Weighted average exercise price £**	**Number of shares**	**Intrinsic Value £' M**
Outstanding as at beginning of period	-	-	
Granted	7.17	449,490	
Exercised	-	-	
Forfeited	-	-	
Outstanding as at end of period	7.17	449,490	6.0
Exercisable as at end of period		-	-

0.4 million stock-settled share appreciation rights were granted over ordinary shares under the Portfolio Share Plan - Part A. These options were granted with exercise prices equivalent to the market value on the date of grant. The weighted average fair value of options granted in the year to December 31, 2006 was £2.58.

Stock-settled share appreciation rights over ordinary shares outstanding as at December 31, 2006 have the following characteristics:

Number of options outstanding	Exercise prices £	Weighted Average Remaining Contractual term Years	Weighted average exercise price of options outstanding £	Number of options exercisable	Weighted average exercise price of options exercisable £
2,919,223	6.01-10.10	4.5	8.54	-	-

Year to December 31, 2006 American depositary shares	Weighted average exercise price $	Number of ADSs	Intrinsic Value $' M
Outstanding as at beginning of period	37.80	937,392	
Granted	50.10	2,138,356	
Exercised	-	-	
Forfeited	41.71	(109,950)	
Outstanding as at end of period	46.4	2,965,798	45.3
Exercisable as at end of period		-	-

2.1 million stock-settled share appreciation rights were granted over American depositary shares (equivalent to 6.3 million ordinary shares) under the Portfolio Share Plan - Part A. These options were granted with exercise prices equivalent to the market value on the date of grant. The 3.0 million stock-settled share appreciation rights over ADSs outstanding at December 31, 2006 are equivalent to 9.0 million ordinary shares. The average fair value of options granted in the year to December 31, 2006 is $14.70.

Year to December 31, 2005 American depositary shares	Weighted average exercise price $	Number of ADSs	Intrinsic Value $' M
Outstanding as at beginning of period	-	-	
Granted	37.80	940,392	
Exercised	-	-	
Forfeited	37.70	(3,000)	
Outstanding as at end of period	37.80	937,392	1.3
Exercisable as at end of period		-	-

0.9 million stock-settled share appreciation rights were granted over American depositary shares (equivalent to 2.8 million ordinary shares) under the Portfolio Share Plan - Part A. These options were granted with exercise prices equivalent to the market value on the date of grant. The 0.9 million stock-settled share appreciation rights over ADSs outstanding at December 31, 2006 are equivalent to 2.8 million ordinary shares. The average fair value of options granted in the year to December 31, 2006 is $14.92.

Stock-settled share appreciation rights over American depositary shares outstanding as at December 31, 2006 have the following characteristics:

Number of options outstanding	Exercise prices $	Weighted Average Remaining Contractual term (years)	Weighted average exercise price of options outstanding $	Number of options exercisable	Weighted average exercise price of options exercisable

2,965,798	35.01 - 50.00	4.4	46.48	-	-

(c) Performance share plan

Portfolio Share Plan - Part B

Performance share awards granted under the Portfolio Share Plan - Part B are exercisable subject to certain performance criteria. In respect of any award made to executive directors performance conditions will be based on relative total shareholder return. Vesting will depend on relative total shareholder return performance against two comparator groups. For one-third of an award, the comparator group will be the Financial Times Stock Exchange 100 constituents (excluding financial institutions) and for two-thirds of the award the comparator group will be a group of international companies from the pharmaceutical sector. In addition, before awards granted to executive directors will vest, the Committee must be satisfied that the underlying performance of the Company is sufficient to justify this. Where median performance is achieved, 33 1/3 per cent of performance shares will vest, rising on a straight-line basis to full vesting at upper quartile performance.

A summary of the status of the Company's stock-settled share awards as at December 31, 2006 and of the related transactions during the periods then ended is presented below:

Performance share awards - Ordinary shares	**Number of shares**	**Aggregate intrinsic value £'M**	**Weighted average remaining life**
Outstanding as at beginning of period	-		
Granted	130,406		
Outstanding as at end of period	130,406	1.4	2.6
Exercisable as at end of period	-	N/A	N/A

Performance share awards - American Depositary Shares	**Number of ADSs**	**Aggregate intrinsic value $'M**	**Weighted average remaining life**
Outstanding as at beginning of period	-		
Granted	175,341		
Outstanding as at end of period	175,341	10.8	2.6
Exercisable as at end of period	-	N/A	N/A

Exercises of employee share-based awards

The total intrinsic value of share-based awards exercised for the period to December 31, 2006, 2005 and 2004 was $65.5 million, $14.9 million and $6.6 million, respectively. The total cash received from employees as a result of employee share option exercises for the period to December 31, 2006, 2005 and 2004 was approximately $82.0 million, $37.1 million and $13.4 million, respectively. In connection with these exercises, the excess tax benefits realized by the Company and charged to additional paid-in capital for the period to December 31, 2006, 2005 and 2004 were $nil, $0.2 million and $0.4 million, respectively.

The Company will settle future employee share award exercises with either newly listed common shares or with shares held in an employee share ownership plan (ESOP). The number of shares held in the ESOP at December 31, 2006 was 6.2 million.

Valuation methodologies

The Company estimates the fair value of share based awards without market-based performance conditions using a Black-Scholes valuation model and awards with market-based performance conditions are valued using a binomial valuation. This is consistent with the provisions of SFAS No. 123(R), Securities and Exchange Commission (SEC) Staff Accounting Bulletin No. 107 and the Company's prior period pro forma disclosures of net earnings, including stock-based compensation (determined under a fair value

method as prescribed by SFAS No. 123). Key input assumptions used to estimate the fair value of share-based awards include the grant price of the award, the expected stock-based award term, volatility of the Company's share, the risk-free rate and the Company's dividend yield. The Company believes that the valuation technique and the approach utilized to develop the underlying assumptions are appropriate in estimating the fair values of Shire's stock-based awards. Estimates of fair value are not intended to predict actual future events or the value ultimately realized by employees who receive equity awards, and subsequent events are not indicative of the reasonableness of the original estimates of fair value made by the Company under SFAS No. 123(R).

The fair value of share awards granted was estimated using the following assumptions:

Period ended December 31,	2006	2005	2004
Risk-free interest rate	4.7-5.0 %	3.9-4.6%	2.5-4.2%
Expected dividend yield	0.5%	0.6%	0%, 0.6%
Expected life (1)	4 years	7 years	7 years
Weighted average volatility	30%	48%	49%
Forfeiture rate	5%	5%	5%

(1) stock awards made in the year to December 31, 2006 expire 5 years from the date of issue (2005: 10 years)

32. Subsequent events

Acquisition of New River

On February 20, 2007 Shire announced that it has agreed to acquire New River for $64 per New River share, or approximately $2.6 billion for the fully diluted equity interest, in an all cash transaction unanimously recommended by the Boards of both companies. The acquisition is structured as a tender offer for all outstanding shares of New River followed by a merger. The acquisition is subject to the approval of Shire plc's shareholders as well as the satisfaction of certain customary conditions, including the tender of a majority of the outstanding New River shares on a fully-diluted basis and the expiration or earlier termination of the Hart-Scott-Rodino waiting period. For accounting purposes, the acquisition of New River will be accounted for as a purchase business combination in accordance with SFAS No. 141.

The total consideration for the acquisition of New River amounts to approximately $2.6 billion in cash. Shire has entered into new bank facilities of $2.3 billion to provide part of the financing for the acquisition. This new facility is conditional upon, amongst other things, approval being given by Shire plc's shareholders at an Extraordinary General Meeting for Shire plc to exceed the limit on its aggregate borrowings set out in Shire's Articles of Association.

Shire plc has also raised approximately $900 million through the private placement of 42,883,721 new ordinary shares to certain institutional investors worldwide at a price of 1075 pence per share. The newly issued shares represent approximately 8.4 per cent of Shire plc's issued ordinary share capital prior to the placing.

Quarterly results of operations (unaudited)

The following table presents summarized unaudited quarterly results for the years to December 31, 2006 and 2005.

2006	**Q1**	**Q2**	**Q3**	**Q4**
	$'M	**$'M**	**$'M**	**$'M**
Total revenues	411.0	439.1	449.4	497.0
Operating income	14.4	82.2	106.2	80.3
Net income	61.1	61.3	87.2	68.6

Earnings per share - basic	12.1c	12.2c	17.3c	13.6c
Earnings per share - diluted	12.0c	12.0c	17.1c	13.4c

2005	[1] **Adjusted Q1 $'M**	[1] **Adjusted Q2 $'M**	[1] [2] **Adjusted and restated Q3 $'M**	[1] **Adjusted Q4 $'M**
Total revenues	333.7	424.6	376.1	465.0
Operating income/(loss)	8.3	134.1	(762.1)	94.9
Net income/(loss)	15.4	109.8	(772.7)	69.0
Earnings per share - basic	3.1c	22.0c	(154.4c)	13.8c
Earnings per share - diluted	3.1c	22.0c	(154.4c)	13.7c

[1] Retrospectively adjusted following the adoption of SFAS No.123(R); see notes 3 and 31 for additional information.
[2] Restated for a correction to the value ascribed to IPR&D acquired with the acquisition of TKT; see note 3 (a) .

SCHEDULE II

VALUATION AND QUALIFYING ACCOUNTS

Provision for sales rebates, returns and coupons	**Beginning balance $'M**	**Provision charged to income [1] $'M**	**Costs incurred/ utilization [1] $'M**	**Ending balance $'M**
2006 :				
Accrued rebates - Medicaid and Health Maintenance Organizations (HMOs)	105.4	263.3	(242.3)	126.4
Sales returns reserve	31.8	34.1	(29.4)	36.5
Accrued coupons	5.2	8.8	(1.0)	13.0
	142.4	306.2	(272.7)	175.9
2005 :				
Accrued rebates - Medicaid and Health Maintenance Organizations (HMOs)	99.4	188.8	(182.8)	105.4
Sales returns reserve	22.5	35.3	(26.0)	31.8
Accrued coupons	15.9	12.3	(23.0)	5.2
	137.8	236.4	(231.8)	142.4
2004 :				
Accrued rebates - Medicaid and HMOs	59.2	136.6	(96.4)	99.4
Sales returns reserve	8.3	35.6	(21.4)	22.5
Accrued coupons	4.1	29.0	(17.2)	15.9
	71.6	201.2	(135.0)	137.8

[1] In the analysis above, due to systems limitations, it is not practical and has not been necessary to break out current versus prior

year activity. When applicable, Shire has performed general ledger reviews of sales deduction provisions charged to income, and the utilization of these provisions in subsequent years. Shire has determined that adjustments made in each year as a result of changes to estimates that related to prior year sales, and adjustments made as a result of differences between prior period provisions and actual payments, did not have a material impact on the Company's financial performance or position either in each individual year, or in the Company's performance over the reported period.

SIGNATURES

Pursuant to the requirements of Section 13 of 15(d) of the Securities and Exchange Act of 1934, the Company has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

SHIRE PLC
(Registrant)

Date: March 1, 2007

By: /s/ Matthew Emmens
Matthew Emmens, Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the date indicated.

Signature	Title	Date
/s/ James Henry Cavanaugh JAMES HENRY CAVANAUGH	Non-executive Chairman	March 1, 2007
/s/ Matthew Emmens MATTHEW EMMENS	Chief Executive Officer	March 1, 2007
/s/ Angus Charles Russell ANGUS CHARLES RUSSELL	Chief Financial Officer and Principal Accounting Officer	March 1, 2007
/s/ James Andrews Grant JAMES ANDREWS GRANT	Non-executive Director	March 1, 2007
/s/ Robin Buchanan ROBIN BUCHANAN	Non-executive Director	March 1, 2007
/s/ David Kappler DAVID KAPPLER	Non-executive Director	March 1, 2007
/s/ Patrick Langlois PATRICK LANGLOIS	Non-executive Director	March 1, 2007
/s/ Kate Nealon KATE NEALON	Non-executive Director	March 1, 2007
/s/ Jeffrey Leiden JEFFREY LEIDEN	Non-executive Director	March 1, 2007

Exhibit Index

Exhibit number	Description
3.1	Articles of Association of Shire plc as adopted by special resolution on September 19, 2005 (1) .
10.1*	Settlement Agreement, dated August 14, 2006 by and between Shire Laboratories Inc. and Barr Laboratories, Inc. (2)
10.2*	Product Development and License Agreement, dated August 14, 2006 by and between Shire LLC and Duramed Pharmaceuticals, Inc. (2)
10.3*	Product Acquisition and License Agreement, dated August 14, 2006 by and among Shire LLC, Shire plc and Duramed Pharmaceuticals, Inc. (2)
21	List of Subsidiaries.
23.1	Consent of Deloitte & Touche LLP.
31.1	Certification of Matthew Emmens pursuant to Rule 13a - 14 under The Exchange Act.
31.2	Certification of Angus Russell pursuant to Rule 13a - 14 under The Exchange Act.
32	Certification of Matthew Emmens and Angus Russell pursuant to Section 906 of the Sarbanes - Oxley Act of 2002.

* Certain portions of this exhibit have been omitted intentionally, subject to a confidential treatment request. A complete version of this agreement has been filed separately with the Securities and Exchange Commission.

(1) Incorporated by reference to Exhibit 3.01 to Shire's Form 8-K filed on November 25, 2005.
(2) Incorporated by reference to Shire ' s Form 10-Q filed on November 7, 2006.

EXHIBIT 21

LIST OF SUBSIDIARIES

Principal subsidiary/undertaking	Jurisdiction of incorporation
Shire Pharmaceuticals Group Limited	England and Wales
Shire LLC	State of Kentucky, USA
Shire Pharmaceuticals Limited	England and Wales
Shire Pharmaceuticals Development Limited	England and Wales
Shire International Licensing BV	Netherlands
Shire Pharmaceuticals, Inc.	State of Delaware, USA
Shire Development, Inc.	State of Delaware, USA
Shire Regulatory, Inc.	State of Delaware, USA
Shire France S A	France
Shire Deutschland GmbH & Co. KG	Germany
Shire US, Inc.	State of New Jersey, USA
Shire Pharmaceuticals Ireland Limited	Republic of Ireland
Shire Italia SpA	Italy
Shire Pharmaceuticals Iberica S.L.	Spain
Shire Pharmaceuticals US Development, Inc.	State of Maryland, USA
Shire BioChem, Inc.	Canada
Shire Pharmaceutical Contracts Limited	England and Wales
Shire US Manufacturing, Inc.	State of Maryland, USA
Shire Human Genetic Therapies, Inc. (formerly Transkaryotic	

Therapies, Inc.)	State of Delaware, USA
Shire Human Genetic Therapies AB (formerly TKT Europe AB)	Sweden

All subsidiary undertakings of Shire plc are beneficially owned (directly or indirectly) as to 100% and are all consolidated in the consolidated financial statements of Shire plc.

EXHIBIT 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in Shire plc's Registration Statements on Form S-8 (Nos. 333-09168, 333-93543, 333-60952, 333-91552, 333-111579, 333-129961, 333-129960 and 333-111108), Form S-4 (No. 333-55696) and Form S-3 (Nos. 333-72862-01, 333-38662 and 333-39702) of our report dated March 1, 2007 which expresses an unqualified opinion and includes an explanatory paragraph relating to the adoption of a new accounting principle as discussed in Note 31 and restatement as discussed in Note 3(a), appearing in this Annual Report on Form 10-K of Shire plc for the year ended December 31, 2006.

/s/ Deloitte & Touche LLP

DELOITTE & TOUCHE LLP
Reading, United Kingdom
March 1, 2007

EXHIBIT 31.1

CERTIFICATION OF MATTHEW EMMENS RELATING TO

FORM 10-K FOR THE YEAR TO

DECEMBER 31, 2006 OF

SHIRE PLC

I, Matthew Emmens, certify that:

I have reviewed this Annual Report on Form 10-K of Shire plc;

Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as at, and for, the periods presented in this report;

The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the Registrant and have:

(a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the Registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) evaluated the effectiveness of the Registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as at the end of the period covered by this report based on such evaluation; and

(d) disclosed in this report any change in the Registrant's internal control over financial reporting that occurred during the Registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the Registrant's internal control over financial reporting; and

The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

(a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2007

/s/ Matthew Emmens
Matthew Emmens
Chief Executive Officer

EXHIBIT 31.2

CERTIFICATION OF ANGUS RUSSELL RELATING TO

FORM 10-K FOR THE YEAR TO

DECEMBER 31, 2006 OF

SHIRE PLC

I, Angus Russell, certify that:

1. I have reviewed this Annual Report on Form 10-K of Shire plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as at, and for, the periods presented in this report;

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the Registrant and have:

   (a) designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the Registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) evaluated the effectiveness of the Registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as at the end of the period covered by this report based on such evaluation; and

   (d) disclosed in this report any change in the Registrant's internal control over financial reporting that occurred during the Registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the Registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of registrant's board of directors (or persons performing the equivalent functions):

   (a) all significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 1, 2007

/s/ Angus Russell
Angus Russell
Chief Financial Officer

EXHIBIT 32

The certification set forth below is being submitted in connection with the Annual Report of the Registrant on the Form 10-K for the year to December 31, 2006 (the Report), for the purpose of complying with Rule 13a-14(b) or Rule 15d-14(b) of the Securities Exchange Act of 1934 (the “Exchange Act”) and Section 1350 of Chapter 63 of Title 18 of the United States Code.

Matthew Emmens, the Chief Executive Officer and Angus Russell, the Chief Financial Officer of Shire plc (the Registrant), each certifies that, to the best of his knowledge:

1. the Report fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and

2. the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Registrant.

Dated: March 1, 2007

/s/ Matthew Emmens

Matthew Emmens
Chief Executive Officer

/s/ Angus Russell

Angus Russell
Chief Financial Officer

Expert Opinion

informa
healthcare

Review of long-acting stimulants in the treatment of attention deficit hyperactivity disorder

Richard H Weisler
Duke University Medical Center, Durham, NC and the Univeristy of North Carolina at Chapel Hill Departments of Psychiatry, Suite 125, 700 Spring Forest Road, Raleigh, NC 27609, USA

A number of long-acting medications for the treatment of attention deficit hyperactivity disorder (ADHD) have recently been developed and approved for use in the US. These compounds are intended to optimize and maintain ADHD symptom control throughout the day, while eliminating problems associated with short-acting medications, such as the need for in-school, midday or multiple daily doses. Recent reports confirm that the safety and tolerability of long-acting medications are similar to those of short-acting medications, although long-acting medications appear to have a lower risk of abuse and diversion and may be associated with significant improvements in medication adherence. Distinctions can be made among the long-acting medications with regard to the onset, magnitude and duration of their clinical effects. Recognition of these differences is important for individualizing treatment for patients with ADHD.

Keywords: atomoxetine, attention deficit hyperactivity disorder, methylphenidate, mixed amfetamine salts, psychostimulants

Expert Opin. Pharmacother. (2007) 8(6):745-758

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is among the most common neurobehavioral disorders, estimated to affect 5 – 10% of children and 2 – 6% of adults [1-3]. ADHD symptoms compromise functioning in school and work settings, social and peer interactions, and family relationships [3,4]. Compared with community or control samples, children and adolescents with untreated ADHD are at higher risk of accidental injury, low grade-point averages in school, dropping out of school and – for those with comorbid conduct disorders – antisocial behavior, such as setting fires [4]. Likewise, adults with ADHD are at greater risk for psychopathology (mood disorders and psychosis, anxiety disorders, developmental disorders and substance use disorders, including nicotine dependence) than are healthy controls or those in the community [5], as well as for receiving lower work-performance ratings and being involved in at-fault car accidents [4]. These findings indicate that, regardless of patient age, the ongoing treatment of ADHD is crucial to managing symptoms and to helping improve functioning.

Psychostimulants have been used for > 40 years to treat ADHD and are the recommended first-line pharmacologic treatment for this disorder [6]. Until fairly recently, prescription stimulants were limited to short-acting, immediate-release (IR) formulations, requiring patients to take two or three doses each day to manage their symptoms. The need for multiple daily dosing raised practical challenges, such as the management of in-school, midday dosing for children [7]. In addition, the greater possibility of drug misuse/diversion with short-acting versus long-acting stimulants [8,9] is of concern, especially considering recent data revealing the relatively easy accessibility of amfetamines on high school and college campuses [101,10]. However, and perhaps most importantly, the use of a short-acting stimulant that must be taken in multiple

daily doses fosters poor treatment adherence, often leads to discontinuation after only several months of treatment [11,12] and yields suboptimal therapeutic benefits.

In response to these limitations, new, long-acting stimulant formulations have been developed, approved and added to the armamentarium rapidly over the last several years. A long-acting nonstimulant, atomoxetine (ATM), with once-daily dosing and minimal abuse potential, is also available for the treatment of ADHD. These formulations and new compounds have gradually become widely prescribed by healthcare providers.

Are the long-acting stimulant formulations really equivalent to their short-acting counterparts, only longer acting? Do they indeed result in better adherence, a lower risk of abuse and improved outcomes? What role does the long-acting nonstimulant ATM warrant in the ADHD armamentarium? This review attempts to address these questions, comparing and contrasting efficacy, tolerability, and safety of the available long-acting stimulants and the nonstimulant ATM with those of short-acting agents and of one another, where direct comparative evidence exists.

2. Methylphenidate

Four long-acting oral methylphenidate (MPH) formulations (Ritalin® LA: MPH long-acting [MPH LA], Novartis Pharmaceuticals Corporation; Metadate® CD: MPH controlled delivery [MPH CD], CellTech Pharma Ltd; Concerta®: osmotic, controlled-release MPH [OROS MPH], ALZA; Focalin XR™: dexmethylphenidate extended-release [dMPH XR], Novartis Pharmaceuticals Corporation) and one transdermal formulation (Daytrana™: MPH transdermal system [MTS], Shire US Inc.) are approved for use in the US, and contain the same active ingredient. In general, all long-acting MPH formulations exhibit bimodal plasma drug concentration–time profiles and higher trough values than those seen with short-acting MPH formulations. For this discussion, clinical data for MPH LA and MPH CD will be considered together, as the drug delivery systems and modified-release mechanisms of these two products are essentially identical.

2.1 Methylphenidate extended-release capsules

Both MPH LA and MPH CD (corresponding products available in Europe are Medikinet® retard, by Medice; and Equasym® retard by Celltech Pharmaceuticals) are soluble capsules containing a mixture of IR and enteric-coated, delayed-release MPH beads. MPH LA contains 50% IR and 50% extended-release (ER) beads; MPH CD contains 30% IR and 70% ER beads. With early-morning dosing, both of these formulations produce bimodal plasma concentration–time profiles [13-16] marked by a rapid rise in drug concentrations in the morning hours, a slower and smaller rise again during the early afternoon and a decline throughout the rest of the day. In this way, both of these long-acting formulations approximate the plasma drug concentration–time profile seen with twice-daily administration of MPH IR.

2.2 OROS methylphenidate tablets

OROS MPH is a tablet with 22% of the MPH dose in the IR overcoat and the remainder in the core tablet, which dissolves slowly via an osmotic pump process [17]. OROS MPH exhibits a biphasic plasma drug concentration–time profile marked by a rapid increase after morning dosing, a continuing increase into the afternoon, and slowly decreasing drug levels throughout the remaining daytime hours. In a 2002 study of adults by Gonzalez *et al.*, the AUC was similar with OROS MPH 18 mg/day (41.8 ng/h/ml) and MPH IR 5 mg t.i.d. (38.0 ng/h/ml) [17]. In another study [18], a linear dose-response effect was observed such that up to 75% of subjects demonstrated clinically significant reductions on the Attention Deficit/Hyperactivity Disorder Rating Scale – version IV (ADHD-RS-IV) scores at the 36- or 54-mg doses versus the 18-mg dose.

2.3 Dexmethylphenidate extended-release capsules

dMPH XR is a long-acting formulation of the *d-threo* enantiomer of racemic MPH. As dMPH lacks the clinically inactive enantiomer of racemic MPH, typically half the usual MPH dose is necessary for clinical benefit to be seen [19,20]. dMPH XR is a capsule formulation that, as with MPH LA, consists of a mixture of 50% IR beads and 50% enteric-coated, delayed-release beads. The plasma drug concentration–time profile is bimodal and is similar to that seen with twice-daily dosing of dMPH IR [20].

2.4 Methylphenidate transdermal system

The MTS was recently approved by the FDA for the full-day treatment of ADHD in children 6 – 12 years of age. It uses DOT Matrix® technology [21], whereby concentrated drug cells are evenly dispersed within an adhesive layer on the patch. A multipolymeric, adhesive matrix enables continuous absorption of dMPH from the skin into the bloodstream [21]. The MTS patch is designed to provide continuous MPH delivery over a 12-h period. Because transdermal delivery results in less first-pass metabolism of both the d- and l-MPH isomers than occurs through oral administration, a dose delivered via MTS will yield greater drug exposure compared with the same dose delivered orally. A 12.5-cm^2 patch provides 10 mg MPH and yields exposure of dMPH over 12 h equivalent to that seen with 18 mg OROS MPH. Moreover, the rate of MPH delivery and absorption is increased with temperature and during application to inflamed skin. For patients transitioning from an oral MPH formulation to MTS, given the differences in MPH isomer bioavailability between the transdermal and oral formulations, the manufacturer advises using the same titration schedule as for MPH-naive patients (e.g., beginning with the 10-mg dose patch and increasing the dose by 5 mg at weekly intervals until adequate clinical response is achieved) [21]

2.5 Efficacy of long-acting methylphenidate products: overview

Table 1 provides an overview of the clinical efficacy and safety trials of long-acting medications included in the present review. These trials show that long-acting MPH formulations are more effective than placebo at improving core ADHD symptoms [22-31]. For example, in a double-blind trial, after 2 weeks of treatment with MPH LA 10 – 40 mg/day, children aged 6 – 14 years showed a 10.7-point decrease in the Conners' ADHD Teacher Rating Scale versus a 2.8-point decrease with placebo, and 70% of children given MPH LA were considered much improved or very much improved versus 40% on placebo [25]. Similar positive findings have been seen in numerous trials evaluating other long-acting MPH formulations [22-31]. In laboratory school investigations, long-acting MPH formulations exhibited sustained efficacy superior to that of placebo 10 – 12 h after morning dosing [32-34]. Symptom control similar in magnitude and duration to that seen with an oral MPH formulation (e.g., OROS MPH) has been reported more recently with the newly available MTS [30,31]. In a randomized, placebo-controlled, 7-week trial in children with ADHD [31], MTS and OROS MPH produced similar, statistically significant reductions from baseline in ADHD-RS-IV scores versus placebo ($p < 0.0001$ for both comparisons). MTS and OROS MPH also significantly improved Clinical Global Impression-Improvement ratings (73% and 67%, respectively) compared with patients given placebo [31]. Although they were not directly compared with one another, outcomes with MTS and OROS MPH appeared to be largely comparable.

In all MPH trials so far, the safety and tolerability profiles of the long-acting formulations also appeared to be comparable to those of their short-acting counterparts, with the most common adverse events being headache, insomnia, abdominal pain, decreased appetite and weight loss. In addition to the adverse effects typically associated with stimulants, minor application-site irritation is the most commonly reported adverse event with MTS [21].

In real-world clinical practice, evidence suggests that the efficacy of long-acting MPH medications may be superior to that of bioequivalent doses of short-acting MPH; this may be explained by better adherence to the medication regimen or by smaller fluctuations in plasma drug concentrations across the day. Steele *et al.* compared the efficacy of short- versus long-acting MPH in a randomized, real-world effectiveness trial [35]. Children aged 6 – 12 years old with ADHD (n = 143), attending an out-patient clinic, were randomized to receive either OROS MPH daily in the morning or usual care with MPH IR for 8 weeks. Although prescribed end point doses were comparable between the two treatment groups, 84% of patients in the MPH IR group reported missing doses compared with 54% of the OROS MPH group. Remission (defined as a score of 0 or 1 on all items of the Swanson, Nolan and Pelham Rating Scale version IV [SNAP-IV]) for ADHD and oppositional defiant disorder [36]) was achieved by 44% of patients given OROS MPH versus 16% of those given MPH IR, and scores on the SNAP-IV decreased by ~ 50% versus 34% with MPH IR ($p = 0.004$) [36]. In the 24-month Multimodal Treatment Study of Children with ADHD, similar superiority in terms of remission rates (although of lesser magnitude) for OROS MPH over MPH IR was seen even with the rigorous application of three daily doses of an MPH IR regimen (37 versus 28%, respectively). [37] Such results indicate that both the high rate of nonadherence to MPH IR and the rapid fluctuations in plasma drug levels with three-times-daily dosing of MPH IR may account for the lagging therapeutic results observed with these formulations, compared with those seen with long-acting medications.

Relatively few head-to-head, controlled, clinical trials comparing long-acting MPH formulations have been conducted so far [23,32-34,37,38]. Notable are the COMACS study, which compared MPH CD and OROS MPH given to children aged 6 – 14 years with ADHD in a laboratory school setting [23,32] and a direct pharmacokinetic comparative study [38]. With regard to pharmacokinetics, Markowitz *et al.* observed higher peak concentrations and more plasma drug concentration variability with MPH LA versus OROS MPH, which showed a smoother drug delivery profile [38]. In the COMACS study, plasma drug concentrations were monitored over 12 h postdose, and behavioral ratings were obtained using the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) scale [39], among other devices, at intervals throughout the day as the children participated in a school-like routine. Differences in pharmacokinetics with OROS MPH and MPH CD appeared to have a significant impact on magnitude, timing and/or duration of clinical benefits with MPH CD and OROS MPH [32]. At any given time point, the best behavioral control was seen with the drug that had the highest plasma MPH concentration. For the morning hours, superior symptom control was seen with MPH CD, which delivers 30% of its total dose in a rapidly absorbed bolus. For 1.0 – 7.5 h postdose, overall better average behavioral control was seen with MPH CD. By contrast, OROS MPH yielded better symptom control in the latter part of the day and early evening. This late-day symptom control was in line with the timing of gradual delivery of 78% of the OROS MPH dose throughout the afternoon hours (Figure 1) [32]. Such studies indicate that subtle, but potentially important differences exist between long-acting MPH formulations, with regard to timing, magnitude and duration of optimal clinical effects. Evidence so far is still limited regarding the new MTS delivery system. However, the timing and magnitude of symptom control appear to be similar to those seen with OROS MPH [31]. Although all of the MPH formulations may be effective, inherent differences allow for treatment to be tailored to individual patient needs.

Table 1. Clinical safety and efficacy trials reviewed in the current discussion .

Trial	Duration	Treatment (dose/day)		Baseline patient age
Methylphenidate (n = 1456)				
Biederman (2003) [22]	2 weeks	Placebo MPH LA (10 – 40 mg)	n = 71 n = 66	Range 6 – 14 Mean 8.8
Sonuga-Barke (2004) [23]	3 weeks	Placebo MPH CD (20, 40, 60 mg) OROS MPH (18, 36, 54 mg)	n = 184*	Range 6 – 12 Mean NA
Hoare (2005) [24]	52 weeks	OROS MPH (18 – 54 mg)	n = 89	Range 6 – 16 Mean NA
Wilens (2006) [25]	2 weeks	Placebo OROS MPH (18 – 72 mg)	n = 90 n = 87	Range 13 – 18 Mean 14.6
Biederman (2006) [26]	6 weeks	Placebo OROS MPH (mean: 80.9 mg)	n = 77 n = 72	Range 19 – 60 Mean NA
Greenhill (2005) [27]	7 weeks	Placebo dMPH ER (5 – 30 mg)	n = 48 n = 49	Range 6 – 17 Mean NA
Silva (2005) [28]	6 weeks	Placebo MPH ER (20, 40 mg) OROS MPH (18, 36 mg)	n = 53*	Range 6 – 12 Mean 9.4
Adler (2005) [29]	29 weeks	Placebo dMPH ER (20 – 40 mg) MPH	n = 221 n = NA n = NA	Range ≥18 Mean NA
McGough (2006) [30]	6 weeks	Placebo MTS (10 – 27 mg)	n = 38 n = 41	Range 6 – 12 Mean 9.1
Melmed (2006) [31]	7 weeks	Placebo OROS MPH (18 – 54 mg) MTS (10 – 30 mg)	n = 85 n = 89 n = 96	Range 6 – 12 Mean NA
Mixed amfetamine salts (n = 2229)				
McCracken (2003) [44]	7 weeks	Placebo MAS (10 mg) MAS XR (10 – 30 mg)	n = 51*	Range 6 – 12 Mean 9.5
Spencer (2005) [45]	24 weeks	MAS XR (10 – 60 mg)	n = 138	Range 13–17 Mean 14.4
Weisler (2006) [46]	4 weeks	Placebo MAS XR (20 – 60 mg)	n = 60 n = 188	Range 18 – 76 Mean 39.2
Spencer (2006) [47]	4 weeks	Placebo MAS XR (10 – 40 mg)	n = 52 n = 226	Range 13 – 17 Mean 14.2
Biederman (2005) [48]	104 weeks	MAS XR (20 – 60 mg)	n = 221	Range 18 – 76 Mean 39.8
McGough (2005) [49]	104 weeks	MAS XR (10 – 30 mg)	n = 568	Range 6 – 12 Mean 8.7
Goodman (2005) [50]	10 weeks	MAS XR (10 – 60 mg)	n = 725	Range NA Mean 36.9
D-amfetamine XR (n = 35)				
James (2001) [53]	8 weeks	MAS (5 – 30 mg) *d*-amp IR (5 – 30 mg) *d*-amp XR (5 – 30 mg)	n = 35*	Range 7 – 12 Mean 9.1

ATM: Atomoxetine; CD: Controlled delivery; ER: Extended release; IR: Immediate release; LA: Long acting; MAS XR: Mixed amfetamine salts extended release; MPH: Methylphenidate; NA: Not available; OROS: Osmotic, controlled-release.

*Crossover design.

Table 1. Clinical safety and efficacy trials reviewed in the current discussion (continued).

Trial	Duration	Treatment (dose/day)		Baseline patient age
Atomoxetine (n = 3635)				
Michelson (2003) [59]	10 weeks	Placebo ATM (60 – 120 mg)	n = 266 n = 270	Range ≥18 Mean 41.2
Spencer (1998) [60]	7 weeks	Placebo ATM (mean: 76 mg)	n = 22*	Range 19 – 60 Mean 34.0
Spencer (2002) [61]	9 weeks	Placebo ATM (≤60 mg) MPH (≤90 mg)	n = 124 n = 129 n = 38	Range 7 – 13 Mean 9.8
Michelson (2002) [62]	6 weeks	Placebo ATM (1.0 or 1.5 mg/kg)	n = 85 n = 85	Range 6 – 16 Mean 10.5
Weiss (2005) [63]	7 weeks	Placebo ATM (up to 1.8 mg/kg)	n = 52 n = 101	Range 8 – 12 Mean 9.9
Kelsey (2004) [64]	8 weeks	Placebo ATM (up to 1.8 mg/kg)	n = 64 n = 133	Range 6 – 12 Mean 9.5
Adler (2005)[67]	97 weeks	ATM (up to 160 mg)	n = 384	Range NA Mean 42.4
Kratochvil (2002) [67]	10 weeks	MPH ATM	n = 44 n = 184	Range 7 – 15 Mean 10.4
Kemner (2005) [68]	3 weeks	OROS MPH (18 – 72 mg) ATM (10 – 80 mg)	n = 850 n = 473	Range 6 – 12 Mean 8.9
McGough (2005) [69]	NA	MAS XR (NA) ATM (NA)	n = 33 n = 38	Range 7 – 12 Mean NA
Biederman (2006) [70]	18 days	MAS XR (30 mg) ATM (1.2 mg/kg)	n = 26 n = 31	Range 6 – 12 Mean 8.7
Wigal (2005) [71]	3 weeks	MAS XR (30 mg) ATM (1.2 mg/kg)	n = 102 n = 101	Range 6 – 12 Mean 8.7

ATM: Atomoxetine; CD: Controlled delivery; ER: Extended release; IR: Immediate release; LA: Long acting; MAS XR: Mixed amfetamine salts extended release; MPH: Methylphenidate; NA: Not available; OROS: Osmotic, controlled-release.

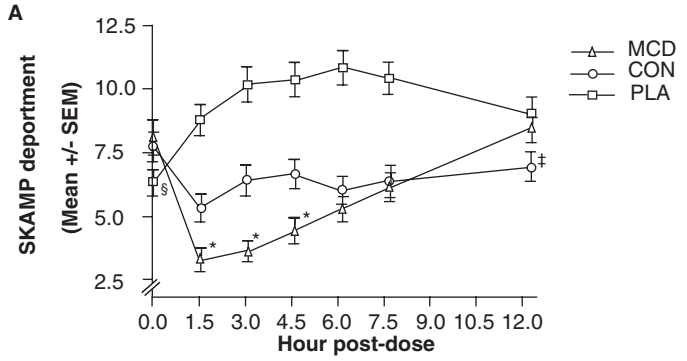
*Crossover design.

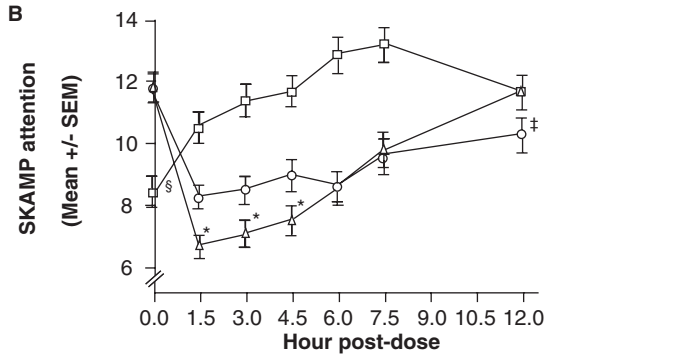
3. Mixed amfetamine salts

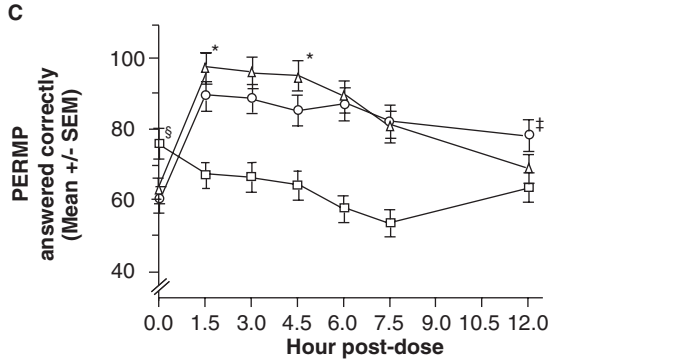
Mixed amfetamine salts extended release (MAS XR; Adderall XR®, Shire Pharmaceuticals, Inc.) is a mixture of neutral salts of dextroamfetamine sulfate, amfetamine sulfate, the dextro isomer of amfetamine saccharate, and D,L-amfetamine aspartate. It is formulated as a capsule that contains 50% IR beads and 50% slow-release beads that deliver active drug ~ 4 h after ingestion. Pharmacokinetic studies of MAS XR for adolescents (Figure 2) [40] and adults [41,42] show that a single dose of this agent (10 – 40 mg) yields a dose-proportional, linear plasma concentration-time profile. Moreover, absorption and plasma concentration of each active component of MAS XR do not appear to be altered over time if the beads are sprinkled over apple sauce or if administered in the fasted or fed state [41].

The efficacy of MAS XR for ADHD symptoms has been demonstrated in short-term, placebo-controlled trials, with clear evidence of dose-related symptom improvement [43-47]. In a 3-week, placebo-controlled trial with children 6 – 12 years of age with ADHD [43], statistically significant ($p < 0.001$) symptom improvement was apparent within 1 week with MAS XR 10 – 30 mg/day versus placebo; at end point, dose-related, statistically significant ($p < 0.001$) decreases from baseline were seen in Conners' Global Index Scale – Teacher version scores (5.3 to 6.4 points). Similar dose-related improvements have been reported in other short-term trials with children, adolescents, and adults with ADHD [44,46,47]; the dose-response of efficacy may be a function of illness severity, such that patients with more severe cases of ADHD experience significantly greater improvements with the higher doses of MAS XR [46,47].

As with other psychostimulant medications for ADHD, the efficacy of MAS XR is maintained with long-term use [45,48-50]. In a 6-month, open-label study of MAS XR 10 – 60 mg/day for adolescents with ADHD [45], mean ADHD-RS-IV scores were decreased from baseline by an average of 7.9 points. In a similar open-label, 2-year study among adults given MAS XR 10 – 60 mg/day [48],







Effect size at each hour post-dose							
	0.0	1.5	3.0	4.5	6.0	7.5	12.0
SKAMP deportment							
MCD	-0.23	0.82	0.89	0.80	0.76	0.54	0.06
CON	-0.18	0.52	0.50	0.50	0.66	0.51	0.25
SKAMP attention							
MCD	-0.59	0.70	0.72	0.66	0.65	0.50	0.00
CON	-0.58	0.41	0.48	0.42	0.64	0.53	0.20
PERMP number correct							
MCD	-0.27	0.57	0.56	0.59	0.58	0.50	0.10
CON	-0.33	0.42	0.42	0.40	0.54	0.53	0.28

Figure 1. Efficacy of placebo, OROS MPH, and MPH CD, based on SKAMP deportment and attention scores and math test scores 0 – 12 h postdose. SKAMP deportment **(A)**, SKAMP Attention **(B)**, and number correct on PERMP (Permanent Product) math test **(C)** among children given OROS MPH (CON), MPH CD (MCD) or placebo (PLA). The corresponding effect sizes for MCD and CON at each session are shown in the table.

SWANSON JM, WIGAL SB, WIGAL T *et al.*: A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs Study). *Pediatrics* (2004) **113**(3 Pt 1):e206-e216 [32]. Copyright 2004 by the American Academy of Pediatrics. Reprinted by Permission of the American Academy of Pediatrics.

* Times at which MCD was significantly better than CON.

‡ Times at which CON was significantly better than MCD and PLA.

§ Times at which PLA was significantly better than both MCD and CON.

CD: Controlled delivery; MPH: Methylphenidate; OROS: Osmotic, controlled-release; SKAMP: Swanson, Kotkin, Agler, M-Flynn and Pelham.

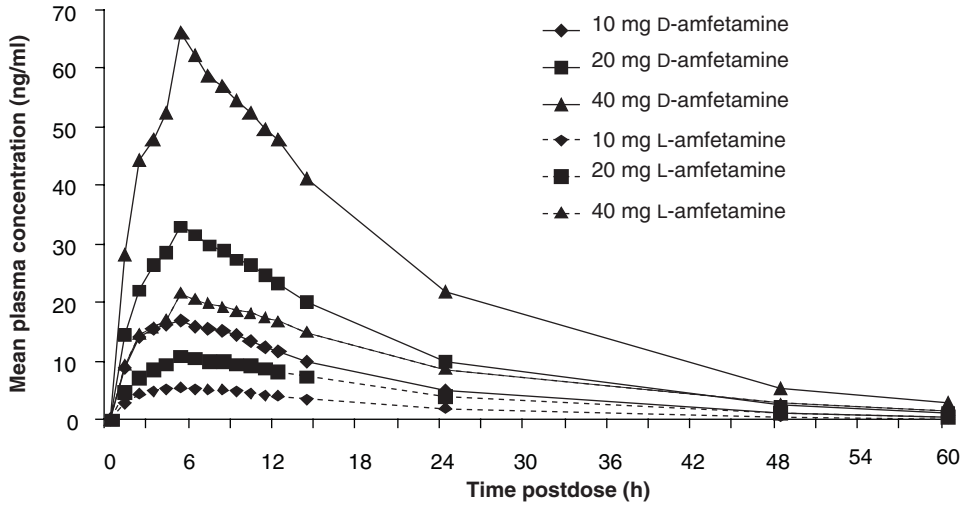


Figure 2. Plasma drug concentration – time profile of *D*-amfetamine and *l*-amfetamine with various doses of mixed amfetamine salts extended release, in adolescents with attention deficit hyperactivity disorder.

KRAMER WG, READ SC, TRAN BV *et al.*: Pharmacokinetics of mixed amphetamine salts extended release in adolescents with ADHD. *CNS Spectr.* 2005 10(Suppl.15):6-13. Copyright 2005 by MBL Communications. Reprinted by Permission of MBL Communications [40].
MAS XR: Mixed amfetamine salts extended release.

ADHD-RS-IV scores were decreased from baseline by an average of 7.2 points. In these and other long-term studies [49,50], efficacy was maintained with no need for dose escalation; in the study by Spencer *et al.* [45] most participants (> 80%) were receiving MAS XR 20 – 40 mg/day at study end.

The most common adverse events associated with MAS XR are decreased appetite/anorexia, headache, weight loss, insomnia and nervousness [45,48,49], which are in line with events expected following the administration of psychostimulant agents. The safety and tolerability of MAS XR are, thus, similar to those of its short-acting counterpart and of other long-acting stimulants [37]; MAS XR also demonstrates minimal cardiovascular effects following long-term use in otherwise healthy adults with ADHD [51].

4. Dextroamfetamine extended release

A long-acting, ER formulation of dextroamfetamine (dAMPH XR; Spansule®, GlaxoSmithKline) is now available in the US, as tablets or capsules, for the treatment of ADHD [52]. In adults, the bioavailability of dAMPH is comparable between a 15-mg XR capsule and three 5-mg doses of the short-acting formulation. Maximum plasma concentration occurs at ~ 3 h postdose, and the $t_{½}$ of dAMPH XR is ~ 12 h [52]. Published information regarding the efficacy and safety of dAMPH XR in ADHD is very limited. One of the few reports identified compared the efficacy of dAMPH XR capsules with that of dAMPH IR and MAS IR for children with ADHD [53]. Using a three-way, crossover design, the investigators found that behavior ratings and measures of locomotor activity were improved with all three drugs up to 12 h after morning dosing. However, in the morning hours, dAMPH XR was less effective than dAMPH IR and MAS IR. Certain measures, including parent behavior ratings, showed more improvement with dAMPH XR than with dAMPH IR and MAS IR during the latter part of the observation day [53]. Safety and tolerability of dAMPH XR appear to be similar to those of short-acting formulations and common adverse events, such as decreased appetite, insomnia and irritability, are consistent with those of other psychostimulants. In the study by James *et al.*, mild weight loss and decreased sleep duration were seen significantly more often with dAMPH XR than with placebo ($p = 0.001$ for both) [53].

5. Lisdexamfetamine dimesilate

Lisdexamfetamine (LDX) was recently approved by the FDA and is awaiting Drug Enforcement Agency scheduling for the treatment of ADHD. It is a pharmacologically inactive prodrug in which D-amfetamine is bound to L-lysine; the bond is severed via metabolism, leading to a gradual release of pharmacologically active D-amfetamine. This compound is thought to be comparable in efficacy and tolerability to once-daily stimulants, but has reduced potential for abuse diversion or overdose toxicity because the lysine binding cannot be broken synthetically. A pharmacokinetic comparison of LDX and D-amfetamine determined that the maximum plasma concentration values of LDX after nasal inhalation and

intravenous administration were 96 and 75% lower, respectively, than for D-amfetamine [54]. Available data on LDX suggest it has efficacy and adverse-event profiles similar to MAS XR and a lower abuse potential than other stimulants [55,56].

6. Atomoxetine

Atomoxetine (ATM; Strattera®, Eli Lilly and Company) differs from other medications used for the management of ADHD in that it is not a psychostimulant, but rather is believed to exert its therapeutic effects via highly specific blockade of the noradrenergic presynaptic transporter. Given the different mechanism of action of ATM from that of psychostimulants, symptom improvement may not begin until after 7 – 10 days of treatment, or longer. Its subjective effects also differ from those of psychostimulants, and it is not associated with abuse or diversion; therefore, it is not designated as a controlled substance in the US. The pharmacokinetic profile of ATM is marked by rapid initial absorption, achievement of the C_{max} after 2 h, and a $t_{½}$ of ~ 5 h. In addition, absorption and clearance do not appear to be affected by food [57,58]. Because metabolism of ATM is influenced by CYP2D6 and is genetically determined, individuals are either extensive or poor metabolizers. Dosage adjustments may be needed for patients who are poor metabolizers and for patients taking other medications, such as fluoxetine and paroxetine, which inhibit the CYP2D6 enzymatic pathway. Drug exposure may be increased by 5- to 10-fold under such circumstances [57], and because of potential toxicity, it should not be co-administered with a monoamine oxidase inhibitor.

Efficacy of once- or twice-daily dosing of ATM for ADHD has been shown in placebo-controlled trials with children, adolescents, and adults [59-64]. Children and adolescents given 0.5 – 1.5 mg/kg/day ATM once-daily for 6 weeks showed an average 12.8-point decrease in ADHD-RS-IV scores from baseline versus a 5.0-point decrease with placebo [62]. Symptom improvement was not limited to one symptom dimension, as subscale scores for inattentiveness and impulsivity were reduced by similar degrees [62]. A graded dose-response effect was observed in another pediatric study, whereby the 0.5-mg/kg/day dose was associated with lower rates of efficacy than the 1.2-mg/kg/day and 1.5-mg/kg/day doses [65]. Similar positive findings have been reported with twice-daily ATM (25 – 60 mg b.i.d.) for adults with ADHD [59,66]. Recent findings for children with ADHD suggest that despite the short half-life of ATM, symptom control may extend into the evening hours and predose morning hours, based on parent ratings of behavior 12 – 22 h after morning dosing [64]. The efficacy of ATM appears to be maintained with long-term treatment (up to 97 weeks) [66].

Conflicting evidence has been reported regarding the relative efficacy of ATM and psychostimulants [67-71]. A randomized, 10-week, open-label trial with children [67] detected no significant differences in efficacy, based on the ADHD-RS-IV, between ATM and short-acting MPH. ATM resulted in a 19.0-point decrease in ADHD-RS-IV scores from baseline, and MPH was associated with a 17.8-point decrease. In this study, symptom improvement continued up to 8 weeks after ATM treatment initiation [67]. In contrast, a number of head-to-head trials of ATM versus long-acting stimulants suggest that ADHD symptom improvement throughout the day with ATM is of lesser magnitude and duration than with stimulants. In a 3-week, community-based, randomized, open-label study of children with ADHD, the efficacy of OROS MPH and ATM was compared [68]. At study end, decreases from baseline in ADHD-RS-IV scores were greater with OROS MPH than with ATM, and significantly ($p < 0.001$) more participants given OROS MPH exhibited treatment response, with a > 25% decrease from baseline in ADHD-RS-IV scores. Other comparative studies between ATM and long-acting stimulants have yielded similar findings [69-71]. In an 18-day, randomized, laboratory school investigation of children with ADHD, who had baseline Clinical Global Impression-Severity scores indicating marked or severe impairment and who were given MAS XR [69], 82% exhibited improvement from baseline on the SKAMP deportment and attention scores at end point, whereas only 34% of those given ATM displayed such an improvement. However, McGough *et al*. [69] observed that patients who exhibited relatively less severe ADHD symptoms at baseline demonstrated a more robust response to ATM than patients with relatively greater baseline ADHD symptom severity. In a separate laboratory classroom investigation [71], MAS XR was also found to exert significantly ($p < 0.0001$) better symptom control over the 12-h postdose period than did ATM (Figure 3).

The safety and tolerability profile of ATM is in line with that expected for an agent that modulates noradrenergic tone and, in general, is similar to those of psychostimulants. A slight decrease in weight and small increases in heart rate and blood pressure have been reported [66,72]. No changes in QT interval have been observed. Other commonly reported adverse events with ATM treatment include, upper abdominal pain, transient vomiting, dyspepsia, dizziness, decreased appetite, headache and erectile dysfunction. Suicidal ideation has been reported in a small number of pediatric patients treated with ATM in clinical trials (5 out of 1347 patients, all < 12 years of age) [57], and, although no patients given ATM in these trials committed suicide, physicians are instructed to alert parents or caregivers to this potential and to watch for unusual changes in behavior of children treated with ATM [49]. Rare cases of severe liver injury have also been reported with ATM [57].

7. Conclusion

Long-acting stimulant medications used to treat ADHD are generally as effective as, and possibly more effective than, short-acting medications. ATM is an effective nonstimulant

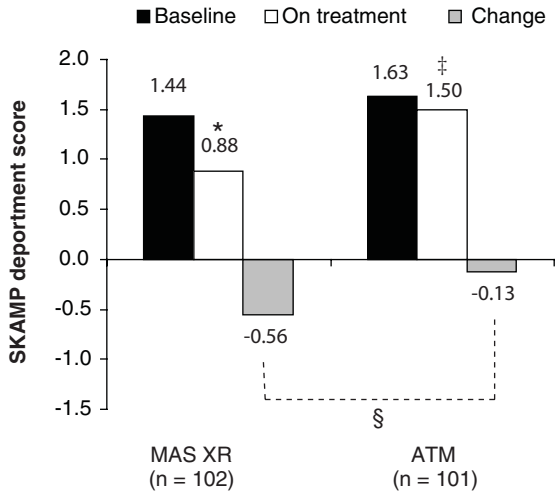


Figure 3. SKAMP deportment scores with MAS XR versus ATM in children with ADHD. SKAMP attention and SKAMP deportment scores up to 12 h following administration of MAS XR or ATM to children 6 – 12 years of age. 'On treatment' indicates average of scores obtained across 3 weeks of active treatment.

WIGAL SB, MCGOUGH JJ, MCCRACKEN JT *et al.*: A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. *J. Atten. Disord.* 2005 **9** (1): 275-289, Copyright 2005 by Sage Publications, Inc. Reprinted by Permission of Sage Publications [71].

ADHD: Attention deficit hyperactivity disorder; ATM: Atomoxetine; MAS XR: Mixed amfetamine salts extended release; SKAMP: Swanson, Kotkin, Agler, M-Flynn and Pelham.

* $p < 0.0001$.

‡ $p = 0.0496$ compared with baseline score based on a 1-sample t test.

§ $p < 0.0001$ comparing treatment effect of MAS XR with ATM is based on ANCOVA; the ANCOVA model included treatment (MAS XR and ATM), site, and corresponding baseline scores as the covariate.

alternative to stimulant treatments. The comparative efficacy of ATM relative to long-acting psychostimulants has been widely studied, but remains unclear. Improvements in efficacy with long-acting stimulant formulations may be accounted for by both pharmacokinetic and behavioral factors. With long-acting stimulants, trough plasma drug concentrations tend to be higher than with short-acting stimulants, and the biphasic drug concentration profile that broadly mimics twice-daily dosing of short-acting stimulants (marked by 2 phases of rapid absorption spaced ~ 4 – 6 h apart) ensures better symptom control during the drug absorption phase. A once-daily treatment regimen, regardless of whether it consists of a stimulant or a nonstimulant, may also lead to improved efficacy, as patients who use such medications show improved compliance, miss fewer doses, and adhere to treatment over a longer period of time [34,36]. There is a lower risk of abuse/diversion with long-acting than with short-acting medications. Tolerability may also be slightly improved with some long-acting formulations, as drug absorption occurs in a more gradual fashion, and associated adverse events are similar in nature and frequency to those seen with their short-acting counterparts.

8. Expert opinion

Whereas short-acting medications may be useful for some patients for initial dosage-adjustment purposes, long-term symptom management appears to be best undertaken for most patients with a long-acting, once-daily medication. Our review of the literature indicates that long-acting stimulants for the treatment of ADHD are at least as effective as short-acting stimulants and the nonstimulant ATM. Long-acting medications exhibit pharmacokinetic and behavioral profiles that would be expected to offer significant therapeutic benefits for 9 – 12 h following a single morning dose. Recent reports indicate that superior efficacy with long- versus short-acting stimulants may be expected in real-world clinical settings, attributable to both better patient adherence and less variable plasma drug concentration profiles [73-75].

Because of its nonstimulant nature and low abuse potential, ATM is useful for patients who should not (e.g., history of recent drug abuse or other contraindications) or cannot tolerate a stimulant medication. ATM offers the advantages of once-daily dosing, but it is unclear whether its therapeutic effects are as robust or long-lasting as those of long-acting stimulant medications. Because improvements may continue to escalate through 8 weeks of ATM treatment [68], short-term comparative studies may not have been of sufficient duration to compare efficacy adequately between the different treatments. Moreover, certain subsets of patients may respond differently to ATM; those who are less impaired exhibit a more robust response than those who may be severely impaired [69]. To better define the factors that may account for these differences in efficacy, further investigations with longer treatment periods and larger sample sizes are needed. Such studies may help physicians to better select patients who would be likely to respond optimally to ATM and to adjust their own and their patients' expectations about when maximal therapeutic benefits might be expected to emerge with this drug.

The safety and tolerability of long-acting psychostimulants are well characterized and appear to be at least comparable to those of short-acting stimulants. All of the long-acting medications reviewed here offer effective and well-tolerated symptom control for the majority of patients with ADHD, while eliminating the need for multiple daily doses, the social stigma linked to midday in-school dosing, and the potential for dose skipping by adult patients who may fail to perceive their need for symptom control.

Moreover, from an abuse/diversion risk perspective, there is greater concern with short-acting than with long-acting medications. The LDX prodrug formulation of D-amfetamine offers additional advantages in that blood levels of the compound are significantly reduced after intranasal and intravenous administration when abused; in addition, blood levels are reported as being reduced after overdose because of

the rate-limiting step of lysine cleavage. The MTS formulation can be placed or removed at any time and delivers drugs at a constant rate over the dosing period. This allows for greater flexibility than is possible with oral formulations, with regard to timing the onset and offset of drug delivery, and is a valuable option for patients who cannot swallow pills. However, this flexibility may be a limitation for older children or adolescents with oppositional defiant disorder, who may remove the patch at will.

Although psychostimulants are generally well tolerated, they are not appropriate for all patients. In 2006, the FDA placed a warning on the labeling of all psychostimulant compounds, stating that stimulants should not be used in children or adults with structural cardiac abnormalities based on rare cases of sudden death associated with stimulants given at usual doses. Psychostimulants should be used with caution in patients with other major medical or psychiatric conditions, such as psychosis, epilepsy or history of seizures, heart disease, hypertension, hypothyroidism, or any condition that might be compromised by an increase in blood pressure or heart rate. In general, adults being treated with any stimulant medication should undergo routine blood pressure and heart rate monitoring.

Although similar precautions must also be exercised with ATM [76,77], this agent also carries other significant safety risks, notably including an early, transient increase in suicidal ideation and a small risk of liver toxicity; both of these potential consequences warrant closer monitoring per FDA guidance for visit frequency, particularly during the first several months of ATM treatment. Any signs or symptoms of liver injury, including unexplained flu-like symptoms, should be investigated appropriately [53].

The various technologies that give rise to the ER characteristics of the long-acting psychostimulant formulations also make it necessary for physicians to be fully aware of the prescribing information for each psychostimulant formulation before prescribing treatment. For example, the long-acting OROS MPH formulation should be used with caution in patients with gastrointestinal conditions that compromise the ability to swallow or with conditions that alter motility or transit time, since the time-release characteristics depend on the osmotic-release mechanism of the slowly dissolving tablet. Such caution is not necessary with the use of capsule formulations, which contain polymer-coated beads that can be sprinkled on food. Furthermore, acid-reducing or acid-suppressing agents interact in opposing ways with MPH LA and amfetamine compounds. Specifically, the modified-release characteristics of MPH LA are pH dependent; acid-suppressing agents, such as proton pump inhibitors or antacid medications, would be likely to decrease or further slow down drug absorption. By contrast, absorption of amfetamines is enhanced with acid-suppressing or alkalinizing agents and should not be co-administered with MAS or d-AMP agents.

Whether long-acting medications improve adherence and health outcomes has not yet been addressed fully. Emerging data indicate that patient adherence may range from modestly to dramatically higher with long-acting treatments [11,73,75]. In their recent report based on a retrospective claims analysis of patients prescribed OROS MPH or MPH IR, Kemner and Lage found that fewer patients who were prescribed OROS MPH had 30-day gaps in their medication supplies (77 versus 95%), and fewer patients switched medications (27 versus 68%) [73]. Moreover, those taking OROS MPH stayed on treatment nearly twice as long (199 days) as did those prescribed MPH IR (108 days). Lage and Hwang also described superior health outcomes with OROS MPH over those with MPH IR, marked by decreased emergency room visits and fewer injuries [74].

Clinicians should recognize that long-acting medication regimens can improve outcomes for patients with ADHD only to a certain extent. Specific patient and psychosocial factors are likely also to play a strong, perhaps even primary role in determining treatment success. With school-age children, researchers have found that those who are younger at the time of diagnosis have more teacher-rated symptoms, are not diagnosed with comorbid oppositional defiant disorder, and experience less psychosocial adversity, are the most likely to continue with stimulant treatment [71]. For older children and those with parents or siblings who also have ADHD or other psychiatric morbidity and/or familial dysfunction, optimal outcomes are unlikely to be achieved without the initiation of a family-based treatment plan. However, the greater ease of a long-acting medication regimen for ADHD may help bring even such at-risk patients and their families to a point where they can participate productively in behavioral and psychosocial intervention plans. Clinicians should be increasingly alert to using improved medication adherence as a springboard for implementing multidisciplinary therapeutic approaches for patients who would otherwise not experience optimal treatment outcomes.

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Review of long-acting stimulants in the treatment of attention deficit hyperactivity disorder

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Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

ABSTRACT

This practice parameter describes the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder (ADHD) based on the current scientific evidence and clinical consensus of experts in the field. This parameter discusses the clinical evaluation for ADHD, comorbid conditions associated with ADHD, research on the etiology of the disorder, and psychopharmacological and psychosocial interventions for ADHD. *J. Am. Acad. Child Adolesc. Psychiatry*, 2007;46(7):894–921. **Key Words:** attention-deficit/hyperactivity disorder, evaluation, treatment, practice parameter.

Attention-deficit/hyperactivity disorder (ADHD; American Psychiatric Association, 2000) is one of the most common childhood psychiatric conditions. It has been the focus of a great deal of scientific and clinical study during the past century. Upon reviewing the voluminous literature on ADHD, the American Medical Association's Council on Scientific Affairs (Goldman et al., 1998) commented, "Overall, ADHD is one of the best-researched disorders in medicine, and the overall data on its validity are far more compelling than for many medical conditions." Although scientists and clinicians debate the best way to diagnose and treat ADHD, there is no debate among competent and well-informed health care professionals that ADHD is a valid neurobiological condition that causes significant impairment in those whom it afflicts. These guidelines seek to lay out evidence-based guidelines for the effective diagnosis and treatment of ADHD.

In this parameter, the term *preschoolers* refers to children ages 3 through 5 years, the term *children* refers to children ages 6 through 12 years, and the term *adolescents* refers to minors ages 13 through 17 years. *Parent* refers to parent or legal guardian. *Patient* refers to any minor with ADHD. The terminology in this practice parameter is consistent with that of *DSM-IV-TR* (American Psychiatric Association, 2000).

METHODOLOGY

The list of references for this parameter was developed by searching *PsycINFO*, *Medline*, and *Psychological Abstracts*; by reviewing the bibliographies

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This parameter was developed by Steven Pliszka, M.D., principal author, and the AACAP Work Group on Quality Issues: William Bernet, M.D., Oscar Bukstein, M.D., and Heather J. Walter, M.D., Co-Chairs; Valerie Arnold, M.D., Joseph Beitchman, M.D., R. Scott Benson, M.D., Allan Chrisman, M.D., Tiffany Farchione, M.D., John Hamilton, M.D., Helene Keable, M.D., Joan Kinlan, M.D., Jon McClellan, M.D., David Rue, M.D., Ulrich Schoettle, M.D., Jon A. Shaw, M.D., and Saundra Stock, M.D. AACAP Staff: Kristin Kroeger Ptakowski and Jennifer Medicus.

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From July 2006 to September 2006, this parameter was reviewed by a Consensus Group convened by the Work Group on Quality Issues. Consensus Group members and their constituent groups were as follows: Work Group on Quality Issues (Oscar Bukstein, M.D., Allan Chrisman, M.D., R. Scott Benson, M.D., and John Hamilton, M.D.), Topic Experts (Larry Greenhill, M.D., and Russell Barkley, Ph.D.), AACAP Work Group on Research (Larry Greenhill, M.D.), AACAP Assembly of Regional Organizations (Joan Gerring, M.D., and Guy Palmes, M.D.), and AACAP Council (Cynthia W. Santos, M.D., and Catherine Jaselskis, M.D.).

Disclosures of potential conflicts of interest for authors and Work Group chairs are provided at the end of the parameter. Disclosures of potential conflicts of interest for all other individuals named above are provided on the AACAP Web site on the Practice Information page.

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of book chapters and review articles; by asking colleagues for suggested source materials; and from the previous version of this parameter. The searches were conducted from September 2004 through April 2006 for articles in English using the key word "attention-deficit/hyperactivity disorder." The search covered the period 1996 to 2006 and yielded approximately 5,000 references. Recent authoritative reviews of literature, as well as recent treatment studies that were in press or presented at scientific meetings in the past 2 to 3 years, were given priority for inclusion. The titles and abstracts of the remaining references were reviewed for particular relevance and selected for inclusion when the reference appeared to inform the field on the diagnosis and/or treatment of ADHD.

EPIDEMIOLOGY AND CLINICAL COURSE

Recently, epidemiological studies have more precisely defined the prevalence of ADHD and the extent of its treatment with medication. Rowland et al. (2002) surveyed more than 6,000 parents of elementary school children in a North Carolina county. Ten percent of the children had been given a diagnosis of ADHD and 7% were taking medication for ADHD. Parents of 2,800 third through fifth graders were surveyed in Rhode Island; 12% of parents reported that their child had been referred for evaluation and 6% were receiving medication (Harel and Brown, 2003). An epidemiological study of nearly 6,000 children in Rochester, MN, found a cumulative incidence of ADHD in the elementary and secondary school population of 7.5% (95% confidence interval 6.5–8.4; Barbaresi et al., 2002), which was similar to a 6.7% prevalence of ADHD found by the U.S. National Health Interview Survey for the period 1997–2000 (Woodruff et al., 2004). The Centers for Disease Control and Prevention (2005) conducted the National Survey of Children's Health during January 2003–2004, asking parents of more than 100,000 children ages 4 to 17 years whether their child had ever been diagnosed with ADHD or received medication treatment (as opposed to currently being treated). The rate of lifetime childhood diagnosis of ADHD was 7.8%, whereas 4.3% (or only 55% of those with ADHD) had ever been treated with medication for the disorder.

Follow-up studies have begun to delineate the life course of ADHD. A majority (60%–85%) of children with ADHD will continue to meet criteria for the disorder during their teenage years (Barkley et al., 1990; Biederman et al., 1996; Claude and Firestone, 1995), clearly establishing that ADHD does not remit with the onset of puberty alone. Defining the number of children with ADHD who continue to have problems as adults is more difficult because of methodological issues reviewed by Barkley (2002). These include changes in informant (parent versus child), use of different instruments to diagnose ADHD in adults, comorbidity of the other psychiatric disorders in the childhood sample (less comorbid samples have better outcome), and issues with the *DSM-IV* diagnostic criteria themselves. The criteria are designed for school-age children with regard to the number of symptoms required to meet the diagnostic threshold (i.e., six of the nine symptoms for inattention and/or hyperactivity/impulsivity), which may be developmentally inappropriate for adults. That is, an adult may suffer significant impairment even though he or she suffers from fewer than six of nine symptoms in these areas. The persistence of the full syndrome of ADHD in young adulthood has been found to range from 2% to 8% when self-report is used (Barkley et al., 2002; Mannuzza et al., 1993). In contrast, when parent report is used, the prevalence increases to 46% and when a developmental definition of disorder is used (98th percentile), it increases further to 67% (Barkley et al., 2002). Biederman et al. (2000) found that the rates of ADHD in adults varied according to number of symptoms and level of impairment required for the diagnostic threshold. Although only 40% of 18- to 20-year-old "grown up" ADHD patients met the full criteria for ADHD, 90% had at least five symptoms of ADHD and a Global Assessment of Functioning score below 60. Faraone and Biederman (2005) performed telephone interviews with 966 adults and the prevalence of ADHD using narrow criteria (those who met full criteria and had childhood onset) was 2.9%, but 16.4% had subthreshold symptoms. Furthermore, adults with a childhood history of ADHD have higher than expected rates of antisocial and criminal behavior (Barkley et al., 2004), injuries and accidents (Barkley, 2004), employment and marital difficulties, and health problems and are more likely to have teen pregnancies (Barkley et al., 2006) and children out of

wedlock (Johnston, 2002). Recently, the National Comorbidity Survey Replication screened a probability sample of 3,199 individuals ages 19 to 44 years and estimated the prevalence of adult ADHD to be 4.4% (Kessler et al., 2005). Although this practice parameter concerns the assessment and treatment of the preschooler, child, or adolescent with ADHD, it is critical to note that many children with ADHD will continue to have impairment into adulthood that will require treatment.

COMORBIDITIES

It is well established that ADHD frequently is comorbid with other psychiatric disorders (Pliszka et al., 1999). Studies have shown that 54%–84% of children and adolescents with ADHD may meet criteria for oppositional defiant disorder (ODD); a significant portion of these patients will develop conduct disorder (CD; Barkley, 2005; Faraone et al., 1997). Fifteen percent to 19% of patients with ADHD will start to smoke (Milberger et al., 1997) or develop other substance abuse disorders (Biederman et al., 1997). Depending on the precise psychometric definition, 25%–35% of patients with ADHD will have a coexisting learning or language problem (Pliszka et al., 1999), and anxiety disorders occur in up to one third of patients with ADHD (Biederman et al., 1991; MTA Cooperative Group, 1999b; Pliszka et al., 1999; Tannock, 2000). The prevalence of mood disorder in patients with ADHD is more controversial, with studies showing 0% to 33% of patients with ADHD meeting criteria for a depressive disorder (Pliszka et al., 1999). The prevalence of mania among patients with ADHD remains a contentious issue (Biederman, 1998; Klein et al., 1998). The National Institute of Mental Health (NIMH) Multimodal Treatment of ADHD (MTA) study (Jensen et al., 2001a) did not find it necessary to exclude any child with ADHD because of a diagnosis of bipolar disorder, but Biederman et al. (1992) found that 16% of a sample of ADHD patients met criteria for mania, although a chronic, irritable mania predominated. Comorbidity in adult ADHD patients is similar to that of children, except that antisocial personality replaces ODD or CD as the main behavioral psychopathology and mood disorders increase in prevalence (Biederman, 2004). Clinicians should be prepared to encounter a wide range of psychiatric symptoms in the course of managing patients with ADHD.

ETIOLOGY

Neuropsychological studies have shown that patients with ADHD have deficits in executive functions that are "neurocognitive processes that maintain an appropriate problem solving set to attain a future goal" (Willcutt et al., 2005). Specifically, a meta-analysis of 83 studies with more than 6,000 subjects showed that patients with ADHD have impairments in the executive functioning domains of response inhibition, vigilance, working memory, and some measures of planning (Willcutt et al., 2005). Nonetheless, not all patients with ADHD show executive function deficits, suggesting that although these deficits are a major factor in the disorder, other neuropsychological problems must be present as well. There is growing evidence that the principal cause of ADHD is genetic (Faraone et al., 2005b). Faraone et al. (2005b) reviewed 20 independent twin studies that estimated the heritability (the amount of phenotypic variance of symptoms attributed to genetic factors) to be 76%. Recent genome scan studies suggest ADHD is complex; ADHD has been associated with markers at chromosomes 4, 5, 6, 8, 11, 16, and 17 (Muenke, 2004; Smalley et al., 2004). Faraone et al. (2005b) identified eight genes in which the same variant was studied in three or more studies; seven of which showed statistically significant evidence of association with ADHD (the dopamine 4 and 5 receptors, the dopamine transporter, the enzyme dopamine β-hydroxylase, the serotonin transporter gene, the serotonin 1B receptor, and the synaptosomal-associated protein 25 gene). Nongenetic causes of ADHD are also neurobiological in nature (Nigg, 2006), consisting of such factors as perinatal stress and low birth weight (Mick et al., 2002b), traumatic brain injury (Max et al., 1998), maternal smoking during pregnancy (Mick et al., 2002a), and severe early deprivation (Kreppner et al., 2001). In the latter case, the deprivation must be extreme, as often occurs in institutional rearing or child maltreatment; there is no evidence that ordinary variations in child-rearing practices contribute to the etiology of ADHD.

Neuroimaging is a valuable research tool in the study of ADHD, but it is not useful for making a diagnosis of

ADHD in clinical practice or in predicting treatment response (Zametkin et al., 2005). Children with ADHD have reduced cortical white and gray matter volume relative to controls, although there is much overlap between the groups. Furthermore, such volume deficits are more pronounced in treatment-naïve children with ADHD than in those who have received long-term medication treatment (Castellanos et al., 2002). Sowell et al. (2003) also found decreased frontal and temporal lobe volume in children with ADHD relative to controls; gray matter deficits have also been found in the unaffected siblings of children with ADHD (Durston et al., 2004). Although the functional imaging of ADHD is in a preliminary stage, it has been shown that when patients with ADHD perform tasks requiring inhibitory control, differences in brain activation relative to controls have been found in the caudate, frontal lobes, and anterior cingulate (Bush et al., 2005).

RECENT ADVANCES IN TREATMENT

At the time of publication of the first AACAP practice parameter for ADHD in 1997 (American Academy of Child and Adolescent Psychiatry, 1997), the literature devoted to the treatment of ADHD was already voluminous. Stimulant treatment of ADHD was also the subject of an AACAP practice parameter (American Academy of Child and Adolescent Psychiatry, 2002). Most of that literature focused on the short-term treatment of ADHD, either with medication or psychosocial interventions. At the time of the first parameter, the intensive study of the pharmacokinetics and pharmacodynamics of stimulant medications was undertaken, pioneered by the group at the University of California at Irvine. Analog classroom settings were used to examine the hour-by-hour effects of stimulant medications on behavior and cognition and its relationship to serum stimulant medications (Swanson et al., 1998b, 2002b). Such studies lead to the development of Concerta (Swanson et al., 1999a, 1998b, 2000, 2002a, 2003), Adderall XR (Greenhill et al., 2003; McCracken et al., 2003), Metadate CD (Swanson et al., 2004; Wigal et al., 2003), and Focalin (Quinn et al., 2004).

Subsequently, numerous large-scale clinical trials prove the efficacy of these new agents (Biederman et al., 2002; Greenhill et al., 2002, 2005; McCracken et al., 2003; Pelham et al., 1999; Wigal et al., 2005; Wolraich, 2000; Wolraich et al., 2001) and atomoxetine (Michelson et al., 2001, 2003). A methylphenidate transdermal patch (Findling and Lopez, 2005; Pelham et al., 2005) has been recently approved for use. With these newer agents, efficacy has been established by rigorous, double-blind, placebo-controlled, multicenter trials. Longer term, open-label studies of these agents, often lasting up to 2 years, have also been performed, giving the field more data about efficacy and safety after prolonged use.

The role of psychosocial interventions in the treatment of ADHD has also been much studied. The NIMH MTA study (MTA Cooperative Group, 1999a, 2004a) and the Multimodal Psychosocial Treatment study (M+MPT, also known as the New York/Montreal study; Klein et al., 2004) have examined the unitary and combined effects of pharmacological and behavioral treatments on ADHD symptoms and its associated impairments in social and academic functioning. The MTA study has completed naturalistic follow-ups of their patients up to 22 months after ending the active study treatment phase (Jensen, 2005; Swanson, 2005). These large-scale, long-term, randomized clinical trials have greatly informed the field as to the efficacy of long-term medication treatment and the role of psychosocial interventions in ADHD. In particular, answers to the question of when ADHD should be treated with pharmacological or behavioral therapy (or a combination of the two) can be based on empirical evidence.

EVIDENCE BASE FOR PRACTICE PARAMETERS

The AACAP develops both patient-oriented and clinician-oriented practice parameters. Patient-oriented parameters provide recommendations to guide clinicians toward the best treatment practices. Treatment recommendations are based both on empirical evidence and clinical consensus, and are graded according to the strength of the empirical and clinical support. Clinician-oriented parameters provide clinicians with the information (stated as principles) needed to develop practice-based skills. Although empirical evidence may be available to support certain principles, principles are primarily based on expert opinion and clinical experience.

In this parameter, recommendations for best treatment practices are stated in accordance with the

strength of the underlying empirical and/or clinical support, as follows:

- [MS] *Minimal Standard* is applied to recommendations that are based on rigorous empirical evidence (e.g., randomized, controlled trials) and/or overwhelming clinical consensus. Minimal standards apply more than 95% of the time (i.e., in almost all cases).
- [CG] *Clinical Guideline* is applied to recommendations that are based on strong empirical evidence (e.g., nonrandomized, controlled trials) and/or strong clinical consensus. Clinical guidelines apply approximately 75% of the time (i.e., in most cases).
- [OP] *Option* is applied to recommendations that are acceptable based on emerging empirical evidence (e.g., uncontrolled trials or case series/reports) or clinical opinion, but lack strong empirical evidence and/or strong clinical consensus.
- [NE] *Not Endorsed* is applied to practices that are known to be ineffective or contraindicated.

The strength of the empirical evidence is rated in descending order as follows:

- [rct] *Randomized, controlled trial* is applied to studies in which subjects are randomly assigned to two or more treatment conditions.
- [ct] *Controlled trial* is applied to studies in which subjects are nonrandomly assigned to two or more treatment conditions.
- [ut] *Uncontrolled trial* is applied to studies in which subjects are assigned to one treatment condition.
- [cs] *Case series/report* is applied to a case series or a case report.

SCREENING

Recommendation 1. Screening for ADHD Should Be Part of Every Patient's Mental Health Assessment [MS].

In any mental health assessment, the clinician should screen for ADHD by specifically asking questions regarding the major symptom domains of ADHD (inattention, impulsivity, and hyperactivity) and asking whether such symptoms cause impairment. These screening questions should be asked regardless of the nature of the chief complaint. Rating scales or specific questionnaires containing the *DSM* symptoms of ADHD can also be included in clinic/office registration materials to be completed by parents before visits or in the waiting room before the evaluation. If a parent reports that the patient suffers from any symptoms of ADHD that induce impairment or if the patient scores in the clinical range for ADHD symptoms on a rating scale, then a full evaluation for ADHD as set out in the next recommendation is indicated.

EVALUATION

Recommendation 2. Evaluation of the Preschooler, Child, or Adolescent for ADHD Should Consist of Clinical Interviews With the Parent and Patient, Obtaining Information About the Patient's School or Day Care Functioning, Evaluation for Comorbid Psychiatric Disorders, and Review of the Patient's Medical, Social, and Family Histories [MS].

The clinician should perform a detailed interview with the parent about each of the 18 ADHD symptoms listed in *DSM-IV*. For each symptom, the clinician should determine whether it is present as well as its duration, severity, and frequency. Age at onset of the symptoms should be assessed. The patient must have the required number of symptoms (at least six of nine of the inattention cluster and/or at least six of nine of the hyperactive/impulsive criteria, each occurring more days than not), a chronic course (symptoms do not remit for weeks or months at a time), and onset of symptoms during childhood. After all of the symptoms are assessed, the clinician should determine in which settings impairment occurs. Because most patients with ADHD have academic impairment, it is important to ask specific questions about this area. This is also an opportunity for the clinician to review the patient's academic/intellectual progress and look for symptoms of learning disorders (see Recommendation 4). Presence of impairment should be distinguished from presence of symptoms. For instance, a patient's ADHD symptoms may be observable only at school but not at home. Nonetheless, if the patient must spend an inordinate amount of time completing schoolwork in the evening that was not done in class, then impairment is present in two settings. *DSM-IV* requires impairment in at least two settings (home, school, or job) to meet criteria for the disorder, but clinical consensus agrees that severe impairment in one setting warrants treatment.

After reviewing the ADHD symptoms, the clinician should interview the parent regarding other common

psychiatric disorders of childhood. In general, it is most logical to next gather data from the parent regarding ODD and CD. Then, the clinician should explore whether the patient has symptoms of depression (and associated neurovegetative signs), mania, anxiety disorders, tic disorders, substance abuse, and psychosis, or evidence of a learning disability. Other practice parameters of the AACAP contain specific recommendations on eliciting symptoms of these disorders in children and adolescents (see also Recommendation 5).

The parent should complete one of the many standardized behavior rating scales that have well-established normative values for children of a wide range of ages and genders. Scales in common use are listed in Table 1. These scales not only yield a measure of ADHD behaviors but also tap into other psychiatric symptoms that could be comorbid with ADHD or may suggest an alternative psychiatric diagnosis. It is advisable for the clinician to request a release of information from the parent to obtain a similar rating scale from the patient's teacher(s). It is important to note that such rating scales do not by themselves diagnose ADHD, although parent or teacher ratings of inattention or hyperactivity/impulsivity that fall in the upper fifth percentile for the patient's age and gender are reason for serious concern. If the teacher cannot provide such a rating scale or the parent declines permission to contact the school, then materials from school, such as work samples or report cards, should be reviewed or inquired about.

Family history and family functioning should be assessed. Because ADHD is highly heritable, a high prevalence of ADHD is likely to be found among the patient's parents and siblings. Family history of other significant mental disorders (affective, anxiety, tic, or CD) is helpful in determining the nature of any

TABLE 1

Common Behavior Rating Scales Used in the Assessment of ADHD and Monitoring of Treatment

Name of Scale	Reference
Academic Performance Rating Scale (APRS)	The APRS is a 19-item scale for determining a child's academic productivity and accuracy in grades 1–6 that has 6 scale points; construct, concurrent, and discriminant validity data as well as norms (n = 247) available (Barkley, 1990).
ADHD Rating Scale-IV	The ADHD Rating Scale-IV is an 18-item scale using *DSM-IV* criteria (DuPaul et al., 1998).
Brown ADD Rating Scales for Children, Adolescents, and Adults	Psychological Corporation, San Antonio, TX (*www.drthomasebrown.com/assess_tools/index.html*) (Brown, 2001)
Child Behavior Checklist (CBCL)	Parent-completed CBCL and Teacher-completed Teacher Report Form (TRF) *www.aseba.org/index.html*
Conners Parent Rating Scale–Revised (CPRS-R)[a]	Parent and adolescent self-report versions available (Conners, 1997)
Conners Teacher Rating Scale–Revised (CTRS-R)[a]	Conners, 1997
Conners Wells Adolescent Self-Report Scale	Conners and Wells, 1997
Home Situations Questionnaire–Revised (HSQ-R), School Situations Questionnaire–Revised (SSQ-R)	The HSQ-R is a 14-item scale designed to assess specific problems with attention and concentration across a variety of home and public situations; it uses a 0–9 scale and has test-retest, internal consistency, construct validity, discriminant validity, concurrent validity, and norms (n = 581) available (Barkley, 1990).
Inattention/Overactivity With Aggression (IOWA) Conners Teacher Rating Scale	The IOWA Conners is a 10-item scale developed to separate the inattention and overactivity ratings from oppositional defiance (Loney and Milich, 1982)
Swanson, Nolan, and Pelham (SNAP-IV) and SKAMP Internet site ADHD.NET	The SNAP-IV (Swanson, 1992) is a 26-item scale that contains *DSM-IV* criteria for ADHD and screens for other *DSM* diagnoses; the SKAMP (Wigal et al., 1998) is a 10-item scale that measures impairment of functioning at home and at school.
Vanderbilt ADHD Diagnostic Parent and Teacher Scales	Teachers rate 35 symptoms and 8 performance items measuring ADHD symptoms and common comorbid conditions (Wolraich et al., 2003a). The parent version contains all 18 ADHD symptoms, with items assessing comorbid conditions and performance (Wolraich et al., 2003b).

Note: ADHD = attention-deficit/hyperactivity disorder.

[a] The longer form should be used for initial assessment, whereas the shorter form is often used for assessing response to treatment, particularly when repeated administration is required.

comorbid disorders, although a comorbid disorder should not be diagnosed solely on the basis of a family history of that comorbid disorder. Social history of the family should be examined. Because patients with ADHD perform better in structured settings, any factors in the family that create an inconsistent, disorganized environment may further impair the patient's functioning. Information regarding any physical or psychological trauma the patient may have experienced (including multiple visits to the emergency room) should be gathered as well as any current psychosocial stressors.

The clinician should obtain information about the patient's perinatal history, developmental milestones, medical history, and mental health history (especially any previous psychiatric treatment). Delays in reaching developmental milestones or in social/language development suggest language disorders, mental retardation, or pervasive developmental disorders. Assessment of developmental milestones is particularly important in the evaluation of the preschooler because many developmental disorders are associated with attention problems and hyperactivity.

The clinician should next interview the child or adolescent. For the preschool or young school-age child (5–8 years old), this interview may be done concurrently with the parent interview. Older children and adolescents should be interviewed separately from parents, as older children and teenagers may not reveal significant symptoms (depression, suicide, or drug or alcohol abuse) in the presence of a parent. Clinicians should be prepared to conduct a separate interview even with a younger child in many clinical situations, such as if the patient appears at risk of abuse or there is evidence of significant family dysfunction. The primary purpose of the interview with the child or adolescent is not to confirm or refute the diagnosis of ADHD. Young children are often unaware of their symptoms of ADHD, and older children and adolescents may be aware of symptoms but will minimize their significance. The interview with the child or adolescent allows the clinician to identify signs or symptoms inconsistent with ADHD or suggestive of other serious comorbid disorders. The clinician should perform a mental status examination, assessing appearance, sensorium, mood, affect, and thought processes. Through the interview process, the clinician develops a sense of whether the patient's vocabulary, thought processes, and content of thought are age-appropriate. Marked disturbances in mood, affect, sensorium, or thought process suggest the presence of psychiatric disorders other than or in addition to ADHD.

Recommendation 3. If the Patient's Medical History Is Unremarkable, Laboratory or Neurological Testing Is Not Indicated [NE].

There are few medical conditions that "masquerade" as ADHD, and the vast majority of patients with ADHD will have an unremarkable medical history. Children suffering a severe head injury may develop symptoms of ADHD, usually of the inattentive subtype. Encephalopathies generally produce other neurological symptoms (language or motor impairment) in addition to inattention. Hyperthyroidism, which can be associated with hyperactivity and agitation, rarely presents with ADHD symptoms alone but with other signs and symptoms of excessive thyroid hormone levels. The measurement of thyroid levels and thyroid-stimulating hormone should be considered only if symptoms of hyperthyroidism other than increased activity level are present. Exposure to lead, either prenatally or during development, is associated with a number of neurocognitive impairments, including ADHD (Lidsky and Schneider, 2003). If a patient has been raised in an older, inner-city environment where exposure to lead paint or plumbing is probable, then serum lead levels should be considered. Serum lead level should not be part of routine screening. Children with fetal alcohol syndrome or children exposed in utero to other toxic agents have a higher incidence of ADHD than the general population (O'Malley and Nanson, 2002).

Unless there is strong evidence of such factors in the medical history, neurological studies (electroencephalography [EEG], magnetic resonance imaging, single-photon emission computed tomography [SPECT], or positron emission tomography [PET]) are not indicated for the evaluation of ADHD. Specifically, the Council on Children, Adolescents, and Their Families of the American Psychiatric Association has warned against the exposure of children to intravenous radioactive nucleotides as part of the diagnosis or treatment of childhood psychiatric disorders, citing both a lack of evidence of validity and safety issues (*http://www.psych.org/psych_pract/clin_issues/populations/children/SPECT.pdf*).

Recommendation 4. Psychological and Neuropsychological Tests Are Not Mandatory for the Diagnosis for ADHD, but Should Be Performed if the Patient's History Suggests Low General Cognitive Ability or Low Achievement in Language or Mathematics Relative to the Patient's Intellectual Ability [OP].

Low scores on standardized testing of academic achievement frequently characterize ADHD patients (Tannock, 2002). The clinician must determine whether the academic impairment is secondary to the ADHD, if the patient has ADHD and a learning disorder, or if the patient has only a learning disorder and the patient's inattentiveness is secondary to the learning disorder. Academic impairment is commonly due to the ADHD itself. Many months or years of not listening in class, not mastering material in an organized fashion, and not practicing academic skills (not doing homework, etc.) leads to a decline in achievement relative to the patient's intellectual ability. If the parent and teacher report that the patient performs at (or even above) grade level on subjects when given one-to-one supervision (a patient can do all of the problems on a test when held in from recess), then a formal learning disorder is less likely. In some cases, the patient may engage in leisure activities that require the skill (e.g., reading science fiction novels) but avoid reading a history book in preparation for an exam. In such cases, it is more appropriate to treat the ADHD and then determine whether the academic problems begin to resolve as the patient is more attentive in learning situations. However, if there is no clear evidence of an improvement in academic performance in 1 to 2 months despite improvement of the ADHD, then psychological testing for learning disorders is indicated.

In other cases, symptoms of learning/language disorders are present that cannot be accounted for by ADHD. These include deficits in expressive and receptive language, poor phonological processing, poor motor coordination, or difficulty grasping fundamental mathematical concepts. In such cases, psychological testing will be needed to identify whether these deficits are related to a specific learning disorder. In the vast majority of cases, these learning disorders will be comorbid with the ADHD, and it is recommended strongly that the patient's ADHD be optimally treated before such testing. It could then be firmly concluded that any deficits identified are clearly the result of a learning disorder and not due to inattention to the test materials.

Purely learning-disordered patients are often inattentive when struggling with material in the area of their disability (a reading-disordered patient is inattentive when he or she must read) but do not have problems outside such a restricted academic setting. Patients with learning disorders alone do not show symptoms of impulsivity or hyperactivity. Children and adolescents with learning disorders may be oppositional with regard to schoolwork, and the clinician is consulted as to whether ADHD is the cause of the oppositional behavior. If a careful interview shows the absence of full criteria for ADHD and if the emergence of the oppositional behavior is clearly correlated with academic demands, then a primary learning disorder is more likely.

Psychological testing of the ADHD patient usually consists of a standardized assessment of intellectual ability (IQ) to determine any contribution of low general cognitive ability to the academic impairment, and academic achievement. Neuropsychological testing, speech-language assessments, and computerized testing of attention or inhibitory control are not required as part of a routine assessment for ADHD, but may be indicated by the findings of the standard psychological assessment.

Recommendation 5. The Clinician Must Evaluate the Patient With ADHD for the Presence of Comorbid Psychiatric Disorders [MS].

The clinician must integrate the data obtained with regard to comorbid symptoms to determine whether the patient meets criteria for a separate comorbid disorder in addition to ADHD, the comorbid disorder is the primary disorder and the patient's inattention or hyperactivity/impulsivity is directly caused by it, or the comorbid symptoms do not meet criteria for a separate disorder but represent secondary symptoms stemming from the ADHD.

When patients with ADHD meet full *DSM-IV* criteria for a second disorder, the clinician should generally assume the patient has two or more disorders and develop a treatment plan to address each comorbid disorder in addition to the ADHD. Children with ADHD commonly meet criteria for ODD or CD. In young children these disorders are nearly always present concurrently. Similarly, if a patient meets full *DSM-IV* criteria for major depressive disorder or a specific anxiety disorder, the clinician is most likely dealing

with a comorbid disorder. Most often, the onset of the depressive disorder occurs several years after the onset of ADHD (Spencer et al., 1999), whereas anxiety disorders have an earlier onset concurrent with the ADHD (Kovacs and Devlin, 1998). A comorbid diagnosis of mania should be considered in ADHD patients who exhibit severe mood lability/elation/irritability, thought disturbances (grandiosity, flight of ideas), severe aggressive outbursts ("affective storms"), and decreased need for sleep or age-inappropriate levels of sexual interest. Mania should not be diagnosed solely on the basis of the severity of the ADHD symptoms or aggressive behavior in the absence of the manic symptoms listed above. Acutely manic ADHD patients generally require mood stabilization before treatment of the ADHD. The choice of a treatment regimen, particularly pharmacological intervention, is often influenced by the nature of the patient's comorbid disorder and which disorder is currently the most impairing of major life activities. Older adolescents with ADHD should be screened for substance abuse disorders, as they are at greater risk than teenagers without ADHD for smoking and alcohol and other illegal substance abuse disorders (Biederman et al., 1997; Wilens et al., 1997).

In other cases, another primary psychiatric disorder produces impairment of attention or impulse control. Impaired attention is caused by primary depressive/anxiety disorders, and those with primary mania have impaired impulse control and judgment. If a patient has no history of ADHD symptoms during childhood but develops inattentiveness and poor concentration only after the onset of depression or mania, then the affective disorder is most likely primary. Patients with adolescent-onset ODD or CD are often described as impulsive or inattentive, but often do not meet full criteria for ADHD or had few ADHD symptoms in early childhood.

Finally, some associated problems may stem from the ADHD itself and not be a separate disorder. Patients with ADHD may develop associated symptoms of dysphoria or low self-esteem secondary to the frustrations of living with ADHD. In such cases, the dysphoria is related specifically to the ADHD symptoms and there is an absence of pervasive depression, neurovegetative signs, or suicidal ideation. If such dysphoria is a result of the ADHD, then it should respond to successful treatment of the ADHD. The distractibility or impulsivity of ADHD patients may often be interpreted as oppositional behavior by caretakers or children. Mild mood lability (shouting out, crying easily, quick temper) is also common in ADHD. It is important to note that such associated symptoms do not reach the level of a separate *DSM* disorder; are temporally related to the onset of the ADHD; are often consistent with, although somewhat excessive, for the social context; and dissipate once the ADHD is successfully treated.

TREATMENT

Recommendation 6. A Well-Thought-Out and Comprehensive Treatment Plan Should Be Developed for the Patient With ADHD [MS].

The patient's treatment plan should take account of ADHD as a chronic disorder and may consist of psychopharmacological and/or behavior therapy. This plan should take into account the most recent evidence concerning effective therapies as well as family preferences and concerns. This plan should include parental and child psychoeducation about ADHD and its various treatment options (medication and behavior therapy), linkage with community supports, and additional school resources as appropriate. Psychoeducation is distinguished from psychosocial interventions such as behavior therapy. Psychoeducation is generally performed by the physician in the context of medication management and involves educating the parent and child about ADHD, helping parents anticipate developmental challenges that are difficult for ADHD children, and providing general advice to the parent and child to help improve the child's academic and behavioral functioning. The treatment plan should be reviewed regularly and modified if the patient's symptoms do not respond. Trade books, videos, and some noncommercial Web sites on ADHD may be useful adjunctive material to facilitate this step of treatment.

The short-term efficacy of psychopharmacological intervention for ADHD was well established at the time of the first AACAP practice parameter for ADHD (American Academy of Child and Adolescent Psychiatry, 1997). It is also clear that behavior therapy alone can produce improvement in ADHD symptoms relative to baseline symptoms or to wait-list controls (Pelham et al., 1998). Since then, a substantial focus has

been on the relative efficacy of pharmacological therapy versus psychosocial intervention. Jadad et al. (1999) reviewed 78 studies of the treatment of ADHD; six of these studies compared pharmacological and nonpharmacological interventions. The reviewers reported that studies consistently supported the superiority of stimulant over the nondrug treatment. Twenty studies compared combination therapy with a stimulant or with psychosocial intervention, but no evidence of an additive benefit of combination therapy was found. Most of these studies involved short-term behavioral treatment; a major hypothesis in the early 1990s was that behavior therapy had to be administered for an extended time for patients with ADHD to realize its full benefit (Richters et al., 1995). Thus, the MTA study was designed to look at comprehensive treatments provided over an entire year.

In the MTA study, children with ADHD were randomized to four groups: algorithmic medication treatment alone, psychosocial treatment alone, a combination of algorithmic medication management and psychosocial treatment, and community treatment. Algorithmic medication treatment consisted of monthly appointments in which the dose of medication was carefully titrated according to parent and teacher rating scales. Children in all four treatment groups showed reduced symptoms of ADHD at 14 months relative to baseline. The two groups that received algorithmic medication management showed a superior outcome with regard to ADHD symptoms compared with those that received intensive behavioral treatment alone or community treatment (MTA Cooperative Group, 1999a [rct]). Those who received behavioral treatment alone were not significantly more improved than the group of community controls who received community treatment (two thirds of the subjects in this group received stimulant treatment). The community treatment group had more limited physician follow-up and was treated with lower daily doses of stimulant compared with the algorithmic medication management group. Nearly one fourth of the subjects randomized to receive behavioral treatment alone required treatment with medication during the trial because of a lack of effectiveness of the behavioral treatment. It seems established that a pharmacological intervention for ADHD is more effective than a behavioral treatment alone.

This does not mean, however, that behavior therapy alone cannot be pursued for the treatment of ADHD in certain clinical situations. Behavior therapy may be recommended as an initial treatment if the patient's ADHD symptoms are mild with minimal impairment, the diagnosis of ADHD is uncertain, parents reject medication treatment, or there is marked disagreement about the diagnosis between parents or between parents and teachers. Preference of the family should also be taken into account. A number of behavioral programs for the treatment of ADHD have been developed. Since the review by Pelham et al. (1998), a number of other controlled studies have shown short-term effectiveness of behavioral parent training (Chronis et al., 2004; Sonuga-Barke et al., 2001 [rct], 2002 [rct]). Several manual-based treatments for applying behavioral parent training to ADHD and ODD children are available (Barkley, 1997; Cunningham et al., 1997). Smith et al. (2006) provided an overview of the principles behind such programs. In general, parents are involved in 10 to 20 sessions of 1 to 2 hours in which they (1) are given information about the nature of ADHD, (2) learn to attend more carefully to their child's misbehavior and to when their child complies, (3) establish a home token economy, (4) use time out effectively, (5) manage noncompliant behaviors in public settings, (6) use a daily school report card, and (7) anticipate future misconduct. Occasional booster sessions are often recommended. Parental ADHD may interfere with the success of such programs (Sonuga-Barke et al., 2002), suggesting that treatment of an affected parent maybe an important part of the child's treatment. Generalized family dysfunction (parental depression, substance abuse, marital problems) may also need to be addressed so that psychosocial or medication treatment is fully effective for the child with ADHD (Chronis et al., 2004).

The 1997 practice parameter (American Academy of Child and Adolescent Psychiatry, 1997) extensively reviewed a variety of nonpharmacological interventions for ADHD other than behavior therapy, including cognitive-behavioral therapy and dietary modification. No evidence was found at that time to support these interventions in patients with ADHD, and no studies have appeared since then that would justify their use. Although there has been aggressive marketing of its use, the efficacy of EEG feedback, either as a primary treatment for ADHD or as an adjunct to medication treatment, has not been established (Loo, 2003). Formal social skills training for children with

ADHD has not been shown to be effective (Antshel and Remer, 2003).

Recommendation 7. The Initial Psychopharmacological Treatment of ADHD Should Be a Trial With an Agent Approved by the Food and Drug Administration for the Treatment of ADHD [MS].

The following medications are approved by the U.S. Food and Drug Administration (FDA) for the treatment of ADHD: dextroamphetamine (DEX), D- and D,L-methylphenidate (MPH), mixed salts amphetamine, and atomoxetine.

STIMULANTS

Many randomized clinical trials of stimulant medications have been performed in patients with ADHD during the past 3 decades. Stimulants are highly efficacious in the treatment of ADHD. In double-blind, placebo-controlled trials in both children and adults, 65% to 75% of subjects with ADHD have been determined to be clinical responders to stimulants compared with 4% to 30% of subjects treated with placebo, depending on the response criteria used (Greenhill, 2002). When clinical response is assessed quantitatively via rating scales, the effect size of stimulant treatment relative to placebo is rather large, averaging about 1.0, one of the largest effects for any psychotropic medication. In the MTA study, subjects who responded to short-term placebo treatment did not maintain such gains and 90% of these subjects were subsequently treated with stimulants in the 14-month time frame of the study (Vitiello et al., 2001).

The physician is free to choose any of the two stimulant types (MPH or amphetamine) because evidence suggests the two are equally efficacious in the treatment of ADHD. Immediate-release stimulant medications have the disadvantage that they must be taken two to three times per day to control ADHD symptoms throughout the day. In the past 5 years, extensive trials have been carried out with long-acting forms of MPH (Concerta, Daytrana, Focalin-XR, Metadate, Ritalin LA), mixed salts amphetamine (Adderall XR), and an amphetamine prodrug lisdexamfetamine (Vyvanse; Biederman et al., 2002, 2006; Findling and Lopez, 2005; Greenhill et al., 2002, 2006b; McGough et al., 2006b; Wolraich et al., 2001). These long-acting formulations are equally efficacious as the immediate-release forms and have been shown to be efficacious in adolescents as well as children (Spencer et al., 2006; Wilens et al., 2006). They offer greater convenience for the patient and family and enhance confidentiality because the school-age patient need not report to the school nurse for medication administration. Single daily dosing is associated with greater compliance for all types of medication, and long-acting MPH may improve driving performance in adolescents relative to short-acting MPH (Cox et al., 2004 [rct]). Physicians may use long-acting forms as initial treatment; there is no need to titrate to the appropriate dose on short-acting forms and then "transfer" children to a long-acting form. Short-acting stimulants are often used as initial treatment in small children (<16 kg in weight), for whom there are no long-acting forms in a sufficiently low dose.

Typical dosing of the stimulant medications is shown in Table 2. The AACAP has also issued specific parameters for the use of stimulant medications (American Academy of Child and Adolescent Psychiatry, 2002). These doses represent guidelines; with careful clinical monitoring, these doses may be exceeded in individual cases. Studies of the treatment of adult ADHD shed light on the doses necessary to optimally treat adult-sized adolescents. Spencer et al. (2005 [rct]) conducted a 6-week double-blind, parallel-group study of MPH in 146 adults with ADHD. MPH was highly efficacious (76% response rate on MPH versus 19% on placebo) at a mean oral dose of 1.1 mg/kg/day (mean daily dose 88 ± 22 mg). This would suggest that adult-sized adolescents may need doses of MPH in this range (or the equivalent dose in amphetamine or Concerta) to achieve an adequate response, but careful monitoring for side effects should be undertaken at such doses. There have not been any studies examining the effects of doses of MPH or amphetamine in adolescents of more than 60 mg/day or 72 mg of Concerta. Doses in this range should be used only with caution, with frequent monitoring of side effects. On average, there is a linear relationship between dose and clinical response: that is, in any group of ADHD subjects, more subjects will be classified as responders and there is a greater reduction in symptoms at the higher doses of stimulant. There is no evidence of a global "therapeutic" window in ADHD patients. Each patient, however, has a unique dose-response curve. If a full range of MPH doses are used, then roughly a third of school-age patients will

TABLE 2
Medications Approved by the FDA for ADHD (Alphabetical by Class)

Generic Class/ Brand Name	Dose Form	Typical Starting Dose	FDA Max/Day	Off-Label Max/Day	Comments
Amphetamine preparations					
Short-acting					Short-acting stimulants often used as initial treatment in small children (<16 kg), but have disadvantage of b.i.d.-t.i.d. dosing to control symptoms throughout day
Adderall[a]	5, 7.5, 10, 12.5, 15, 20, 30 mg tab	3–5 y: 2.5 mg q.d.; ≥6 y: 5 mg q.d.–b.i.d.	40 mg	>50 kg: 60 mg	
Dexedrine[a]	5 mg cap	3–5 y: 2.5 mg q.d.			
DextroStat[a]	5, 10 mg cap	≥6 y: 5 mg q.d.–b.i.d.			
Long-acting					Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep Adderall XR cap may be opened and sprinkled on soft foods
Dexedrine Spansule	5, 10, 15 mg cap	≥6 y: 5–10 mg q.d.–b.i.d.	40 mg	>50 kg: 60 mg	
Adderall XR	5, 10, 15, 20, 25, 30 mg cap	≥6 y: 10 mg q.d.	30 mg	>50 kg: 60 mg	
Lisdexamfetamine	30, 50, 70 mg cap	30 mg q.d.	70 mg	Not yet known	
Methylphenidate preparations					
Short-acting					Short-acting stimulants often used as initial treatment in small children (<16 kg) but have disadvantage of b.i.d.-t.i.d. dosing to control symptoms throughout day
Focalin	2.5, 5, 10 mg cap	2.5 mg b.i.d.	20 mg	50 mg	
Methylin[a]	5, 10, 20 mg tab	5 mg b.i.d.	60 mg	>50 kg: 100 mg	
Ritalin[a]	5, 10, 20 mg	5 mg b.i.d.	60 mg	>50 kg: 100 mg	
Intermediate-acting					Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep Metadate CD and Ritalin LA caps may be opened and sprinkled on soft food
Metadate ER	10, 20 mg cap	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Methylin ER	10, 20 mg cap	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Ritalin SR[a]	20 mg	10 mg q.a.m.	60 mg	>50 kg: 100 mg	
Metadate CD	10, 20, 30, 40, 50, 60 mg	20 mg q.a.m.	60 mg	>50 kg: 100 mg	
Ritalin LA	10, 20, 30, 40 mg	20 mg q.a.m.	60 mg	>50 kg: 100 mg	
Long-acting					
Concerta	18, 27, 36, 54 mg cap	18 mg q.a.m.	72 mg	108 mg	Swallow whole with liquids Nonabsorbable tablet shell may be seen in stool.
Daytrana patch	10, 15, 20, 30 mg patches	Begin with 10 mg patch q.d., then titrate up by patch strength	30 mg	Not yet known	
Focalin XR	5, 10, 15, 20 mg cap	5 mg q.a.m.	30 mg	50 mg	
Selective norepinephrine reuptake inhibitor					
Atomoxetine					Not a schedule II medication
Strattera	10, 18, 25, 40, 60, 80, 100 mg cap	Children and adolescents <70 kg: 0.5 mg/kg/day for 4 days; then 1 mg/kg/day for 4 days; then 1.2 mg/kg/day	Lesser of 1.4 mg/kg or 100 mg	Lesser of 1.8 mg/kg or 100 mg	Consider if active substance abuse or severe side effects of stimulants (mood lability, tics); give q.a.m. or divided doses b.i.d. (effects on late evening behavior); do not open capsule; monitor closely for suicidal thinking and behavior, clinical worsening, or unusual changes in behavior

Note: FDA = U.S. Food and Drug Administration; ADHD = attention-deficit/hyperactivity disorder.
[a] Generic formulation available.

have an initial optimal response on a low (<15 mg/day), a medium (16–34 mg/day), or a high (>34 mg/day) daily dose (Vitiello et al., 2001 [rct]). Most, however, will require dose adjustment upward as treatment progresses.

After selecting the starting dose, the physician may titrate upward every 1 to 3 weeks until the maximum dose for the stimulant is reached, symptoms of ADHD remit, or side effects prevent further titration, whichever occurs first. Contact with physician or trained office staff during titrations is recommended. It is helpful to obtain teacher and parent rating scales after the patient has been observed by the adult on a selected dose for at least 1 week. The parent and the patient should be queried about side effects. An office visit should then be scheduled after the first month of treatment to review overall progress and determine whether the stimulant trial was a success and long-term maintenance on the particular stimulant should commence.

Arnold (2000) reviewed studies in which subjects underwent a trial of both amphetamine and MPH. This review suggested that approximately 41% of subjects with ADHD responded equally to both MPH and amphetamine, whereas 44% responded preferentially to one of the classes of stimulants. This suggests the initial response rate to stimulants may be as high as 85% if both stimulants are tried (in contrast to the finding of 65%–75% response when only one stimulant is tried). There is at present, however, no method to predict which stimulant will produce the best response in a given patient. The titration schedule for DEX or mixed salts amphetamine follows a similar practice as for MPH. Patients with ADHD and comorbid anxiety or disruptive behavior disorders have as robust a response of their ADHD symptoms to stimulants as do patients who do not have these comorbid conditions (MTA Cooperative Group, 1999b [rct]).

Treatment of Preschoolers With Stimulants

Stimulants have been widely prescribed by clinicians for this age group, although the number of published controlled trials is limited. Connor (2002) reviewed nine small studies of MPH in children younger than 6 years old, all of which used some type of blind as well as a crossover or parallel-group design. These studies involved 206 subjects and used doses of MPH that ranged from 2.5 to 30 mg/day or 0.15 to 1.0 mg/kg/day. Eight of the nine studies supported the efficacy of MPH in the treatment of preschoolers with ADHD at milligram-per-kilogram doses that were comparable with those used in school-age children. Studies of preschoolers with significant developmental delays suggested this subgroup was prone to higher rates of side effects including social withdrawal, irritability, and crying (Handen et al., 1999 [rct]). Thus, a cautious titration is recommended in this subgroup. In the NIMH-funded Preschool ADHD Treatment Study (PATS), 183 children ages 3 to 5 years underwent an open-label trial of MPH; subsequently, 165 of these subjects were randomized into a double-blind, placebo-controlled, crossover trial of MPH lasting 6 weeks (Kollins et al., 2006). The 140 subjects who completed this second phase went on to enter a long-term maintenance study of MPH. Parents of subjects in this study were required to complete a 10-week course of parent training before their child was treated with medication. Of note, only 37 of 279 enrolled parents thought that the behavior training resulted in significant or satisfactory improvement (Greenhill et al., 2006a).

Results from the short-term, open-label, run-in and double-blind, crossover studies do show that MPH is effective in preschoolers with ADHD (Greenhill et al., 2006a). The mean optimal dose of MPH was found to be 0.7 ± 0.4 mg/kg/day, which is lower than the mean of 1.0 mg/kg/day found to be optimal in the MTA study with school-age children. Eleven percent of subjects discontinued MPH because of adverse events (Wigal et al., 2006). Also relative to the MTA study, the preschool group showed a higher rate of emotional adverse events, including crabbiness, irritability, and proneness to crying. The conclusion was that the dose of MPH (or any stimulant) should be titrated more conservatively in preschoolers than in school-age patients, and lower mean doses may be effective. A pharmacokinetic study done as part of the PATS protocol showed that preschoolers metabolized MPH more slowly than did school-age children, perhaps explaining these results (McGough et al., 2006a).

Atomoxetine

Atomoxetine is a noradrenergic reuptake inhibitor that is superior to placebo in the treatment of ADHD in children, adolescents, and adults (Michelson et al.,

2001 [rct], 2002 [rct], 2003 [rct]; Swensen et al., 2001 [rct]). Its effect size was calculated to be 0.7 in one study (Michelson et al., 2002). Atomoxetine can be given once or twice daily, with the second dose given in the evening; atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although they may produce relatively more nausea or sedation. Dosing of atomoxetine is shown in Table 2.

Michelson et al. (2002) showed that although atomoxetine was superior to placebo at week 1 of the trial, the greatest effects were observed at week 6, suggesting the patient should be maintained at the full therapeutic dose for at least several weeks to obtain the drug's full effect. Atomoxetine has been studied in the treatment of patients with ADHD and comorbid anxiety (Sumner et al., 2005 [rct]). Patients with ADHD or an anxiety disorder (generalized anxiety, separation anxiety, or social phobia) were randomized to either atomoxetine (n = 87) or placebo (n = 89) in a double-blind, placebo-controlled manner for 12 weeks of treatment. At the end of the treatment period, atomoxetine led to a significant reduction in ratings of symptoms of both ADHD and anxiety relative to placebo, showing the drug to be efficacious in the treatment of both conditions. This study is of interest because treatment algorithms for ADHD with comorbid anxiety have recommended treatment of ADHD first with stimulants, then addition of a selective serotonin reuptake inhibitor (SSRI) for treatment of the anxiety (Pliszka et al., 2000). Recently, however, the SSRI fluvoxamine was shown not to be superior to placebo for the treatment of anxiety when added to a stimulant in a small sample (n = 25) of children with ADHD and comorbid anxiety (Abikoff et al., 2005 [rct]). This small study does not invalidate this practice, but the above results of Sumner et al. (2005) suggest that using atomoxetine for the treatment of ADHD with comorbid anxiety is a viable alternative approach. No evidence exists that atomoxetine is effective for the treatment of major depressive disorder, however.

Selection of Agent

The clinician and family face the choice of which agent to use for the initial treatment of the patient with ADHD. The American Academy of Pediatrics (2001), an international consensus statement (Kutcher et al., 2004), and the Texas Children's Medication Project (Pliszka et al., 2006a) have recommended stimulants as the first line of treatment for ADHD, particularly when no comorbidity is present. Direct comparisons of the efficacy of atomoxetine with that of MPH (Michelson, 2004) and amphetamine (Wigal et al., 2004) have shown a greater treatment effect of the stimulants, and in a meta-analysis of atomoxetine and stimulant studies, the effect size for atomoxetine was 0.62 compared with 0.91 and 0.95 for immediate-release and long-acting stimulants, respectively (Faraone et al., 2003). However, atomoxetine may be considered as the first medication for ADHD in individuals with an active substance abuse problem, comorbid anxiety, or tics. Atomoxetine is preferred if the patient experiences severe side effects to stimulants such as mood lability or tics (Biederman et al., 2004). When dosed twice daily, effects on late evening behavior may be seen.

It is the sole choice of the family and the clinician as to which agent should be used for the patient's treatment, and each patient's treatment must be individualized. Nothing in these guidelines should be construed by third-party payers as justification for requiring a patient to be a treatment failure (or experience side effects) to one agent before allowing the trial of another.

Recommendation 8. If None of the Above Agents Result in Satisfactory Treatment of the Patient With ADHD, the Clinician Should Undertake a Careful Review of the Diagnosis and Then Consider Behavior Therapy and/or the Use of Medications Not Approved by the FDA for the Treatment of ADHD [CG].

The vast majority of patients with ADHD who do not have significant comorbidity respond satisfactorily to the agents listed in Recommendation 7. If a patient fails to respond to trials of all of these agents after an adequate length of time at appropriate doses for the agent as noted in Table 2, then the clinician should undertake a review of the patient's diagnosis of ADHD. This does not require the patient to be completely re-evaluated, but the clinician should be certain of the accuracy of the history that led to the diagnosis of ADHD and examine whether any undetected comorbid conditions are present, such as affective disorders, anxiety disorders, or subtle developmental disorders. The clinician should ascertain that these factors are not the primary problems impairing the patient's attention and impulse control. Primary care physicians should

consider referral to a child and adolescent psychiatrist at this point.

Bupropion, tricyclic antidepressants (TCAs), and α-agonists are often used in the treatment of ADHD even though they are not approved by the FDA for this purpose. Although there is at least one double-blind, randomized, controlled trial for bupropion, TCAs, and clonidine, the evidence base for these medications is far weaker than for the FDA-approved agents (Pliszka, 2003). Their doses for clinical use are shown in Table 3. These agents may have effect sizes considerably less than those of the approved agents and comparable with the effectiveness of behavior therapy (Pelham et al., 1998). Thus, it may be prudent for the clinician to recommend a trial of behavior therapy at this point, before moving to these second-line agents. In other cases, the patient may have had a partial response to one of the FDA-approved agents, wherein there is definite improvement over baseline symptoms but impairment at home or school still is present. As noted in Recommendation 12, addition of behavior therapy along with treatment with the FDA-approved agent may provide added benefit in such cases.

Bupropion, TCAs, and α-agonists, although not as extensively studied as the previously discussed

TABLE 3
Medications Used for ADHD, Not Approved by FDA

Generic Class/ Brand Name	Dose Form	Typical Starting Dose	Max/Day	Comments
Antidepressants				
Bupropion				Lowers seizure threshold; contraindicated if current seizure disorder
Wellbutrin[a]	75, 100 mg tab	Lesser of 3 mg/kg/day or 150 mg/day	Lesser of 6 mg/kg or 300 mg, with no single dose >150 mg	Usually given in divided doses, b.i.d. for children, t.i.d. for adolescents, for both safety and effectiveness
Wellbutrin SR	100, 150, 200 mg tab			
Wellbutrin XL	150, 300 mg tab			
Imipramine				Obtain baseline ECG before starting imipramine and nortriptyline
Tofranil[a]	10, 25, 50, 75 mg tab	1 mg/kg/day	Lesser of 4 mg/kg or 200 mg	
Nortriptyline				
Pamelor,[a] Aventil[a]	10, 25, 50, 75 mg cap	0.5 mg/kg/day	Lesser of 2 mg/kg or 100 mg	
α_2-Adrenergic agonists				
Clonidine				May be used alone or as adjuvant to another medication for ADHD
Catapres[a]	0.1, 0.2, 0.3 mg tab	<45 kg: 0.05 mg q.h.s.; titrate in 0.05-mg increments b.i.d., t.i.d., q.i.d.; >45 kg: 0.1 mg q.h.s.; titrate in 0.1-mg increments b.i.d., t.i.d., q.i.d.	27–40.5 kg: 0.2 mg; 40.5–45 kg: 0.3 mg; >45 kg: 0.4 mg	Effective for impulsivity and hyperactivity; modulating mood level; tics worsening from stimulants; sleep disturbances
Guanfacine				May not see effects for 4–6 wk
Tenex[a]	1, 2 mg tab	<45 kg: 0.5 mg q.h.s.; titrate in 0.5-mg increments b.i.d., t.i.d, q.i.d.; >45 kg: 1 mg q.h.s.; titrate in 1-mg increments b.i.d., t.i.d., q.i.d.	27–40.5 kg: 2 mg; 40.5–45 kg: 3 mg; >45 kg: 4 mg	Review personal and family cardiovascular history Taper off to avoid rebound hypertension

Note: ECG = electrocardiogram.
[a] Generic formulation available.

medications, have shown effectiveness in small controlled trials or open trials. The common doses of these agents used in children and adolescents are shown in Table 3. Bupropion is a noradrenergic antidepressant that showed modest efficacy in the treatment of ADHD in one double-blind, placebo-controlled trial (Conners et al., 1996 [rct]). It is contraindicated in patients with a current seizure disorder. It can be given in either immediate-release or long-acting form, but may not come in pill sizes small enough for children who weigh <25 kg.

TCA medications are the most studied of the non-FDA–approved medications for the treatment of ADHD (Daly and Wilens, 1998 [rct]). Imipramine and nortriptyline have been most commonly used in recent years by clinicians. Among the TCAs, desipramine should be used with extreme caution in children and adolescents because there have been reports of sudden death (Biederman et al., 1995; Riddle et al., 1993). Desipramine should be used only if other TCAs have not proven effective or have caused the patient to suffer excessive side effects. For TCAs electrocardiography must be performed at baseline and after each dose increase. Once the patient is on a stable dose of the TCA, a plasma level should be obtained to ensure the level is not in the toxic range. However, if the level is subtherapeutic in terms of the range for the treatment of depression, there is no need to further increase the dose if the symptoms of ADHD are adequately controlled.

α-Agonists (clonidine and guanfacine) have been widely prescribed for patients with ADHD, for the disorder itself, for comorbid aggression, or to combat side effects of tics or insomnia. Extensive controlled trials of these agents are lacking. Connor et al. (1999) performed a meta-analysis of 11 studies of clonidine in the treatment of ADHD. The studies were highly variable in both method and outcome, and open-label studies showed a larger effect than controlled studies. Nevertheless, the review suggested a small to moderate effect size for clonidine in the treatment of ADHD. One small double-blind trial showed the superiority of guanfacine over placebo in the treatment of children with ADHD and comorbid tics (Scahill et al., 2001 [rct]). A gradual titration is required and clinical consensus suggests the α-agonists are more successful in treating hyperactive/impulsive symptoms than inattention symptoms, although this remains to be proven by clinical trials. In recent years clinical consensus has led to the use of clonidine as adjunctive therapy to treat tics or stimulant-induced insomnia rather than as a primary treatment for ADHD. If the α-agonist is deemed ineffective after an adequate trial, the medication should be tapered gradually over 1 to 2 weeks to avoid a sudden increase in blood pressure.

Recommendation 9. During a Psychopharmacological Intervention for ADHD, the Patient Should Be Monitored for Treatment-Emergent Side Effects [MS].

For stimulant medications, the most common side effects are appetite decrease, weight loss, insomnia, or headache. Less common side effects of stimulants include tics and emotional lability/irritability. Treating physicians should be familiar with the precautions and reported adverse events contained in product labeling. Strategies for dealing with side effects include monitoring, dose adjustment of the stimulant, switching to another stimulant, and adjunctive pharmacotherapy to treat the side effects. If one of these side effects emerges, then the physician should first assess the severity of the symptom and the burden it imposes on the patient. It is prudent to monitor side effects that do not compromise the patient's health or cause discomfort that interferes with functioning because many side effects of stimulants are transient in nature and may resolve without treatment. This approach is particularly valuable if the patient has had a robust behavioral response to the particular stimulant medication. If the side effect persists, then reduction of dose should be considered, although the physician may find that the dose that does not produce the side effect is not effective in the treatment of the ADHD. In this case the physician should initiate a trial of a different stimulant or a nonstimulant medication.

After such trials, the physician, family, and patient may find that the one particular stimulant that is most efficacious in the treatment of that patient's ADHD also produces a troublesome side effect. In this case adjunctive pharmacotherapy may be considered. Low doses of clonidine, trazodone, or an antihistamine are often helpful for stimulant-induced insomnia. Clinicians must be aware of the risk of priapism in males treated with trazodone (James and Mendelson, 2004). Some patients become paradoxically excited when treated with antihistamines; anticholinergic effects of some antihistamine agents can be detrimental.

Melatonin in doses of 3 mg has recently been shown to be helpful in improving sleep in children with ADHD treated with stimulants (Tjon Pian Gi et al., 2003 [ut]). A chart review suggested cyproheptadine can attenuate stimulant-induced anorexia (Daviss and Scott, 2004 [cs]).

How often stimulants induce tics in patients with ADHD is less clear. Recent double-blind clinical trials of both immediate-release and long-acting stimulants have not found that stimulants increase the rate of tics relative to placebo (Biederman et al., 2002 [rct]; Wolraich et al., 2001 [rct]). Children with comorbid ADHD and tic disorders, on average, show a decline in tics when treated with a stimulant. This remains true even after more than 1 year of treatment (Gadow et al., 1999 [ut]; Gadow and Sverd, 1990). If a patient has treatment-emergent tics during a trial of a given stimulant, then an alternative stimulant or a nonstimulant should be tried. If the patient's ADHD symptoms respond adequately only to a stimulant medication that induces tics, then combined pharmacotherapy of the stimulant and an α-agonist (clonidine or guanfacine) is recommended (Tourette's Syndrome Study Group, 2002 [rct]).

Side effects of atomoxetine that occurred more often than those with placebo include gastrointestinal distress, sedation, and decreased appetite. These can generally be managed by dose adjustment, and although some attenuate with time, others such as headaches may persist (Greenhill et al., 2007). If discomfort persists, then the atomoxetine should be tapered off, and a trial of a different medication initiated. On December 17, 2004, the FDA required a warning be added to atomoxetine because of reports that two patients (an adult and child) developed severe liver disease (both patients recovered). In the clinical trials of 6,000 patients, no evidence of hepatotoxicity was found. Patients who develop jaundice, dark urine, or other symptoms of hepatic disease should discontinue atomoxetine. Routine monitoring of hepatic function is not required during atomoxetine treatment.

Aggression, Mood Lability, and Suicidal Ideation

Controlled trials of stimulants do not support the widespread belief that stimulant medications induce aggression. Indeed, overall aggressive acts and antisocial behavior decline when ADHD patients are treated with stimulants (Connor et al., 2002 [rct]). A rate of emotional lability of 8.6% was reported in patients taking Adderall XR compared with a rate of 1.9% in the placebo group (Biederman et al., 2002). It should be noted, however, that this 4-week trial used an aggressive titration schedule, and children were randomized to dose condition regardless of weight. The physician must distinguish between aggression/emotional lability that is present when the stimulant is active (i.e., during the day) and increased hyperactivity/impulsivity in the evening when the stimulant is no longer effective. The latter phenomenon (commonly referred to as "rebound") is more prevalent than the former, and it has been shown in laboratory classroom settings that even on placebo, the behavior of children with ADHD is worse in the late afternoon and evening than in the morning (Swanson et al., 1998a [rct]). Thus, the "worsening" behavior observed by the caretaker in the evening was probably present before treatment, but is more noticeable compared with the now improved behavior during the day. The physician may deal with this situation by administering a dose of immediate-release stimulant in the late afternoon. Such a dose is usually smaller than one of the morning doses.

The FDA and its Pediatric Advisory Committee have reviewed data regarding psychiatric adverse events to medications for the treatment of ADHD (U.S. Food and Drug Administration, 2006). Data from both controlled trials and postmarketing safety data from sponsors and the FDA Adverse Events Reporting System, also referred to as MedWatch, was reviewed. For most of the agents, these events were slightly more common in the active drug group relative to placebo in the controlled trials, but with the exception of suicidal thinking with atomoxetine (see below) and modafinil, these differences did not reach statistical significance (Mosholder, 2006). Postmarketing safety data were also reviewed for reports of mania/psychotic symptoms, aggression, and suicidality (Gelperin, 2006). Such reports have many limitations because information about dose, comorbid diagnoses, and concomitant medications is often not available. Nonetheless, for each agent examined (all stimulants, atomoxetine, and modafinil), there were reports of rare events of toxic psychotic symptoms, specifically involving visual and tactile hallucinations of insects. Symptoms of aggression and suicidality (but no completed suicides) were also reported. At the time, the Pediatric Advisory Committee did not recommend a boxed warning

regarding psychiatric adverse events, but did suggest clarifying labeling regarding these phenomena. No changes to the stimulant medication labeling were suggested regarding suicide or suicidal ideation.

In September 2005 the FDA also issued an alert regarding suicidal thinking with atomoxetine in children and adolescents (U.S. Food and Drug Administration, 2005). In 12 controlled trials involving 1,357 patients taking atomoxetine and 851 taking placebo, the average risk of suicidal thinking was 4/1,000 in the atomoxetine-treated group versus none in those taking placebo. There was one suicide attempt in the atomoxetine group but no completed suicides. A boxed warning was added to the atomoxetine labeling. This risk is small, but it should be discussed with patients and family, and children should be monitored for the onset of suicidal thinking, particularly in the first few months of treatment.

If after starting an ADHD medication the patient clearly is more aggressive or emotionally labile or experiences psychotic symptoms, then the physician should discontinue that medication and consider a different agent. Adjunctive therapy with neuroleptics or mood stabilizers is not recommended if the aggressive/labile behavior was not present at baseline and is clearly a side effect of the stimulant.

Cardiovascular Issues

In March 2006 the Pediatric Advisory Committee also addressed the risk of sudden death occurring with agents used for the treatment of ADHD (Villalaba, 2006). The FDA review of events related to sudden death revealed 20 sudden death cases with amphetamine or dextroamphetamine (14 children, 6 adults), whereas there were 14 pediatric and four adults cases of sudden death with MPH. It is important to note that the rate of sudden death in the general pediatric population has been estimated at 1.3–8.5/100,000 patient-years (Liberthson, 1996). The rate of sudden death among those with a history of congenital heart disease can be as high as 6% by age 20 (Liberthson, 1996). Villalaba (2006) estimated the rate of sudden death in treated children with ADHD for the exposure period January 1, 1992 to December 31, 2004 to be 0.2/100,000 patient-years for MPH, 0.3/100,000 patient-years for amphetamine, and 0.5/100,000 patient-years for atomoxetine (the differences between the agents are not clinically meaningful). Thus, the rate of sudden death of children taking ADHD medications do not appear to exceed the base rate of sudden death in the general population. Although an advisory committee 1 month earlier had recommended a boxed warning be issued for cardiovascular events, including stroke and myocardial infarction (Nissen, 2006), the Pediatric Advisory Committee did not support this recommendation. No evidence currently indicates a need for routine cardiac evaluation (i.e., electrocardiography, echocardiography) before starting any stimulant treatment in otherwise healthy individuals (Biederman et al., 2006). The package insert for stimulants states that these medications should generally not be used in children and adolescents with preexisting heart disease or symptoms suggesting significant cardiovascular disease. This would include a history of severe palpitations, fainting, exercise intolerance not accounted for by obesity, or strong family history of sudden death. Postoperative tetralogy of Fallot, coronary artery abnormalities, and subaortic stenosis are known cardiac problems that require special considerations in using stimulants. Chest pain, arrhythmias, hypertension, or syncope may be signs of hypertrophic cardiomyopathy, which has been associated with sudden unexpected deaths in children and adolescents. Before a stimulant trial, such patients should be referred for consultation with a cardiologist for possible electrocardiography and/or echocardiography. If stimulants are initiated, then the patient should also be studied by the cardiologists during the course of treatment.

Side Effects of Non-FDA–Approved Agents

Bupropion may cause mild insomnia or loss of appetite. Extremely high single doses (>400 mg) of bupropion may induce seizures even in patients without epilepsy. TCAs frequently cause anticholinergic side effects such as dry mouth, sedation, constipation, changes in vision, or tachycardia. Reduction in dose or discontinuation of the TCA is often required if these side effects induce impairment. Side effects of α-agonists include sedation, dizziness, and possible hypotension. In the previous decade there was controversy over the safety of the use of α-agonists, particularly clonidine, in children. Swanson and colleagues (1995) noted about 20 case reports of children suffering significant changes in heart rate

and blood pressure, particularly after clonidine dose adjustment. Four cases of death were reported in children taking a combination of MPH and clonidine, but there were many atypical aspects of these cases (Popper, 1995; Swanson et al., 1995, 1999b; Wilens and Spencer, 1999), and Wilens and Spencer (1999) doubted any causative relationship between the stimulant-agonist combination and the patients' deaths. There have been no further reports of severe cardiovascular adverse events associated with clonidine use in ADHD patients. Nonetheless, physicians must be cautious. The patient's blood pressure and pulse should be assessed periodically (Gutgesell et al., 1999), and abrupt discontinuations of the α-agonist are to be avoided. The patient and family should be advised to report any cardiac symptoms such as dizziness, fainting, or unexplained change in heart rate.

Recommendation 10. If a Patient With ADHD Has a Robust Response to Psychopharmacological Treatment and Subsequently Shows Normative Functioning in Academic, Family, and Social Functioning, Then Psychopharmacological Treatment of the ADHD Alone Is Satisfactory [OP].

Whether combined medication and psychosocial treatment of uncomplicated ADHD yields improved outcome relative to medication treatment alone remains a contentious issue. For children with ADHD alone who do not have significant comorbidity, the MTA and M+MPT studies do not for the most part show an additive effect of the psychosocial interventions. In the first set of analyses of the MTA data, the four groups were compared over time on quantitative measures of ADHD symptoms; there was no significant difference between the comprehensive medication management group and the combined treatment group. In a subsequent set of analyses, an advantage for the combined treatment was seen. Swanson et al. (2001 [rct]) created a "categorical" outcome measure using the Swanson, Nolan, and Pelham (SNAP) behavior rating scale. Successful treatment was defined as having an average symptom rating no greater than 1.0 ("just a little"). Using this definition, 68% of the combined group was optimally treated, compared with 56% of the medication-only group, a statistically significant difference. Behavioral treatment alone remained inferior to medication management, with only 34% of the behavioral treatment group maximally improved.

Combined treatment did not yield superior outcome to medication only in the M+MPT study. After 2 years of intensive psychosocial intervention and MPH, children with ADHD (without learning problems or comorbidities) were no different from those treated with medication alone in terms of ADHD symptoms (Abikoff et al., 2004b [rct]), academics (Hechtman et al., 2004 [rct]), or social skills (Abikoff et al., 2004a [rct]). Children in the MTA study were studied for 1 year after the end of active intervention. No benefit of combined treatment was found over medication alone, and stopping medication was strongly related to deterioration (MTA Cooperative Group, 2004a [rct], 2004b [rct]). Overall, the data suggest that for ADHD patients without comorbidity who have a positive response to medication, adjunctive psychosocial intervention may not provide added benefit. Therefore, if a patient with ADHD shows full remission of symptoms and normative functioning, it is not mandatory that behavior therapy be added to the regimen, although parental preferences in this matter should be taken into account.

Recommendation 11. If a Patient With ADHD Has a Less Than Optimal Response to Medication, Has a Comorbid Disorder, or Experiences Stressors in Family Life, Then Psychosocial Treatment in Conjunction With Medication Treatment Is Often Beneficial [CG].

In contrast to the lack of an additive effect of behavioral and pharmacological treatment in children with ADHD alone, the MTA study provided strong evidence that patients with ADHD and comorbid disorders and/or psychosocial stressors benefit from an adjunctive psychosocial intervention. Comorbid anxiety (as reported by the child's parent) predicted a better response to behavioral treatment (March et al., 2000 [rct]), particularly when the ADHD patient had both an anxiety and a disruptive behavior disorder (ODD or CD; Jensen et al., 2001b [rct]). Children receiving public assistance and ethnic minorities also showed a better outcome with combined treatment (Arnold et al., 2003 [rct]; MTA Cooperative Group, 1999b [rct]). Thus, the clinician should individualize the psychosocial intervention for each ADHD patient, applying it

in those patients who can most benefit because of comorbidity or the presence of psychosocial stress.

Recommendation 12. Patients Should Be Assessed Periodically to Determine Whether There Is Continued Need for Treatment or If Symptoms Have Remitted. Treatment of ADHD Should Continue as Long as Symptoms Remain Present and Cause Impairment [MS].

The patient with ADHD should have regular follow-up for medication adjustments to ensure that the medication is still effective, the dose is optimal, and side effects are clinically insignificant. For pharmacological interventions, follow-up should occur at least several times per year. The number and frequency of psychosocial interventions should be individualized as well. The procedures performed at each office visit will vary according to clinical need, but during the course of annual treatment, the clinician should review the child's behavioral and academic functioning; periodically assess height, weight, blood pressure, and pulse; and assess for the emergence of comorbid disorders and medical conditions. Psychoeducation should be provided on an ongoing basis. The need to initiate formal behavior therapy should be assessed and the effectiveness of any current behavior therapy should be reviewed.

The history of medication treatment of ADHD now spans nearly 70 years, which is longer than the use of antibiotics (Bradley, 1937). The MTA clearly showed that once the study treatments ceased at 14 months, the combined and medication groups lost some of their treatment gains, in part because of medication discontinuation and in part because the medication was now being given in the community with less careful monitoring and dose adjustment (MTA Cooperative Group, 2004a [rct], 2004b [rct]). In contrast, in the M+MPT study, all of the medication treatment was performed in the study. There was no deterioration in clinical effect or compliance, even in the second year, when the intensity of psychosocial treatment was greatly reduced (Abikoff et al., 2004b [rct]; Klein et al., 2004 [rct]). Given the high level of maladaptive behavior among adolescents with ADHD (Barkley et al., 2004), continued psychopharmacological intervention through this developmental period is likely to be highly beneficial. At the time of the 1997 AACAP practice parameter on ADHD, few long-term medication treatment studies of children with ADHD were available. One of the first controlled long-term stimulant studies studied the effects of DEX (Gillberg et al., 1997 [rct]). Children with ADHD (n = 62) were successfully treated with DEX in a short-term, open-label trial and then randomized to either placebo or DEX in a double-blind, parallel-group design for up to 1 year of treatment. Significantly more children relapsed in the placebo group (71%) than in the DEX group (29%), and the stimulant group showed significantly more improved ratings on the Conners Parent Rating Scales than the placebo group as the study progressed.

Charach et al. (2004) followed 79 of 91 participants from a clinical trial of MPH for an additional 5 years; 69 of these subjects remained in the study through year 5. Adherence to stimulant (defined as taking the medication at least 5 days a week since the last evaluation with no drug holidays that exceeded 14 weeks) was assessed at each year of the study. At 5 years, adherents showed greater improvement in teacher-reported symptoms than nonadherents; nonetheless, many subjects had discontinued their stimulant medication.

With the introduction of long-acting stimulants and atomoxetine, longer term (1–2 years) open-label follow-up safety studies have been performed. Caution needs to be used when interpreting many of these studies due to their open-label nature and high rates of attrition. Follow-up data from long-term, open-label Concerta studies are available from both the first (Wilens et al., 2003a [ut]) and second year of treatment (Wilens et al., 2005 [ut]). In these studies, 497 children ages 6–13 years who had participated in double-blind, placebo-controlled studies of Concerta were studied regularly over the study period. Patients received adjustment of their daily dose of Concerta according to clinical need. Teacher and Parent Inattention/Overactivity With Aggression (IOWA) Conners Rating Scales were obtained monthly in year 1, and in year 2, global evaluations of the effectiveness of the Concerta were made by parents and teachers every 3 months. In year 1, the subjects' mean Inattention/Overactivity and Aggression/Defiance ratings done by both parents and teachers remained in the normative range throughout the study period. The mean prescribed dose of Concerta rose from 35 mg to 41 mg by the end of year 1. Thirty-one subjects (7.6%) discontinued because of lack of effectiveness. Overall, 289 subjects completed year 1 of treatment. Two hundred twenty-nine subjects

completed year 2; none of these dropped out because of lack of efficacy. Using the last observation carried forward, 85% of parents rated the effectiveness of the medication at the study's end as good or excellent.

A 24-month follow-up study of Adderall XR showed similar long-term effectiveness (McGough et al., 2005 [ut]). Subjects (N = 568) began treatment with Adderall XR with 10 mg/day, and investigators individually titrated doses up to a maximum of 30 mg/day; 273 (48%) completed treatment. By 24 months, the mean dose of Adderall XR was 22.4 ± 6.9 mg. Each quarter of the study period, subjects' parents completed the 10-item Conners Parent Rating Scales; these ratings remained in the normative range throughout the 2-year period.

Long-term atomoxetine treatment was studied in 416 patients ages 6–15 years (Michelson et al., 2004 [ut]). Patients were treated in an open-label study of atomoxetine for 12 weeks, and then they were randomized to either placebo or atomoxetine for 9 months. Atomoxetine was superior to placebo in preventing relapse, with 22.3% of atomoxetine subjects showing a return to baseline severity versus 37.9% in the placebo group. Wilens et al. (2004 [ut]) reported on the follow-up of 601 adolescents with ADHD treated with atomoxetine, of whom 219 had completed 2 years of treatment. Subjects took doses of atomoxetine beginning at 1.2 and 2.0 mg/kg/day with a mean dose of 1.4 mg/kg/day. Ninety-nine (16.5%) discontinued the atomoxetine because of a lack of efficacy. Mean Parent ADHD Rating Scale-IV scores (assessed every 3 months) for the group fell into the normative range by the third month of treatment and remained until the end of the study.

Recent controlled trials of long-acting stimulants have confirmed the lack of any major medical adverse events with this class of medications, with no short-term abnormalities of hematological or chemical measures (Biederman et al., 2002 [rct]; Greenhill et al., 2002 [rct]; McCracken et al., 2003 [rct]; Wolraich, 2000 [rct]; Wolraich et al., 2001 [rct]). Although stimulants are a controlled substance, a meta-analysis of open-label long-term studies of stimulant treatment in ADHD concluded that stimulant treatment does not increase the risk of substance abuse and may even have a protective effect (Wilens et al., 2003b). Side effects that tend to persist in long-term treatment with all stimulants include insomnia, decreased appetite and/or weight loss, and headache (Charach et al., 2004 [ut]; Gillberg et al., 1997 [rct]; McGough et al., 2005 [ut]; Wilens et al., 2005 [ut]). In the long-term Adderall XR study (McGough et al., 2005), 84 patients (15%) discontinued medication because of side effects. In the 2-year Concerta study, 28 (6.9%) discontinued the study because of side effects in the first year, and an additional three subjects did so in the second year (Wilens et al., 2005). Two studies (Gillberg et al., 1997; Law and Schachar, 1999 [rct]) compared outcomes of children with ADHD treated with stimulant or placebo during a 6-month period. Neither study showed that DEX or MPH produced tics at a rate exceeding that of placebo. Gillberg et al. (1997) did not find that DEX-treated children have higher rates of anxiety or depression than those on placebo after 6 months of treatment. Although side effects to medications used in the long-term treatment of ADHD can be problematic and require the attention of the clinician when they occur, they are without serious medical sequelae and of mild to moderate intensity, and generally respond to dose adjustment or change of medication.

As patients with ADHD enter late adolescence, clinicians and the family face the question of whether symptoms of ADHD and social functioning have improved to the point that medication intervention is no longer needed. Long-term follow-up of MTA subjects (now followed for 8 years after they started treatment with data analyzed at the 2-year follow-up point published) has begun to shed some light on this issue. Subjects showed marked improvement during the first 14 months of the active study period, with more gradual improvement thereafter (Jensen, 2005 [ut]). Children who continued to be impaired were more likely to have ODD or CD, both at baseline and at follow-up. For the entire MTA group, treatment group effects (medication versus no medication, combined treatment versus medication alone) at 22 months were no longer significant. Secondary analyses of these data were performed to explore possible reasons for the loss of the effectiveness of the MTA medication management over the longer period of time (Swanson, 2005 [ut]). These analyses found that the ADHD sample fell into three groups: children with initial small improvements followed by gradual improvement over time, children with a large initial improvement who maintained improvement over the 36 months, and children who showed initial improvement but then deteriorated.

This third group had higher levels of aggression and lower IQs at baseline. Medication effects on functioning were significant at follow-up only in the first two groups. The first group showed improved performance if they were on medication at follow-up, whereas the second showed more improvement if they had received the MTA medication titration algorithm at the start of treatment. Interestingly, in the second group, current medication status did not affect outcome, meaning that some children maintained gains even though they were no longer taking medication. This implies that the clinician must be alert to the fact that some patients with ADHD deteriorate in spite of medication (and these are more likely to have comorbidity at baseline), whereas others do show remission of symptoms and may no longer require medication management.

If a patient with ADHD has been symptom free for at least 1 year, then inquiries should be made about whether the patient and family still think the medication provides a benefit. Signs that the ADHD has remitted include lack of any need to adjust dose despite robust growth, lack of deterioration when a dose of stimulant medication is missed, or new-found abilities to concentrate during drug holidays. Low-stress times such as vacations are a good time to attempt a withdrawal from medication, but parents should assign some cognitively demanding tasks (reading a book, practicing mathematics problems) to be sure that remission has occurred. The start of a new school year is not a good time to attempt a drug holiday, but once a patient's school routine is established, the medication can be withdrawn and teacher input solicited. Medication should be reinstituted if the patient, parents, or teachers report deterioration in functioning.

Recommendation 13. Patients Treated With Medication for ADHD Should Have Their Height and Weight Monitored Throughout Treatment [MS].

The effect of stimulant treatment on growth has been a concern for many years. The 1997 practice parameter on ADHD noted that stimulants were associated with small decreases in expected height and weight gain, which were rarely clinically significant (American Academy of Child and Adolescent Psychiatry, 1997). In the late 1990s concern about effects on growth abated, particularly because follow-up studies did not show any long-term effect on ultimate adult height (Gittelman-Klein and Mannuzza, 1988; Kramer et al., 2000; Weiss and Hechtman, 2003). Recently, however, two major reviews (Faraone et al., unpublished data, 2006; Poulton, 2005) examined all of the available data and concluded that stimulant treatment may be associated with a reduction in expected height gain, at least in the first 1 to 3 years of treatment. It is difficult to determine the clinical significance of such changes. The MTA study showed reduced growth rates in ADHD patients after 2 years of stimulant treatment compared with those patients who received no medication (MTA Cooperative Group, 2004b [rct]), and these deficits persisted at 36 months (MTA Cooperative Group, 2006 [rct]). The PATS study followed a group of 140 preschoolers who received MPH for up to 1 year for ADHD (Swanson et al., 2006 [rct]). The subjects had less than expected mean gains in height (−1.38 cm) and weight (−1.3 kg). Interestingly, in both the PATS and MTA studies, ADHD subjects were larger than average (~0.2 SD above the mean) for both height and weight compared with controls or normative data before entry into the study, especially for treatment-naïve subjects. Swanson et al. (2006 [rct]) hypothesized that children with ADHD are bigger, on average, than an age-matched sample of children without ADHD. Thus, clinicians may not observe growth deficits in stimulant-treated children because treatment does not slow the height acquisition rate enough to bring them below the mean height for age. In a review and analysis of cross-sectional data, Spencer et al. (1996) compared the heights of ADHD patients with those of controls in three separate age samples. They found no height deficits relative to controls in childhood, a small but statistically significant reduction in height relative to controls at puberty, but no difference in height in adulthood. There was no relationship between stimulant treatment and height measures, and Spencer et al. (1996) hypothesized that ADHD itself was associated with a slower tempo of growth, which resolved by adulthood, and the shorter stature was unrelated to medication effects. There is also evidence that stimulant-induced growth delays are greater in the first year of treatment but attenuate after that (Faraone et al., 2005a; Spencer, 2003). Charach et al. (2006) found that higher doses of stimulant correlated with reduced gains in height and weight; indeed, the effect did not become significant until the dose in MPH equivalents was >2.5 mg/kg/day for 4 years. Pliszka et al. (2006b) did not find that

children with ADHD treated with monotherapy with either amphetamine or MPH showed any failure to achieve expected height; furthermore, the two stimulant classes did not have any differential effect on height, but amphetamine had somewhat greater effects on weight than MPH. The subjects in this study had drug holidays averaging 31% of time during their treatment course, which may have contributed to the lack of effect of the stimulant on height.

In assessing for clinically significant growth reduction, it is recommended that serial plotting of height and weight on growth charts labeled with lines showing the major percentiles (5th, 10th, 25th, 50th, 75th, 90th, and 95th) be used (Mei et al., 2004). This should occur one to two times per year, and more frequently if practical. If the patient has a change in height or weight that crosses two percentile lines, then this suggests an aberrant growth trajectory. In these cases a drug holiday should be considered if return of symptoms during weekends or summers does not lead to marked impairment of functioning. The clinician should also consider switching the patient to another ADHD medication. It is important for the clinician to carefully balance the benefits of medication treatment with the risks of small reductions in height gain, which as of yet have not been shown to be related to reductions in adult height (Gittelman-Klein and Mannuzza, 1988; Kramer et al., 2000; Weiss and Hechtman, 2003).

SUMMARY

The key to effective long-term management of the patient with ADHD is continuity of care with a clinician experienced in the treatment of ADHD. The frequency and duration of follow-up sessions should be individualized for each family and patient, depending on the severity of ADHD symptoms; the degree of comorbidity of other psychiatric illness; the response to treatment; and the degree of impairment in home, school, work, or peer-related activities. The clinician should establish an effective mechanism for receiving feedback from the family and other important informants in the patient's environment to be sure symptoms are well controlled and side effects are minimal. Although this parameter does not seek to set a formula for the method of follow-up, significant contact with the clinician should typically occur two to four times per year in cases of uncomplicated ADHD and up to weekly sessions at times of severe dysfunction or complications of treatment. Nothing in this parameter should be construed as justification for limiting clinician contact by third-party payers or for regarding more limited contact by the clinician as substandard when clinical evidence documents that the patient is functioning well.

PARAMETER LIMITATIONS

AACAP practice parameters are developed to assist clinicians in psychiatric decision making. These parameters are not intended to define the standard of care, nor should they be deemed inclusive of all proper methods of care or exclusive of other methods of care directed at obtaining the desired results. The ultimate judgment regarding the care of a particular patient must be made by the clinician in light of all of the circumstances presented by the patient and his or her family, the diagnostic and treatment options available, and available resources.

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Evaluation of Psychopathological Conditions in Children With Heavy Prenatal Alcohol Exposure Susanna L. Fryer, MS, Christie L. McGee, MS, Georg E. Matt, PhD, Edward P. Riley, PhD, Sarah N. Mattson, PhD

Objective: This study compared the prevalence of psychopathological conditions in children with heavy prenatal alcohol exposure (N = 39) and nonexposed, typically developing peers (N = 30), matched with respect to age, gender, and socioeconomic status. *Methods:* Caregivers were interviewed with either the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version, or the Computerized Diagnostic Interview Schedule for Children, Version IV. Statistical resampling methods were used to create 95% confidence intervals for the difference between the proportions of children with psychopathological conditions in the exposed and control groups. *Results:* Group differences were seen in the attention-deficit/hyperactivity disorder, depressive disorders, oppositional defiant disorder, conduct disorder, and specific phobia outcome categories. The group difference in the attention-deficit/hyperactivity disorder category was by far the largest effect observed. *Conclusions:* These results suggest that fetal alcohol exposure should be considered a possible factor in the pathogenesis of childhood psychiatric disorders. These data provide clinically relevant information about the mental health problems that children with fetal alcohol exposure are likely to face. **Pediatrics** 2007;119:e733–e741.

Shire's net income almost doubles on sales of Adderall XR, new drugs

(Ref: Bloomberg, CNBC, Financial Times, Forbes, Morningstar, Shire)

April 25th, 2007

By: Alison Fischer

Tags: Top Story Adderall XR Daytrana Dynepo Elaprase Lialda Vyvanse Shire Corporate Affairs

Shire reported Wednesday that net income for the first quarter nearly doubled to $112.7 million over the year-ago period, on sales of attention-deficit hyperactivity disorder drug Adderall XR and new products. Adderall XR's sales increased 21 percent to $249.1 million, beating the $234 million forecast by analysts.

Total first-quarter revenue grew 29 percent to $528.2 million, compared to the prior-year quarter. "The numbers look good. Sales are very positive," remarked Jefferies International analyst, Robin Campbell. Quarterly sales for ADHD patch Daytrana, which was launched in the US in June last year, were lower than analysts had predicted and CEO Matthew Emmens noted that the drug's promotion had been reduced due to a problem with the product, which has since been resolved.

The company is in the process of launching several new drugs, including anaemia drug Dynepo, ulcerative colitis compound Lialda, and Elaprase, for Hunter Syndrome. "Elaprase should go north of $100 million for the year," remarked Canaccord Adams analyst, Karl Keegan. "It's a small but very well defined population."

"The key issue for Shire in 2007 is the switch from Adderall XR to [ADHD drug] Vyvanse," Lehman Brothers analyst Kerry Holford recently commented. Shire acquired the full rights to Vyvanse through its purchase of New River Pharmaceuticals earlier this year and expects to launch the product in the US in the second quarter. Citigroup analysts anticipate that Vyvanse may reach sales of $1.3 billion by 2010.

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- Shire's revenue, profit climb in first quarter on higher ADHD drug sales
- Shire's 4Q net income triples on drug sales
- Publication of Shire's annual report 2008

Reference Articles

- Shire edges 2007 revenue guidance higher; Q1 EPS jumps 39 percent - (Forbes)
- Shire 1Q revenue up 28.5%, outlook unchanged - (Morningstar)
- Shire first-quarter net almost doubles on new drugs - (Bloomberg)
- New products help Shire surge - (Financial Times)
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Press Release

VYVANSE™ (lisdexamfetamine dimesylate) Receives Final DEA Schedule Classification, Clearing Way for Launch of First Prodrug Stimulant for Treatment of ADHD

Basingstoke, U.K., Philadelphia, PA – May 3, 2007 – Shire plc (LSE: SHP, NASDAQ: SHPGY, TSX: SHQ) announced today that the U.S. Drug Enforcement Administration (DEA) has classified VYVANSE (lisdexamfetamine dimesylate, formerly known as NRP104), as a Schedule II controlled substance, following the earlier recommendation of the U.S. Food and Drug Administration (FDA).

The DEA schedule classification of VYVANSE represents the final step in the Federal government's administrative approval process before Shire begins commercialization of this novel ADHD treatment. The DEA has published this decision in the Federal Register today with an effective date of June 4, as required by law. The FDA approved the New Drug Application (NDA) for VYVANSE for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) on February 23, 2007. The product launch of VYVANSE remains on track for Q2 2007.

"The decision by the DEA was anticipated. All ADHD stimulant medications have historically been classified as Schedule II controlled substances," said Matthew Emmens, Shire Chief Executive Officer. "VYVANSE is the first ADHD stimulant to have the results of abuse liability studies reflected in its product label. Shire plans to continue to build the body of evidence in support of a lower abuse potential profile."

VYVANSE is a prodrug stimulant that is therapeutically inactive until metabolized in the body.[1] In clinical studies designed to measure duration of effect, VYVANSE provided consistent ADHD symptom control compared to placebo throughout the day, even at 6:00 pm.[1]

When VYVANSE was administered orally and intravenously in two human studies that evaluated abuse potential, VYVANSE produced subjective responses on a scale of "Drug Liking Effects" (DLE) that were less than *d*-amphetamine at equivalent doses.[1] DLE is used in clinical studies to assess the abuse potential of a drug among known substance abusers.

"VYVANSE will provide physicians with a novel treatment option," said Robert Findling, MD, study investigator and Director, Division of Adolescent and Child Psychiatry, University Hospitals Case Medical Center. "Clinical studies have shown that VYVANSE offers significant efficacy for up to 12 hours and significantly less abuse-related liking effects at equivalent oral doses of the active ingredient, *d*-amphetamine."

On April 20, 2007, Shire announced that it completed its acquisition of New River Pharmaceuticals Inc. ("New River") pursuant to a short-form merger. The completion of the acquisition will allow Shire to drive the launch and future development of VYVANSE and gain the full economic benefits of the treatment.

Additional information about VYVANSE and Full Prescribing Information are available at www.Vyvanse.com.

VYVANSE Important Safety Information

VYVANSE should not be taken by patients who have advanced arteriosclerosis; symptomatic cardiovascular disease; moderate to severe hypertension; hyperthyroidism; known hypersensitivity or idiosyncrasy to sympathomimetic amines; agitated states; glaucoma; a history of drug abuse; or during or within 14 days after treatment with monoamine oxidase inhibitors (MAOIs).

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses in ADHD. Physicians should take a careful patient history, including family history, and physical exam, to assess the presence of cardiac disease. Patients who report symptoms of cardiac disease such as exertional chest pain and unexplained syncope should be promptly evaluated. Use with caution in patients whose underlying medical condition might be affected by increases in blood pressure or heart rate.

New psychosis, mania, aggression, growth suppression, and visual disturbances have been associated with the use of stimulants. Use with caution in patients with a history of psychosis, seizures or EEG abnormalities, bipolar disorder, or depression. Growth monitoring is advised during prolonged treatment.

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic uses or distribution to others and the drugs should be prescribed or dispensed sparingly. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events.

The most common adverse events reported in clinical studies of VYVANSE were loss of appetite, insomnia, abdominal pain, and irritability.

For further information on Shire please contact:

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About ADHD
Approximately 7.8 percent of all school-age children, or about 4.4 million U.S. children aged 4 to 17 years, have been diagnosed with ADHD at some point in their lives, according to the U.S. Centers for Disease Control and Prevention (CDC).[2] ADHD is one of the most common psychiatric disorders in children and adolescents.[3] ADHD is a neurobiological disorder that manifests as a persistent pattern of inattention and/or hyperactivity-impulsivity that is more frequent and severe than is typically observed in individuals at a comparable level of development.[4] To be properly diagnosed with ADHD, a child needs to demonstrate at least six of nine symptoms of inattention; and/or at least six of nine symptoms of hyperactivity/impulsivity; the onset of which appears before age 7 years; that some impairment from the symptoms is present in two or more settings (e.g., at school and home); that the symptoms continue for at least six months; and that there is clinically significant impairment in social, academic or occupational functioning and the symptoms cannot be better explained by another psychiatric disorder.[4]

Although there is no “cure” for ADHD, there are accepted treatments that specifically target its symptoms. The most common standard treatments include educational approaches, psychological or behavioral modification, and medication.[5]

Shire plc
Shire’s strategic goal is to become the leading specialty biopharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on attention deficit and hyperactivity disorder (ADHD), human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire believes that a carefully selected portfolio of products with a strategically aligned and relatively small-scale sales force will deliver strong results.

Shire’s focused strategy is to develop and market products for specialty physicians. Shire’s in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe.

For further information on Shire, please visit the Company’s website: www.shire.com.

"SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995
Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire’s results could be materially affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to the impact of those on Shire’s Attention Deficit and Hyperactivity Disorder (“ADHD”) franchise; patents, including but not limited to, legal challenges relating to Shire’s ADHD franchise; government regulation and approval, including but not limited to the expected product approval dates of SPD503 (guanfacine extended release) (ADHD) and SPD465 (extended release triple-bead mixed amphetamine salts) (ADHD); Shire’s ability to secure new products for commercialization and/or development; Shire’s ability to benefit from its acquisition of New River Pharmaceuticals Inc.; and other risks and uncertainties detailed from time to time in Shire plc’s filings with the Securities and Exchange Commission, particularly Shire plc’s Annual Report on Form 10-K for the year ended December 31, 2006.

# # #

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HEALTH

Shire showcases new ADHD drug to wary doctors

Fri, May 18 09:25 AM EDT

By Ben Hirschler

LONDON (Reuters) - Shire Plc, aiming to convince wary doctors to try its new hyperactivity disorder drug Vyvanse, will use a top U.S. medical meeting starting on Saturday to promote the product ahead of its June launch.

Extensive clinical data, including results of long-term tests, will be presented at the May 19-24 American Psychiatric Association annual meeting in San Diego.

Company spokeswoman Jessica Mann said the congress would be "very important" for Vyvanse, while industry analysts believe it could be key to ensuring early commercial success.

Switching patients onto the next-generation treatment before Shire's older Adderall XR drug faces cheap generic competition from 2009 is pivotal to future profit growth at Britain's third-biggest drugmaker.

Analysts at Citigroup forecast Vyvanse could achieve peak sales of $1.7 billion by 2016, by which time it would account for 31 percent of the U.S. market for attention deficit hyperactivity disorder (ADHD) treatments.

But the new product will have to fight its corner.

A recent survey of 54 pediatricians and psychiatrists found doctors were likely to try Vyvanse but were unconvinced it had advantages over current therapies.

Results of the survey by Anian, a Reuters company that tracks industry trends for institutional investors, suggested Vyvanse could initially capture roughly 20 percent of market share from Adderall XR.

It is also likely to take business from Johnson & Johnson's Concerta and Eli Lilly and Co's Strattera.

One key swing factor will be the price of the new drug, which Shire has yet to announce. Most analysts expect it to be set at parity with Adderall XR, although the use of promotional coupons and a lower average daily consumption will reduce the value per Vyvanse prescription.

Vyvanse, like most other ADHD drugs, is a stimulant, but it cannot be metabolized until it reaches the stomach, which Shire argues makes it less appealing to drug abusers than Adderall XR -- although it is still classified as a controlled substance by the U.S. Drug Enforcement Administration.

It also has other advantages. Its action lasts right through until the evening and it also has a smoother delivery profile, resulting in a more uniform effect among patients.

Although Vyvanse will be launched in the United States next month, the full marketing offensive will only happen after the July 4 holiday, following a sales force meeting at the end of June.

Analysts at Cowen and Co said in a note this effective delay compared to early expectations of an April/May

launch pointed to 2007 sales of around $100 million, against consensus forecasts of $175-200 million. But they expect sales to ramp up to $430 million in 2008.

Shire gained full control of Vyvanse with its $2.6 billion acquisition of New River Pharmaceuticals this year.

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Analyst downgrades Shire's rating over Vyvanse expectations

(Ref: Bloomberg, BusinessWeek, MarketWatch)

July 9th, 2007

By: Daniel Beaulieu

Tags: Top Story Adderall XR Vyvanse Shire ADHD Corporate Affairs

A JP Morgan analyst downgraded Shire's rating on Monday, over concerns that fewer patients than expected would switch to the company's new attention-deficit hyperactivity disorder treatment, Vyvanse, from its older ADHD product, Adderall XR.

"Although Shire has an excellent track record in the attention-deficit hyperactivity disorder market, we see real risk that the Vyvanse switch will undershoot expectations," stated JP Morgan analyst Alistair Campbell, who forecast that sales for Vyvanse in 2010 would be $864 million. "We forecast a 70 percent switch on a patient basis, but toned down by the lower average daily consumption with Vyvanse," he added. Adderall XR's patent is expected to expire in the US in April 2009.

The FDA approved Vyvanse for children in February, and is currently reviewing the product for adults.

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- Shire hikes hyperactivity drug price more than expected
- Shire, New River receive FDA approval for Vyvanse
- DEA classifies Shire's Vyvanse as Schedule II controlled substance
- Shire's Vyvanse wins US approval for use in adults
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The Carlat Psychiatry Blog

Keeping Psychiatry Honest Since 2007

Thursday, July 12, 2007

Vyvanse Watch

Vyvanse (lisdexamfetamine dimesylate) was approved by the FDA in February for the treatment of ADHD in children, and is finally available in pharmacies. Tonight, Shire is presenting its official introduction of Vyvanse to physicians in a live webcast called "ADHD Thursday Night Live."

I don't know a huge amount about Vyvanse yet. I *do* know that Vyvanse is the molecule dextroamphetamine (trade names Dexedrine and Dextrostat) attached to the amino acid lysine. Shire cleverly calls it "lisdexamfetamine," presumably on the theory that using an "f" instead of "ph" in the chemical name will make it less obvious that Vyvanse is simply a fancified version of good old Dexedrine, a mainstay of ADHD treatment of decades.

At any rate, Vyvanse is an inactive “pro-drug” which has no pharmacologic effect until after it is absorbed through the GI tract into the bloodstream, when liver and gut enzymes cleave off the lysine portion and produce the active drug d-amphetamine. The requirement that lysine be lopped off delays the peak concentration of d-amphetamine, but not by very much. To give you a sense of the scale that we are talking about, Dexedrine, which is *pure* dexamfetamine (I'm using Shire's Newspell here) reaches its peak concentration at 3 hours after administration (see Dexedrine prescribing information, accessed at http://www.fda.gov/cder/foi/label/2006/ 017078s040lbl.pdf). Vyvanse reaches *its* peak concentration at 3.5 hours, a delay of 30 minutes. While classified as a Schedule II controlled substance like existing stimulants, Vyvanse produces no high if snorted, and a 100 mg dose made drug abusers less buzzed than a 40 mg dose of Dexedrine. However, at 150 mg of Vyvanse there were no differences between the two on the “drug likeability scale.” (See the manufacturer’s Web site at http://www.vyvanse.com/.)

Over the past 2 weeks in my private practice office I have received 9 different mailings from Shire about Vyvanse, an average of about one every other day, but I expect the pace to pick up significantly. Today, my Vyvanse mailing invited me to a "virtual roundtable series" to "provide feedback on various support materials that Shire provides physicians to help them better understand...Vyvanse." In other words, Shire has invited me and thousands of other physicians to be marketing consultants. No compensation was mentioned, but I was provided with the following number to register: 1-800-635-8730, program 2595. Readers are invited to do their own research on this opportunity.

I'll keep you updated on future promotionals as they flood into my office. This should be interesting, as Shire is the most aggressive pharmaceutical marketer I've ever seen, and they are not shy about using CME programs to promote their products.

at 6:46 PM

Share

6 comments:

scattered said...

I have been taking 30mg Vyvanse for a couple of weeks after a 50 year life of frustrated inability to concentrate on any one thing for very long. It's effect was almost immediate. The downside is that I miss the comic nature of my bouncing brain...my friends and family do not. if nothing else, the mess that is my life now has become painfully apparent. I don't feel completely overwhelmed, but close. i don't understand the medical communities willingness to prescribe speed and not opiods. from my memories of my parents medicine cabinet...not much has really changed since the sixties. It's all just an educated guess with usually inconsistant or worse results, at least for me.

January 29, 2008 at 8:41 AM

Anonymous said...

I really do not care what marketing the companies do as long as the medication does what it says it can do. I have been fighting my insurance company for 9mo to get Vyvanse approved as it was the only medication the worked for me for the short time I was on it.

I was on Concerta, Ritiln, and Adderall XR - They all gave me major side effects like serious cramping and abdominal pain, panic attacks & anxiety, to crashes around 3-4pm when I need to be alert with 3 little kids coming home from school.

Because of my fight to try to get the medication covered, I lost custody of my children temproarily as my ex hisband if saying that my "mental health" is not well managed.

So can you please explain to me that the ONLY medication that worked for me, I can not even get? And not to mention that Ido not have to worry about it's addictive qualities.

August 15, 2008 at 6:38 PM

Gina Pera said...

That's really a shame, anonymous. A medication that could help you to be healthier in mind and body, not to mention keep your family intact, and you can't get it.

Yet, our religion-infused Bush administration is doling out millions and millions of dollars to "faith-based" marriage initiatives carried out by lay people. Yet how many "marriage problems" are caused by brain disorders that remain untreated because community mental health clinics have gone the way of the dodo bird. My guess is, a huge percentage of them.

Leave it up to the grandstanding Grassley and his ilk--so blindly supported by comments elsewhere on this blog--and your insurance will never cover any modern delivery method for your stimulant medication. (Besides, they make so much more money when the insured pay a premium for the higher-cost meds.)

It's just amazing to me. White House staffers are some of the most powerful members of Congress, though they work behind the scenes with their own undisclosed interests. Yet no one questions Grassley's staffers and their motives. Talk about naive!

No one can convince me that Grassley's big insurance-company campaign donor has nothing to do with his crusade against psychiatric researchers and the medications they show to be effective.

Anyone who swallows his office's hype without question probably believed the "smoking gun" in Iraq, too. And look where that got us.

Yes, some pharma reps spook me, too. I've observed docs shortly after reps have gotten to them, and they look like they're fresh out of an an Amway marathon. Scary!

But for people like you and many others, Vyvanse (or Concerta or Daytrana or....) will be the only thing that works. So, we have to remember that behind the reps and the icky marketing moves are scientists who really do care and who've devoted their lives to helping people improve their lives.

Good luck,
Gina

August 23, 2008 at 5:37 PM

Anonymous said...

my psychiatrist seemed to want me to switch to vyvanse. I should have seen through this. I was on Adderall XR and it was pretty damn good. 2 20mg's a day (i should have been on 2 30s because I have a tolerance and am 250 lbs but whatever...screw docs charging like specialists but prescribing likes gp's lil punks, happy to field the easy money grounders and max profits...) anyways, apparently my insur co wanted a prior auth for vyvanse. apparently my doc threw adderall xr under the bus in that form (unbeknownst to me). docs always slying pushign the vyvanse, "oh, studies show its superior in every way...). Except this doc doesn't go outside the pdr, even though he's a specialist. and the pdr for vyvanse is stuck at 70mg, compared to 60 mg for Adderall xr. 70 mg vyvanse, however, translates, in its power, to about 25 or 30 mg of Adderall XR...so, I am getting less of the active ingredient with vyvanse at its max pdr dose compared to adderall xr at its max pdr dose of 60 mg (2 30 mg a day). Now my doc is saying I can't go back on adderall xr and the prior auth for xr was denied. doc says we said xr was not good when we applied for an auth for vyvanse. doc and the ins co are being kind of shifty about letting me see these damn prior auths. i sent in records requests. i want to know is it legal for shire to influence doc to switch me to vyvanse? i got a month free of vyvanse with that card...does he get free cme credits? 12 of those can costs like $500 a year or so (i think)...does he get free classes for switching patients? bcbshield in michigan or something gave docs $100 for every patient they switched over the generics, prompting the ama to issue a legality opinion on that and damning it...also the drug company said they previously appr'd my xr prior auth because it listed only mdd, major depressive disorder, not both mdd and add and said I should tell the doc to resubmit with just mdd, but the doc refused, said that would be wrong...i'm like, you did that before according to the insur co...let me do a document request to prove it and then explain why you are coming up with reasons now to keep me on vyvanse and off xr? ratface punks!

January 25, 2010 at 2:36 AM

Anonymous said...

I was diagnosed with ADHD about half a year ago and was prescribed 50mg Vyvanse as a first course of treatment. I shudder when I remember the one month I was on that drug. Basically, it made me insane. I was beyond irritable and was so jumpy and anxious that I couldn't concentrate on anything. It almost cost me the loving relationship I was in with my boyfriend. He would point out to me things he noticed when I was on the drug such as twitching and dilated pupils. He had fallen into recreational drug use that got out of control when he was a teenager and had to go through a treatment program. He said many of the side effects he saw in me reminded him of people on hard drugs. I would get so focused on one thing that I shut out everything else in the world, including paying bills, being on time to work, or anything else. I would focus on one thing and everything else would be shut out. I played a computer game for two days straight and ignored everything else including my ringing phone, which was my boyfriend trying to find out if I was still alive. I have never done anything like this before or since.

The drug also caused me insomnia and severe constipation. Because of the insomnia my sleep deficit grew over the course of the month. I need at least six hours of sleep a night to function properly and if I don't get that much my mood is more volatile and I am disoriented and depressed, even when I am not on a stimulant med. When Vyvanse was added on top of that I experienced a daily melt-down because I was so sleep-deprived, unhappy, and tense.

I'm a bartender and I found myself arguing with customers for the first time ever and even cursed out two people in my bar. I am usually a very easy going person and love to joke around but this drug changed my whole personality. When on Vyvanse I had zero sense of humor and everything pissed me off. Customers I have known for years would approach me very subtly and ask with great concern in their voice what was wrong. I had no idea what they were talking about and after this happened several times I got very defensive. I must have acted like Michael Douglas in the movie "Falling Down." One of my coworkers described me as having rabies. My driving habits were completely crazy. I would drive as fast as I could everywhere I went, weaving in and out of traffic like a lunatic. If a passenger in my car pointed out the way I was driving I would get angry.

After a few weeks I started taking only a portion of each capsule by cutting it open and dissolving a fraction of its contents in a beverage. This helped a bit but once I had reduced the dose enough to where the side effects started to drop off I also felt no effect from the drug in reducing symptoms of ADHD.

When I next saw my doctor I told him what was going on and he was shocked by what he was hearing. I was his first patient to be prescribed this drug and he told me he had no indication from what he had read about Vyvanse that it would have side effects that were so severe. He prescribed me generic Adderall instead. It treats my ADHD effectively with fewer and much less noticeable side effects. After being off Vyvanse for a few days I realized what had happened to me because I felt so much better. Other people noticed, too. Strangely, while all this was going on I was unaware that I was acting unusually. I had three Vyvanse tablets left over and about a month ago I consumed a third of the powder in one tablet. I had a paper I needed to do for school and I thought the Vyvanse might help me keep going all day. Big mistake! I yelled at my boyfriend a few times that day and was belligerent and confrontational with everyone else. I was so wound up I got very little done on my assignment and basically wasted a whole day. That evening I threw the other two Vyvanse tablets in the garbage.

Not everyone will experience the same side effects but I would recommend to anyone who is prescribed this drug that they be very careful and give their doctor lots of feedback about what's going on.

April 28, 2010 at 6:12 AM

Andrew Kinsella said...

The data re the minimal difference between Vyanse and dexamphetamine are interesting.

I was actually on dexamphetamine for my ADHD for 20 months. It was an excellent treatment- and stabilised my attention so well that I learned to meditate-(and that is now the mainstay of my ADHD treatment.I have not needed medication now for 16 months).

However dexamphetamine is a dirt cheap drug. There is no profit in it for the likes of Shire. No wonder that they want a glossy new drug to market- Vyanse is a much better cash cow.

October 22, 2011 at 7:48 AM

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Shire plc: 2007 Guidance Upgraded as Revenue Growth Accelerates

BASINGSTOKE, England and PHILADELPHIA, July 26, 2007 /PRNewswire-FirstCall/ -- Shire plc the global specialty biopharmaceutical company announces results for the second quarter 2007.

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    Q2 2007 Financial Highlights

    - Product sales up 34% to US$504 million;

    - Total revenues up 31% to US$575 million;

    - Net cash provided by operating activities up 33% to US$183 million;
and
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- 2007 revenue growth is now expected to be at least 25% (previous guidance: low 20% range).

Matthew Emmens, Chief Executive Officer, commented:

"We continue to execute our strategy effectively and this is reflected in the delivery of an excellent second quarter. Revenues were up 31%, led by ADDERALL XR and DAYTRANA in a growing ADHD market. ELAPRASE also made a significant contribution to overall growth as did our other new products FOSRENOL and LIALDA. For the half year, total revenues grew by 30%, with strong operating cash generation.

Importantly, we have just launched VYVANSE, our next generation ADHD product. We believe this product is best in class and early results are promising with positive feedback from both physicians and patients. In addition, we have received two FDA approvable letters in the ADHD category - for INTUNIV, a non-stimulant treatment for ADHD, and SPD465, a longer acting version of ADDERALL XR for the treatment of adult ADHD.

Our business continues to broaden into biopharmaceuticals. Our in-licensing of JUVISTA, a protein candidate for the prevention and reduction of scarring in connection with both therapeutic and cosmetic surgery, fits well within our model of focusing on the specialist physician. JUVISTA could become the first agent with such an indication and has the potential to create a substantial market.

With established positions in major pharmaceutical territories, we are now expanding into selected newer, faster growing markets in a measured way.

Shire has never been stronger and we now expect revenue growth in 2007 to be not less than 25%. We have impressive and well focused product franchises and we continue to bring in new projects, strengthening our pipeline."

Business Highlights

JUVISTA(R) (Human TGFBeta3)

On June 19, 2007 Shire signed an agreement with Renovo Limited ("Renovo") to develop and commercialize JUVISTA, Renovo's novel drug candidate in late Phase 2 development. JUVISTA is being studied for the prevention and reduction of scarring in connection with both cosmetic and therapeutic surgery; areas often paid for "out of pocket" by patients choosing elective surgery. Under the terms of the agreement Shire has the exclusive right to commercialize JUVISTA worldwide, with the exception of EU member states. Phase 3 trials for JUVISTA are expected to commence in mid 2008.

Following the expiration of the Hart Scott-Rodino ("HSR") waiting period of 30 days commencing July 11, 2007, Shire will pay Renovo US$75 million (expensed as R&D for US GAAP purposes) and will make an equity investment in Renovo Group plc of US$50 million (at a subscription price of GBP2 per share, which represents approximately 7% of Renovo's share capital). In addition, Shire will pay Renovo US$25 million on filing of JUVISTA with the US Food and Drug Administration ("FDA"), up to US$150 million on FDA approval, royalties on net sales of JUVISTA and up to US$525 million on the achievement of very significant sales targets.

Issue of Convertible Bonds

In May 2007 Shire issued US$1.1 billion principal amount of Convertible Bonds due 2014. The proceeds of the issue were used by Shire to repay borrowings under its bank facilities previously drawn to partially fund the acquisition of New River Pharmaceuticals Inc. ("New River"). The bonds are convertible into ordinary shares of Shire plc, have a semi-annual coupon of 2.75% per annum and an initial conversion price of US$33.5879 per ordinary share (equivalent to US$100.7637 per American Depository Share ("ADS")).

New River Acquisition

On April 19, 2007 Shire completed the acquisition of New River by way of a short-form merger for US$64 per share, or approximately US$2.6 billion. The acquisition of New River allows Shire to capture the full economic value of VYVANSE(TM) and gain control of the future development and commercialization of this product.

Product Highlights

VYVANSE(TM) (lisdexamfetamine dimesylate) - Attention Deficit Hyperactivity Disorder ("ADHD").

On May 3, 2007 the US Drug Enforcement Administration ("DEA") classified VYVANSE as a Schedule II controlled substance, consistent with the earlier recommendation of the FDA. VYVANSE is indicated for the treatment of ADHD in children aged six to twelve years old. The VYVANSE launch meeting took place in the week commencing June 25, 2007. Shire's ADHD sales force is now actively promoting this product.

LIALDA(TM) (mesalamine) - Ulcerative colitis

On March 19, 2007 LIALDA was launched in the US. By July 13, 2007 LIALDA had achieved a US market share of 4.2%. Preparations are underway for the launch of the product, known as MEZAVANT(TM) in the EU, in the second half of this year.

DYNEPO(R) (epoetin delta) - Anemia associated with chronic kidney disease

Following the launch of DYNEPO in Germany in Q1 2007, this quarter saw the launch of DYNEPO in the UK.

FOSRENOL(R) (lanthanum carbonate) - Hyperphosphatemia

FOSRENOL was launched in Italy and Canada in Q2 2007. FOSRENOL has now been launched in 21 countries. FOSRENOL's European sales for the three months to June 30, 2007 were US$9.0 million (2006: US$0.3 million). In addition sales of FOSRENOL in the US have increased from US$5.9 million in Q2 2006 to US$15.5 million in Q2 2007.

ELAPRASE(TM) (idursulfase) - Hunter syndrome

On June 14, 2007 Health Canada (under priority review) approved ELAPRASE for sale and marketing in Canada. ELAPRASE had been made available on a limited basis to Canadian patients since January 2007 through Health Canada's Special Access Program and reimbursement discussions across Canada are now underway to enable widespread access. In less than eleven months since its first approval in the US, ELAPRASE is now available in 25 countries and sales for the three months to June 30, 2007 were US$42.7 million.

Pipeline Highlights

VYVANSE - ADHD (adult)

On June 29, 2007 Shire submitted a supplemental New Drug Application to the FDA for VYVANSE for the treatment of ADHD in adults. This application is subject to a ten month FDA review period. Shire expects to release results from the Phase 3 clinical trials in Q4 2007.

INTUNIV(TM) (guanfacine) extended release (previously known as SPD503) - ADHD

On June 21, 2007 Shire received an approvable letter from the FDA for INTUNIV, a non-stimulant selective alpha-2A-receptor agonist. Shire is seeking approval of INTUNIV as monotherapy for the treatment of ADHD symptoms throughout the day in children aged six to 17 years. Shire is working with the FDA to provide a full and timely response to the agency's request.

Amphetamine transdermal system ("ATS") - ADHD

In June 2007 following completion by Noven Pharmaceuticals Inc. ("Noven") of Phase 1 studies for ATS, Shire paid US$5.9 million to Noven to acquire exclusive development rights to ATS.

SPD465 - ADHD

On May 19, 2007 Shire received an approvable letter from the FDA for SPD465, an investigational oral stimulant intended to provide symptom control of ADHD in adults for up to 16 hours with one daily dose. Shire is evaluating its response to the approvable letter.

ELAPRASE (idursulfase) - Hunter Central Nervous System ("Hunter CNS")

In June 2007 Shire HGT had a pre-Investigational New Drug meeting with the FDA to finalize plans for the Phase 1 clinical trial program for Hunter CNS. The program remains on track for initiation of clinical trials in 2008.

Q2 2007 Unaudited Results

	Q2 2007		
	US GAAP	Adjustments	Non GAAP(1)
	US$M	US$M	US$M

Revenues	574.9	-	574.9
(Loss)/Income from ongoing operations(2)	(1,786.4)	1,935.5	149.1
Net (loss)/income	(1,811.3)	1,925.2	113.9
Diluted earnings/(loss) per:			
Ordinary share	(331.0c)	351.4c	20.4c
ADS	(993.0c)	1,054.2c	61.2c

	Q2 2006		
	US GAAP	Adjustments	Non GAAP(1)
	US$M	US$M	US$M
Revenues	439.1	-	439.1
(Loss)/Income from ongoing operations(2)	83.8	39.3	123.1
Net (loss)/income	61.3	28.3	89.6
Diluted earnings/(loss) per:			
Ordinary share	12.0c	5.6c	17.6c

ADS	36.1c	16.7c	52.8c

Note: Average exchange rates for Q2 2007 and Q2 2006 were US$1.98: GBP1.00 and US$1.83: GBP1.00 respectively.

(1) Non GAAP income from ongoing operations, Non GAAP net income and Non GAAP diluted earnings per ordinary share and per ADS exclude intangible asset amortization charges, the New River in-process R&D charge of US$1,896 million, the accounting impact of share-based compensation and other items as described on page 6. For an explanation of why Shire's management believes that these non-GAAP financial measures are useful to investors, see page 6. For a reconciliation of these non-GAAP financial measures to the most directly comparable financial measures prepared in accordance with US GAAP, see pages 24-25.

(2) (Loss)/income from continuing operations before income taxes and equity in earnings of equity method investees.

2007 Financial Outlook

Following the strong performance this quarter, we have amended the previous guidance given as part of the Q1 2007 results:

- 2007 revenue growth is now upgraded to be not less than 25% (previous guidance: low 20% range) assuming prescription growth in the ADHD market of 5-7% (previous guidance: 4-6%);

- As in 2006, earnings for 2007 will be impacted by the costs associated with the continued development, launch and roll-out of new products. We currently expect these costs to be at the upper end of the ranges set out below, which include products and projects arising from the recent acquisition of New River and JUVISTA:

- Research and development spend for 2007 will be in the range of US$340 - US$360 million (unchanged from previous guidance).

- SG&A costs for 2007 will be in the range of US$930 - US$960 million (unchanged from previous guidance). The level of quarterly SG&A expenditure is expected to increase over the Q2 2007 spend as VYVANSE is launched in the US and MEZAVANT is launched in Europe.

- In addition:

- The depreciation charge for the year is expected to increase by approximately 20% compared to 2006 (unchanged from previous guidance); and

- The effective tax rate for 2007 is expected to be approximately 26% (unchanged from previous guidance).

Shire reports its non GAAP earnings based on net income/(loss) adjusted for certain items, and as from Q1 2007, excluding intangible asset amortization charges and the accounting impact of SFAS123R for share based compensation. The financial outlook for the full year stated above excludes the following items (all of which will be excluded from non GAAP net income):

- Intangible asset amortization charges, which are expected to rise by up to 80% over the 2006 charge of US$57.4 million (including US$1.1 million of impairments);

- The accounting impact of SFAS 123R estimated at approximately US$45 million (US$22 million for the 6 months ended 30 June 2007) (split for GAAP purposes between cost of product sales, R&D and SG&A in the approximate ratio of 10%, 20% and 70%, respectively);

- The in-process research and development ("IPR&D") charge related to New River (US$1.9 billion);

- Up front payments for JUVISTA of US$75 million;

- Integration costs (including bridging finance costs) for the New River acquisition which are estimated to be approximately US$10 million (US$9.2 million incurred to date including bridging finance costs of US$7.9 million); and

- Other items as described on page 6 under Non GAAP Measures.

Dividend

In respect of the six months ended June 30, 2007, the Board resolved to pay an interim dividend of 2.147 US cents per ordinary share (2006: 1.935 US cents per share).

Dividend payments will be made in Pounds Sterling to Ordinary Shareholders, in US Dollars to holders of American Depository Shares and in Canadian Dollars to holders of Exchangeable Shares. A dividend of 1.048 pence per ordinary share (2006: 1.048 pence), 6.441 US cents per ADS (2006: 5.804 US cents) and 6.715 Canadian cents per Exchangeable Share (2006: 6.584 Canadian cents) will be paid. The Board resolved to pay the dividend on October 4, 2007 to persons whose names appear on the register of members of the Company (or to persons registered as holders of Exchangeable Shares in Shire Acquisition Inc.) at the close of business on September 14, 2007.

This is consistent with Shire's stated policy of paying a dividend semi-annually, set in US cents per share. Dividend growth for the full year will be reviewed by the Board when the second interim dividend is determined. Shire intends to pursue a progressive dividend policy.

Non-Executive Director Changes

As part of the Board's ongoing review of corporate governance matters, the following Non-Executive changes were announced on July 25, 2007: David Kappler, Chair of Shire's Audit, Compliance and Risk Committee will take on the additional role of Senior Independent Director; Kate Nealon will take on the role of Chair of the Remuneration Committee; and Dr Jeff Leiden will join the Remuneration and Nomination Committees, each with immediate effect. Dr Barry Price has stepped down as Senior Independent Director, Chair of the Remuneration Committee and as a member of the Audit, Compliance and Risk Committee. Dr Price remains a Board member and a member of the Company's Nomination Committee.

On May 10, 2007 non-executive director the Hon. James Grant Q.C. retired from the Board following completion of his term of office. The board thanks Mr Grant for his contribution during his six year term in office.

High resolution images are available for the media to view and download free of charge from http://www.vismedia.co.uk

Matthew Emmens, Chief Executive Officer and Angus Russell, Chief Financial Officer will host the investor and analyst meeting and conference call at 14:30 BST/9:30 EDT at the offices of Financial Dynamics, Holborn Gate, 26 Southampton Buildings, London WC2A 1PB.

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    The details of the conference call are as follows:


    UK dial in: 0800-953-0810
```

US dial in: 1866-789-2220

International dial in: +44-(0)-1452-560-068

Password/Conf ID: 10176864#

Live Webcast: http://gaia.world-television.com/shire/20070726/

Notes to editors

SHIRE PLC

Shire's strategic goal is to become the leading specialty biopharmaceutical company that focuses on meeting the needs of the specialist physician. Shire focuses its business on ADHD, human genetic therapies (HGT), gastrointestinal (GI) and renal diseases. The structure is sufficiently flexible to allow Shire to target new therapeutic areas to the extent opportunities arise through acquisitions. Shire believes that a carefully selected portfolio of products with a strategically aligned and relatively small-scale sales force will deliver strong results.

Shire's focused strategy is to develop and market products for specialty physicians. Shire's in-licensing, merger and acquisition efforts are focused on products in niche markets with strong intellectual property protection either in the US or Europe.

For further information on Shire, please visit the Company's website: http://www.shire.com

THE "SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to the impact of those on Shire's Attention Deficit and Hyperactivity Disorder ("ADHD") franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval date of INTUNIV(TM) (guanfacine) extended release (ADHD); Shire's ability to secure new products for commercialization and/or development; Shire's ability to benefit from its acquisition of New River Pharmaceuticals Inc.; the successful development of JUVISTA(R) (human TGFBeta3) and other risks and uncertainties detailed from time to time in Shire plc's filings with the Securities and Exchange Commission, particularly Shire plc's Annual Report on Form 10-K for the year ended December 31, 2006.

Non-GAAP Measures

This press release contains financial measures not prepared in accordance with US GAAP. These measures are referred to as "non GAAP" measures and include Non GAAP income from ongoing operations, Non GAAP net income, Non GAAP diluted earnings per ordinary share and Non GAAP diluted earnings per ADS. These non GAAP measures exclude the effect of certain cash and non-cash items, both recurring and non-recurring, that Shire's management believes are not related to the core performance of Shire's business.

These non GAAP financial measures are used by Shire's management to make operating decisions because they facilitate internal comparisons of the Company's performance to historical results and to competitors' results. These measures are also considered by Shire's Remuneration Committee in assessing the performance and compensation of employees, including its executive directors.

The non GAAP measures are presented in this press release as the Company's management believe that they will provide investors with a means of evaluating, and an understanding of how Shire's management evaluates, the Company's performance and results on a comparable basis that is not otherwise apparent on a GAAP basis, since many one-time, infrequent or non-cash items that the Company's management believe are not indicative of the core performance of the business may not be excluded when preparing financial measures under US GAAP.

However, these non GAAP measures should not be considered in isolation from, as substitutes for, or superior to financial measures prepared in accordance with US GAAP.

The following are trademarks of Shire or companies within the Shire Group which are the subject of trademark registrations in certain territories:

ADDERALL XR(R) (mixed salts of a single-entity amphetamine)

CALCICHEW(R) range (calcium carbonate with or without vitamin D3)

CARBATROL(R) (carbamazepine) extended-release capsules

DAYTRANA(TM) (methylphenidate transdermal system)

ELAPRASE(TM) (idursulfase)

FOSRENOL(R) (lanthanum carbonate)

INTUNIV(TM) (guanfacine) extended release

LIALDA(TM) (mesalamine)

MEZAVANT(TM) (mesalazine)

REMINYL(R) (galantamine hydrobromide) (UK and Republic of Ireland)

REMINYL XL(TM) (galantamine hydrobromide) (UK and Republic of Ireland)

REPLAGAL(R) (agalsidase alfa)

VYVANSE(TM) (lisdexamfetamine dimesylate)

XAGRID(R) (anagrelide hydrochloride)

The following are trademarks of third parties referred to in this

press release:

3TC (trademark of GlaxoSmithKline (GSK))

DYNEPO (trademark of Sanofi Aventis)

JUVISTA (trademark of Renovo)

PENTASA (trademark of Ferring)

RAZADYNE (trademark of Johnson & Johnson)

RAZADYNE ER (trademark of Johnson & Johnson)

REMINYL (trademark of Johnson & Johnson, excluding UK and Republic of

Ireland) REMINYL XL (trademark of Johnson & Johnson, excluding UK and

Republic of Ireland) ZEFFIX (trademark of GSK)

OVERVIEW OF US GAAP FINANCIAL RESULTS

1. Introduction

Summary of Q2 2007

Revenues from continuing operations for the three months to June 30, 2007 increased by 31% to US$574.9 million (2006: US$439.1 million).

The loss from continuing operations (before income taxes and equity in earnings of equity method investees) for the three months to June 30, 2007 was US$1,786.4 million (2006: income of US$83.8 million). The loss was due to the US$1,896.0 million write-off of IPR&D acquired as part of the US$2.6 billion acquisition of New River. This adjustment is required under US GAAP and represents the value of acquired intangible assets still under development, including the adult indication of VYVANSE.

Cash inflow from operating activities for the three months to June 30, 2007 increased by 33% to US$183.0 million (2006: US$137.4 million). This increase resulted mainly from higher sales in Q2 2007 compared to Q2 2006, partially offset by increased cash expenditure on operating costs and expenses.

Cash and cash equivalents, restricted cash and short-term investments at June 30, 2007 totaled US$638.0 million (December 31, 2006: US$1,156.7 million). The decrease in cash and cash equivalents during the first half of the year of US$528.4 million was primarily due to the acquisition of New River being partly funded from Shire's pre-acquisition cash resources. The remaining funding for the New River acquisition comprised cash of US$0.9 billion raised from the equity placing during Q1 2007 and US$1.3 billion drawn from Shire's loan facilities during Q2 2007.

2. Product sales

For the three months to June 30, 2007 product sales increased by 34% to US$504.2 million (2006: US$376.0 million) and represented 88% of total

revenues (2006: 86%).

Product Highlights

Product	Sales US$M	Sales Growth (2)	US Rx Growth (1) (2)	US Market Share at June 30, 2007 (1)
ADDERALL XR	255.1	16%	9%	26%
DAYTRANA	19.9	-	-	2%
PENTASA	40.2	17%	6%	17%
LIALDA	5.0	-	-	4%
FOSRENOL	24.5	295%	10%	9%
REPLAGAL	31.9	13%	n/a	n/a
ELAPRASE	42.7	-	n/a	n/a
CARBATROL	17.9	10%	-4%	41%
XAGRID	17.1	21%	n/a	n/a

(1) IMS Prescription Data - Product specific

(2) Compared to Q2 2006.

ADDERALL XR - ADHD

ADDERALL XR is the leading brand in the US ADHD market with an average market share of 26% during Q2 2007 (2006: 26%). US ADHD market growth of 8% resulted in a 9% increase in US prescriptions for ADDERALL XR for the three months to June 30, 2007 compared to the same period in 2006.

Sales of ADDERALL XR for the three months to June 30, 2007 were US$255.1 million, an increase of 16% compared to the same period in 2006 (2006: US$220.7 million). Product sales growth was higher than prescription growth due primarily to a price increase in January 2007.

Litigation proceedings concerning Shire's ADDERALL XR patents are ongoing. Further information on this litigation can be found in our filings with the US Securities and Exchange Commission ("SEC"), including our Annual Report on Form 10-K for the year to December 31, 2006.

As previously disclosed, the United States Federal Trade Commission ("FTC") informed Shire on October 3, 2006 that it was reviewing the ADDERALL XR patent litigation settlement agreement

between Shire and Barr Laboratories, Inc. ("Barr"). On June 22, 2007, the Company received a civil investigative demand requesting that it provides information to the FTC relating to its settlement with Barr and its earlier settlement with Impax Laboratories, Inc. The Company is cooperating fully with this investigation and believes that the settlements are in compliance with all applicable laws.

VYVANSE - ADHD

VYVANSE was launched in the US in June 2007 following receipt of required regulatory approvals. Launch stocks of US$55.9 million (before sales deductions) were shipped to wholesalers during June 2007. In accordance with US GAAP, sales of these launch stocks have been deferred pending satisfaction of revenue recognition criteria. All launch stocks are expected to be recognized into revenue by the end of 2007.

DAYTRANA - ADHD

Following its launch in June 2006, DAYTRANA achieved an average market share during Q2 2007 of 2%, consistent with the previous quarter. Net sales for the three months to June 30, 2007 were US$19.9 million, compared to net sales of US$11.9 million for the first quarter of 2007. Net sales growth of US$8.0 million over the first quarter of 2007 is primarily due to a reduction in the redemption of coupons issued to support the product's launch.

The addition of DAYTRANA, combined with the ADDERALL XR market share has helped Shire grow its total share of the US ADHD market to 28% at June 30, 2007 compared to 27% at June 30, 2006 (which included a 1% share relating to ADDERALL, which Shire subsequently divested).

PENTASA - Ulcerative colitis

PENTASA's US average market share of the oral mesalamine prescription market remained stable at 17% for Q2 2007 compared to the same period in 2006. US prescriptions of PENTASA for the three months to June 30, 2007 were up 6% compared to the same period in 2006. This was primarily due to a 5% increase in the US oral mesalamine prescription market.

Sales of PENTASA for the three months to June 30, 2007 were US$40.2 million, an increase of 17% compared to the same period in 2006 (2006: US$34.5 million). Sales growth is higher than prescription growth primarily due to an increasing shift to the 500mg strength capsules as well as the impact of a price increase in November 2006.

LIALDA - Ulcerative colitis

In Q2 2007 LIALDA's average market share of the US oral mesalamine prescription market was 2.5% following the launch of LIALDA in Q1 2007. Net sales of US$5.0 million for three months to June 30, 2007 were impacted by US$2.1 million in sales deductions, primarily stocking discounts and coupons.

The initial launch stock of US$34.3 million (before sales deductions) continues to be worked through the wholesaler pipeline. In accordance with US GAAP, sales of LIALDA are being recognized as the conditions for revenue recognition are met. All launch stock is expected to be recognized into revenue by the end of the year.

FOSRENOL - Hyperphosphatemia

In Europe, FOSRENOL has now been launched in Germany, France, UK, Italy and a number of other countries. Launches will continue throughout 2007 in the EU including Spain, subject to finalization of national marketing authorizations and the conclusion of pricing and reimbursement negotiations. European sales of FOSRENOL for the three months to June 30, 2007 were US$9.0 million (2006: US$0.3 million).

US sales of FOSRENOL for the three months to June 30, 2007 were US$15.5 million (2006: US$5.9

million) giving worldwide FOSRENOL sales of US$24.5 million for the quarter (2006: US$6.2 million). US IMS Retail Audit prescriptions for the three months to June 30, 2007 were up 10% compared to the same period in 2006 due to FOSRENOL increasing its average market share to 8.5% during Q2 2007 (2006: 8.1%) and market growth of 4% over the same period. The increase in net sales is significantly higher than retail audit prescription growth due to a combination of a price increase in July 2006, growth in use of the higher strengths (launched in early 2006), lower sales deductions, wholesaler de-stocking in 2006 of initial launch stocks and the growth of non-retail business.

REPLAGAL - Fabry disease

Sales for the three months to June 30, 2007 were US$31.9 million (2006: US$28.3 million). This increase of 13% is primarily due to higher unit sales in Europe and Canada and the impact of favorable exchange rates.

ELAPRASE - Hunter syndrome

ELAPRASE was successfully launched in the US in August 2006 and in several major European markets during the first half of 2007. ELAPRASE is now sold in 25 countries. Sales for the three months to June 30, 2007 were US$42.7 million compared to US$26.6 million in the first quarter of 2007, an increase of US$16.1 million.

CARBATROL - Epilepsy

US prescriptions for CARBATROL for the three months ending June 30, 2007 were down 4% compared to the same period in 2006. This was primarily due to a comparable decline in the US extended release carbamazepine prescription market.

Sales of CARBATROL for the three months to June 30, 2007 were US$17.9 million, an increase of 10% compared to the same period in 2006 (2006: US$16.2 million). Although there was a decrease in US prescriptions, sales rose due to price increases in July 2006 and April 2007.

Patent litigation proceedings relating to CARBATROL are ongoing. Further information about this litigation can be found in our filings with the SEC, including our Annual Report on Form 10-K for the year to December 31, 2006.

XAGRID - Thrombocythemia

Sales for the three months to June 30, 2007 were US$17.1 million, an increase of 21% compared to the same period in 2006 (2006: US$14.1 million). Expressed in transaction currencies (XAGRID is primarily sold in Euros), sales increased by 13% due to growth in many of Shire's markets. In addition, there was an 8% benefit from favorable exchange rate movements against the US dollar.

3. Royalties

Royalty revenue increased to US$64.0 million for the three months to June 30, 2007 (2006: US$60.4 million).

Royalty Highlights

Product	Royalties to Shire US$M	Royalty (1) Growth %

3TC	39.0	2%
ZEFFIX	10.4	24%
Other	14.6	7%
Total	64.0	6%

(1) Compared with 2006.

3TC - HIV infection and AIDS

Royalties from sales of 3TC for the three months to June 30, 2007 were US$39.0 million, an increase of 2% compared to the same period in 2006 (2006: US$38.3 million). The impact of foreign exchange movements has contributed 4% to the reported growth; excluding foreign exchange movements there has been a decline of 2% compared to the same period in 2006.

Shire receives royalties from GSK on worldwide 3TC sales. GSK's worldwide sales of 3TC for the three months to June 30, 2007 were US$284 million, a decrease of 2% compared to the same period in 2006 (2006: US$290 million). The nucleoside analogue market for HIV has continued to grow, however competitive pressures within the market have increased, leading to a decline in 3TC sales.

ZEFFIX - Chronic hepatitis B infection

Royalties from sales of ZEFFIX for the three months to June 30, 2007 were US$10.4 million, an increase of 24% compared to the same period in 2006 (2006: US$8.4 million). The impact of foreign exchange movements has contributed 9% to the reported growth, excluding foreign exchange movements there has been an increase of 15% compared to the same period in 2006.

Shire receives royalties from GSK on worldwide ZEFFIX sales. GSK's worldwide sales of ZEFFIX for the three months to June 30, 2007 were US$88 million, an increase of 20% compared to the same period in 2006 (2006: US$73 million). This increase was mainly due to strong growth in the Chinese and Korean markets and favorable foreign exchange movements.

OTHER

Other royalties are primarily in respect of REMINYL and REMINYL ER (known as RAZADYNE and RAZADYNE ER in the US), a product marketed worldwide (excluding the UK and the Republic of Ireland) by Janssen Pharmaceutical N.V. (Janssen), an affiliate of Johnson & Johnson. Shire has the exclusive marketing rights in the UK and the Republic of Ireland. Sales of the REMINYL/RAZADYNE range, for the symptomatic treatment of mild to moderately severe dementia of the Alzheimer's type, continue to grow.

Barr and other companies have filed Abbreviated New Drug Applications ("ANDA") with the FDA for generic versions of RAZADYNE and Janssen and Synaptech Inc. ("Synaptech") have filed lawsuits against some of those ANDA filers. A trial was held during the week of May 21, 2007. No decision from the court has been issued at this time.

In June 2006 Janssen and Synaptech filed a lawsuit against Barr for infringement of their patent rights relating to RAZADYNE ER as a result of Barr filing an ANDA with the FDA for a generic version of RAZADYNE ER. Janssen and Synaptech also filed suit against Sandoz Inc. in May 2007. No court date has been set in either proceedings.

4. Financial details

Cost of product sales

For the three months to June 30, 2007 the cost of product sales was 14% of product sales (2006: 16%). The cost of product sales for REPLAGAL in 2006 included a US$16.7 million adjustment in respect of inventories acquired through the acquisition of Transkaryotic Therapies, Inc. (TKT). This fair value adjustment increased Shire's cost of product sales as a percentage of product sales for the three months to June 30, 2006 by 4%. Excluding the impact of this fair value adjustment in 2006, cost of product sales as a percentage of product sales in the three months to June 30, 2007 was 2% higher than for the three months to June 30, 2006 due to changes in the product sales mix.

For the three months to June 30, 2007 cost of product sales included a charge of US$0.9 million for share based compensation under SFAS 123R (2006: US$0.7 million).

Research and development (R&D)

R&D expenditure increased from US$72.6 million in the three months to June 30, 2006 to US$102.1 million in the three months to June 30, 2007. Phase 3(b) and Phase 4 studies to support new product launches and the continuation of Phase 3 trials on GA-GCB, the development of the Women's Health and New River franchises, pre-clinical development of three HGT projects, two new Phase 1 projects and two further pre-clinical projects have contributed to this increase.

Expressed as a percentage of total revenues, R&D expenditure was 18% for the three months to June 30, 2007 (2006: 17%).

For the three months to June 30, 2007 R&D included a charge of US$3.2 million for share based compensation under SFAS 123R (2006: US$1.3 million) and a payment to Noven of US$5.9 million to acquire the exclusive rights to ATS.

Selling, general and administrative (SG&A)

SG&A expenses increased from US$197.3 million in the three months to June 30, 2006 to US$253.1 million in the three months to June 30, 2007, an increase of 28%.

The increase, as planned, in SG&A expenses included the impact of the following:

- An increase in the ADHD sales force to promote VYVANSE;

- The cost of the new GI sales force in the US; and

- The launches of DYNEPO, LIALDA and VYVANSE.

As a percentage of product sales, SG&A expenses were 50% (2006: 52%). For the three months to June 30, 2007 SG&A included a charge of US$7.7 million for share based compensation under SFAS 123R (2006: US$5.7 million), representing 2% of product sales (2006: 2%).

Depreciation and amortization

The depreciation charge for the three months to June 30, 2007 was US$14.6 million (2006: US$10.5 million). The increase in depreciation follows investment in Shire's infrastructure to support the continuing growth of the Company.

The amortization charge for the three months to June 30, 2007 was US$17.6 million (2006: US$13.3 million). The increase in amortization is primarily due to the commencement of amortization of capitalized intangibles for DAYTRANA and DYNEPO following their launches in June 2006 and March 2007 respectively. The amortization of capitalized intangibles for VYVANSE will commence in

July 2007.

Integration Costs

For the three months to June 30, 2007 Shire incurred US$1.3 million of costs associated with the integration of the New River business (2006: US$1.6 million relating to the TKT acquisition). New River is now fully integrated and no further integration costs are anticipated.

In-process R&D (IPR&D)

During the three months to June 30, 2007, as required under US GAAP (business combination accounting), Shire expensed the portion of the New River purchase price allocated to IPR&D of US$1,896.0 million. This amount represents the value of those acquired development projects which, at the acquisition date, had not been approved by the FDA or other regulatory authorities, including the adult indication of VYVANSE.

Gain on disposal of product rights

For the three months to June 30, 2007 Shire recognised a gain on the disposal of certain non core product rights of US$5 million (2006: US$nil)

Interest income

For the three months to June 30, 2007 Shire received interest income of US$14.9 million (2006: US$10.0 million). Interest income primarily relates to interest received on cash balances. Interest income for the three months to June 30, 2007 is significantly higher than for the three months ending June 30, 2006 due to increases in the US dollar interest rate and higher average cash balances.

Interest expense

For the three months to June 30, 2007 the Company incurred interest expense of US$28.0 million (2006: US$6.5 million). The increase in interest expense follows the acquisition of New River which was partly funded by US$1.3 billion of term loans, utilized under the US$2.3 billion banking facility. These term loans were subsequently partially repaid using the US$1.1 billion proceeds from the convertible bonds issued in May 2007. The remaining US$0.2 billion of the term loans was also repaid during the quarter. Interest expense for 2007 includes a US$7.9 million write-off of deferred financing costs following the repayment of these term loans.

The original US$2.3 billion banking facility has been reduced to US$1.2 billion and its terms have been renegotiated on a more favorable basis. Further details are set out in Shire's Form 8-K dated July 25, 2007. As at June 30, 2007 no drawings under this facility were outstanding.

In the three months to June 30, 2007 and 2006 part of the interest expense relates to a provision for interest, which may be awarded by the Court in respect of amounts due to those ex-TKT shareholders who have requested appraisal of the acquisition consideration payable for their TKT shares. The original trial date for the appraisal rights litigation was set for April 23, 2007, but this trial date has since been deferred, and the Company is awaiting a new trial date. Further information about this litigation can be found in our filings with the SEC, including our Annual Report on Form 10-K for the year to December 31, 2006.

Taxation

The effective rate of tax for the three months to June 30, 2007 was -1% (2006: 28%). The significant difference from the prior year effective rate is due to the IPR&D charge of US$1,896.0, which is not tax deductible. Excluding the IPR&D charge the effective rate of tax was 23%. At June 30, 2007 net deferred tax liabilities of US$135 million (December 31, 2006: net deferred tax asset of US$261 million) were recognized. Shire has moved from a net deferred tax asset to a net deferred tax liability

position following the recognition of a deferred tax liability of US$433.6 million in respect of intangible assets acquired with New River, and a deferred tax asset of US$51.8 million relating to New River's net operating loss carry forwards.

Equity in earnings of equity method investees

Net earnings of equity method investees of US$0.7 million were recorded for the three months to June 30, 2007 (2006: US$0.8 million). This comprised earnings of US$3.1 million from the 50% share of the anti-viral commercialization partnership with GSK in Canada (2006: US$1.6 million), offset by losses of US$2.4 million being the Company's share of losses in the GeneChem, AgeChem and EGS Healthcare Funds (2006: losses of US$0.8 million).

Unaudited US GAAP results for the six months to June 30, 2007

Consolidated Balance Sheets

	June 30, 2007 US$M	December 31, 2006 US$M
ASSETS		
Current assets:		
Cash and cash equivalents	598.5	1,126.9
Restricted cash	39.5	29.8
Accounts receivable, net	413.4	310.8
Inventories	177.6	131.1
Deferred tax asset	97.7	105.7
Prepaid expenses and other current assets	107.3	106.0
Total current assets	1,434.0	1,810.3
Non current assets:		
Investments	69.5	55.8

Property, plant and equipment, net	295.1	292.8
Goodwill	238.2	237.4
Other intangible assets, net	1,872.4	762.4
Deferred tax asset	102.0	155.3
Other non-current assets	28.7	12.4
Total assets	4,039.9	3,326.4
LIABILITIES AND SHAREHOLDERS' EQUITY		
Current liabilities:		
Accounts payable and accrued expenses	681.6	566.1
Liability to dissenting shareholders	465.6	452.3
Other current liabilities	44.5	313.6
Total current liabilities	1,191.7	1,332.0
Non-current liabilities:		
Convertible bonds, non current	1,100.0	-
Deferred tax liability	334.7	-
Other non-current liabilities	377.0	52.1
Total non-current liabilities	1,811.7	52.1

Total liabilities	3,003.4	1,384.1

Unaudited US GAAP results for the six months to June 30, 2007

Consolidated Balance Sheets (continued)

	June 30, 2007 US$M	December 31, 2006 US$M
Shareholders' equity:		
Common stock of 5p par value; 750.0 million shares authorized; and 553.2 million shares issued and outstanding (2006: 750.0 million shares authorized; and 506.7 million shares issued and outstanding)	48.3	43.7
Exchangeable shares: 1.2 million shares issued and outstanding (2006: 1.3 million)	57.0	59.4
Treasury stock	(194.7)	(94.8)
Additional paid-in capital	2,421.8	1,493.2
Accumulated other comprehensive income	79.1	87.8

(Accumulated deficit)/retained earnings	(1,375.0)	353.0
Total shareholders' equity	1,036.5	1,942.3
Total liabilities and shareholders' equity	4,039.9	3,326.4

Unaudited US GAAP results for the three and six months to June 30, 2007

Consolidated Statements of Operations

	3 months to June 30, 2007 US$M	3 months to June 30, 2006 US$M	6 months to June 30, 2007 US$M	6 months to June 30, 2006 US$M
Revenues:				
Product sales	504.2	376.0	965.7	722.0
Royalties	64.0	60.4	123.5	121.4
Other revenues	6.7	2.7	13.9	6.7

Total revenues	574.9	439.1	1,103.1	850.1
Costs and expenses:				
Cost of product sales(1)	70.3	61.6	133.8	123.6
Research and development	102.1	72.6	183.0	200.0
Selling, general and administrative	253.1	197.3	466.8	379.3
Depreciation and amortization(1)	32.2	23.8	61.1	46.7
Integration costs	1.3	1.6	1.3	3.9
Gain on sale of product rights	(5.0)	-	(5.0)	-
In-process R&D charge	1,896.0	-	1,896.0	-
Total operating expenses	2,350.0	356.9	2,737.0	753.5
Operating (loss)/income	(1,775.1)	82.2	(1,633.9)	96.6
Interest income	14.9	10.0	34.7	24.2
Interest expense	(28.0)	(6.5)	(35.8)	(12.1)
Other income/(expenses), net	1.8	(1.9)	2.3	(1.4)

Total other (expenses)/income, net	(11.3)	1.6	1.2	10.7
(Loss)/income from continuing operations before income taxes and equity in earnings of equity method investees	(1,786.4)	83.8	(1,632.7)	107.3
Income taxes	(25.6)	(23.3)	(67.1)	(29.8)
Equity in earnings of equity method investees	0.7	0.8	1.2	4.3
(Loss)/income from continuing operations	(1,811.3)	61.3	(1,698.6)	81.8
Gain from discontinued operations (net of income tax expense of US$nil)	-	-	-	40.6
Net (loss)/income	(1,811.3)	61.3	(1,698.6)	122.4

(1) Cost of product sales does not include amortization of intangible assets relating to intellectual property rights acquired, which is separately presented in Depreciation and amortization.

Unaudited US GAAP results for the three and six months to June 30, 2007

Consolidated Statements of Operations (continued)

	3 months to June 30, 2007 US$M	3 months to June 30, 2006 US$M	6 months to June 30, 2007 US$M	6 months to June 30, 2006 US$M
Earnings per share - basic				
(Loss)/income from continuing operations	(331.0c)	12.2c	(317.5c)	16.2c
Gain on disposition of discontinued operations	-	-	-	8.1c
(Loss)/earnings per ordinary share - basic	(331.0c)	12.2c	(317.5c)	24.3c
Earnings per share - diluted				
(Loss)/income from continuing operations	(331.0c)	12.0c	(317.5c)	16.0c
Gain on disposition of discontinued operations	-	-	-	8.0c
(Loss)/earnings per				

ordinary share - diluted	(331.0c)	12.0c	(317.5c)	24.0c
(Loss)/earnings per ADS - diluted	(993.0c)	36.1c	(952.5c)	72.0c
Weighted average number of shares:				
Basic	547.3	504.4	535.0	503.7
Diluted	547.3	509.5	535.0	509.8

Unaudited US GAAP results for the three and six months to June 30, 2007

Consolidated Statements of Cash Flows

	3 months to June 30, 2007 US$M	3 months to June 30, 2006 US$M	6 months to June 30, 2007 US$M	6 months to June 30, 2006 US$M
CASH FLOWS FROM OPERATING ACTIVITIES:				
Net (loss)/income	(1,811.3)	61.3	(1,698.6)	122.4
Adjustments to reconcile				

net income to net cash provided by operating activities:				
Depreciation and amortization:				
- cost of product sales	1.3	1.0	2.6	2.1
- in other costs and expenses	32.2	23.8	61.1	46.7
Amortization of deferred financing charges	9.2	-	9.2	-
Share based compensation	11.8	7.7	22.4	16.7
In-process R&D charge	1,896.0	-	1,896.0	-
Write down of long-term investments	-	2.0	-	2.0
Gain on sale of product rights	(5.0)	-	(4.9)	-
Equity in earnings of equity method investees	(0.7)	(0.8)	(1.2)	(4.3)
Gain on disposition of discontinued operations	-	-	-	(40.6)
Changes in operating assets and liabilities, net of acquisitions:				
(Increase)/decrease in accounts receivable	(25.2)	(42.6)	(103.0)	13.8
(Decrease)/increase in				

sales deduction accrual	(10.8)	8.1	18.9	13.0
(Increase)/decrease in inventory	(26.6)	3.2	(40.0)	8.3
Decrease/(increase) in prepayments and other current assets	25.1	(4.5)	11.3	18.1
Decrease in other assets	9.8	0.4	0.7	2.8
Movement in deferred taxes	0.1	9.2	13.8	(1.0)
Increase in accounts and notes payable and other liabilities	25.1	59.3	7.6	54.8
Increase in deferred revenue	52.0	9.3	88.5	6.0
Net cash provided by operating activities(A)	183.0	137.4	284.4	260.8

Unaudited US GAAP results for the three and six months to June 30, 2007

Consolidated Statements of Cash Flows

	3 months to June 30, 2007	3 months to June 30, 2006	6 months to June 30, 2007	6 months to June 30, 2006

	US$M	US$M	US$M	US$M
CASH FLOWS FROM INVESTING ACTIVITIES:				
Movements in short-term investments	55.8	-	55.8	5.5
Movements in restricted cash	(9.2)	1.4	(9.6)	1.1
Purchases of subsidiary undertakings, net of cash acquired	(2,458.6)	-	(2,458.6)	(0.8)
Expenses related to the New River acquisition	(57.3)	-	(60.4)	-
Purchases of long-term investments	(3.7)	(8.8)	(5.8)	(9.3)
Purchases of property, plant and equipment	(15.7)	(24.1)	(33.6)	(50.6)
Purchases of intangible assets	(3.6)	(50.0)	(31.8)	(50.2)
Deposits received for sale of product rights	3.5	-	10.5	-
Proceeds received from sale of product rights	6.3	-	6.3	-
Proceeds from property, plant and equipment sales	-	0.8	-	0.8
Proceeds from loan repaid by IDB	-	-	-	70.6

Returns of equity investments	1.0	0.3	2.2	0.3
Net cash used in investing activities(B)	(2,481.5)	(80.4)	(2,525.0)	(32.6)
CASH FLOWS FROM FINANCING ACTIVITIES:				
Proceeds from drawings under bank facility	1,300.0	-	1,300.0	-
Repayment of drawings under bank facility	(1,300.0)	-	(1,300.0)	-
Proceeds from issue of 2.75% convertible bonds due 2014	1,100.0	-	1,100.0	-
Redemption of Shire convertible bonds due 2011	-	-	-	(0.1)
Redemption of New River convertible notes	(279.4)	-	(279.4)	-
Proceeds from exercise of New River purchased call option	141.8	-	141.8	-
Payment of debt arrangement and issuance costs	(29.8)	-	(32.7)	-
Proceeds from exercise of options	1.7	3.9	24.1	17.7
(Costs)/proceeds from issue of common stock, net	(1.0)	-	877.3	-

Proceeds from exercise of warrants	-	-	7.0	-
Excess tax benefit of share based compensation, charged directly to equity	-	0.8	-	2.0
Payment of dividend	(29.4)	(22.6)	(29.4)	(22.6)
Payments to acquire treasury stock	(55.5)	-	(99.9)	(2.0)
Net cash provided by/(used in) financing activities(C)	848.4	(17.9)	1,708.8	(5.0)
Effect of foreign exchange rate changes on cash and cash equivalents (D)	2.4	3.6	3.4	5.4
Net (decrease)/increase in cash and cash equivalents(A) +(B) +(C) +(D)	(1,447.7)	42.7	(528.4)	228.6
Cash and cash equivalents at beginning of period	2,046.2	842.4	1,126.9	656.5
Cash and cash equivalents at end of period	598.5	885.1	598.5	885.1

US GAAP results for the three and six months to June 30, 2007

Selected Notes to the Unaudited US GAAP Financial Statements

(1) (Loss)/Earnings per share

	3 months to June 30, 2007 US$M	3 months to June 30, 2006 US$M	6 months to June 30, 2007 US$M	6 months to June 30, 2006 US$M
(Loss)/income from continuing operations	(1,811.3)	61.3	(1,698.6)	81.8
Gain on disposition of discontinued operations	-	-	-	40.6
Numerator for basic and diluted EPS	(1,811.3)	61.3	(1,698.6)	122.4
Weighted average number of shares:				
Basic	547.3	504.4	535.0	503.7

Effect of dilutive shares:				
Stock options(1)	-	4.6	-	5.5
Warrants(1)	-	0.5	-	0.6
Diluted	547.3	509.5	535.0	509.8

(1) Calculated using the treasury stock method

The share equivalents not included in the calculation of the diluted weighted average number of shares are shown below:

	3 months to June 30, 2007	3 months to June 30, 2006	6 months to June 30, 2007	6 months to June 30, 2006
	No. of shares Millions(1)	No. of shares Millions(2)	No. of shares Millions(1)	No. of shares Millions(2)
Stock options out of the money	1.1	2.9	1.4	2.9
Stock options in the money(3)	36.5	-	34.4	-
Warrants(3)	0.6	-	0.6	-
Convertible debt	32.7	-	32.7	-
	70.9	2.9	69.1	2.9

(1) For the three and six months ended June 30, 2007, all share options, warrants and convertible bonds were excluded from the calculation of the diluted weighted average number of shares, because the Company made a net loss during the calculation period.

(2) For the three and six months ended June 30, 2006, certain stock options have been excluded from the diluted EPS because their exercise prices exceeded Shire plc's average share price during the calculation period.

(3) For the purpose of computing the denominator for Non GAAP diluted EPS these equate in total to 6.8 million shares and 7.7 million shares for the three months and six months to June 30, 2007 respectively, as calculated by the treasury stock method.

Unaudited US GAAP results for the three months to June 30, 2007

Selected Notes to the US GAAP Financial Statements (continued)

(2) Analysis of revenues

	3 months to June 30, 2007	3 months to June 30, 2006	3 months to June 30, 2007	3 months to June 30, 2007
	2007 US$M	2006 US$M	% chan	% of total

Posted: July 2007

TOP NEWS

Modest launch seen so far for Shire drug Vyvanse

Thu, Aug 23 05:53 AM EDT

LONDON, Aug 23 (Reuters) - Shire Plc's (**SHP.L**) new hyperactivity drug Vyvanse has had a modest launch so far in the United States, partly reflecting the school holiday period, according to industry analysts.

A spokesman for Britain's third largest drugmaker said on Thursday the firm was very pleased with the launch to date, in particular the fact Vyvanse was winning market share from rival products and not just Shire's older Adderall XR.

Analysts, however, said the overall level of demand had been subdued, with Vyvanse's market share at 2.4 percent of total prescriptions after eight weeks on the market rather less than hoped.

Vyvanse is a key new product for Shire. The company is hoping it will replace its current top-selling attention deficit hyperactivity disorder (ADHD) drug Adderall XR, which could face generic competition from 2009.

Anian -- a Reuters business that tracks industry issues and trends for institutional investors -- said the launch data to date had been both positive and negative.

While it was encouraging that Vyvanse was taking share from products like Johnson & Johnson's (**JNJ.N**) Concerta and Eli Lilly and Co's (**LLY.N**) Strattera, feedback from pharmacies suggested demand so far had been underwhelming.

An Anian survey of 14 urban and suburban U.S. pharmacies found only two had dispensed Vyvanse, while five stocked the drug.

Dealers reported Credit Suisse analysts said in a note earlier this week that the penetration and ramp-up rate to date was "somewhat disappointing", although the market share gains from rivals were promising, indicating a mixed launch overall.

The Shire spokesman said take-up was inevitably muted by the school holidays, when schoolchildren use less medication and many doctors are on holiday, reducing the scope for heavy marketing.

"The bottom line is we are really pleased with the launch so far," he said.

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UBS
Global Life Sciences Conference

Michael Cola
President, Specialty Pharmaceuticals
Shire plc

September 24, 2007

THE "SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

Statements included herein that are not historical facts are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially affected. The risks and uncertainties include, but are not limited to, risks associated with: the inherent uncertainty of pharmaceutical research, product development, manufacturing and commercialization; the impact of competitive products, including, but not limited to the impact of those on Shire's Attention Deficit and Hyperactivity Disorder ("ADHD") franchise; patents, including but not limited to, legal challenges relating to Shire's ADHD franchise; government regulation and approval, including but not limited to the expected product approval date of INTUNIV™ (guanfacine) extended release (ADHD); Shire's ability to secure new products for commercialization and/or development; Shire's ability to benefit from its acquisition of New River Pharmaceuticals Inc.; the successful development of JUVISTA® (human TGFβ3) and other risks and uncertainties detailed from time to time in Shire plc's filings with the Securities and Exchange Commission, particularly Shire plc's Annual Report on Form 10-K for the year ended December 31, 2006.

Introduction

- Continue to execute on strategy effectively
- Excellent half year results
  - Revenue growth accelerating with new product launches - (up 30% for H1 2007 on previous year)
- Upgrading revenue growth guidance to at least 25% (previous guidance low 20% range)
- VYVANSE Launch – rapid uptake
- Good progress in strengthening our R&D pipeline

Q2 2007 Highlights

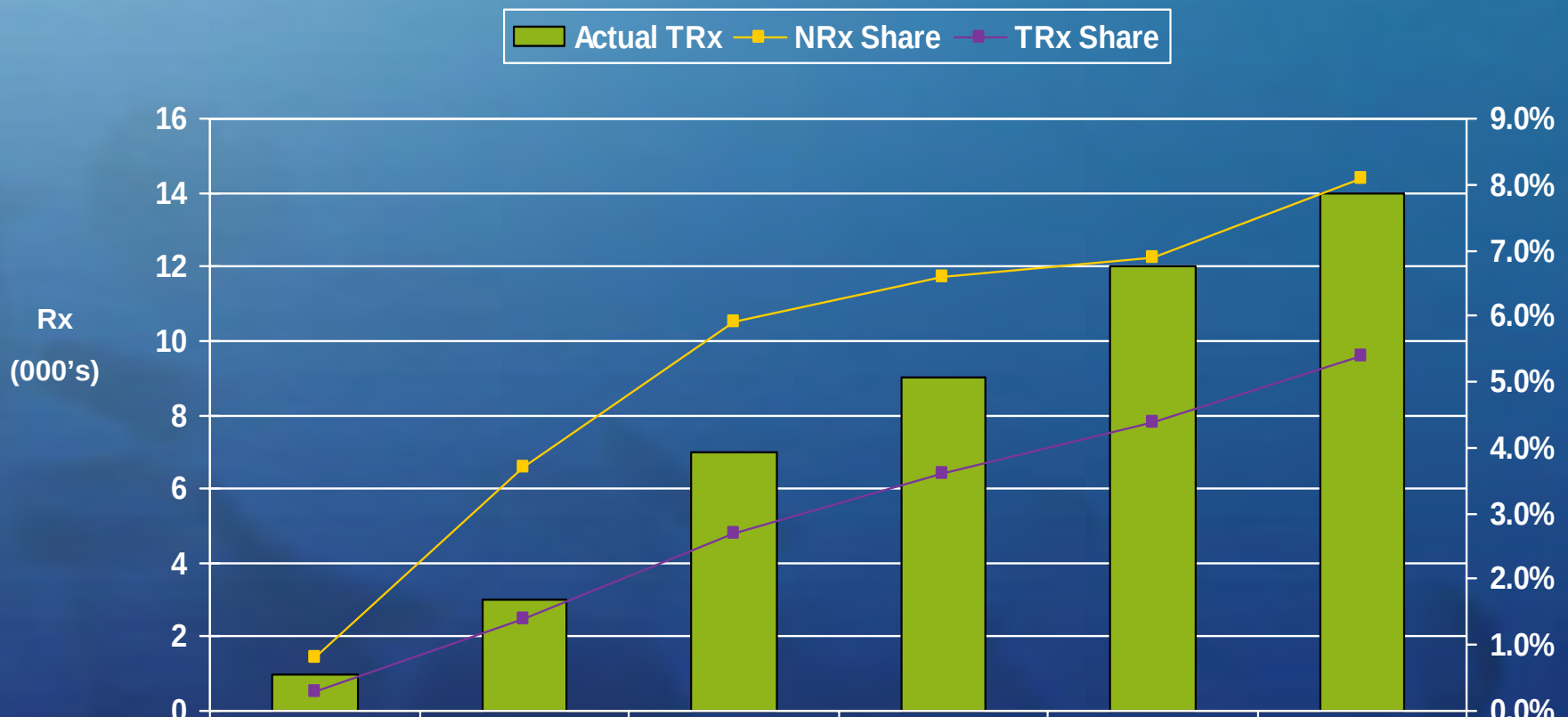
- New River acquisition
- JUVISTA license agreement with Renovo
- $1.1 billion convertible bond
- ADHD
  - VYVANSE
    - Launched July 2 – 2.8% market share*
    - sNDA for adult indication filed during the quarter
  - INTUNIV (SPD503) – Approvable letter received
  - SPD465 – Approvable letter received
- GI
  - LIALDA
    - Launched in Q1
    - Latest weekly market share – 8.7% of NRx and 6% of TRx *
    - Very positive reaction from patients and physicians

SOURCE: IMS NGPS – as at September 7, 2007

Portfolio Highlights

- Human Genetic Therapies
  - ELAPRASE
    - Now available in 33 countries
  - REPLAGAL
    - Approved in 41 countries;
    - REPLAGAL sales continue to show significant growth with new patients starting therapy through in European markets as well as through geographic expansion into Canada, Latin America and Japan;
  - GA-GCB
    - Phase 3 clinical program consisting of 3 trials is currently enrolling patients
- Renal
  - FOSRENOL
    - Now available in 21 countries
    - Launched in Italy, Canada, and Slovak Republic
  - DYNEPO
    - Launched in Germany, UK, Ireland and Italy

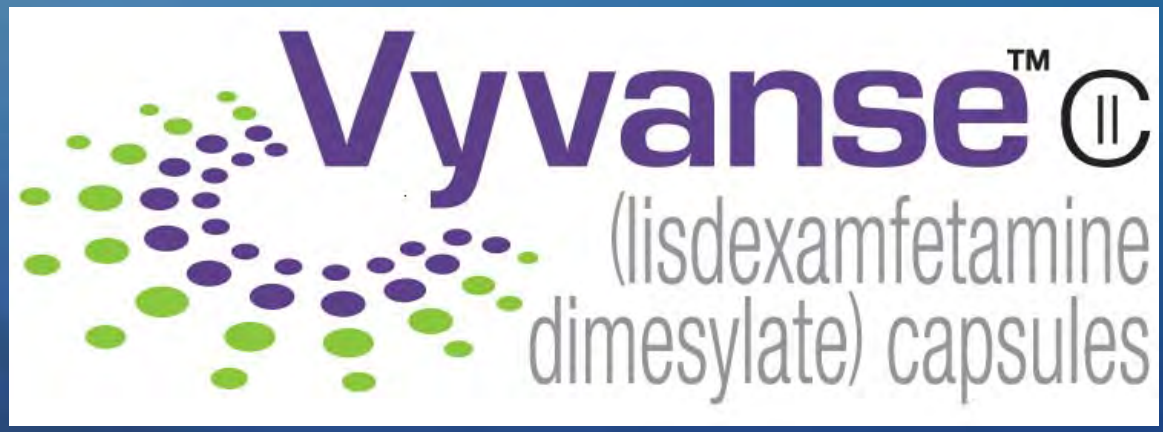
LIALDA – Good Launch Uptake



	March	April	May	June	July	Aug
Actual TRx	1	3	7	9	12	14
NRx Share	0.8%	3.7%	5.9%	6.6%	6.9%	8.1%
TRx Share	0.3%	1.4%	2.7%	3.6%	4.4%	5.4%

Source: IMS NGPS

VYVANSE – Launch update



VYVANSE is positioned as a new class of ADHD medication not just a replacement to Adderall XR

NEW Vyvanse™ (lisdexamfetamine dimesylate) capsules

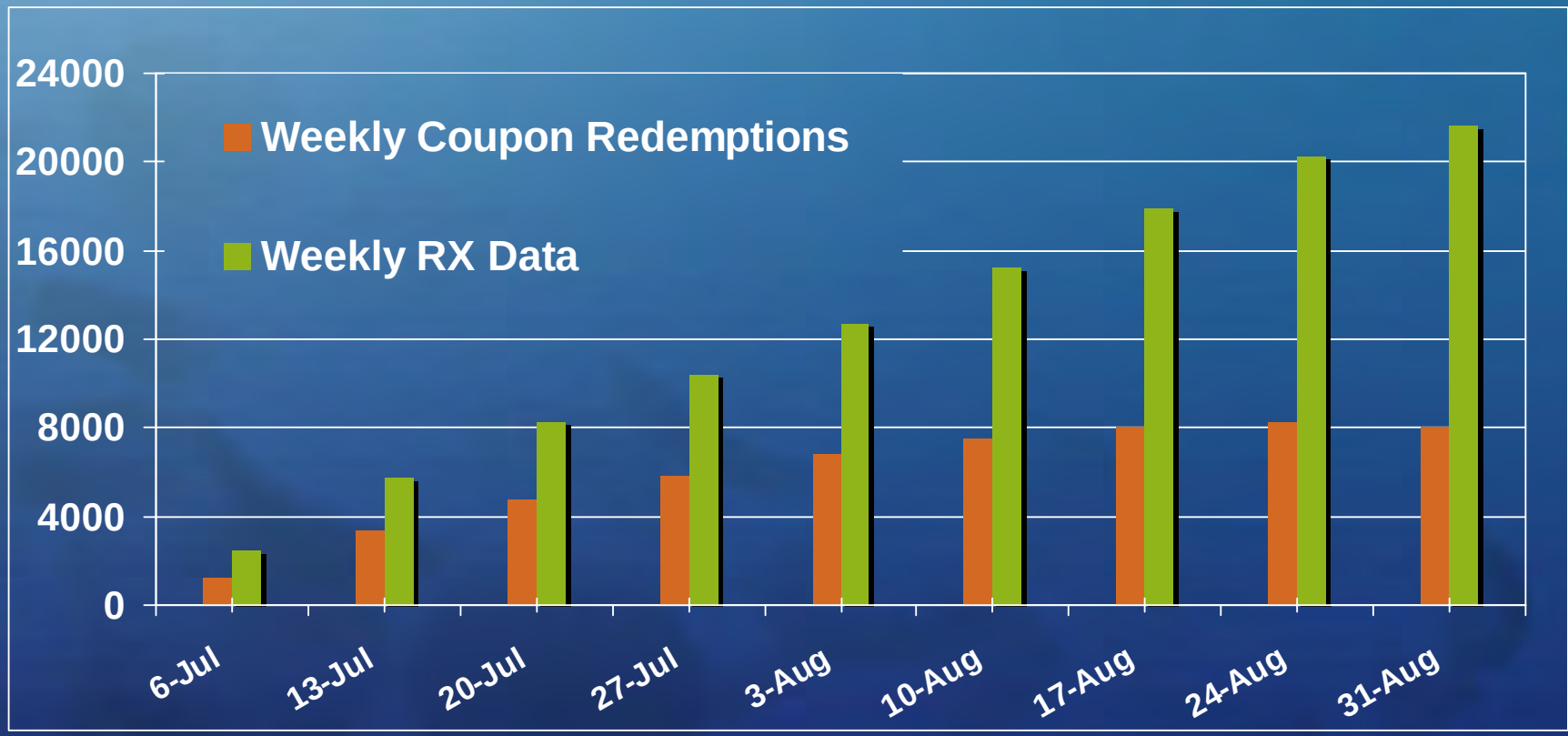
The First Prodrug Stimulant

Ex. 6, Page 735

Key attributes to support VYVANSE as an NCE in a new class

- The first Pro-drug Stimulant
- Consistent time to maximum concentration of d-amphetamine from patient to patient
- Significant efficacy throughout the day, even at 6:00 PM
- Adverse event profile that is mild to moderate in severity and incidence decreases over time
- Significantly lower abuse related liking effect than an equivalent oral dose of d-amphetamine

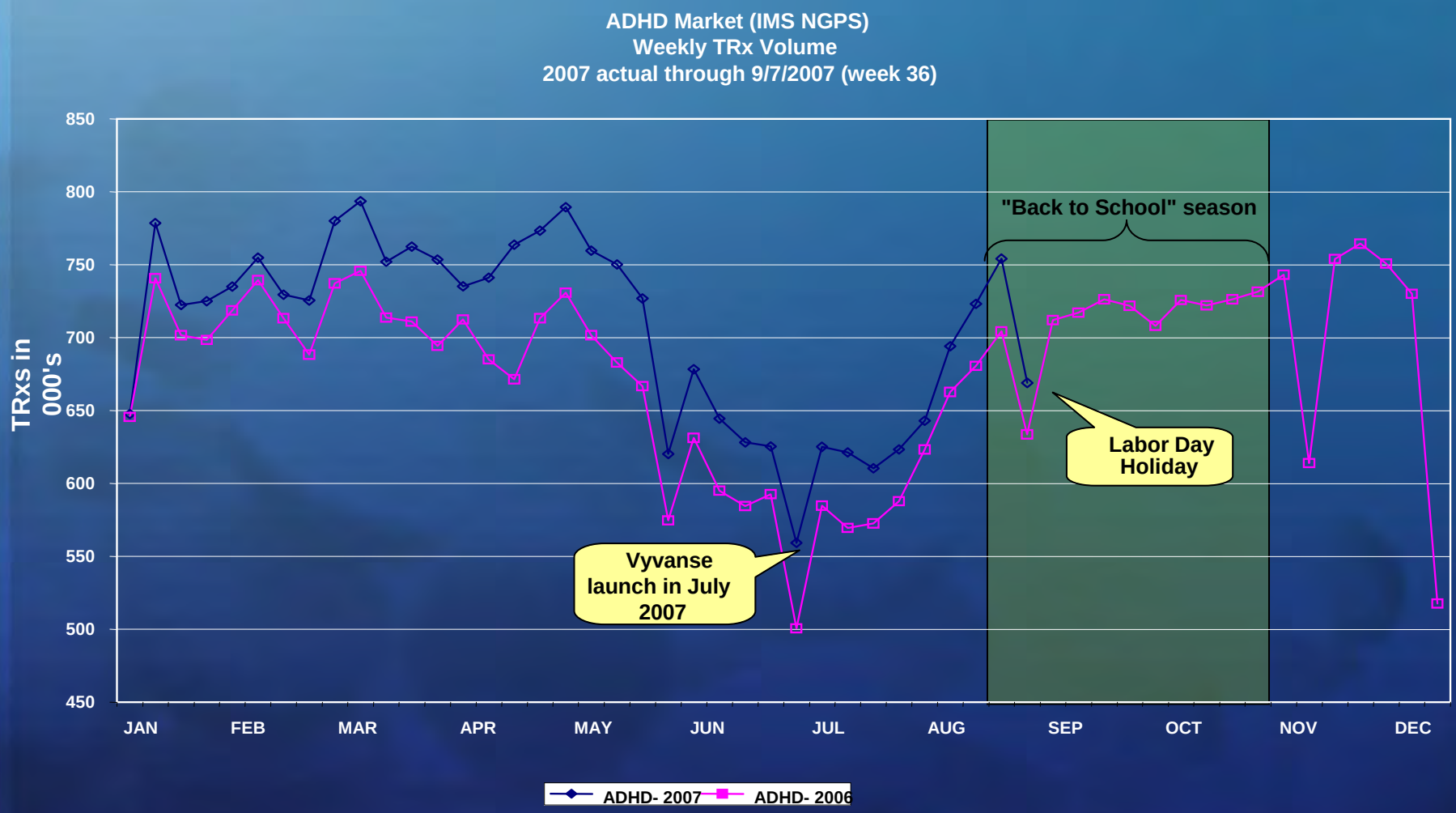
Weekly TRxs are separating from weekly coupon redemptions demonstrating that patients are refilling



- Every redeemed coupon is accompanied by an Rx
- Only one coupon (30 capsules) can be redeemed per patient

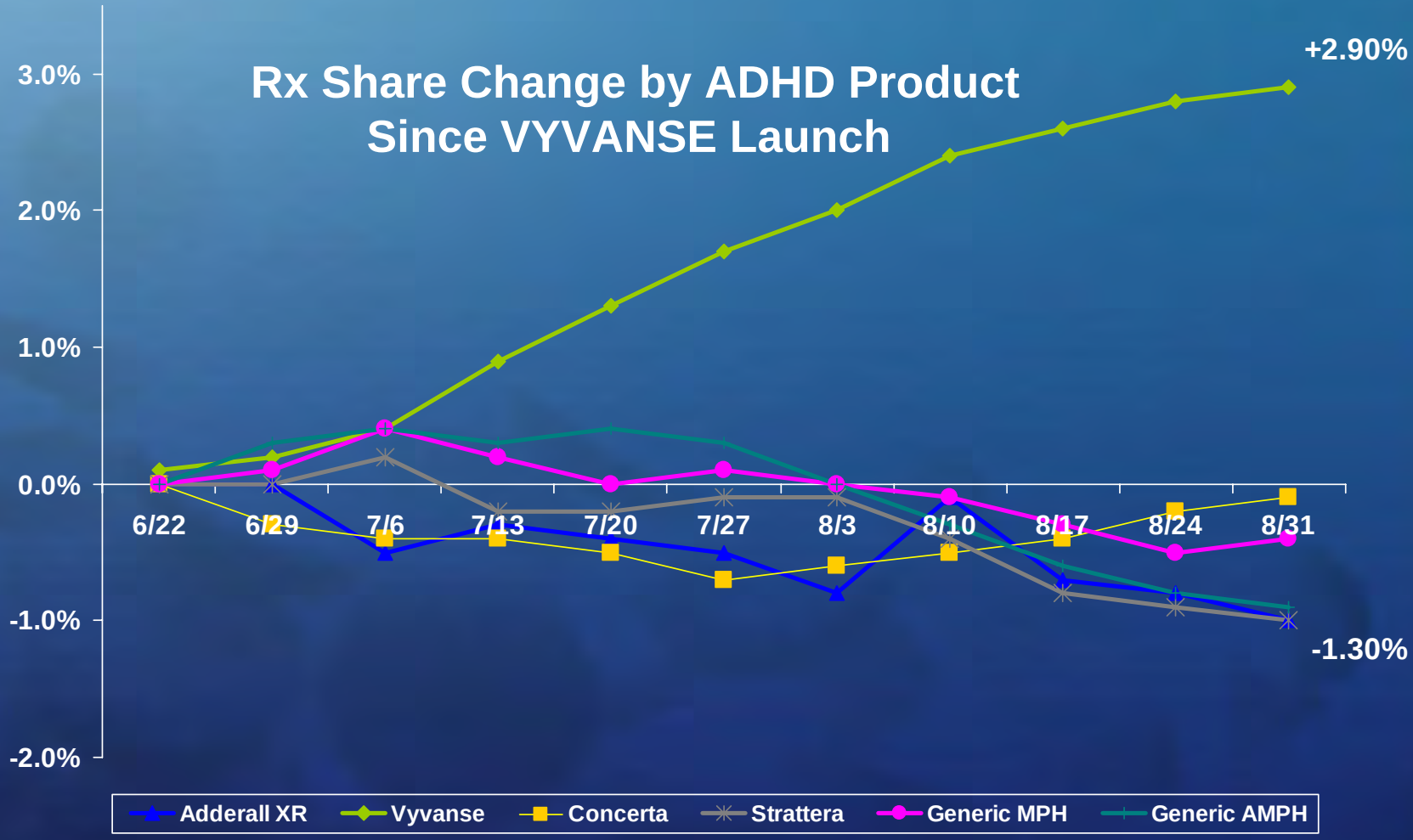
SOURCE: IMS Daily Rx & PSKW

Back to School is not a one-two week event; It runs through October



Ex. 6, Page 738

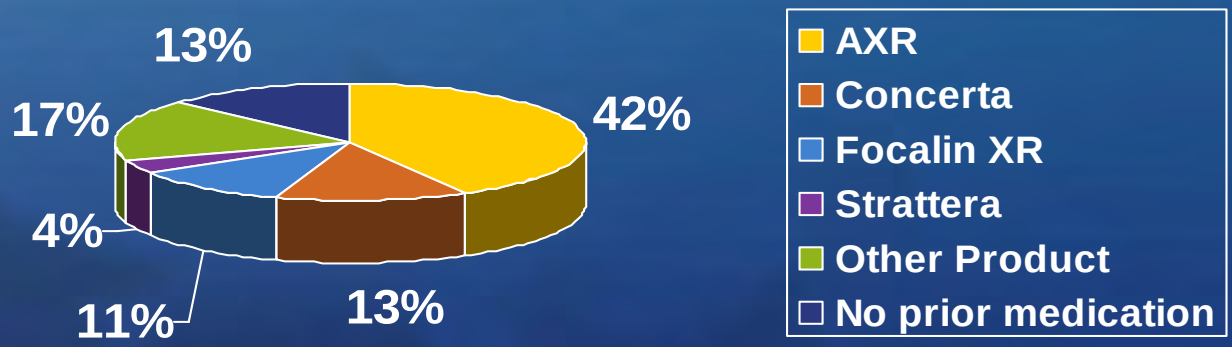
VYVANSE is taking market share from all products in the ADHD category, not just ADDERALL XR



SOURCE: IMS NGPS - Universe

VYVANSE patients are coming from Adderall XR and other brands

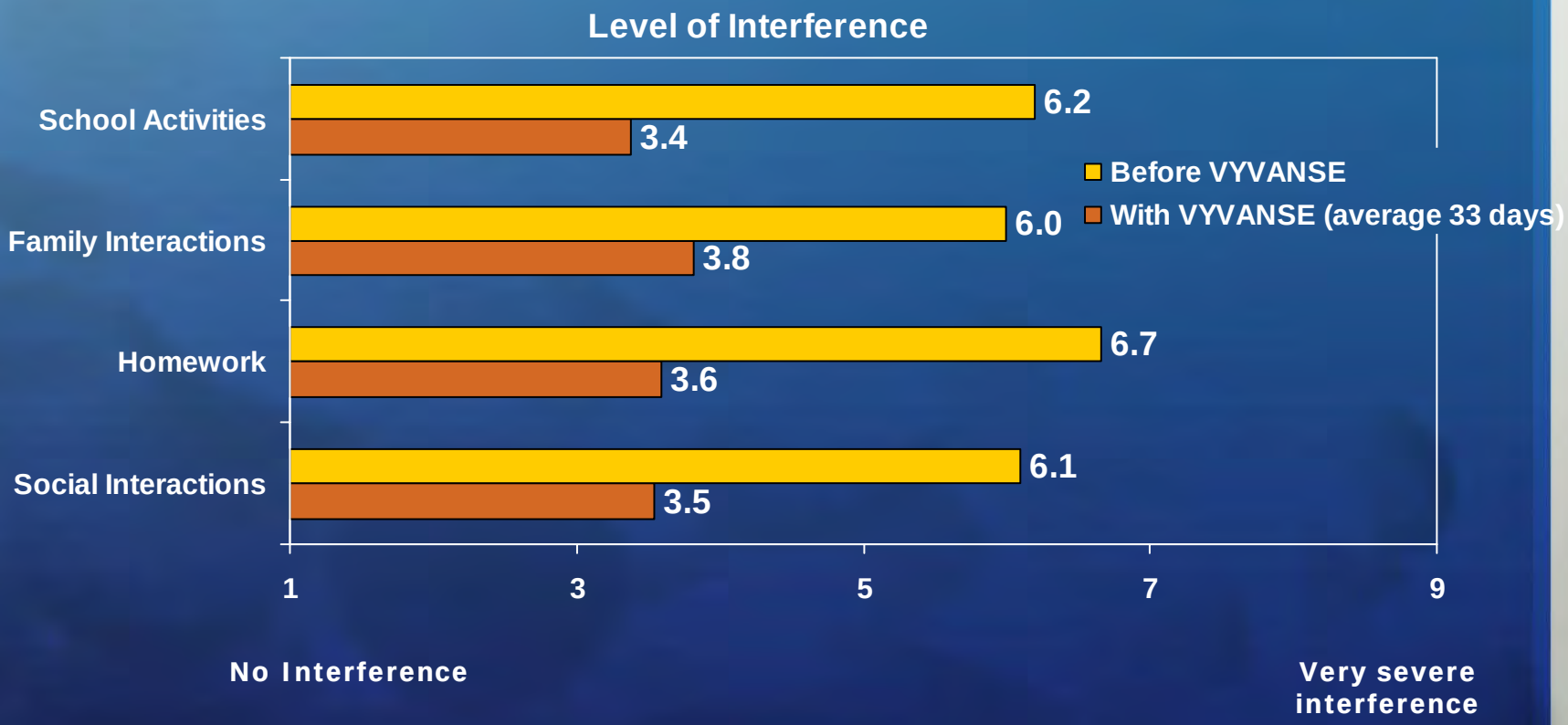
- 5,335 patients started on VYVANSE have enrolled and completed baseline surveys
- 87% had used a prescription for ADHD prior to VYVANSE



Source: VYVANSE New Start Patient Experience program

Ex. 6, Page 740

With use of VYVANSE, ADHD interfered significantly less with life's activities among children previously using ADDERALL XR

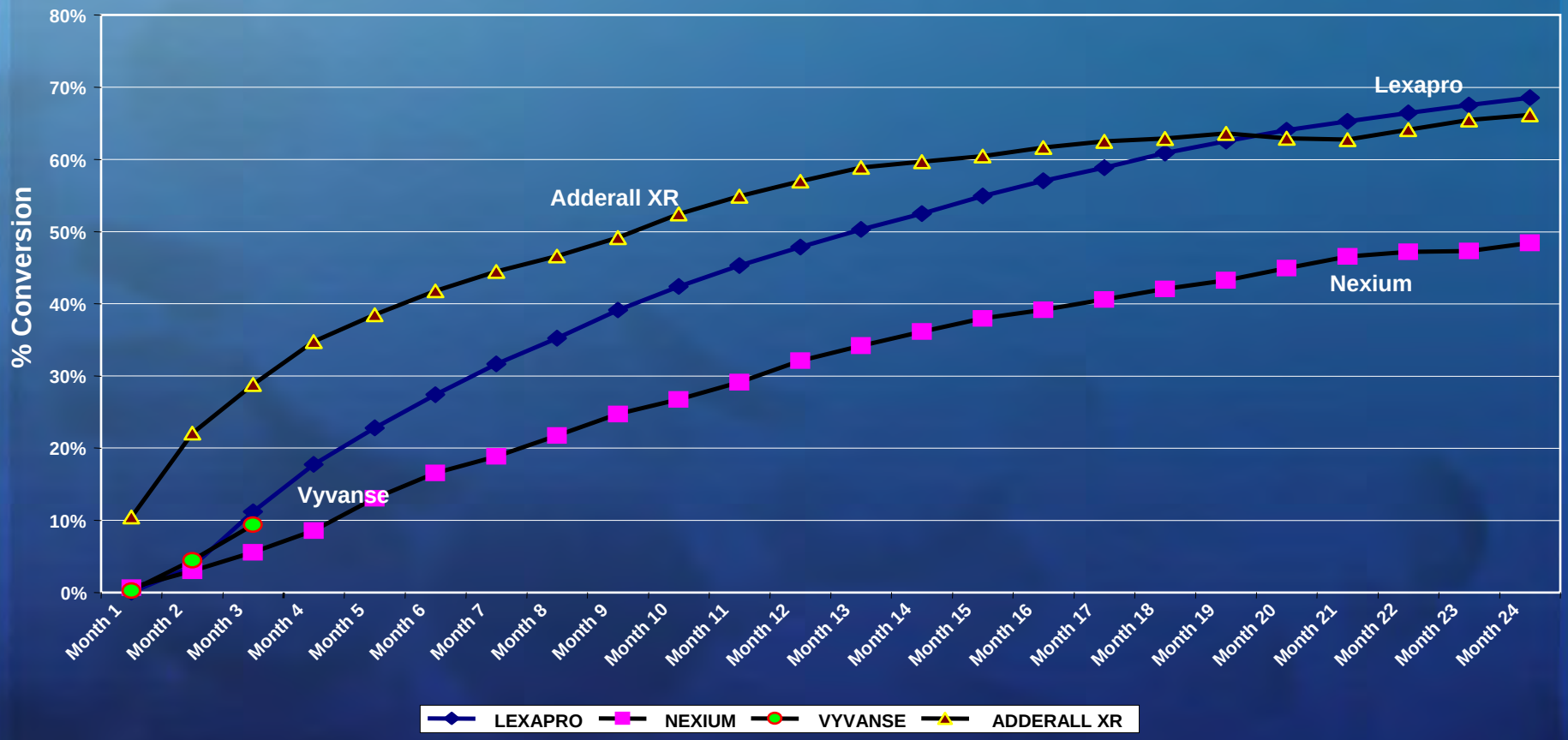


n=125

Ex. 6, Page 741

Successor Molecules (Lexapro, Nexium) follow a different pattern than line extensions such as AXR

Successor Molecule Launch
% Conversion of Original Brand & Generics (based on TRx volume)



% Conversion = New Product TRx/ (New Product TRx + Original Brand TRx + Generic of Original TRx)

Ex. 6, Page 742

Managed Care update

- Coverage is progressing as planned:
  - 6-9 month post-launch review period on adding new products to formulary is common
  - All targeted plans have received clinical information on VYVANSE
  - Negotiations with numerous plans are progressing
  - Parity with AXR formulary status expected by 18 months

Managed Care Tier Status has only modest impact on share in ADHD

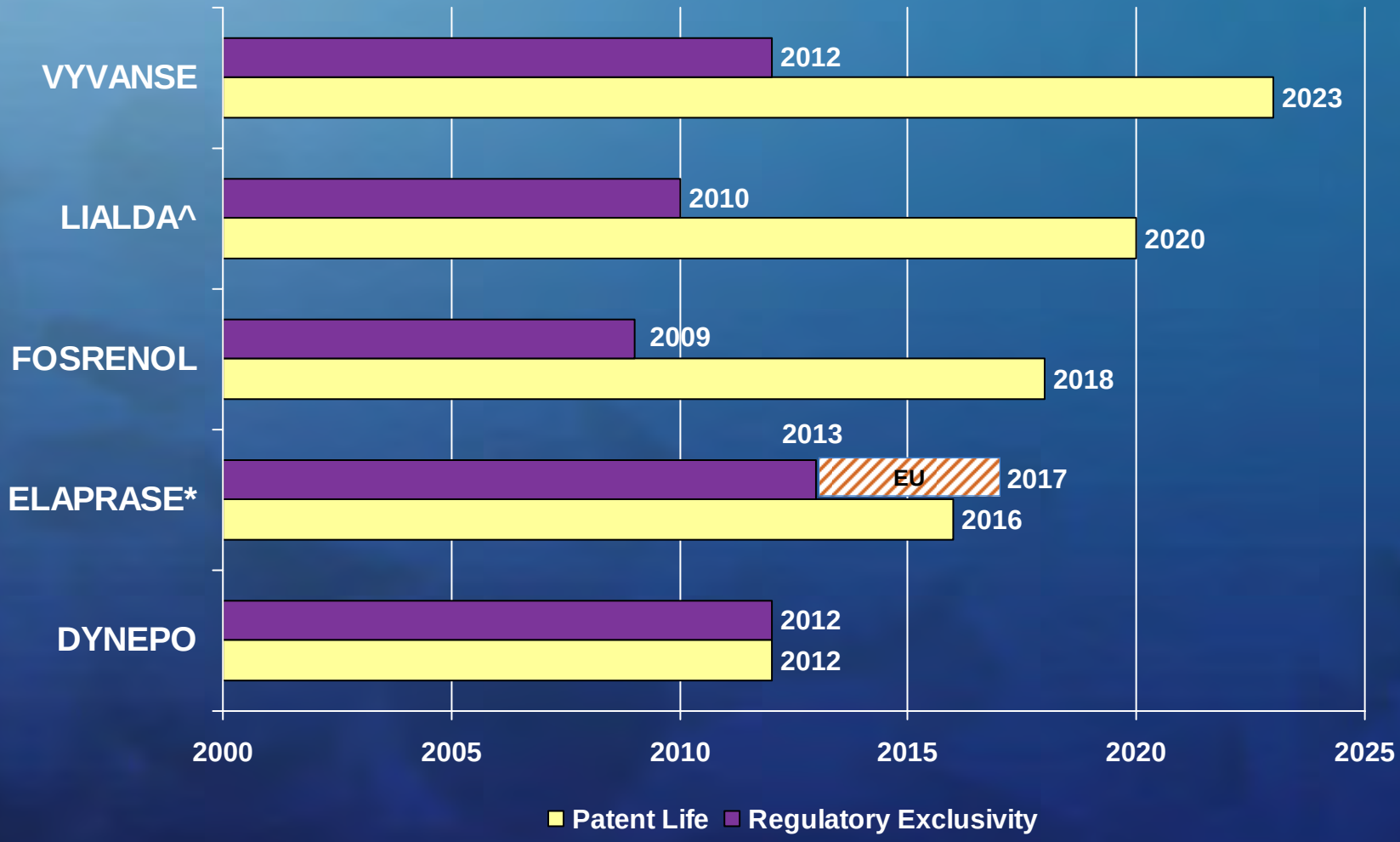
	Tier 2	Tier 3
Adderall XR	28.1%	25.3%
Concerta	22.8%	19.9%
Strattera	10.0%	9.2%

Source: IMS PlanTrak June 2007

Summary

- VYVANSE rapid launch uptake
- Tracking in line with the industry's best successor molecule launches
- Patients starting on coupons are refilling Rxs
- Back to school is not a one-two week event, but lasts at least two full months
- Physicians and Patients are providing very positive feedback on their clinical experience with VYVANSE
- Coverage is progressing as planned
- VYVANSE has tremendous growth potential beyond 2009
  - Very strong IP
  - Europe
  - Potential for other indications

Strong market exclusivity for growth drivers



^ Currently no generic approval pathway for locally acting drugs
*Orphan Drug

Shire has one of the strongest late- stage pipelines in the Specialty Pharma sector

Product Launches

2007	2008	2009	2010	2011-2015
▪ VYVANSE	▪ INTUNIV*	▪ SEASONIQUE	▪ GA-GCB	▪ ELAPRASE CNS
▪ DYNEPO	▪ SPD465*		▪ VYVANSE EU	▪ SANFILIPPO
▪ LIALDA / MEZAVANT	▪ DAYTRANA EU			▪ MLD
▪ FOSRENOL EU				▪ CEPO
▪ ELAPRASE EU			▪ FOSRENOL - CKD	▪ SPD493
				▪ JUVISTA

- Eight potential launches over a 30 month period from 2006-2008

* Approvable letter received

Ex. 6, Page 747

Concluding Remarks

- 2007 guidance upgraded as revenue growth accelerates
  - revenue growth to be at least 25% for 2007 (previous guidance low 20% range)
- Excellent H1 '07 results
  - Successful ongoing launches
  - Continuing to demonstrate our ability to execute
  - VYVANSE rapid launch uptake – 2.8% market share*
  - ELAPRASE – rapid uptake in US and EU
  - LIALDA – 8.7% NRx, 6% TRx*
  - FOSRENOL – strong start in Europe
  - DYNEPO – launched in Q1 2007, good reception
- Good progress in strengthening our R&D pipeline

SOURCE: IMS NGPS – as at September 7, 2007

Questions and Answers

Shire shares fall on concerns over sales of Vyvanse

(Ref: Bloomberg, BusinessWeek, MarketWatch)

September 14th, 2007

By: Daniel Beaulieu

Tags: Top Story Adderall XR Vyvanse Shire Marketing & Sales

Shares in Shire fell as much as 7.5 percent after some analysts expressed disappointment with sales of recently-launched attention-deficit hyperactivity disorder treatment, Vyvanse. However, Shire's chief financial officer, Angus Russell, responded that "we're quite comfortable that things are going extremely well."

"If Vyvanse share stalls in coming months, we will have serious doubts over our forecasts. The Vyvanse share of the combined Adderall XR/Vyvanse volume has been disappointing at just over 10 percent after 12 weeks," remarked JPMorgan analysts Alistair Campbell and Craig Maxwell. Nonetheless, Shire's Russell commented that "this note has chosen to highlight very short-term data with a very narrow focus. We certainly don't think this is any indication of a long-term trend."

Cowen & Co's Ken Cacciatore also reduced his Vyvanse sales estimates through 2011, although he and several other analysts cautioned against selling off Shire shares as the treatment is new to the market and is not expected to face generic competition before 2023. David Buck of Buckingham Research added that prescriptions for Vyvanse doubled from July to August, and forecast that the drug would account for 20 percent of Shire's ADHD franchise by the end of 2007. "We believe that Shire's 2007 Vyvanse sales should hit our $74 million forecast....We would characterise Vyvanse as making strong progress; however, some estimates seem overly aggressive in 2007 for this product," Buck indicated.

Shire purchased New River Pharmaceuticals earlier this year to gain the full rights to Vyvanse, which is expected to be a successor to Shire's ADHD drug Adderall XR. The older ADHD treatment is scheduled to lose patent protection in 2009.

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Insight, Analysis and Views

- ViewPoints: Forecasts rise for Pharmacyclics' Imbruvica on back of impressive Q2 sales
- Physician Views Poll Results: Gastroenterologists see significant need for NASH drugs, but cite non-invasive diagnostics as key to market penetration
- FirstWord Lists: Pharma's biggest pipeline drugs

Tweeter

Related News

- Shire, New River receive FDA approval for Vyvanse
- DEA classifies Shire's Vyvanse as Schedule II controlled substance
- Shire's Vyvanse wins US approval for use in adults
- Shire, New River shares soar on FDA "approvable" letter for ADHD drug
- US requests documents from Shire to aid inquiry into marketing of ADHD drugs

Reference Articles

- Shire falls on Vyvanse worries - (BusinessWeek)
- Shire shares fall on concerns on Vyvanse sales growth - (Bloomberg)
- Shire shares drop amid doubts over Vyvanse market share - (MarketWatch)

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Third Quarter Results to September 30, 2007

Shire plc

November 1, 2007

REFERENCE 39

THE "SAFE HARBOR" STATEMENT UNDER THE PRIVATE SECURITIES LITIGATION REFORM ACT OF 1995

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Agenda

Introduction and Q3 Highlights	Matthew Emmens
Q3 Financial Review	Angus Russell
Recent Product Launches	Matthew Emmens
Questions & Answers	All

Matthew Emmens
CEO

Introduction and Q3 Highlights

Introduction

- Strategy on track
- Excellent third quarter results
  - Strong product sales reflecting good results and successful product launches across all areas of our business
- Upgrading revenue growth guidance to at least 30% (previous guidance: at least 25%)

Q3 Financial Highlights

- Product sales up 41% to $543 million
- Total revenues up 35% to $609 million
- Net cash provided by operating activities up 51% to $124 million

Q3 Portfolio Highlights

- ADHD franchise exceeds 30% US market share
  - VYVANSE
    - Launched July 2 – 4.1% market share*
    - Adult indication PDUFA date – April 28, 2008
  - DAYTRANA
    - Voluntary market withdrawal of a limited quantity
    - New patches are now manufactured with enhanced process and improved ease of use
- GI franchise exceeds 23% share of 5-ASA market
  - LIALDA
    - Latest weekly market share – 9.3% of NRx and 6.9% of TRx *
    - Prescriptions being generated from both new patients and switches from other brands
- JUVISTA license agreement with Renovo
  - Positive Phase 2 clinical trial results

SOURCE: IMS NPA – as at October 19, 2007

REFERENCE 39

Q3 Portfolio Highlights

- Human Genetic Therapies
  - ELAPRASE
    - Now available in 34 countries
    - Approved and launched in Japan
  - REPLAGAL
    - Approved in 41 countries;
    - REPLAGAL sales continue to show significant growth with new patients starting therapy in European markets as well as through geographic expansion into Canada, Latin America and Japan
  - GA-GCB
    - Phase 3 clinical program consisting of 3 trials is ongoing on a worldwide basis
- Renal
  - FOSRENOL
    - Now available in 23 countries
    - Launched in Canada, Slovak Republic, and Poland
  - DYNEPO
    - Launched in Ireland and Italy during Q3

Ex. 6, Page 759

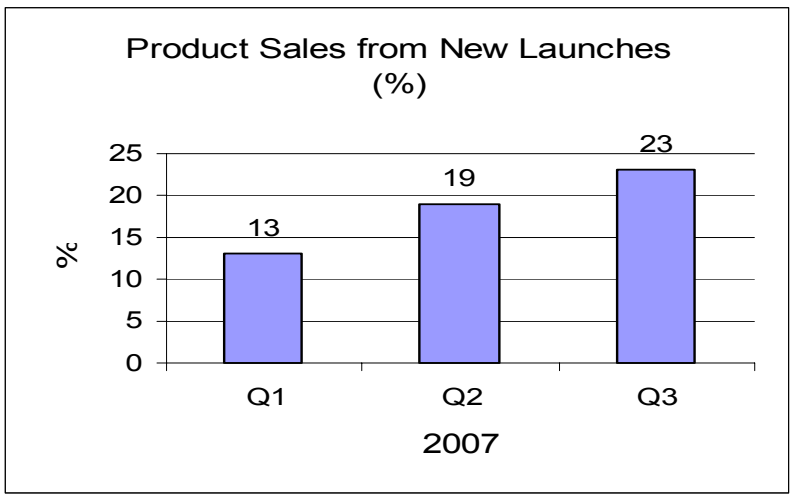
Angus Russell
CFO

Q3 Financial Review

Total Revenues

	Q3 07 $m	Q3 06 $m	Growth %
Product Sales	543.1	386.2	41%
Royalties	61.9	60.4	
Other Revenues	3.7	2.8	
Total Revenues	608.7	449.4	35%

		Q3 07 $m	Q3 06 $m	Growth %
Product Sales (excl. new launches)	77%	**418.6**	**359.8**	**16%**
ELAPRASE		55.1	4.3	
LIALDA		16.3	0.0	
FOSRENOL US		16.3	11.4	
FOSRENOL EU	23%	12.4	0.8	
VYVANSE		10.6	0.0	
DAYTRANA		9.4	9.9	
DYNEPO		4.4	0.0	
Product Sales	100%	**543.1**	**386.2**	**41%**

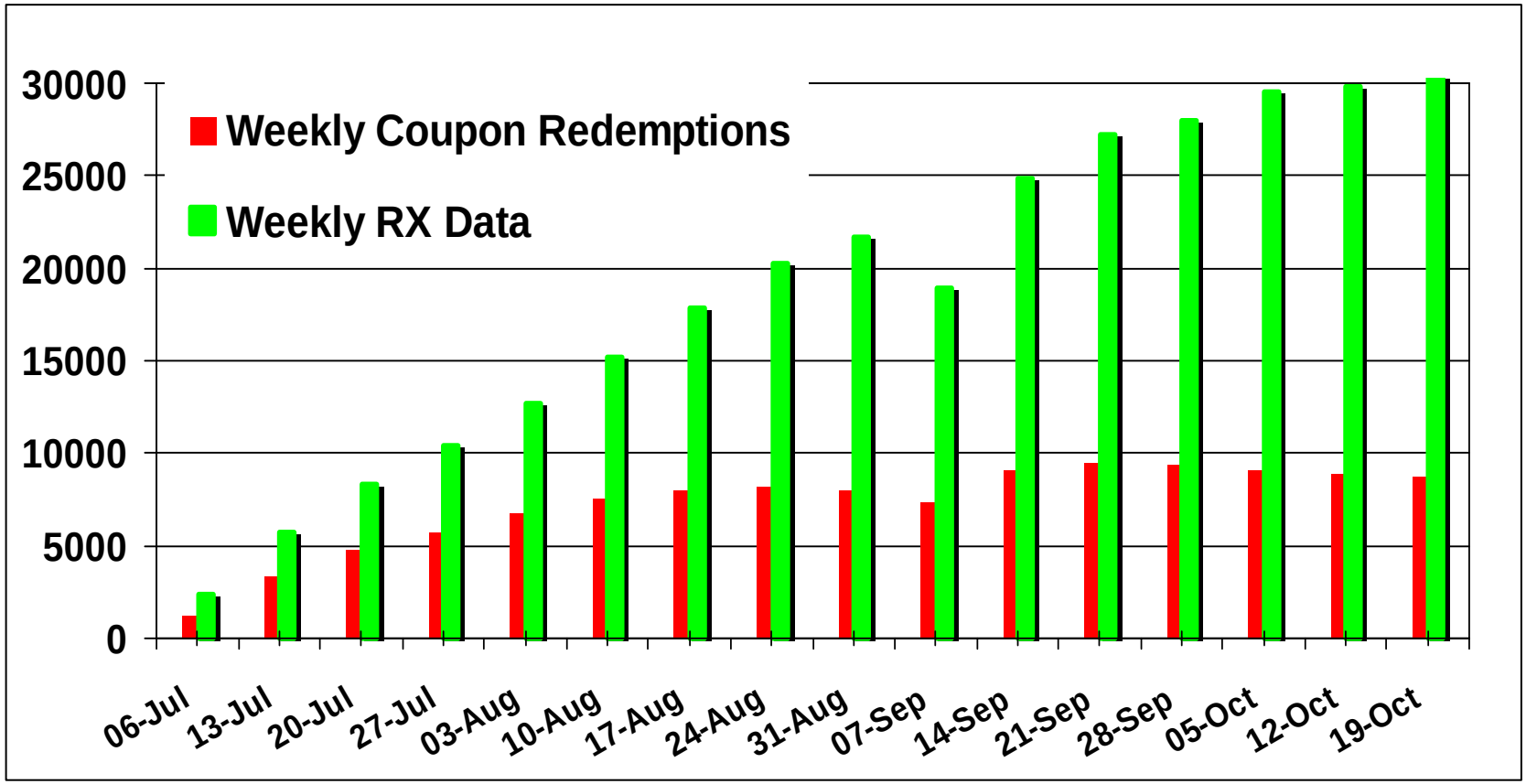


Major Product Sales

	Q3 07 $m	Q3 06 $m	Sales Growth	US RX* Growth
ADDERALL XR	249.0	207.6	20%	3%
VYVANSE	10.6	-	n/a	n/a
DAYTRANA	9.4	9.9	-5%	64%
PENTASA	43.7	36.9	18%	2%
LIALDA	16.3	-	n/a	n/a
ELAPRASE	55.1	4.3	n/m	n/a
REPLAGAL	40.7	32.4	26%	n/a
FOSRENOL	28.7	12.2	135%	0%
CARBATROL	19.3	20.4	-5%	-5%
XAGRID	16.8	13.3	26%	n/a

* Source: IMS Data

VYVANSE TRxs are growing and separating from coupon redemptions showing that patients are refilling



- Every redeemed coupon is accompanied by an Rx
- Only one coupon (30 capsules) can be redeemed per patient
- Over 300,000 Rx written since launch

SOURCE: IMS Rx & PSKW

Ex. 6, Page 763

VYVANSE – Gross to Net Sales (Q3 2007)

	Q3 TRx ('000)*	$m		Notes
Sales Demand	217	20.9		Price per TRx = 28.3 (tablets per TRx) x $3.41 (price per tablet)
Restocking		10.2		
Underlying gross sales		31.1	100%	
Sales coupons		(12.3)	39%	66%
Wholesaler discounts & rebates		(8.2)	27%	
Net Sales		10.6	34%	

Q2 deferred revenue sales	55.9
Add Q3 deferred sales	1.9
Less Q3 sales demand	(20.9)
Deferred revenue at 9/30/07	36.9

Sales deductions will trend towards a long term rate of approximately 28%.

*per IMS

DAYTRANA – Gross to Net Sales (Q3 2007)

	Q3 TRx ('000)*	$m		Notes
Sales Demand	183	21.7		Price per TRx = 29.8 (patches per TRx) x $3.98 (price per patch)
Destocking		(0.1)		
Underlying gross sales		21.6	100%	
Sales coupons		(3.9)	18%	
Returns		(4.0)	18%	56%
Wholesaler discounts and rebates		(4.3)	20%	
Net Sales		9.4	44%	

Coupon expense to moderate at 10% in 2008.

Voluntary market withdrawal. This is a one off charge for Q3

Sales deductions are expected to trend towards a long term rate of approximately 25%.

*per IMS

Royalties

	Q3 07 $m	Q3 06 $m	Growth (%)
3TC	36.7	36.5	1% *
ZEFFIX	10.2	9.3	10% **
Other ***	15.0	14.6	3%
Total	61.9	60.4	2%

*Foreign exchange movements have contributed +4% to reported growth
**Foreign exchange movements have contributed +6% to reported growth
***Includes REMINYL/RAZADYNE

Financial Ratios (% of net product sales)

(on a non-GAAP basis)

	Q3 07	Q3 06	YTD 07	FY 06
COGS	14%	14%	14%	13%
Gross margin	86%	86%	86%	87%
R&D	19%	19%	18%	20%
SG&A	46%	54%	47%	52%
Operating EBITDA (1)	21%	14%	22%	16%
Operating EBITDA margin (% Total Revenue)	29%	26%	31%	28%

(1) Excluding royalties

This slide contains non GAAP financial measures. They exclude intangible asset amortization in respect of intellectual property charges, the accounting impact of share-based compensation and the effect of certain cash and non-cash items, both recurring and non-recurring, that Shire's management believes are not related to the core performance of Shire's business.

Net Income/EPS

Net income ($m)	Q3 07	Q3 06	Growth (%)	YTD 07
- GAAP	34.7	87.2		
- Adjustments	91.5	(1.5)		
- Non GAAP [1]	126.2 [2]	85.7	47%	
EPS - ADS (diluted)				
- GAAP	18.9c	51.3c		
- Non GAAP [1]	66.3c [2]	50.4c	32%	200.4c

[1] These are non GAAP financial measures. They exclude intangible asset amortization charges, the accounting impact of share-based compensation and the effect of certain cash and non-cash items, both recurring and non-recurring, that Shire's management believes are not related to the core performance of Shire's business.

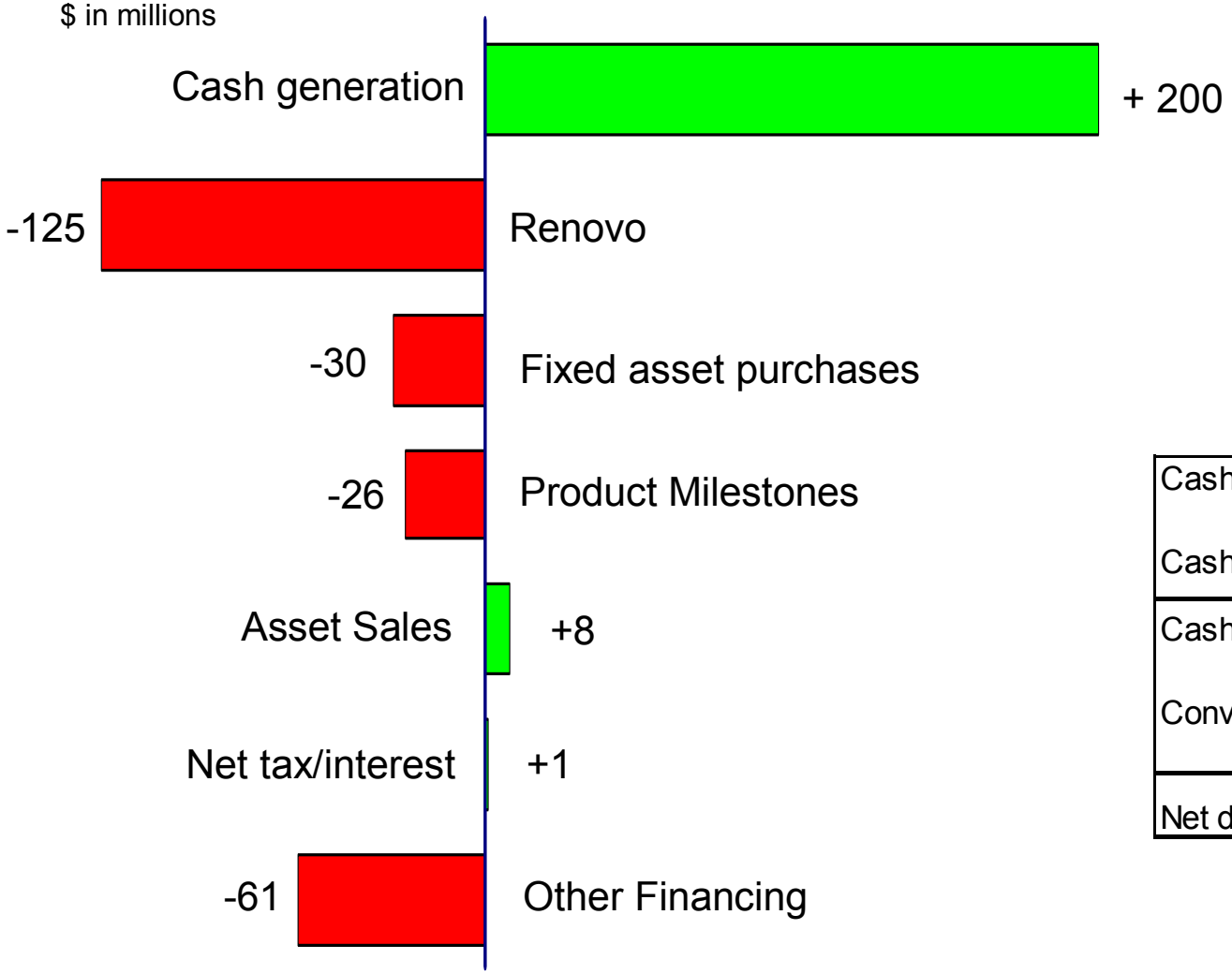
[2] The Q3 Non GAAP tax rate was 15% *(see slide 21)* compared to a guidance rate of 26%. This low tax rate was primarily due to a higher level of tax deductible expenditure than forecast in high-tax territories (principally the US) and reductions in specific tax liabilities relating to tax reviews and tax filings which have now been finalised. The impact of this credit was to increase Non GAAP income by approximately $15m and Non GAAP earnings per ADS by approximately 7c.

EPS Reconciliation

	Q3 07 $m	Q3 07 cents/ADS	Q3 06 $m	Q3 06 cents/ADS
Net income for diluted EPS (ADS)	**34.7**	**18.9c**	**87.2**	**51.3c**
Cost of product sales fair value adjustment	-	-	6.7	3.9c
In-licensing payments	75.0	39.0c	30.5	18.3c
Gain on disposal of product rights	(7.1)	(3.6c)	(63.0)	(37.5c)
Legal settlement provision	27.0	13.8c	-	-
Intangible asset amortization	31.1	15.9c	14.6	8.7c
SFAS 123R effect	11.7	6.0c	9.1	5.4c
Taxes on above adjustments	(46.2)	(23.7c)	0.6	0.3c
Non GAAP net income / EPS (ADS)	**126.2**	**66.3c**	**85.7**	**50.4c**

Cash flow – Q3 2007

$ in millions



Cash at 30/6/07	**638**
Cash outflow Q3 07	(33)
Cash at 30/9/07 (1) (2)	**605**
Convertible debt	(1,100)
Net debt at 30/9/07	**(495)**

(1) Shire's balance of cash and cash equivalents at 30 Sept 2007 includes $42m of restricted cash and is available to finance payments due to TKT dissenting shareholders (provision at 30 Sept 2007 of $473m)

(2) Shire has a revolving credit facility of $1.2bn which was undrawn at 30 Sept 2007

Net cash outflow for Q3 2007 : -33

Updated FY 2007 Guidance

	Q3 07 Actual	YTD 07 Actual	Updated FY Guidance	Q2 FY Guidance
Revenue growth	35%	32%	> 30%	> 25%
R&D - GAAP ($m)	180.7	363.7		
Less **SFAS 123R**	(3.3)	(8.8)		
Noven	-	(5.9)		
Renovo	(75.0)	(75.0)		
R&D - Non GAAP ($m)	102.4	274.0	$365m to $375m	$340m to $360m
SG&A - GAAP ($m)	286.7	753.5		
Less **SFAS 123R**	(7.5)	(22.7)		
Legal settlement provision	(27.0)	(27.0)		
SG&A - Non GAAP ($m)	252.2	703.8	$955m to $975m	$930m to $960m

Updated FY 2007 Guidance (cont.)

	Q3 07 Actual	YTD 07 Actual	Updated FY Guidance	Q2 FY Guidance
D&A - GAAP ($m)	46.3	107.4		
Less amortization	(31.1)	(64.0)	Up 70%	Up 80%
Depn - Non GAAP ($m)	15.2	43.4	Up 30%	Up 20%
Tax charge (credit) - US GAAP	(23.2)	43.9		
Less non GAAP adjustments	46.2	63.5		
Non GAAP Charge	23.0	107.4		
Non GAAP-Income before tax	148.7	477.4		
Effective Tax rate	15%	22%	Low 20%'s	26%

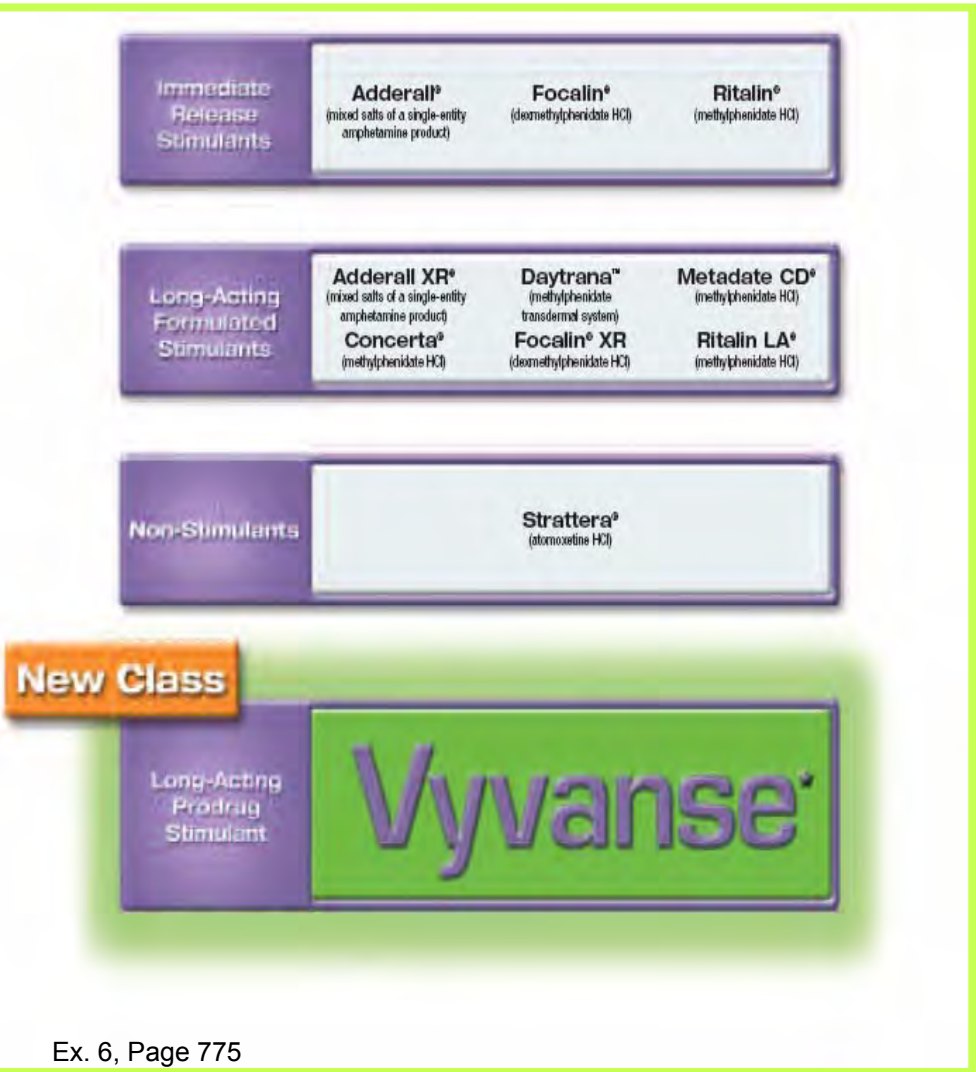
Matthew Emmens
CEO

Product Launches

VYVANSE – Launch update

REFERENCE 39

VYVANSE is positioned as a new class of ADHD medication not just a replacement to AXR



NEW Vyvanse™ (lisdexamfetamine dimesylate) capsules

The First Prodrug Stimulant

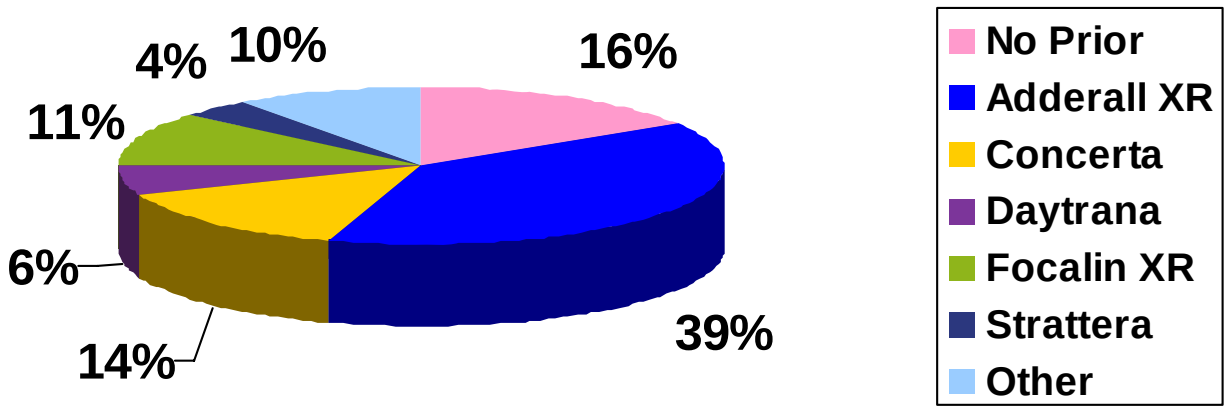
Ex. 6, Page 775

Key attributes to support VYVANSE as an NCE in a new class

- The first Pro-drug Stimulant
- Consistent time to maximum concentration of d-amphetamine from patient to patient
- Significant efficacy throughout the day, even at 6:00 PM
- Adverse event profile that is mild to moderate in severity and incidence decreases over time
- Significantly lower abuse related liking effect than an equivalent oral dose of d-amphetamine

VYVANSE patients reported coming from ADDERALL XR and other brands

- **10,045 patients started on VYVANSE have enrolled and completed baseline surveys**
- **At baseline, 84% had used a prescription for ADHD prior to VYVANSE**

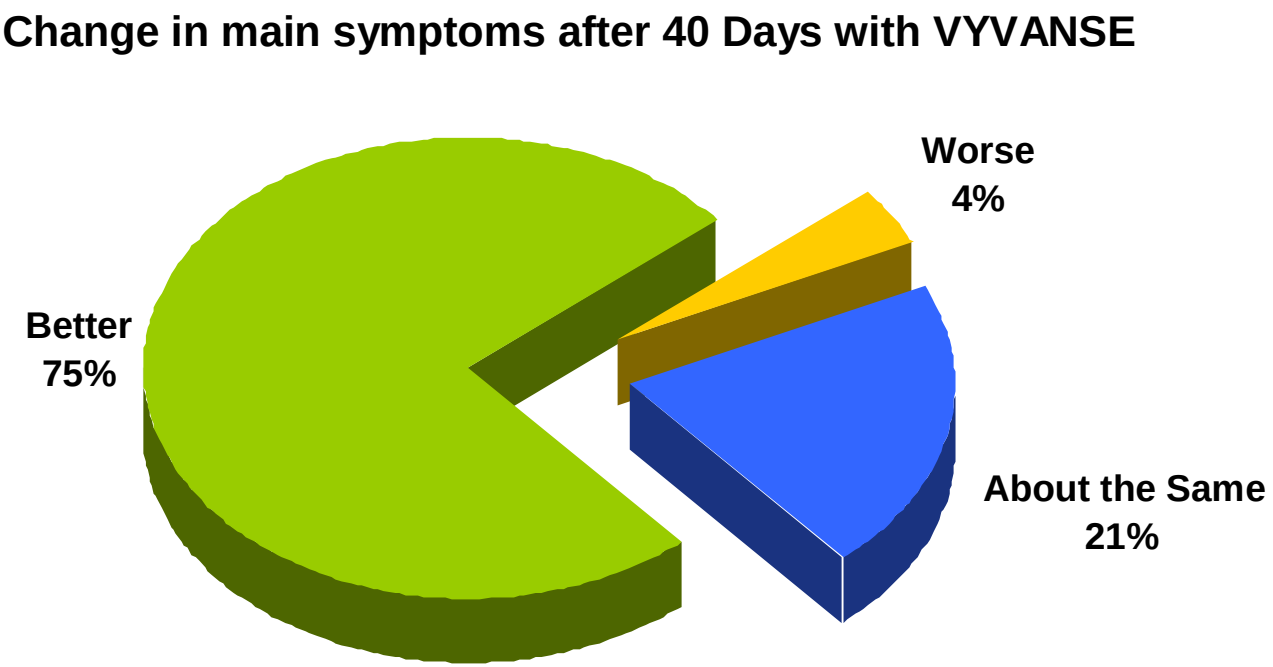


N = 10,045

Ex. 6, Page 777

Source: VYVANSE New Start Patient Experience program

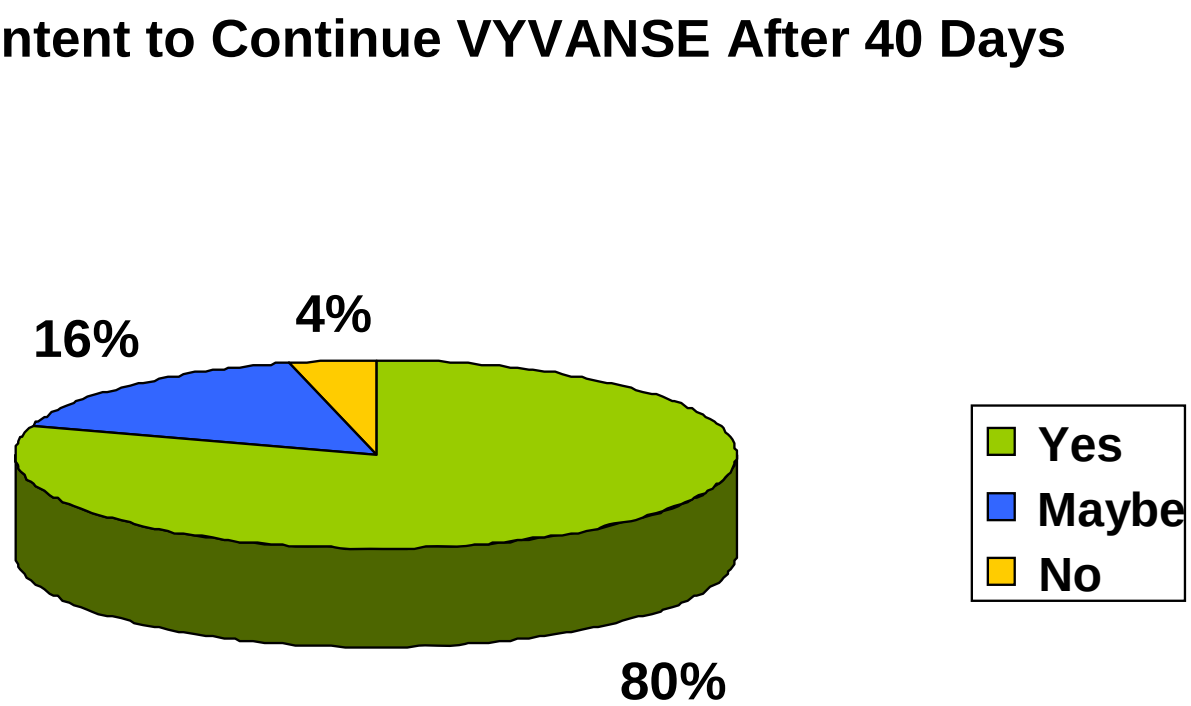
Among patients who switched from ADDERALL XR to VYVANSE, 75% reported further improvement in their most bothersome symptom



n=455

Source: VYVANSE New Start Patient Experience program including over 10,000 patients surveyed of whom 39% were formerly ADDERALL XR users. Among these patients, more than half reported that they still experienced the most bothersome symptoms of ADHD.
Notes: Most bothersome symptoms reported: First: inattention, second: hyperactivity and third: impulsiveness.

8 out of 10 parents reported they intend to continue their child on VYVANSE after switching from ADDERALL XR

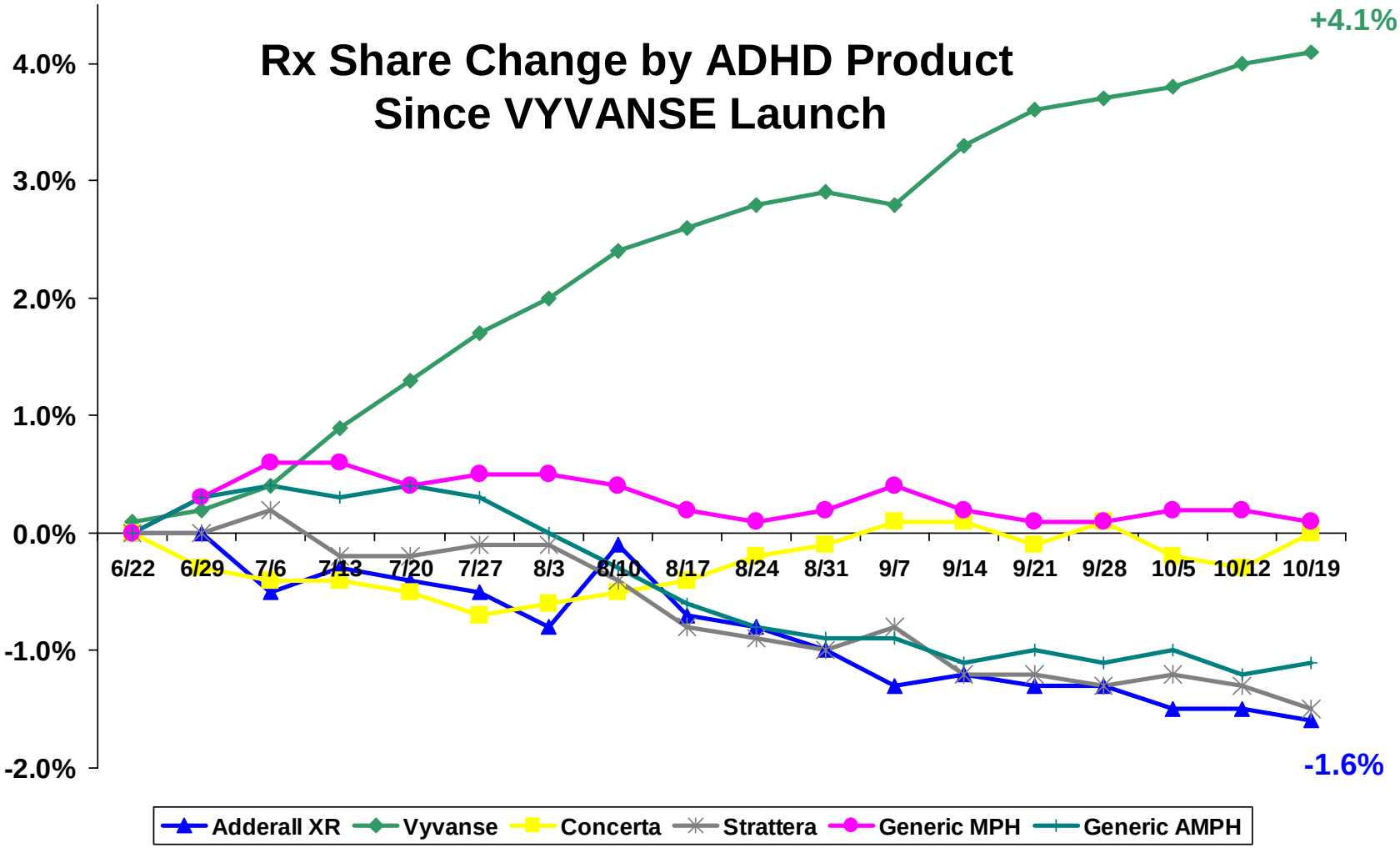


N=455

Source: VYVANSE New Start Patient Experience program

VYVANSE is taking market share from all products in the ADHD category, not just ADDERALL XR

REFERENCE 39



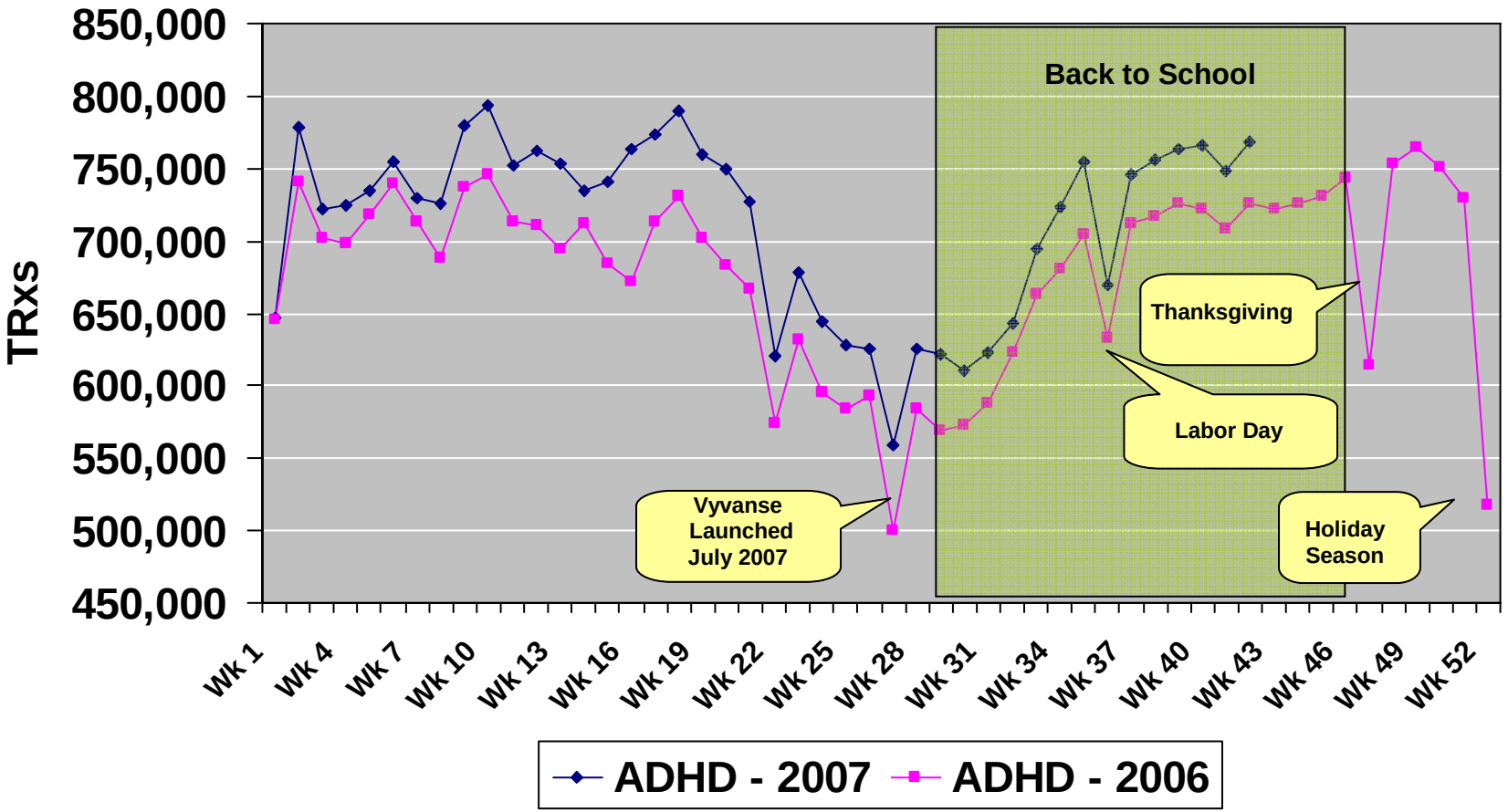
SOURCE: Ex. 6, Page 780 IMS NGPS - Universe

Back to School is not a one-two week event; It runs through October

ADHD Market

Weekly TRx volume

2007 Actual through 10/19/07



Ex. 6, Page 781

Managed Care update

- Coverage is progressing as planned:
  - 6-9 month post-launch review period on adding new products to formulary is common
  - Early success – 3 of top 6 targeted MCO's have added VYVANSE with preferred status
  - Negotiations with numerous plans are progressing
  - Parity with ADDERALL XR formulary status expected by 18 months

REFERENCE 39

VYVANSE demonstrated strong efficacy in Adults with ADHD in a very large Phase III study

- The study was a double-blind, placebo-controlled, 4-week study with forced dose escalation in 420 adult subjects aged 18 to 55 years with moderate to severe symptomatic ADHD
- All VYVANSE doses (30, 50, or 70 mg/d) were highly effective compared with placebo, as shown by ADHD-RS-IV (the primary endpoint)
- Significant improvements in ADHD symptoms were observed within the first week of treatment
- Adverse event profile was similar to that seen with other ADHD trials in adults. A/Es were mild to moderate in severity and incidence decreased over time
- VYVANSE did not worsen sleep quality

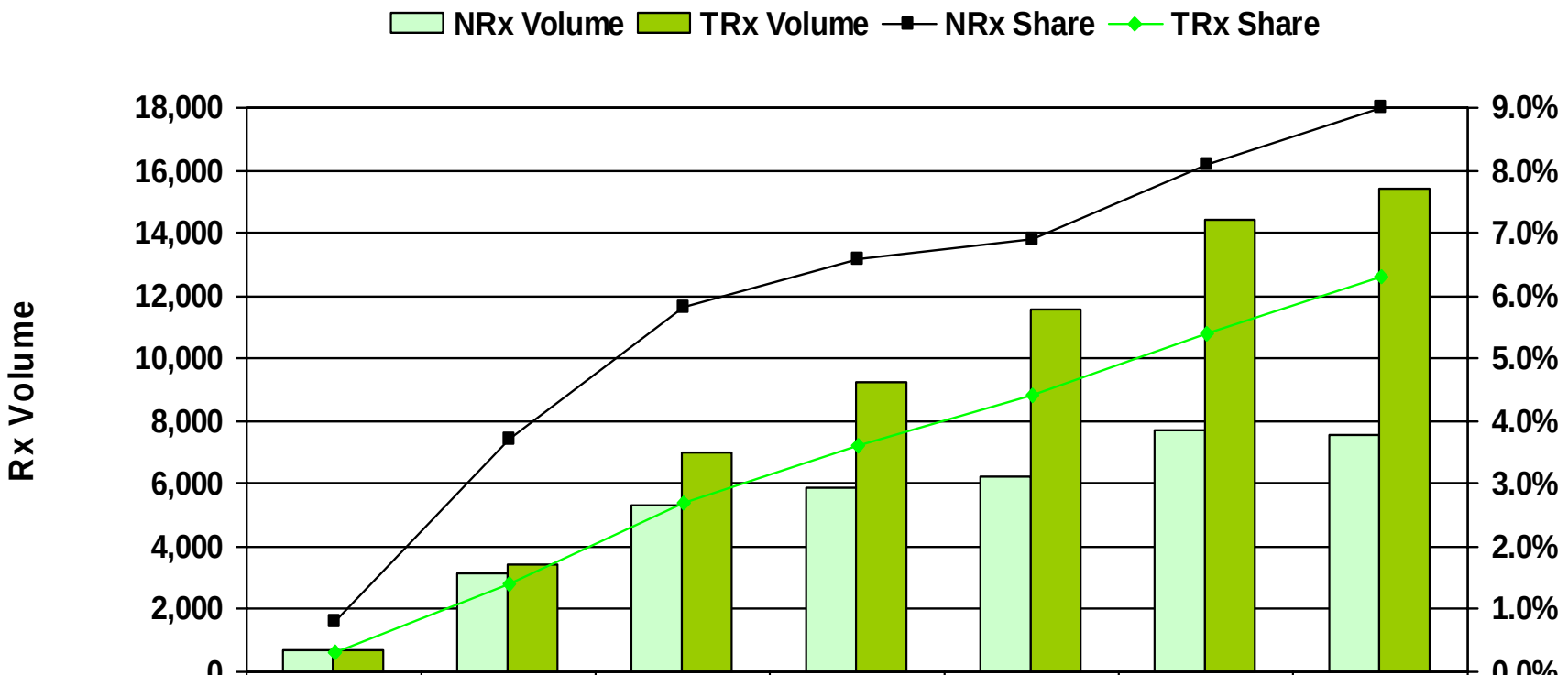
Ex. 6, Page 783

VYVANSE Summary

- VYVANSE rapid launch uptake
- Tracking in line with the industry's best successor molecule launches
- Patients starting on coupons are refilling Rxs
- Back to school is not a one-two week event, but lasts a few months
- Physicians and Patients are providing very positive feedback on their clinical experience with VYVANSE
- Managed Care coverage is progressing as planned
- VYVANSE has tremendous growth potential beyond 2009
  - Very strong IP
  - Europe
  - Potential for other indications

LIALDA – Launch update

LIALDA's growth continues with 6.3% monthly TRx share and 9.0% NRx monthly share in September

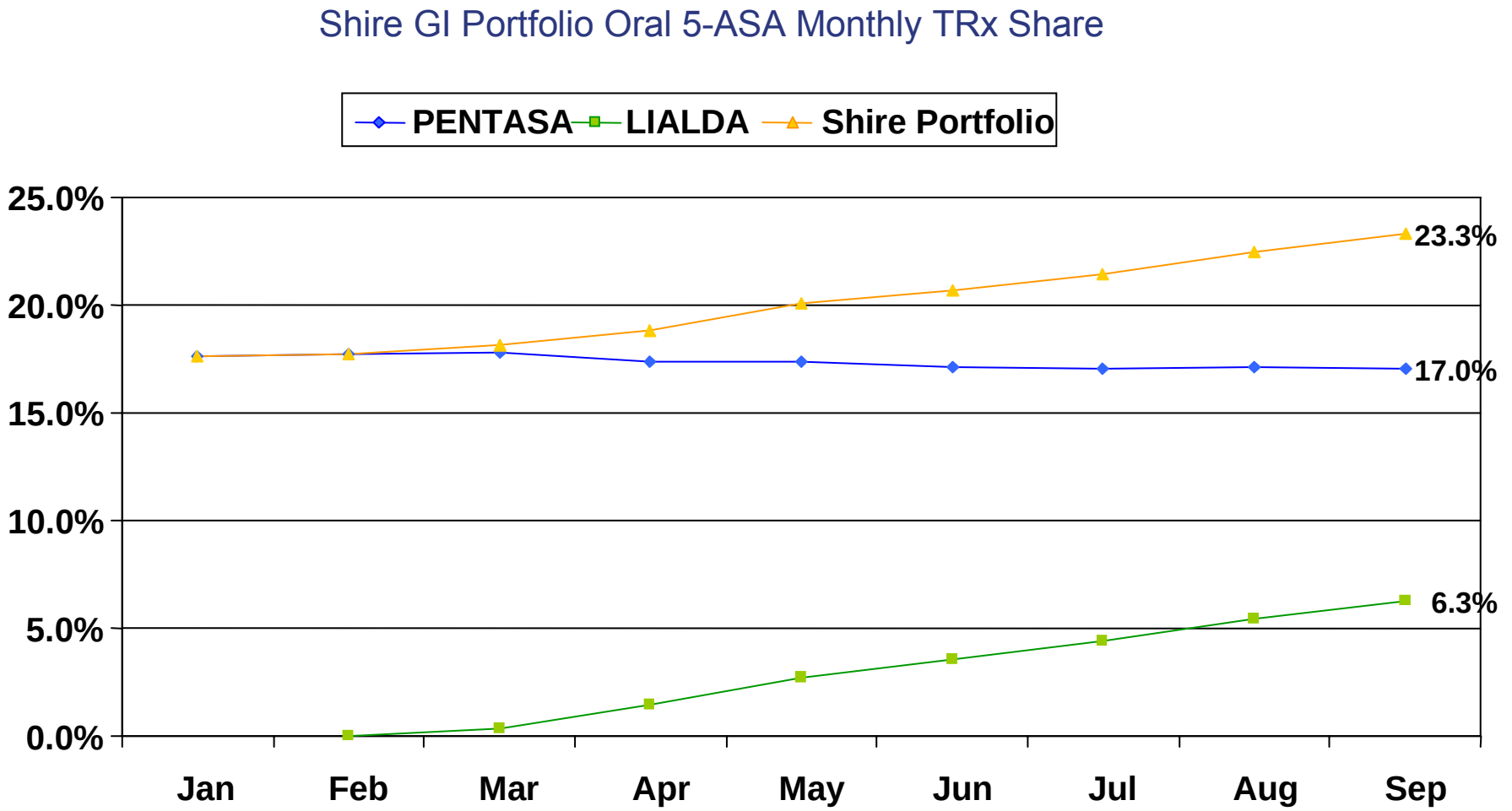


	March	April	May	June	July	Aug	Sept
NRx Volume	722	3,143	5,340	5,896	6,268	7,689	7,594
TRx Volume	725	3,427	7,020	9,258	11,583	14,452	15,429
NRx Share	0.8%	3.7%	5.8%	6.6%	6.9%	8.1%	9.0%
TRx Share	0.3%	1.4%	2.7%	3.6%	4.4%	5.4%	6.3%

Ex. 6, Page 786

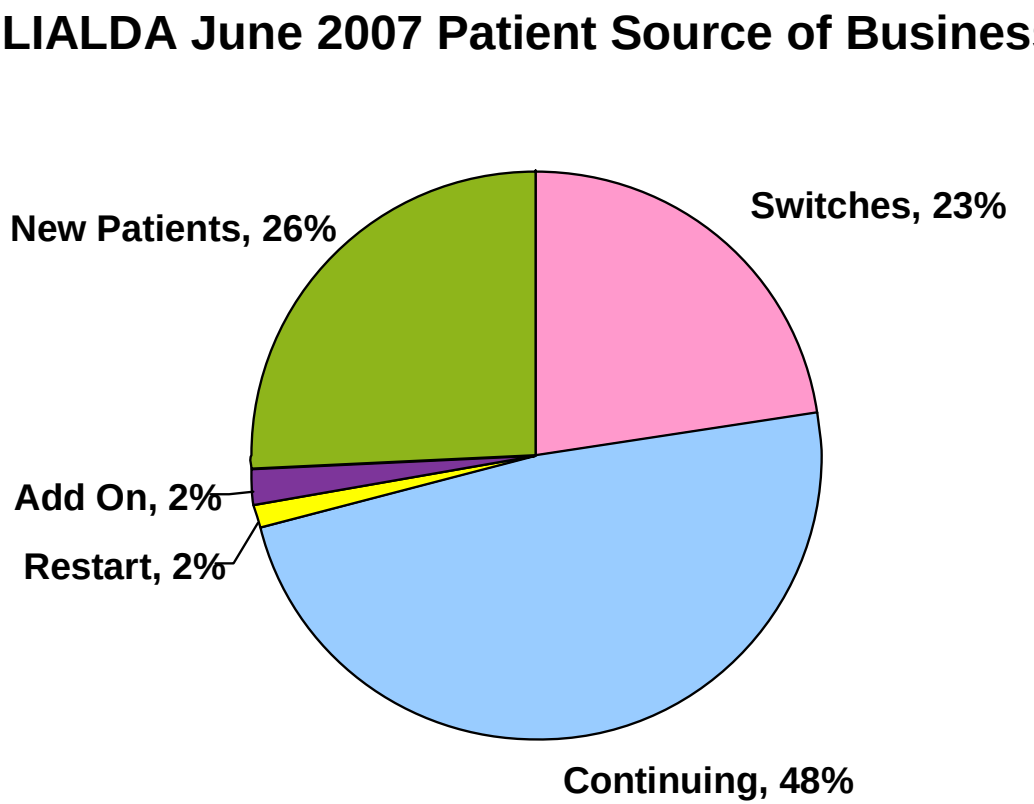
Source: IMS Monthly NGPS September 2007

Total Shire GI monthly share reached 23.3% of 5-ASA Market



Source: IMS Monthly NPA (NGPS) Restated Feb-June 2007 Data
Oral 5-ASA Market Definition: LIALDA, PENTASA, Asacol, Colazal and Dipentum

LIALDA's prescriptions are being generated from both new patients and conversions from other brands



Source: Verispan Patient Parameters Source of Business, June 2007

Concluding Remarks

- 2007 guidance upgraded as revenue growth accelerates
  - revenue growth to be at least 30% for 2007 (previous guidance: at least 25%)
- Excellent Q3 results
  - Successful ongoing launches
  - Continuing to demonstrate our ability to execute
  - VYVANSE – enthusiastic response from physicians and caregivers
  - ELAPRASE – rapid uptake in US and EU
  - LIALDA – growth continues
  - FOSRENOL – strong start in Europe
  - DYNEPO – launched in Q1 2007, good reception
- Good progress in strengthening our R&D pipeline

Questions and Answers

All

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Shire plc Q3 2007 Earnings Call Transcript

Nov. 4, 2007 2:24 AM ET | About: Shire PLC (SHPG)

Shire plc (SHPGY)

Q3 2007 Earnings Call

November 1, 2007, 10:30 AM ET

Executives

Cléa Rosenfeld - VP, IR

Matthew Emmens - CEO and Chairman of the Management Committee

Angus Russell - CFO

Analysts

Brian White - Deutsche Bank AG London

Corey Davis - Natexis Bleichroeder Inc.

David Buck - Buckingham Research Group Inc.

Dani Saurymper - Goldman Sachs Equity Securities (UK)

David Steinberg - Deutsche Bank Securities Inc.

Frank H. Pinkerton - Banc of America Securities

Ken Cacciatore - Cowen and Company, LLC.

Graham Parry - Merrill Lynch International

John Boris - Bear, Stearns & Co.

Martin Wales - UBS Warburg (UK)

Presentation

Operator

Thank you for standing by and welcome to the Shire's Third Quarter Results Conference Call. At this time, all participants are in a listen-only mode. There will be a presentation followed by a question and answer session. [Operator Instructions] I must advise you that this conference is being recorded today, Thursday, the 1st of November, year 2007.

I would now like to hand the conference over to your speaker today, Cléa Rosenfeld, Vice President, Investor Relations. Please go ahead.

Cléa Rosenfeld - Vice President, Investor Relations

Thank you very much Sabrina. Good morning and good afternoon everyone. Thank you for joining us today for Shire's third quarter 2007 financial results. By now you should all have received our press release and should be viewing our presentation via our website on www.shire.com. If for some reason you have not received the press release or unable to access our website, please contact Souheil in our U.K. Investor Relations department on 44-1256-894-160, as he will be happy to help you.

Our speakers today are Matthew Emmens, Chief Executive Officer; and Angus Russell, Chief Financial Officer.

Before we begin and as always, I would refer you to the slides, the second slide of our presentation and remind you that any statements made during this call, which are not historical statements, will be forward-looking statements, and as such, will be subject to risks and uncertainties, which, if they materialize, could materially affect our results.

Today's agenda is as follows. We begin with a summary of Shire's third

quarter performance and third quarter highlights from Matthew Emmens, and Angus Russell will continue with the financial review of the quarter, then finally Matt will summarize the key points for this quarter. We will then open up for your questions. Could I please ask again, in the interest of time and so that everyone gets a chance to ask the questions on this call, that you limit yourself to two questions? As always, Eric and I will be more than happy to follow up with any subsequent questions at the end of this call or after. Thank you very much for your understanding.

And now over to you Matt.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Thank you Cléa, thanks for your interest in Shire and welcome to our 3Q. I will start out by saying that our strategy of a rapidly growing biopharmaceutical company is certainly on track with very strong quarterly results. You'll see that both total income and our top line is very, very strong. We are upgrading our revenue growth guidance to at least 30% from our previous level of at least 25%, and as you have seen the numbers, you'll see why.

Looking at highlights on page 6, our product sales were up 41% to $543 million. Our total revenues were up 35% to $609 million, and our net cash provided by operating activities was up 51% to $124 million.

Moving on to page 7, a look at our portfolio highlights. Our ADHD franchise now exceeds 30% of U.S. market share. Moving to VYVANSE, which was launched July 2nd, you are seeing a 4% total market share now, so we've basically been able to get 1 percentage share for each month in the market. We'll have more to say on that in a minute, but we are pleased with that launch.

Our adult indication PDUFA date is April 28th of next year, so we are excited about that as that represents a very large opportunity, not only in the U.S., but in Europe and other countries.

Looking at DAYTRANA, as you know, we had some issues with the backing, the liner, and we had a limited withdrawal of a limited quantity of those patches, and we are now manufacturing... Noven is now manufacturing those

with an enhanced process that provides improved ease of use.

Moving to our GI franchise, it now exceeds 23% share of the total 5-ASA market. LIALDA, our latest weekly market share is 9.3% of new prescriptions and 6.9% of total prescriptions. Noteworthy there is that we are not losing it on the PENTASA side, so we are very pleased with that. We are getting prescriptions from both new patients and switches from other brands.

Looking at JUVISTA, our license with Renovo, we had positive Phase 2 clinical trial results recently. We continue to be very encouraged by the product's potential.

Moving on the page 8, we look at Human Genetic Therapies, ELAPRASE is now available in 34 countries and it's approved and launched in Japan. It's becoming a major contributor to our total portfolio. Looking at REPLAGAL, it continues to grow, it's now in 41 countries. We have significant growth for the quarter with new patients starting therapy in European markets, as well as through geographic expansions in Canada, Latin America, and also Japan.

Our Phase 3 clinical trails for GA-GCB, at least three of them are ongoing and we are enrolling patients at a better pace than we did last quarter.

Moving on to Renal, FOSRENOL is now available in 23 countries and we recently launched the product in Canada, the Slovak Republic, and Poland. I would tell you also that FOSRENOL sales, 40% of the total FOSRENOL sales are coming from Europe now, very rapidly growing in Europe. And DYNEPO was recently launched in Ireland and Italy, and we are having very good results in Germany and you are seeing that have some sales for the first time this quarter that are significant.

With that, I will move on and introduce Angus Russell, who will go more in depth with our numbers.

Angus Russell - Chief Financial Officer

Thanks Matt. If you just turn to the next slide, slide 10 and look at total revenues in a little bit more detail. As Matt already mentioned, total product sales were are up 41% and overall revenues were up 35. If you look beneath that and look at the proportion of the sales growth that's coming from products just launched really in the last two years, you can see that analyzed

in the top right hand corner in the table there. The first point I would make is to highlight that even the base business, prior to the launch of all these new products is growing at 16%, very, very healthy performance in its own right from products that have been on the market for quite a few years. But if we look at this wave of new products launched in the next two years, interesting to note that they are now contributing 23% of our entire sales base, and that's in contrast to the same period last year when these products were only contributing about 7%. And if you look at it in dollar terms, it means we've added almost $100 million of new sales between this quarter and the comparable quarter last year.

At the bottom, you can see how our growth has accelerated in the proportion of new sales across the course of this year. In the first quarter, I reported that this number was 13% of sales, last quarter it was 19% and now 23%. And I think this trend will continue certainly through the rest of this year and well into the first half of next year.

If we look at the next page, slide 11, and look at the usual analysis of our major products sales, looking at the movement between the underlying script growth and total sales growth, ADDERALL XR, underlying growth in that, in script terms was 3%, that's a 6% growth in the ADHD market during this period, but that has been reduced for ADDERALL XR because obviously we are now beginning to lose share as we put VYVANSE into the market and patients are converting from ADDERALL XR use to VYVANSE. The difference largely between the 3% and the reported 20% is 7% price increase that we took in January this year, and then some wholesaler stock movements that occurred between the two periods.

VYVANSE and DAYTRANA, I'd like to take you through in a little bit more detail on the next few slides, so we'll come back to those in a moment; but carrying on down, PENTASA, 2% in the underlying market growth of this product, that's 4% growth in the 5-ASA market and a very minor decline from 17.4% to 17.1% during the period. I think that's a lot less than anybody expected in terms of concerns that we would cannibalize our own drug with the launch of LIALDA, that's not occurred, we have been able to maintain and actually grow the sales of PENTASA during this period. Difference between the 2% and the 18% is really to do with some price increases in the preference for the new 500 milligram dose strength over the

250 milligram dose strength.

LIALDA, as I said, is an excellent launch, and Matt will cover this in more detail when he talks about launches later on again, but obviously we had no sales in the comparable period, the product only launched about six months ago, six and a half months ago; we've got $16.3 million worth of sales in the quarter.

ELAPRASE continues very rapid uptake and new patients being signed quite rapidly and introduced to treatment and reimbursements being negotiated very successfully. So you can see an excellent result of $55 million of sales in this quarter.

REPLAGAL, again for a product that's been in the market some years, we entered new markets this period. It's driven the growth up 26%. That is a little bit flattered, there is an 8% foreign exchange benefit in that number of 26%, but nonetheless still very good strong underlying growth.

And FOSRENOL, rather large number there, 135%, a lot of that is to do with the very rapid uptake and the excellent performance again by European marketing teams in launching that drug across multiple markets now in Europe, and that contributed two-thirds of that 135% rise. The other third of that came from, if you remember, a de-stocking in the comparable period last year to do with what we call the optimized formulation when some of the older formulation came back to us and was de-stocked by the wholesalers. Stock levels this year are totally unaffected there, quite normal throughout this year.

CARBATROL, one of older products but still producing nice cash return, the market decline for carbamazepine is actually 5%. We are in line with that having held on to our share and there is no pricing benefits or stock movements there really worth talking about, and you see the reported number also 5%.

And finally, XAGRID, again excellent performance as an open drug across the European markets, very strong growth in the period of again 26% here with a 9% foreign exchange benefit included within that.

Now let's move on looking at the next slide and talk a lot more about VYVANSE and DAYTRANA, which are quite complex this period because of

launch issues and in the case of DAYTRANA, as Matt already touched on, the withdrawal of some of the products from the market.

First off, with VYVANSE on slide 12 wanted to show you this chart just to demonstrate why the figures are as they are during the quarter. What's clear hopefully from this chart, which is a week by week representation of the prescriptions and the coupons that have been redeemed in the period, as you can see and as we would expect, in the early weeks of Q3, as the product went out, by definition, most of the scripts were being offered in the form of coupon redemptions. So a lot of the scripts that were out there, people were getting as free treatment.

I just draw you attention to the bullet points at the bottom of this slide. Every redeemed coupon is accompanied by a script. I put that in there because there has been a lot of confusion judging by some of the calls we have taken in last few weeks where I think people are thinking about the products in the industry where you get free samples and free samples do not have an accompanying script. With a coupon, I stress again, it's only a form of payment, if you like, or free supply of that script, the script actually does get recorded, but it comes for 30 days completely free.

Next point is significant, related to that, is that it's only for the first 30 days treatment. Thereafter, you would have to pay for script as normal and we keep you know records of that to ensure that it's only the first 30 days. You can see statistically over 300,000 scripts now have been written since launch.

Final two points, I draw your attention to on the slide is the coupons having risen up in the early weeks have now reached a fairly consistent stable level, and those are the red bars that you see on the slide in recent weeks. That's good in the sense that we are getting a very constant level of new starts on the drug week-by-week, but you can now see that as a proportion of the total scripts being written, which is the green line, in these most recent weeks, couponing now has fallen to a much, much lower level than you can see to the left hand side of the chart in the early weeks, which are the weeks that are of course included in this Q3 results.

So, let's turn and look at the next slide and see how does that translate into effective numbers. So, let me walk you through this slide. Sales demand in the left hand column you can see, during Q3 was 217,000 scripts for

VYVANSE, and on the right hand side you can see, I have given you the numbers to how you multiply, there's on average 28.3 capsules per script at a price of $3.41. That gives you a total demand for the quarter of $20.9 million.

On top of that, we actually made new shipments to refill wholesalers who would dispatch material to pharmacies during the quarter and unlike the first shipment we made, which, as you know, has to be deferred under revenue recognition, we can instantly book the restocking of the pipes. So, in the quarter, we actually shipped another 10.2 refills for the wholesalers. So, that gives a total underlying gross sales number of 31.1, as you can see on the slide.

Against that, as I've just said from the prior chart, you can see very clearly that a lot of that material that went out in the early weeks was given to patients as a free trial for 30 days. Therefore, couponing is very high in this particular quarter, 39% of sales, $12.3 million.

On top of that, there are both normal wholesaler discounts and rebates being offered, but it's a higher number in this period because a significant amount of the 8.2 you see here was actually a one-time discounted offer to the wholesalers to enable us to ship a very large quantity, the $56 million that appears on the box on the right hand side. For them to hold that amount of working capital intake, a personal risk themselves on our product launch, we have to provide some incentives, discounts to cushion them on that, and so that's included as a one-time item within the $8.2 million.

So when you look at this, you see that, a mix of all that, is that two-thirds of the sales were reduced by these early sales coupons and discounts and rebates. What I've then included in the box on the right is to say that we believe that somewhere in the second half of next year, as we get towards the back-end of next year, this 66% number will fall back to about a 28% number in terms of gross to net discounts and rebating on a very small, I imagine by then, level of couponing compared to total scripts being written each week.

Just to give you a calibration, ADDERALL XR today has a gross to net discount of about 24%. So to be at 20% just 18 months after launch, puts us pretty close to ADDERALL XR like economics. Right now, I could say already

that in these current weeks as we move from October into November, we're probably already at discount ranges of coupons and rebates combined at 66%, is probably in about a 40% to 45% range as we speak.

Just on the other box on the right hand side, let me just reconcile for you again the deferred revenues. You can see, as I said, that we shipped almost $56 million, $55.9 million in Q2. We made a very early shipment in Q3, which by then also had to be deferred because there was no real demand yet at the beginning of the quarter. So that brought the total shipments up to almost $58 million, against that $57 million, $58 million. Against that, you can see then we booked this 20.9 of true sales demand. So at the moment, we still have revenue deferral of $37 million. It's my expectation that by the end of this year, we will have worked our way through that remaining $37 million and to remind you that on top of that, like, as you can see what happened in this quarter, any fresh shipments will be booked straight into the sales line.

Now turning to the next slide and looking at the similar analysis for DAYTRANA, you can see again and I'll walk you through in the same way, 183,000 scripts during the period for DAYTRANA and with the economics of that shown again on the right hand side, you can see that produced true sales demand of $21.7 million during the quarter, a very small piece of destocking, but $21.6 million then of underlying sales.

Our couponing went up again compared to prior quarter and that was a lot to do with the issue about product withdrawal and trying to resolve the liner issues during the past quarter, to obviously incent patients to stay on the drug, whilst we resolve those issues, we did again offer a short-term couponing program to keep the market incented to keep taking the drug.

On top of that, you can see the returns, $4 million we booked as returns, which was linked specifically to the one-time withdrawal of a proportion of the patches... the older patches that have the liner problem and then there is the normal level of wholesaler discounts and rebates. You can see, again, I am saying that the combined 56%, I expect will, towards the end of this year and certainly into next year, will fall back to a level of 25%, which, as I said, when you compare to ADDERALL XR as well in the normal range of our gross to net discounts.

Now, turning to next page looking at our royalties line, again, very good performance from the royalties given how long this royalty stream has been in existence and the longevity of these products is still very impressive. 3TC shows 1% improvement, although you can see from the footnote, there is a 4% currency benefit, but I still think an underlying 3% decline is an excellent performance for a product at this lifecycle stage of, the 3TC is now in.

In regards to ZEFFIX, you can see a 6% currency benefit within the 10% that means a still good 4% underlying growth, particularly now coming from the Chinese market, but also other markets like Japan and Korea and Asia continue to provide growth for this product. And finally, REMINYL, which is up 3% in total during the quarter.

We look at financial ratios on the next page. I think given despite the level of discounting and rebating and couponing, the broadly based growth across many other fast growing products has meant that our gross margins are only down about 1% compared to the full year last year, and actually year-to-date in Q3, as you can see, at 86%, so are in line with each other, and I would hope that we can sustain that through to the end of this year.

In terms of R&D, you can see that's up at 19% in the quarter, but year-to-date is 18%, and when I talk about full year guidance, I think our year-to-date figure is getting pretty close to how we will end up as a percent of sales and this is in line with our indicated position on R&D as a percent of product sales.

SG&A, again, very happy to say this, I think it's trending down to where my expectation has been for some time and as I have talked with many of you before, last year remember, and you can see it shown on the right, we were at 52% because we had to put a lot of infrastructure and cost upfront before we actually made many of these product launches. Now with a strong revenue performance, we are seeing that full... down to 46% in this quarter, 47% year-to-date, and I think that range is a pretty good anchor for the year in total. And that's, as you can see, something like a 5% to 6% improvement in operating margin across the course of this year.

And then looking at that operating margin itself, maybe starting with the bottom line, first looking at as a percentage of total revenue, obviously 28% last year, 31% year-to-date this year, and 29 in this quarter, I think the

current, again, quarter and year-to-date numbers something in that range, maybe around the 30% level is fair, but of course this does get flattered by the revenues coming from royalties, which dropped straight into this number.

So, I'll try to give you a representation as how we look at the business and run it a lot internally, which is to think about our product sale performance, and there you see at the low point with all the costs that we have to put in last year drove that figure down to 16% for the year, but already year-to-date we are back up to 22%. We were 21% in the quarter; again I think it's a good range for this year. And as I've said to you... many of you before, I would hope that we continue a gradual improvement across the course of the next one to two years to get us back up maybe to a 25% number across that to one to two-year period.

Now turning to the next page and looking at net income and EPS. The anchor number that you are well aware in terms of EPS and what we are looking at is a non-GAAP, as we call it, cash EPS number of 66.6 cents, and you can see that effectively represents 32% growth compared to the same equivalent period last year.

If we look over now in terms of the reconciling items between GAAP EPS and this non-GAAP number. Obviously one of the biggest items is the fact that we have to expense in the R&D line, the in-licensing payment to Renovo that was made to secure the JUVISTA license, and that's $75 million or so expensed in R&D. We have got a small gain on the disposal of product right, the EQUETRO, we sold for 7.1, we have no book value, it is an enhanced development, and therefore we were able to book the entire 7.1 cash disposal in these numbers as a profit.

In terms of the next item that we can relates back to TKT. There were a number of minor litigations going on, it's around the time of TKT acquisition. This is one of the slightly larger litigations in that group of various litigations. This was related to the class action suit regarding the share price drop after the fact that REPLAGAL in the U.S. was rejected by the FDA, and there was a share price fall and a class action suit was brought against the company. I am pleased to say we've reached the settlement; the gross settlement is $50 million. We have been able to make a claim for $23 million of insurance. So what we've booked here is the remaining provision of $27 million and that closes that particular litigation.

We've got some intangible asset amortization going through and that's the piece that we take out, remember to get our cash EPS number. It's risen quite a bit this quarter because now of course we are bringing the VYVANSE amortization on to the books. And then there is a normal FAS 123 adjustment and tax effects on all those above items.

If you move on to next slide, look at cash generation, again very strong performance. I mean, this business these days is not throwing off between $700 million to $800 million a year of underlying cash flow. Against that, we have got the $75 million that I just mentioned, payment to Renovo plus the additional amount of $50 million that we bought 6% of the equity in Renovo, so all of that has gone out in this period as a cash payment to Renovo as $125 million.

We have got some fixed asset purchases broadly based across the business, mainly plant and equipment of $30 million. We have got some product milestones, $26 million, and the largest item is the $25 million that we paid to Noven for DAYTRANA with its annual sales having gone through $50 million and that's as per the original business development agreement.

Asset sales, well, $7 million of the $8 million is the EQUETRO item I just talked about, money coming in. And our net interest received of $8 million has just outweighed our tax paid in the period of $7 million, so a small cash inflow.

And finally, other financing is the shares that we have to buy in the market to fulfill option grants; there was a net $61 million outflow in regards to some of those purchases.

On the right hand side, you can see in the books our net debt position is shown at $495 million, within the cash at $638 million. Just to remind you there's a substantial proportion... that's shown in the footnote to the left, there's a $473 million provision within that 638 in regard to the pending litigation for the dissenting shareholder case with TKT.

On to the next page then; and the last two slides; really to talk about the guidance for the full year; so we've upgraded our revenue growth. You can see revenues in the quarter of 35% to 32% to-date, very strong performance. Given us the confidence to now say that clearly our revenues

will be at no less than 30% for the full-year, another full 5% upgrade on the previous quarter.

R&D has risen a little bit against the previous range, not so really having seen this very strong line... strong top-line performance immersion across the year, we've decided to invest and initiate faster some of our R&D programs. We have very large IIIb/IV programs in place now to support and drive that top-line. That will continue certainly into next year to continue to support this strong top-line performance.

SG&A similar story. We've marginally increased the previous range really again in respect to driving that top-line and investing in promotional costs, which is having a very beneficial effect to the top-line growth. In terms of our... and putting in this product... in percentages to product sales, R&D, I expect it should end up, as I said, around the 18%, maybe 17% to 18% range for the full-year product sales. And with SG&A, I expect this to be in the 46% to 47% range compared to product sales.

As we turn over the page here and look finally at the other elements that we have given you some forecasting help with in the past. D&A less amortization and you can see the amortization, our guidance is down a little bit now, up 70%, we said 80% previously, but it's moderated a bit in our forecast now. And depreciation going the other way, up from 20% to 30%. So bring them together and the guidance is pretty much the same across the total D&A category.

And then on tax charge, obviously we have had some one-time benefits in this quarter. Some of that came from revelation of various reviews and audits. Like any company, we obviously are subject to tax audit and review. Some of those concluded during this quarter and concluded in a favorable manner to us and we have been able to take a favorable review in our tax provisioning in respect to that.

And finally, obviously the deduction of the substantial amounts of marketing expense in the U.S., particularly associated with the VYVANSE launches let us be able to deduct those costs against our U.S. profits and obviously the U.S. environment for us is one of the higher tax jurisdictions. So in the mix of our entire global operations being able to deduct all those expenses has been quite beneficial in the quarter. So that's now enabling us to take the tax

charge for this year down from 26% to probably something around the lower 20s for the year as a whole.

And that's it. With that, let me hand back to Matt to give you a lot more detail about a couple of the big product launches.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Thank you, Angus. It's no secret there has been a lot of interest in our launch as I thought I would take a minute and give you our view of how they are going and what the prospects are.

First I will turn over to VYVANSE, which is going to be... and we will flip to page 24, the first page of that. I think there has been some misunderstanding. I would like to just go over kind of where we are positioning this drug and why we are doing that. It is positioned as a new class of ADHD medication and it is not, I repeat not a replacement for AXR. We used the word switch, that's probably unfortunate. That's one way of looking at it, but basically if we had chosen to have this product as a substitute for ADDERALL XR, we would by that nature of that, limit ourselves to what the market would be, A, and we would suggest that this drug could be substituted. It is not a new chemical entity, it is not a line extension and it is not substitutable in the broader sense.

So later on that's going to become important, but we now have a very distinctive profile of this drug, not just because we are saying there... if you look to the left of this slide, there is immediate release stimulants, there is long-acting formulated stimulants, there is non-stimulants in this new class called long-acting prodrug stimulants.

The drug is intrinsically long-acting and we are getting feedback from parents, physicians and patients that take this drug that has a different profile than any drug in the market, and you will see by where we are getting the business from that they are voting with their hands in their prescriptions.

The drug has a broad appeal. It is not just a line extension as I talked about and patients are actually seeing a difference when... they feel different, when they take this drug they feel better, I will get to that in a minute.

The other flaw I think is that for some reason everybody thinks that the growth of this drug will stop in April 2008. We have this big deadline coming up... it's '09. And that's not the case. This drug is a new chemical entity and it is showing the growth rates that we'd expect of it and we expect that growth to continue well on beyond that in terms of a typical new chemical entity profiles. So there is no magic date there. Yes, that will affect ADDERALL XR, but this drug is being perceived as a different drug and being prescribed as a different drug.

So let me get in to that, turning to page 25; we call it the first prodrug stimulant. This is the intrinsically long-acting thing that gives us a predictable blood profile, and activity at least to 6 PM. We have consistent time to maximum concentration and that's very different than what we get from ADDERALL XR or IR or some of the other drugs in the market. They are unpredictable in terms of their onset and offset and their overall length of activity or effectiveness. We have seen significant efficacy throughout the day, even at 6 PM., and patients and physicians routinely tell us that that's the difference they see with this product. The adverse event profile is very similar to what we have expected and in fact we get better remarks on this drug than we get from ADDERALL XR. And you see the same thing you do with all stimulants. You get more adverse effects in the first week or two and then they decrease rapidly in the second and third weeks. So the liking effect is the third thing that we stressed, but however the most important thing is length of activity and smoothness.

Turning to page 26; VYVANSE patients reported coming from ADDERALL XR and other brands; we studied 10,045 patients that were started on VYVANSE and have enrolled and completed the baseline surveys. This is part of the couponing program as we get data back from these patients.

At baseline, 84% had used the prescription for ADHD prior to VYVANSE, so they are coming off of other drugs and you can see where they are coming from. Obviously about 40% from ADDERALL XR, but you can see that we are getting them from everywhere, including CONCERTA and STRATTERA, which is very interesting because that's exactly what our strategy is, is to go after the broad market. And it's interesting that we are getting quite a bit from STRATTERA because that is perceived as to be the safest drug in the market. So some of that liking effect safety we think is attracting people to prescribe

this drug as an alternative to other drugs in the stimulant class.

Moving to 27; among patients who switched from ADDERALL XR to VYVANSE, 75% reported further improvement in their most bothersome symptoms. Now, what they did in this study is the same database that I just described, but they took another sample out of this of 455 patients, and they asked them what their most bothersome symptom was. The first was obviously inattention, and the second was hyperactivity, and the third was impulsiveness. Interesting, 96% of people in this survey said that they are either better, 75%, or about the same, 21%, adding up to 96% people think that they are better on this drug than anything else that they were on before that. That's amazing.

28; if we look at 8 out of 10 parents reported they intend to continue their child on VYVANSE after switching from ADDERALL XR, and this was when they were on drug for 40 days. So again, 96% said they either would, that was 80%, or maybe 16%, they're still thinking about it. But you don't see a lot of negative here. Usually by this time, two or three months out from the sales force, we would know if we have an Achilles' heel, a problem, a hook that the competition has to get at us, and I can tell you that we don't see any of that. Basically we see physicians trying the drug, getting very positive results, and very positive feedback from parents regarding how long the drug is acting and how smooth it is. We don't seem to get some of the effect drop off at the end of the day that you do, it's a personality effect that this drug doesn't seem to have at the same rate. So that's what they feed back to us, we can't promote that obviously, but we're just listening.

If we go to page 29; I mentioned we're taking product share from all products in the category and you can see how that's happening. That's a good thing. It means that they perceive this drug to be not only better than ADDERALL XR, but everything else out there, and that will help us over time. The perception of the drug is positive. The patients' willingness to stay on is positive. The leading indicators qualitatively don't get much better than this.

Turning to page 30; we have emphasized this once before, we want to do it once again. There has been a lot of projection based on weeklies and monthlies. We just want to show you how this market works and basically you can see when there is a holiday in summer, the prescriptions to total markets go down dramatically, 40% or so. And then when you see a Labor

Day or a Thanksgiving or a holiday season coming up in December, you can expect the market to go down. So I think there has been some overreaction to that. We just want to show you historically how that's affected, and emphasized that the Back to School... we still got several more weeks to Back to School season. You can see it doesn't really fall off till the end of this month.

If we go to page 31; there has been some things written about Managed Care which are puzzling. There has been some things written about pricing and sensitivity in the market. We have not seen this. I would tell you our coverage is progressing as planned. It takes usually about 6 to 9 months to get a significant amount of Managed Care formulary acceptance and we are about a third of the way right now of getting the status that ADDERALL XR has. So we are well on track to meet that. We are not having the difficulties that people seem to be explaining to us; it's a mystery to us.

We've had... three of the top six targeted Managed Care organizations have added VYVANSE to preferred status basically in the last four weeks. We have a lot of negotiations ongoing and as I said, we expect parity with ADDERALL XR formulary status within 18 months and we are not getting the resistance that has been described in some of the papers I read. I don't understand it.

Okay, 32; VYVANSE demonstrated strong efficacy in adults with ADHD. You probably know that. We just presented it at one of the large meetings in a double-blind study, placebo-controlled, 4-week study with forced dose escalation in 420 adults. The adults were 18 to 55 years of age in that study. All doses were effective compared with the placebo as measured by the standard in this therapy class. We saw significant improvements. The adverse effect profile was similar to that seen with other ADHD drugs and trials in adults. And one of the big things that everybody was saying because it lasted longer probably disturbs sleep, it did not in this, the quality of sleep was the same. So pretty straight forward, this was the basis for our filing and we didn't have any surprises here. We think this will be a terrific ADHD adult product.

Moving on to 33, just to summarize; we had good uptake, we are getting to about a percent share a month. We are getting it from all sectors based on their participation. We are getting switching from drugs that were perceived to be the safer drugs, drugs like STRATTERA, and we are getting

prescriptions from CONCERTA. So the strategy for this drug was to go to broad appeal and have a larger opportunity than there would be if just... if it was just an ADDERALL switch, which probably in itself if we had done that would basically make people think that you could substitute that. And based on the favorable clinical profile of this drug's substitution, I think we would have a lot of resistance based on the patients and based on the physicians because of the symptom release... the symptom relief, excuse me.

We are tracking in line with the industry's best successor molecule launches. Again, this is a not a line extension, it's not like XR to IR, it's a new chemical entity and has a patent to go along with that and basically the clinical profile is markedly different in the minds of physicians and us. I say markedly in that they can... they basically tell us back that they are seeing longer activity to 6:00 P.M. and sometimes beyond, and they are telling us that they see more smoothness in the uptake and the offset of this product.

So we are getting good refill of the prescriptions, good data. We have got a few more weeks to Back to School. I mentioned the positive feedback. The Managed Care coverage is going as planned, in fact, maybe a little bit better. And VYVANSE has a tremendous growth potential beyond 2009. We do not believe that the absence of ADDERALL XR in this setting, albeit at a lower price, a generic price, is going to have a significant impact on the growth of this product.

We will bring the product to Europe. We believe there is a tremendous opportunity to build that market there, particularly the adult market, and we also have the potential for other indications and are doing exploratory work for that right now. So, VYVANSE is going to be around for a while based on our patents. It's going to be geographically diverse. We are going to take it to other places and we are going to take it to other indications.

Moving on to LIALDA launch update, it's on page 35. Growth continues, you can see by the chart it's fairly steady. You can see a nice separation between, and the same growth path between the news and the refills. That shows that we are still in a very good launch trajectory. Our growth continues. We have 6.3 monthly total Rx share and 9% of the news in September. So this is healthy. This is a successful launch.

If we turn to page 36, you can see that we have not harmed our own

PENTASA too much of a degree at all. And I think some of the models had significant erosion and that we are not seeing there. And our total share of the market has reached 23.3%. So we are pretty pleased with that and we expect to see continued share growth in the market.

Moving on to 37, one of the big things is where is this going to come from and how often do these patients flare, when do they come in, et cetera. So, if we look at early data from June, you can see that it was roughly split 26% new patients, 23% switches, and then we had refills in there already. So, it's coming from all sectors and we are getting not just when they flare and that's very healthy. We are getting new patients, but we are getting switches off existing drugs, and you see that in the market share data.

So to conclude, we've upgraded our guidance. We are pleased to do that. The business is very healthy and that health is coming broadly from many products and areas of our business. Our revenue growth will be at least 30% in 2007, up from our previous guidance, which was at least 25%. Our launches are going very well. I think we are demonstrating a high level of ability to execute VYVANSE, we are getting enthusiastic response from physicians, all our leading indications are positive. We've had over 300,000 prescriptions to-date. We have had roughly 40% of physicians that have been willing to try this drug to-date, and we have had nothing but positive feedback. The buzz out there is very, very good, and patients like it, moms and dads as you saw want to keep their kids on it. And we expect that to continue to help this product grow.

ELAPRASE has had a rapid uptake in the U.S. and now the EU. As you know, it has been a very positive contributor. This drug is now running significant numbers that help our top and bottom lines.

LIALDA growth continues, I just said that. FOSRENOL, strong growth in Europe. Europe represents about 40% of FOSRENOL business just in less than a year out there. So it's really a runaway success in Europe. And DYNEPO as you know, launched in Q1, we've had great reception in Germany, moving into other countries now, and starting to see the dollar show up. And our R&D pipeline is moving forward.

With that, we will take questions.

Cléa Rosenfeld - Vice President, Investor Relations

Go ahead Sabrina.

Question And Answer

Operator

Thank you. We will now begin the question and answer session. [Operator Instructions]. Your first question comes from Brian White from Deutsche Bank. Please ask your question.

Brian White - Deutsche Bank AG London

Good afternoon. Just a couple of quick questions. Firstly, looking at the data you've supplied, based on the reception to VYVANSE, does this mean that there's really no need for products like INTUNIV in the future? I guess, we haven't had much of an update on that for a while. And then just secondly, have you seen much off-label usage of VYVANSE in adults?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, Brian, I'll answer those backwards for you. Generally, ADDERALL had about 40% adults, the last data I saw it was about 30% adults. For VYVANSE you know we can't promote this, it's just the physicians now believe that these drugs work in all kinds of patients. And we will have the indication and the ability to promote in April of next year. And the INTUNIV we believe has a place in the market. We have some interesting data on that product. As you know, we're in negotiations, we have an approvable letter. We haven't been in a big hurry to launch simply because we want to solve those things, get the best label we can. And in the meantime, it allows us to focus on VYVANSE, which I think is the superior opportunity.

Brian White - Deutsche Bank AG London

Okay, thank you.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Thanks, Brian.

Operator

Your next question comes from Corey Davis from Natexis. Please ask your question.

Corey Davis - Natexis Bleichroeder Inc.

Thanks very much. I just have a couple of them. First, I realize JUVISTA is still a ways away, but... does it makes sense at some point, would you have to buy a commercial infrastructure to get into that market, i.e., a company already in that space or is it such a focused market that it's just as easy to set up your own sales force in that area?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, good question, Corey. We've certainly thought about it. Obviously, when you license a product that has that potential, you start to think about how you're going to do it. And we think we could do it either way. We're going to try to do it in a very thoughtful way. We haven't made any decisions on that yet. We certainly reviewed our alternatives and what the implications for cost and return might be. Stay tuned.

And we see it as a regenerative business, not as a potion and lotion type of answer. We don't want to be out there with just derm products. We really want to go towards what the future is, and more importantly, we want to go towards out of pocket pay, in that segment about 70%... 75% of all those procedures and drugs are paid out of the patient's pocket with no third party reimbursement. So that certainly takes the pressure off of any pricing squeeze that may be coming now or in the future.

So, stay tuned. You're thinking like we're thinking. But again that infrastructure, we're not too excited about traditional derm business, would be my point.

Corey Davis - Natexis Bleichroeder Inc.

Okay. Great answer. Second question, I'm not sure if you addressed this at all or if I missed it. VYVANSE in '08, you've got estimates on the Street all over the place. How should we think about this without asking you for

guidance? Should we straight line the current trajectory of scripts or is there something that can happen to accelerate the slope of that line?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, it's a little bit tough to call. We're getting so much positive qualitative, it could accelerate... that's an unknown. I think the 1% a month that we're seeing is a good rate. It's certainly a good rate if you take ADDERALL XR out of your mind and you start looking at some of the other products that have been introduced over the last five years, you start to see that as a benchmark of a pretty good launch. Not pretty good, a great launch actually, it's among the best.

A straight line of that would be okay. I don't know which one to tell you. Certainly we're out there full force, we're out there with a favorable market. I mean, I'll tell you, I've never seen products with this willingness to treat and this willingness to come back and this perception that it's giving better relief than something out there. So... and there's really nothing negative here there could be... you could have some uptick. But I wouldn't give you guidance to that. I would say it could happen. I don't see any problem with a straight line, but again, this is all forward-looking and a best guess.

Corey Davis - Natexis Bleichroeder Inc.

Very helpful. Thanks, Matt.

Operator

Your next question comes from David Buck from Buckingham Research. Please ask your question.

David Buck - Buckingham Research Group Inc.

Yes, thanks for taking the question. Matt, you talked a little bit about the couponing impact, which I think is helpful. Can you talk a little bit about what impact you think managed care is going to have on the growth of VYVANSE? You mentioned that you're only about a third of where you expected to be on...

Matthew Emmens - Chief Executive Officer and Chairman of the

Management Committee

No, no, no, no.... what I said is that we're a third of the way to where we are with ADDERALL XR. Please, please let's get that straight. That's not true. If anything, we're ahead of where we expected to be, a little bit, because that's our... again, our standard is XR in terms of acceptance by managed care.

I would tell you, we are not getting huge pushback. I would tell you another thing. One of the pieces of our strategy, which we emphasize when we see you on one-to-ones is that we want symptomatic disorders. And here it really comes into play. You have a patient that feels better and believes that this is a better drug on this drug, and you have a parent that wants that drug, I think managed care will be very careful in terms of considering this drug for approval because it is better.

And secondly, I don't believe when ADDERALL XR does go away in '09 that this will be substitutable. The profiles of these drugs are different enough where we don't have to prompt somebody to tell us they're different. And they're going to feel different if they change them and that's going to be a problem.

So as I said, we're not seeing any problem in managed care. That is a misnomer. People have written about it and I don't know where they're getting that from. We're not having a problem. I talked to our sales people yesterday, and they told me right now with three months' effort, they're a third of the way where they are with ADDERALL XR in terms of acceptance and also tiering.

So it's a little better than we expected. We think that we can be where ADDERALL XR was in the same timeframe that ADDERALL XR got there, which we said was about 18 months.

David Buck - Buckingham Research Group Inc.

Just to put it another way. I mean, why [inaudible] acceleration that in VYVANSE if the managed care does pick up towards ADDERALL XR levels, why wouldn't it be above the 1% or so script growth?

Matthew Emmens - Chief Executive Officer and Chairman of the

Management Committee

I think it's just a matter of physicians trying it. It's a new chemical entity, they want to see what it does and I think they want to get feedback from their patients and that's starting to happen.

David Buck - Buckingham Research Group Inc.

Okay. And one other one on... you talked in the past, Matt, about the ability as we get past some of the launch phase to leverage the SG&A as a percentage of sales. Can you give current thoughts on that, what you're seeing in terms of...

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, you're seeing it already and I'll let Angus comment on it, but you're basically seeing that start to happen. We were above 50% SG&A before all this started and I think Angus just mentioned that. You're seeing us now in the high 40s and our goal would be to get it down to the, well, lower than that at some point. And we're working to... we're going the right way. Angus, do you want to make some comments about that?

Angus Russell - Chief Financial Officer

Yes. Just going to back to it, I thought... we sort of said that on page 16, I mean that was the point I was making, Dave, which is that we're at 52% last year, we're at 47% year-to-date this year and 46 in the quarter. And I said I, the full year guidance, even with a small dollar increase, it calibrates to being still in that range of 46% to 47%.

So I reiterate again, that's a whole 5% to 6% improvement in operating margin that's come from reducing SG&A. And I also said when I was presenting that slide a moment ago that I expect that over the next one to two years, we will see that continue to improve. Not perhaps by the same degree we've seen in this full year because we've got growth of over 30% now on the top line. But certainly, I do expect to see a continuous improvement going forward and we will anchor that a bit more when we get to give some guidance for next year.

David Buck - Buckingham Research Group Inc.

Great. Okay, thank you.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Thanks, David.

Operator

Your next question come Dani Saurymper from Goldman Sachs. Please ask your question.

Dani Saurymper - Goldman Sachs Equity Securities (UK)

Yes, a couple of quick questions if I may. Just Angus, coming back to the divestment of products to Almirall, can you just talk us though... you've given us the quantity of sales, any indication of profitability of those revenues? And related to those divestitures, should we anticipate any further divestments as you look through your portfolio and review that? Secondly, when can we expect the further abuse testing studies to come through on VYVANSE? And I will leave it just there. Thanks.

Angus Russell - Chief Financial Officer

Okay, yes, the Almirall products, I think you said previously, the sales of that were in the sort of mid 50s type range. And the EBIT on that is... it's like $10 million, $12 million, something like that. It's sort of around that sort of range. I mean, clearly they move around a bit from time, but that would give you a range of EBIT to take out your models. So I'd say just put low 50s of sales or mid 50s of sales and about a 10 to 12 EBIT. Sorry, what was your second part, Dani, you were saying that other thing, other divestments?

Dani Saurymper - Goldman Sachs Equity Securities (UK)

Well, potential for further portfolio reviews?

Angus Russell - Chief Financial Officer

Yes, it's an interesting point. I mean I'm keen and I think lots of people I talk to know that the point I always stress that it's as important in this industry... I strongly believe it's as important to clean up your portfolio over time as

well as making good acquisitions to make good divestments. I think we feel that that divestment we've just done is good, in the sense that it allows us to concentrate on our core products. I think it's good for both parties. I think for Almirall, they're looking for good products for Europe and these products as I just said, are profitable and growing still. And that's been a good deal for both parties.

But for us, what we're trying to do here is move from products that were, if you like, part of Shire's history, not a lot of those were small regional products. What we're trying to focus the business on is now the big core global franchises that we're trying to build. So as we build up the global ones, we're looking gradually through the portfolio. If these products are very cash-generative, like a CARBATROL or a XAGRID, then they're cash generators for us to keep. And a single product of that magnitude is still worth having. But there are other things we're focusing on, and other things that you will see us probably do over the course of the next 12 months in continuing to clear up the portfolio.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Angus likes to think he's in sales. And when he sells, he runs in and says 'I sold something!' And I tell him it's more important to sell things over time. Sorry about that. Anyway.

Angus Russell - Chief Financial Officer

And then there was the final question you had as well. What was that?

Dani Saurymper - Goldman Sachs Equity Securities (UK)

Yes, I think there's some further abuse testing studies to come...

Angus Russell - Chief Financial Officer

Yes, that's right, yes we did say that. We were interested obviously in the first studies that were run by the New River folks. We've continued to look at that and we have run some slightly larger studies and they're being evaluated. There's a series of those and I don't think we will be in a position to comment on that until probably around the middle of next year. So stay

tuned for that. But I would suggest that no one should be banking on anything there. As I say, it was interesting information, we want to explore it further, but not till the middle of next year.

Operator

Your next question comes from David Steinberg from Deutsche Bank. Please ask your question.

David Steinberg - Deutsche Bank Securities Inc.

Okay. Thanks. On FOSRENOL, it looks like your marketing initiatives in Europe are doing well and the product has done nicely in the first year. In the U.S. though you've enlisted a bigger company to help you and despite all these efforts, you are still at about 9% share. Is there any new initiatives you can take or are the prescribing habits of the prescriber base entrenched so that you are just not going to move the needle there? How should we think about trends going forward in the U.S. for FOSRENOL? And then secondly, Angus, on the tax rate, I know you had a benefit this quarter. Any spillover into '08 and '09 in terms of potential lower tax rates?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Okay. Just on FOSRENOL, you pointed out an issue, we are disappointed with the U.S. We are ecstatic with the European performance. It's interesting we did some of the perceptual work recently on the product in the U.S. and it's perceived as the most effective, which is nice. There is this lingering doubt in their mind about metals, and we have six years' data now and we haven't had any issues with it being a metal, but our competition has successfully planted that in their mind. I am not so sure we can ever change that, so I don't... there is a limited time in which we will invest in the rate in the U.S. that we continue to. We haven't pulled that plug yet. But obviously Europe is doing terrific and the drug is going to be a couple... it's going towards a couple of hundred million dollars if we keep going in the right direction. So it's a significant contributor.

But I would say the U.S., I don't have great hopes for it, it's late in the game now. Usually when you get this far out it's difficult to change a trend and make it meaningful. So I am disappointed. I think our guys tried really hard.

I think that the two year jump that our competition had on us allowed them to put a lot of doubts, none of which were substantiated by the way in the minds of physicians, but they have caused it to be reserved and we often get either second or third line therapy, and that's very, very difficult to change at this point.

So, I would say we are going to give it one more little push, we are trying something new. I won't mention what it is in terms of what we are going to do with our reps in the doctors' office. For competitive reasons I won't mention it, but again I don't think you are going to see it jump to a 50% growth rate or something. So...

Angus Russell - Chief Financial Officer

Tax rate. Tax rate David...

David Steinberg - Deutsche Bank Securities Inc.

Yes.

Angus Russell - Chief Financial Officer

Yes, just go back to what I said, let's just recap again because it then allows me to talk about what how that rolls forward. I said there were two issues really about the benefit in this quarter on the tax. One was this mix effect was that, say, with the large amounts of upfront expense in Q3 in regard to VYVANSE launch and one or two of the other launches in the U.S. From a mix effect across a global company, we were able obviously to have deductible tax expense in the quarter in a relatively high tax jurisdiction. So that's a mix effect and that is difficult until we sort of got some of our budgets in and we know first we have to decide our budgets and we are in the middle of that process right now, then we look at the mix of all the profits and what that means for our tax charge. So that's something we are sort of working on this part of the budgeting process.

The other one was really just a one-time benefit associated with these reviews and tax audits that have come to conclusion. They take 6, 9 months to run and they have come to conclusion in this quarter and that's allowed us to get a much clearer picture of the liabilities in various markets, it was principally the U.S. and the UK where a sort of a regular normal reviews,

annual reviews were being done by the revenue authorities. So, one of them I'd say I'd characterize those latter ones as just one-time befits. A mix effect, I have got to look at that in the context. So what I would I ask as I say I think is that you continue with your 26 projection for next year and then as part of the guidance when I come out with that probably, obviously next Q, we will give you a much more specific steer on the tax. But I hope that we can do something, but I don't know that. So I'd just ask you to leave it at the 26 level for now.

David Steinberg - Deutsche Bank Securities Inc.

Fair enough, thanks.

Operator

Your next question comes from Frank Pinkerton from Banc of America. Please ask your question.

Frank H. Pinkerton - Banc of America Securities

Hi, first question, just to clarify on the earlier question that was asked about abuse. Is that the New River pain products that you gave guidance, you wouldn't update until middle of '08?

Angus Russell - Chief Financial Officer

No sorry, Frank, that was... I think the question was in respect to abuse liability in regard to VYVANSE in ADHD, so it was that question.

Frank H. Pinkerton - Banc of America Securities

Can you then please update us or give us any update you have on the... I guess the products that were in New River that were abuse deterrent pain products and if those are going to be carried forward and where those stand?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, we are continuing to work. In fact, we are encouraged by the possibility of a pain product based on the New River technology. We had to reformulate and do some things, so we are being a little bit quiet about it. But we think there is a product there that works and would have... would be attractive to

the market for some of the reasons that have been previously cited. Stay tuned. Yes, it's going to be middle of next year also just coincidence, but our guys are working on it, we should have an update for you. We are planning on doing some R&D overviews for you next year of what we are working on. We haven't done that in a while.

Angus Russell - Chief Financial Officer

Probably worth adding, it came up earlier, but just to reinforce because it's part of the whole thing Matt mentioned on the slide, final wrap-ups, in VYVANSE we're looking at other indications for VYVANSE. And again, we've started a couple of programs there, we don't speak about them yet because they are obviously going through sort of proof of concepts and early evaluation, but we try... I think what we try and do is some time in the first half next year, is give broad update on the VYVANSE molecule and its application, both in abuse liability in ADHD, the pain product in terms of looking at carrier wave, if you like, in other uses, and then VYVANSE in other indications. So, we'll try and do an overall summary of that some time around the middle of next year may be.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, we have some other interesting ideas for carrier wave technology tank at this point.

Frank H. Pinkerton - Banc of America Securities

Okay, great. And then just as follow-up, can you explain, I guess rationale or the strategy you are going to employ with pricing between all of your ADHD kind of drugs going forward? Is... are certain ones going to be priced at a premium, is there a way to drive adoption or sales of certain products by changing prices in other products? What's the kind of goal and philosophy you guys are going to take on the pricing side?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

We don't discuss prospective pricing for many obvious reasons, but I would tell you that this is not a particularly price-sensitive situation. I've said that,

people don't believe it. So I'll tell you what I believe. I believe that the most effective drug in this market will be paid for by both third parties and out-of-pocket as it is now. And I don't think any creative pricing strategy is going to have a marked effect on adoption. It's about effectiveness, it's about what the psychiatrist or the treating physician wants and it's about the feedback they get from their patients in this market, it is an unusual market. Psychiatry in general is that way and there is a huge patient loyalty in this market to a product that works for them and I just don't see it being a huge factor and I don't think that it's one we want to pin our success on.

Angus Russell - Chief Financial Officer

Just for clarity, because it's a post-quarter event and I think a lot of people are aware of it, it's a publicly announced price increase. But just for the record, basically we put an 8% price increase through in ADDERALL XR on the 1 of October. So just to make sure everybody... I know most people are aware that because like I say it's a publicly announced price increase, but just to make sure for the record everybody does know that.

Cléa Rosenfeld - Vice President, Investor Relations

Next question?

Operator

Your next question comes from Ken Cacciatore from Cowen and Company. Please ask your question.

Ken Cacciatore - Cowen and Company, LLC.

Hi, thanks. Just a couple of questions. First, from my understanding of the press release, you indicated that you might be able to launch a couple of the lower doses of VYVANSE. So I was wondering if you could let us know what part of the market maybe this has hindered you at, or how does it compare to ADDERALL XR in terms of the lower doses? And then, Matt, more of a theoretical question, as you continue to do work with VYVANSE and build the safety dossier on it on the lower abuse, at what point do you stop feeling comfortable that you... as you're manufacturing ADDERALL XR, if you believe it's actually less safe than VYVANSE and you have a lot of time with VYVANSE, do you just stop feeling comfortable manufacturing ADDERALL XR,

or go to the agency and ask... and kind of discuss that with them?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Okay, two questions in that. We don't think that ADDERALL XR is unsafe, and based on just ethics, I wouldn't withdraw the drug. I think it would look like you were trying to manipulate the market. I think that the thing to do is gradually let it die or naturally as it dies ultimately in 2009. I don't think you are going to see us do anything like that. I think that we have a superior drug in VYVANSE. I think the market recognizes it, and I think the adoption will be a steady growth that will be impressive over time.

As far as the intermediate dose, as we call them, they are not lower doses. And there hasn't been a dosage issue with any of the feedback we've received in the market in this drug. As you know, we got three... we have three doses now. We have some in between doses for better titration coming, simply because it's an offering that allows the physician more flexibility. I can tell you that the perceived need of it is not going to knock your socks off in terms of any changing growth.

Angus Russell - Chief Financial Officer

We did the same with XR, Ken, just so you're aware. Historically, I mean, it's been our patent, we launch with three dose strengths and then as Matt said, we call these betweeners, the in-between thing doses and we did the same with XR. We launched with three and then within about six months we added the final three, so that gave us a range of six every sort of 5 milligram strength and this is just replicating that -

Ken Cacciatore - Cowen and Company, LLC.

Okay.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Our impression is there is actually less of a need for in-between doses, although we will have them in this drug because of the smoothness it has. You don't get the spiking which seems to be a little more noticeable when you're using XR.

Ken Cacciatore - Cowen and Company, LLC.

Okay. And I don't know if I saw it in the presentation, but can you give us a sense of the target physician penetration rate with your sales force at this point?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, we cover roughly half of the prescribers. We basically aim the representatives' efforts at the physicians that prescribe the most and we do it in deciles like everybody else does, and we've basically gone to... we used to do, say, the top three deciles because they wrote about 75% or 80% of the business. It's usual in the business. We are actually covering a little better than that now, over 40%

Ken Cacciatore - Cowen and Company, LLC.

Okay, thanks, guys.

Operator

Your next question comes from Graham Parry from Merrill Lynch. Please ask your question.

Graham Parry - Merrill Lynch International

Thanks for taking my questions. First of all, could you just quantify the stoking benefits both in ADDERALL XR, but also for the total revenue line in dollar terms across the entire portfolio?

And then, secondly, on tax, the $46 million of tax adjustments that you've used to get to the cash EPS number, could you just clarify whether that includes or excludes the $23 million or so of write-backs that you have booked in the reported number? So does the cash EPS include or exclude that tax benefit? Also, what tax rate are you using to get to that $46 million? So is it 34% excluding the write-back or is it 17% on the non-cash items plus the write-back?

And then, finally, one for Angus on growth rate into 2008 on costs.

Obviously, you are early in your budgeting process at the moment, but you previously talked about some slowing off in cost growth, I think, to sort of high single to low double digit rate. Is that still way you're talking at the moment, without giving any specific guidance?

Angus Russell - Chief Financial Officer

Yes, I think all those tax effects, Graham, I would suggest, in the interest of time and everybody else on the call, give us a separate call, we can talk to you about... talk you through the non-GAAP and all the tax effects because that's quite complicated, so.

Cléa Rosenfeld - Vice President, Investor Relations

Yes, we will do it offline, Graham.

Angus Russell - Chief Financial Officer

Yes, we will do that offline. But 2008, well, as I said before, I mean, that was the other question. Again, I said we've made a substantial improvement this year in terms of SG&A costs as a percent of product sales. I say again, and I told you already the financial full year guidance for this year, '07 is going to put us in the 46% to 47% of product sales, not of total revenues, a product sales range, down from 52% last year. As I just said, I hope that we can continue that trend. So, yes, there the is a point is I do expect both the dollar increase in both R&D and SG&A costs, we are working through all of that with our colleagues in the businesses, as you said, in our budget process, which hopefully will be complete around the middle of December. And then, so whilst dollars go up, I expect, with what I imagine will be a good still strong line top performance... top line performance, that we will see some improvement. It's not going to be clearly at the same rate of a 5% and 6% benefit on SG&A in just one year with that top line performance this year we have been able to deliver that. But I certainly want to continue making progress and I will set those targets for you all next year.

Graham Parry - Merrill Lynch International

And the stocking effects?

Angus Russell - Chief Financial Officer

Stocking effects, I mean, again, maybe it's something we should do offline with your particular interest in that. I mean, just because they are different on every product, so trying to express that is meaningless across the entire product range.

But I mean, what I would say is stock levels are normalized. I mean, what we now have is 3... 80%, more than 80%, 85% of our business is basically with three wholesalers in the U.S., the three, Big Three. Within there, we now have these contracts which anchor us into a range, which is about the range of between... it's around three weeks of demand in terms of the stocks they have to hold and there is a few days flexibility, but it's a lot tighter in these new contracts that have been introduced in the past year or so that limits their ability to flex that in any other way. So you don't see the old de-stocking, stocking effects that used to go through everybody's books years ago with big swings and the wholesalers.

So, general overview I would make on here is the stocking, de-stocking is pretty small across the entire product range, with the only exception being that aberration I mentioned on FOSRENOL in last year, where we saw those provisions put through for returns of one of the dose strengths that we launched earlier in the year. But absent that, I mean, stock levels are at a very normalized level on every major product and the movements in this quarter are relatively small. But we can talk to the specific numbers offline with you if you have an interest.

Graham Parry - Merrill Lynch International

That's great, thanks.

Operator

Your next question comes from John Boris from Bear Stearns. Please ask your question.

John Boris - Bear, Stearns & Co.

Okay, thanks for taking the question. It's a two-part question related to VYVANSE. First part, Matt, you indicated about the 300,000 scripts generated, I think you have given about a little over 130,000 coupons. Can you just comment on how you might be tracking the stickiness of those

coupons? By stickiness I just mean how many of them have shifted to being a cash paying customer from initial 30 days supply. And then, where do you see as the rate of couponing going forward? And then, just a follow-up on the abuse liability studies.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, hi, John. Basically, you're going to see the couponing gradually fall-off over the next, say, 18 months to a lower level and Angus will give you that... kind of where we end up with that. And we get a very, very high refill rate out of the coupon people, if they are willing to go do that and try it, it's... again, the guys told me it was over 90% and maybe we've got a better number as Angus looks at this, let's see.

Angus Russell - Chief Financial Officer

Yes, hi John. I mean, this goes back to slide 12. I don't know if you were there to pull up the slide, but that was what I took you through on slide 12, which is a representation of this exact picture, which is that the red bars on the slide... if you are in glorious Technicolor... the red bars are the level of coupon redemptions and, as I said, what you're seeing is they rose up in the early weeks, but now you can see a pattern of several weeks of very consistent leveling of couponing. In other words, we are getting a very consistent number of new patients who just got this first 30 days for a coupon. No one can get more than 30 days and what you are seeing, obviously, is a continuous refilling growth of the scripts.

So, I mean, I think this chart... if you look at just the calibration and the scaling here, you can see that we're somewhere between 25% to 30% of scripts now being couponed. And that's substantially down from when the early weeks, we were half to sort of 60% in some of the early weeks of Q3, which is why you have such a high couponing discount against them. But I think if you look at that slide and then the specific slide on the numbers, which was on slide 13, where I said we are at 39% discounts as an average across the quarter starting at 60% to 70% of all scripts in the beginning of the quarter, probably falling off to this 25% to 30% range by the end of the quarter. And now we are seeing it at this sort of 25% to 30%, but it's going to come down now as we get refills because we are holding the level of

coupons, we are not accreting that and that's very clear, I hope from slide 12.

John Boris - Bear, Stearns & Co.

Okay, thanks.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

It would be unlikely that we would go up in coupons -

John Boris - Bear, Stearns & Co.

Okay.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

So it's either going to stay the same or go down and become a smaller percentage as the sales improve.

John Boris - Bear, Stearns & Co.

Thanks for the clarification on that. And then, just on the abuse liability studies that you have ongoing. Can you just comment on timing of filing and then any kind of negotiations you have had with DEA, FDA about the ability of those studies to be able to move the product from C2 to C3?

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

Yes, I wouldn't bet the ranch on C2 to C3. We have always kind of cautioned on that and I would tell you that probably timing of any kind of data that we have will be the middle of next year. We have a number of studies, it's not just one, and we have some that are ending now that we are analyzing, but we'll probably put it together as a package. I think the real thing is the important is... you got to remember that, from a physician standpoint, when New River was touting this drug, basically, their primary thing was about safety and abusability and all that stuff. That didn't play well with physicians. As we got out there later, as we bought the product and started doing our soft... the softer research, we... basically, it came... the most important thing

and the thing that bothered them is the duration of activity, particularly as it relates to inattention. And the second one was the smoothness, this onset, offset, causes... can cause personality differences in kids, especially they tend to get a flat affect when they come off the drug or else they might get a little buzz when they go into it. And this drug does not do that, and that is very important to them. The third attribute was this whole abusability thing, they just... it's kind of like, not my patients. So it's nice to have, but the other two are the ones that are going to drive the business.

So again, as I said, I wouldn't hang my hat on it because I think it's going be difficult to change the C2 to C3 thing. I just... we always thought that was a challenge because it's basically an interpretation and it's a big statement when you say it. But I think the perception of the physician that this gets better would be helpful, but, again, remember it's the third attribute. So we are spending some more of our time focusing on the length of activity, also in some of our Phase 4 trials to reinforce that. But I will tell you the number one sales person for this product seems to be the parents of the kids that go on it. They come back in and they tell them that it works late into the day, which they like as the kid comes from school at that time. And that's often very dysfunctional for a family, and they say they feel better on this drug. And the parents notice that the behavior change is marked during that afternoon period. And that's the number one thing we get and that's what the doctors tell us back, and that kind of reinforcement circle is a very powerful thing for us and it reinforces certainly the message that our guys bring in.

John Boris - Bear, Stearns & Co.

Thanks.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

I think we can take one more question. I don't want to drag on forever. As you know, you can always call us and we try to get back to you pretty quickly and especially with specific information. But I will take one more.

Operator

Your next question comes from Martin Wales from UBS. Please ask your question.

Martin Wales - UBS Warburg (UK)

Hello, one more question. Your R&D spend, which, obviously, at the start... or I think at the end of last year you commented on a certain level of spend, it appeared you weren't going to spend that money, at the end of... I guess, for the full year results, then it became apparent, obviously, you started to invest more in Phase 3, 4 studies to drive the products forward. Can you just give me a sense on how much money you are spending on clinical trials versus how much is, I guess, maintenance should we call it, i.e., how much is to feed the people -

Angus Russell - Chief Financial Officer

Yes, it's an interesting ratio. If I understand... well, you are saying maintenance. I don't know if you are talking about sort of overhead, if you like, people, we look at infrastructure and people and then how much is pure project spend, money just spent with CROs or whatever in the actual project. Is that what you were referring to?

Martin Wales - UBS Warburg (UK)

That's exactly it, yes.

Angus Russell - Chief Financial Officer

Yes, we are sort of around the industry standard. I mean, when we benchmark this, when you look it. It's about a one to one ratio, generally speaking. I mean, we have had a lot of benchmarking work, as I said, done as part of our performance review of everything and that's the normal feedback that you get about a development-based company like this, is that it's somewhere around one to one. We have been a little bit below that in the past, which I think was demonstrable of sort of perhaps the lack of some areas, the sort of areas we have beefed up and that's particularly important ahead of these... this degree of launches with things like medical liaison to support the product launches, and we have recruited quite a lot of new medics in the past year to support and they have been giving us great support and really helping drive these products launches. So it brought us up and we are sort of now beginning to move towards that one to one. It's probably still slightly beneath it, but we are getting near it and I think, as we

move into next year, we will probably achieve that sort of ratio.

Martin Wales - UBS Warburg (UK)

But in general terms, it's almost a virtuous circle, if sales growth continues to grow strongly, you continue to invest in supportive studies, which hopefully in turn drives the sales growth. Is that right, what you think about it?

Angus Russell - Chief Financial Officer

That's absolutely it, Martin. I mean, it's pretty normal in the industry again to invest for one to two years post these launches. We think there is a lot of strong clinical data we can bring by doing more IIIb/IV programs to continue to drive the top line and that's what we made a decision on. We were holding back some of those programs until we saw how well the product's done. With clearly this sort of top line performance and the acceleration across this year, that's what we put in the press release, that we have now initiated some of those programs probably about a quarter earlier than we otherwise would have done.

Martin Wales - UBS Warburg (UK)

Nice one. I will save my other questions for offline.

Angus Russell - Chief Financial Officer

Okay. Thanks, give us a call.

Matthew Emmens - Chief Executive Officer and Chairman of the Management Committee

We appreciate everybody coming on the call today. I would just say I think it would be hard to find a company that's growing at this rate at this size in this segment. Our growth is coming across a broad range of products and geographies and we are continuing to invest in the business and I think our future is bright and sustainable. So we appreciate it, and we look forward to seeing each of you on an individual basis as we usually do. Thanks. Have a good day.

Operator

This concludes our conference for today. Thank you for participating. You

may all disconnect.

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Louis Sanfilippo, MD, is an Assistant Clinical Professor of Psychiatry at Yale School of Medicine and is also in private practice. He is a Managing Partner of Cenestra Health, a biotech company focused on developing empirically validated nutraceutical products. Dr. Sanfilippo teaches on Psychopharmacology to Yale Psychiatry residents with a focus on antidepressants, mood stabilizers, antipsychotics, and psychostimulants. His clinical expertise is in the treatment of anxiety, depression, ADHD, and bipolar disorder in adults, college students, athletes and executives. Dr. Sanfilippo has published articles, chapters, and books across a wide range of topics, including psychotic disorders, principles of psychopharmacology in young adults, mood disorders and suicide, forensic and ethical issues in psychiatry, the philosophy of mind, as well as a review of psychiatry for medical students. He has presented on sports psychiatry and has been a fellow with American Psychoanalytic Association.

Topics

- Recent developments in the treatment protocol for attention deficit hyperactivity disorder (ADHD)
- Prescribing patterns, reimbursement, and generic competition for stimulants
- Novel therapeutics in clinical development

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REFERENCE 41

Diagnosis & Assessment of ADHD

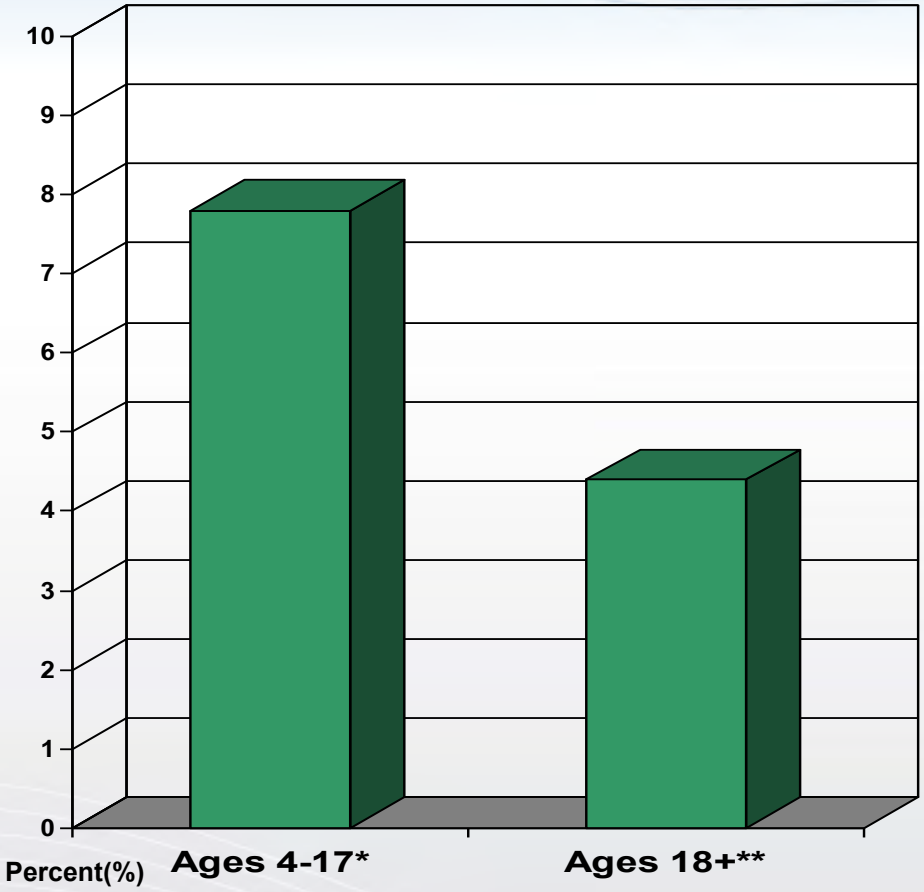
- Clinical Diagnosis of ADHD
  - Inattention Symptoms (at least 6 of 9 symptoms) or Hyperactivity/ Impulsivity Symptoms (at least 6 of 9)
  - Symptoms present for 6 months
  - Some symptoms before 7 years of age
  - Symptoms cause impairment in 2 or more settings
- Spectrum of Severity
- Collateral History
- Neuropsychological Testing
- Assessment of Comorbid Disorders (Different for Children & Adults)
  - Learning/Communication
  - Oppositional Defiant
  - Anxiety
  - Mood (Depression & Bipolar)
  - Substance Abuse Disorders

Ex. 6, Page 839

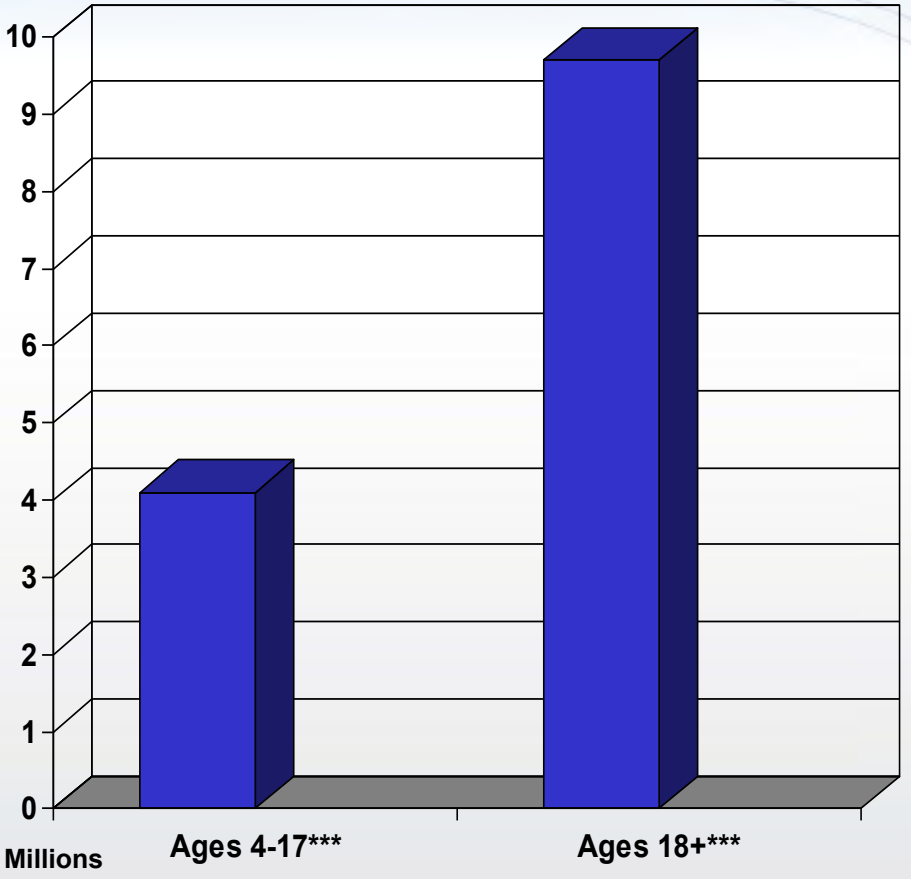
REFERENCE 41

Prevalence of ADHD in the U.S. Population

Prevalence of ADHD (in percentages)



Prevalence of ADHD (in millions)



* Mental health in the United States: Prevalence of diagnosis and medication treatment for attention-deficit hyperactivity disorder, United States, 2003. *MMWR, September 2, 2005; 54(34):842-847.*

** Kessler RC, et. al. The prevalence and correlates of adult ADHD in the United States from the National Comorbidity Survey Replication. *Am J Psychiatry. 2006; 163:716-723.*

***US Census Bureau, Statistical Abstract of the United States, 2006. Numbers derived from 2004 data. At http://www.census.gov/prod/2005pubs/06statab/pop.pdf Ex. 6, Page 840

REFERENCE 41

ADHD:
Trends in Medication Treatment

Ex. 6, Page 841

REFERENCE 41

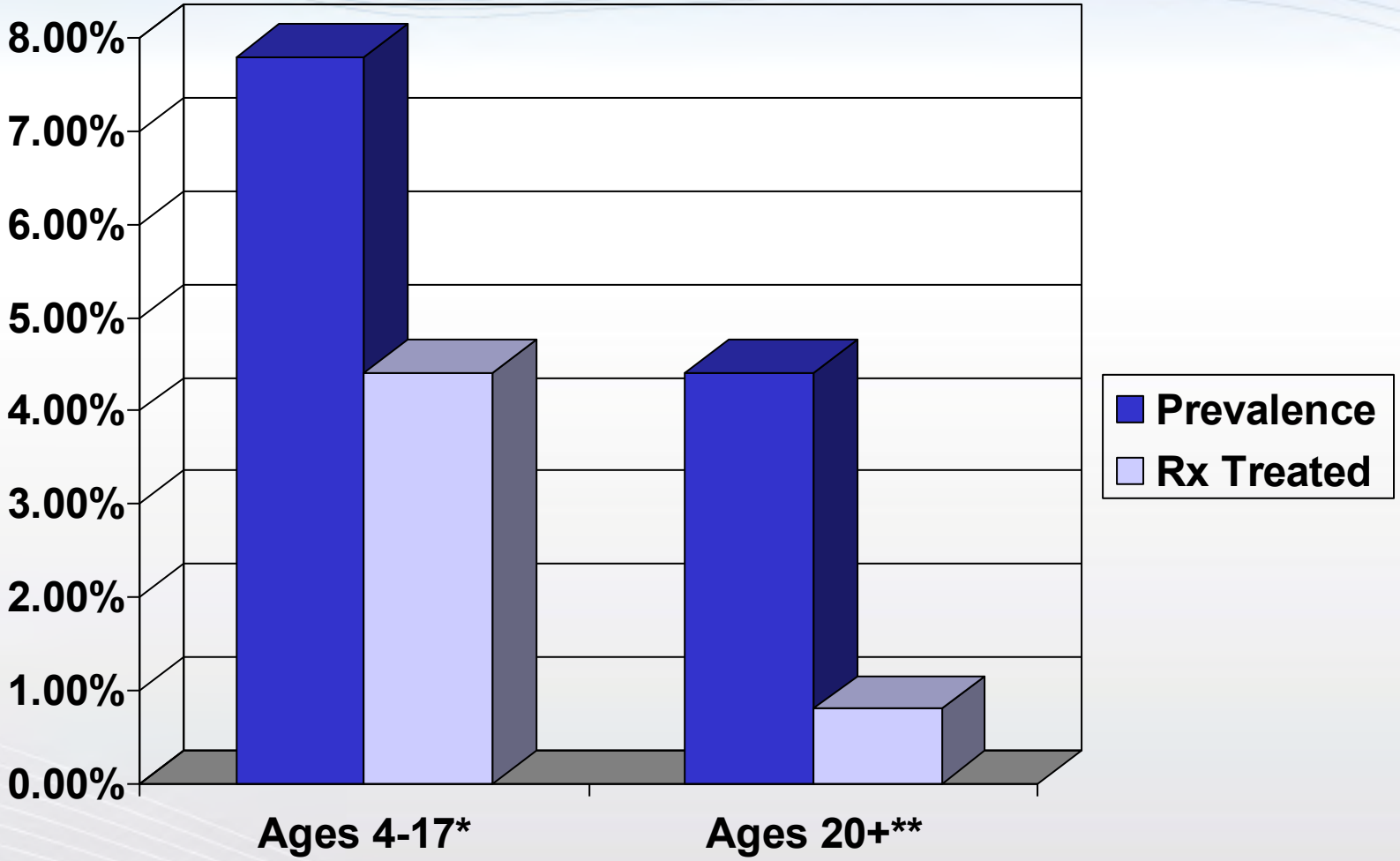
Overview: Medication Treatments for ADHD

- **FDA-Approved Treatments**
  - Stimulants
    - Schedule II Drugs
    - Potentiate dopamine/norepinephrine neurotransmission
  - Atomoxetine (Strattera; Eli Lilly)
    - Non-stimulant
    - Norepinephrine reuptake inhibitor
- **Off-Label Treatments**
  - Modafanil (Provigil; Cephalon) – arousal-promoting
  - Guanfacine - alpha-2 agonist
  - Clonidine - alpha-2 agonist
  - Bupropion (Wellbutrin family) – norepinephrine/dopamine reuptake inhibitor
  - Tricyclic Antidepressants

Ex. 6, Page 842

REFERENCE 41

ADHD Prevalence vs. Medication Treatment, U.S.



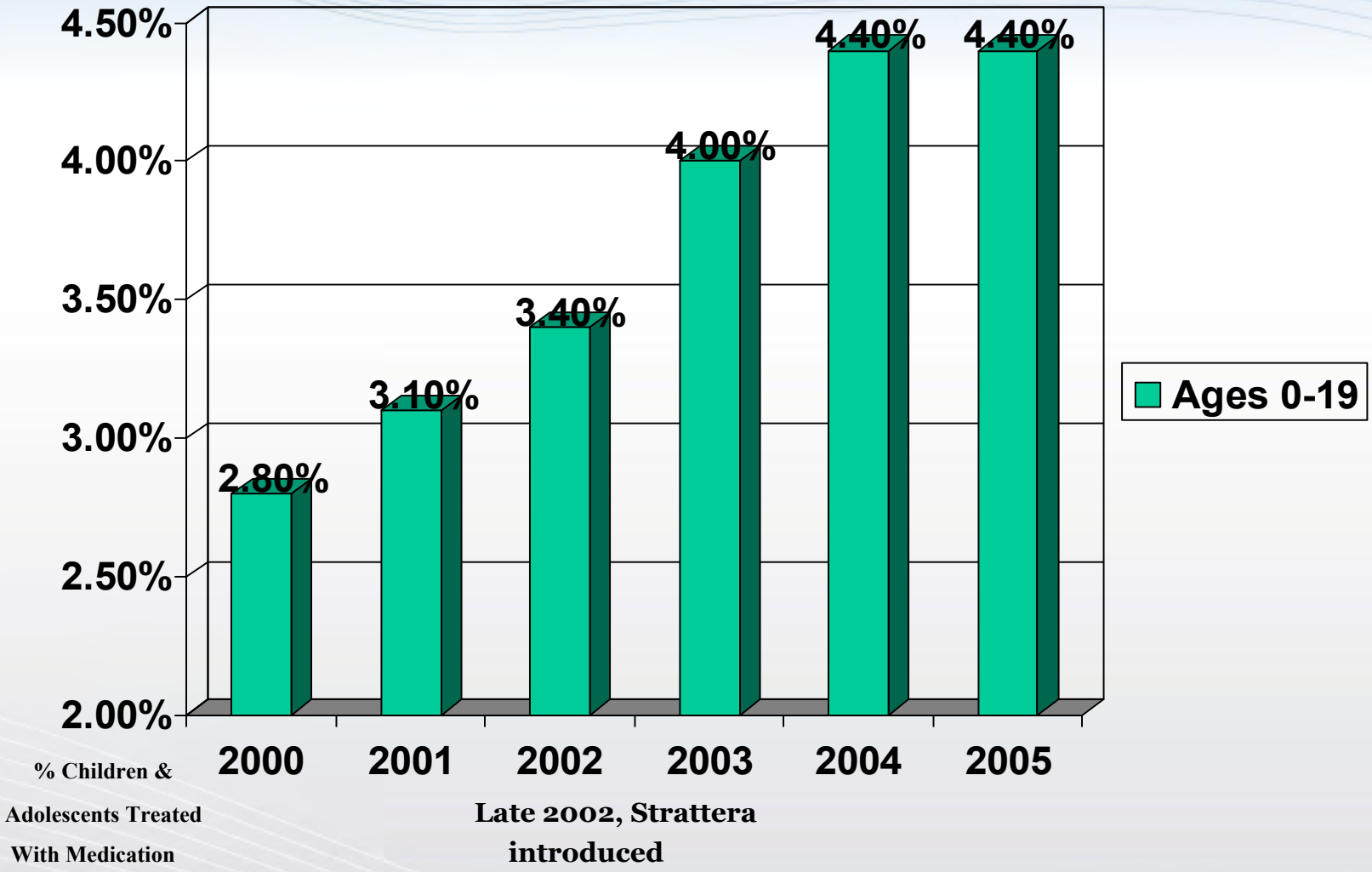
*Kessler RC, et. al.; The prevalence and correlates of adult ADHD in the United States from the National Comorbidity Survey Replication. *Am J Psychiatry*. 2006; 163:716.723.

**Castle, L, et. al.; Trends in Medication Treatment for ADHD. *Journal of Attention Disorders*. 2007; 335-342.

Ex. 6, Page 843

REFERENCE 41

ADHD Medication Treatment Trends, Ages 0-19 (2000-2005)*



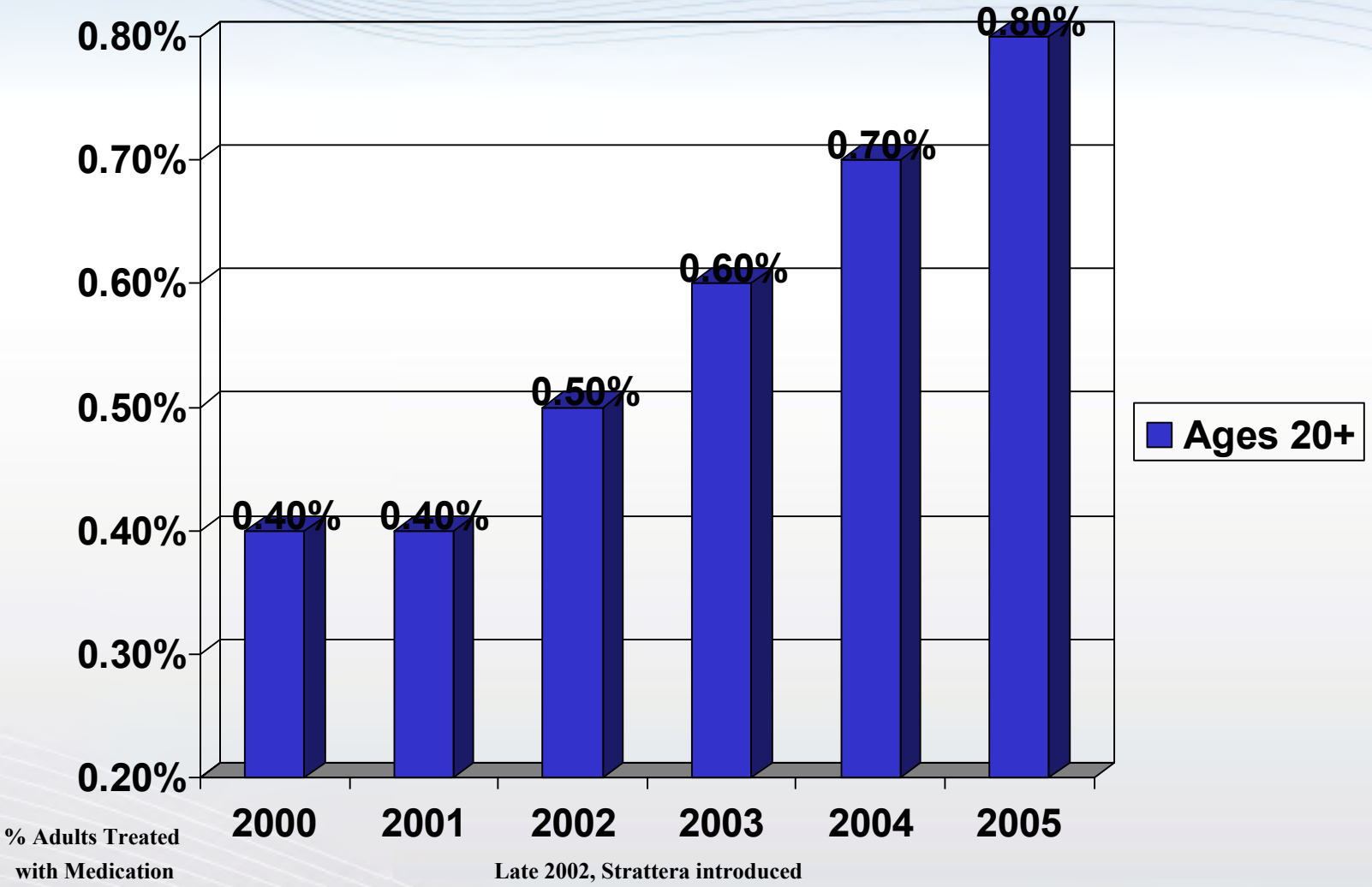
ANNUAL GROWTH RATE = 9.5% (2000-2005)

Ex. 6, Page 844

*Castle, L, et. al.; Trends in Medication Treatment for ADHD. *Journal of Attention Disorders*. 2007; 335-342.

REFERENCE 41

ADHD Medication Treatment Trends, Ages 20+ (2000-2005)*



ANNUAL GRWOTH RATE = 15.3% (2000-2005)

Ex. 6, Page 845

*Castle, L, et. al.; Trends in Medication Treatment for ADHD. *Journal of Attention Disorders*. 2007; 335-342.

Trends: ADHD Diagnosis & Medication Treatment

- Up to 65% children with ADHD will continue to have symptoms into adulthood *
- Pharmacologic treatment of Adult ADHD doubled between 2000-2005**
- Marketing New Drug Treatments May Increase Public & Clinician Awareness
- Most Rapid Rate of Growth in Pharmacologic Treatment (2000-2005)**
  - Children ages 0-9
  - Adults ages 20-64
- Medication Patterns (in 2005)**
  - Children & Adolescents (Extended Release Formulations account for 68.3%)
    - Amphetamine mix, 32.4% (does not include dextroamphetamine products)
    - Methylphenidate, 46.9% (does not include dexmethylphenidate products)
    - Atomoxetine, 16.7%
  - Adults (Extended Release Formulations account for 43.7%)
    - Amphetamine mix, 43.4%
    - Methylphenidate, 34.5%
    - Atomoxetine, 13.7%

*American Academy of Child & Adolescent Psychiatry. Practice Parameters for the assesment and treatment of children, adolescents, and adults with attention-deficit/hyperactivity disorder, J Am Acad Child Adolesc Psychiatr. 1997; 36 (10 Suppl); 85S-121S.

**Castle, L., et. al.; Trends in Medication Treatment for ADHD. *Journal of Attention Disorders*. 2007; 335-342.

REFERENCE 41

AN OVERVIEW:
Clinical Decision-Making in ADHD Pharmacotherapy

- The Stimulant Landscape: Drugs & Companies
- Pharmacotherapy Approaches: Choosing the Initial Type of Drug
  - Stimulant vs. Non-Stimulant
  - Comorbidities
- Treatment with Stimulants: Which One to Choose?
  - Practical Concepts in ADHD Medication Treatment
  - Which Class: Amphetamine or Methylphenidate?
  - Which Form: Immediate-Release, Intermediate-Release, or Extended Release?
- VYVANSE (lisdexamfetamine)
- Clinical Practice

Ex. 6, Page 847

REFERENCE 41

The Stimulant Landscape: Drugs & Companies

Amphetamine Line

- **Extended Release Formulations (up to 12 hours) –once daily**
  - Vyvanse capsules (Shire) – lisdexamfetamine, d-amphetamine/L-lysine prodrug; approved 2/07, launched 2nd quarter 2007
  - Adderall XR capsules (Shire) – mixed amphetamine salts of dextroamphetamine & racemic d/l-amphetamine
  - Dexedrine SR spansules (GlaxoSmithKline) & generic versions of Dexedrine SR - dextroamphetamine
- **Immediate Release Formulations (3-6 hours) – 2-3 times daily**
  - Adderall tablets (Barr/Duramed-Shire Deal)
  - Generic versions of Adderall (ie, "mixed amphetamine salts")
  - Dexedrine tablets (GlaxoSmithKline) - dextroamphetamine
  - Generic versions of Dexedrine

Methylphenidate Line

- **Extended Release Formulations (up to 12 hours) – once daily**
  - Concerta tablets (McNeil Pediatrics) - methylphenidate
  - Focalin XR capsules (Novartis) - dexmethylphenidate
  - Daytrana Transdermal Patch (Shire) - methylphenidate
- **Intermediate-Release Formulations, Second-Generation (6-8 hours) – 1-2x daily**
  - Ritalin LA capsules (Novartis; Celgene); ANDA filed for generics 11/2007 with Paragraph IV certification
  - Metadate CD Capsules (UCB) - methylphenidate +metadate ER
- **Intermediate-Release Formulations, First-Generation (3-6 hours) – 1-2x daily**
  - Ritalin SR tablets (Novartis) & generic versions - methylphenidate
  - Metadate ER tablets & generic versions – methylphenidate
- **Immediate Release Formulations (2-4 hours), 2-4x daily**
  - Ritalin tablets (Novartis) & generic versions – methylphenidate
  - Focalin tablets (Novartis) & generic versions (approved 2/07) - dexmethylphenidate

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REFERENCE 41

ADHD Pharmacotherapy: Choosing the Initial Type of Drug

- Stimulants: 1st Line Treatments for ADHD (without comorbidities)*
  - Texas Algorithm for Children: if one stimulant trial fails, use drug from alternative stimulant class (ie, if amphetamine first, then try methylphenidate product)*
  - Efficacious and generally well-tolerated
  - High Effect Size
    - ~60-70% respond favorably to stimulant medication initially and over time
    - more significant with stimulants (0.95 long-acting; 0.91 short-acting) than with atomoxetine (0.62)**
- When might stimulants not be considered1st or 2nd Line?
  - Comorbid Tic Disorders
    - Strattera
    - Stimulant, with alpha-agonist or atypical antipsychotic
  - Anxiety Disorders
    - Strattera
    - Stimulant, with SSRI for anxiety
  - Substance Abuse Disorders
    - Stattera
    - Long-Acting Stimulant
  - Other clinical conditions in which most severe comorbidity should be treated first (ie, depression, aggression)

*Pliska SR, et al. The Texas Children's Medication Algorithm Project: revision of the algorithm for pharmacotherapy of attention-deficit/ hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry.* 2006; 45:642-657.

**Farone SV, Biederman J, et al. Comparing the efficacy of medications for ADHD using metaanalysis. *MedGenMed.*2006;8:4.

Ex. 6, Page 849

Practical Concepts in ADHD Stimulant Treatment

REFERENCE 41

One Drug May Not Fit All …*but are some better?*

- ADHD pharmacotherapy should be tailored to each patient
  - Drug dose-response curves are unique for each patient
  - Patients may respond better to one drug class than another
  - Other clinical factors (ie, lifestyle, comorbidities, abuse liabilities)
- Be clinically rational, accept trial & error
- Patients/parents have preferences
  - Extended-release formulations
    - are easy with once daily dosing
    - offer continuous effect through much of the day
    - decrease concern medication will wear off too early or at an important time
  - Immediate-release formulations
    - offer flexibility of dosing
    - achieve faster, higher peak levels; may optimize performance situations
    - help avoid “feeling on” all day
- Clinicians have preferences

Ex. 6, Page 851

REFERENCE 41

Stimulant Treatment Often Involves A Combination Drug Strategy

- Combining different formulations may help optimize efficacy and is common practice
  - ER form in the morning, IR form ("booster") in the afternoon
    - Concerta in the am, IR-methylphenidate in mid-late afternoon
    - Adderall XR in the am, Adderall in late afternoon
    - Concerta + IR-methylphenidate booster in the am, with IR-methylphenidate in afternoon
  - Other variations on the theme
- Combination Rx is typically within the same drug class (ie, amphetamine: Adderall XR with its IR form) but not always
- Vyvanse: ER form in the am + IR form in the pm, all-in-one?

Ex. 6, Page 852

Which Class: Methylphenidate or Amphetamine?

- More important than the class of stimulant is which time-release formulation is chosen and its associated properties
- Patient and/or clinician factors that may influence the use of one class of stimulant over the other
  - Family history (ie, positive or negative response)
  - Patient preference/bias
  - Clinician preference/bias
  - Clinical relevance of the type of encapsulation or delivery
    - Sprinkles for food (able with Adderall XR; not with Concerta)
    - Patch (Daytrana) only with methylphenidate
- Insurance Factors (covered later)
- Dextroamphetamine & dexmethylphenidate much less commonly used

Ex. 6, Page 853

REFERENCE 41

Which Form: Immediate, Intermediate, or Extended Release?

- Extended-Release Formulations Generally Favored
  - Easier, for parents and patients
  - No need for in-school dosing
  - Stability of effect for most of day
  - Improved treatment adherence
  - Less abuse/misuse potential
  - Better profile for patients at risk for subtance abuse
- Short-Acting
  - For patient seeking flexible dosing options
  - Useful as boosters
  - Higher peak levels may be better for some patients
  - Very low dose titrations may be better for very young children
- Intermediate-Acting

Ex. 6, Page 854

REFERENCE 41

VYVANSE

(LDX:lisdexamfetamine dimesylate)

Ex. 6, Page 855

REFERENCE 41

OVERVIEW: How Does/Will VYVANSE Fit Into the Stimulant & ADHD Treatment Landscape?

- Efficacy Data
- Distinguishing Clinical Features
- Current Clinical Trials
- Practice Patterns: What Am I Doing? What Are Colleagues Doing?
- Other (Clinical & Non-Clinical) Factors That May Affect Prescribing Patterns

Ex. 6, Page 856

REFERENCE 41

VYVANSE: Efficacy Data for ADHD

- It Works: Results from Phase II, III Studies, High Effect Sizes
- Study NRP-104-201 (Phase II)*
  - Vyvanse & Adderall XR vs. placebo
  - Children ages 6-12, n=52
  - Significant results vs. placebo on primary efficacy measure: SKAMP-DS Rating Scale (attention/ deportment), analog classroom ($p<0.001$)
  - Significant results vs. placebo on secondary measures: PERMP, Clinical Global Impression ($p<0.001$)
- Study NRP-104-301 (Phase III)**
  - Children ages 6-12, n=290
  - Significant results vs. placebo on primary efficacy measure ADHD-RS-IV (50-59% decrease in ADHD-RS scores vs. 15% decrease for placebo, $p<0.001$)
- Study NRP-104-302***
  - Long-term open-label study
  - Significant improvement (>60%) from baseline in the ADHD-RS at endpoint
- Pivotal Adult Phase III ADHD Trial****
  - sNDA before FDA
  - Adults 18-55, n=414
  - "Significant reduction" in ADHD-RS-IV scores; 57-61% improved/very imprv (similar to MAS SR trials)
- Conclusions
  - Children: Effect Sizes very high, dose-related (? better than other stimulants)
  - Adults: looks efficacious

*Biederman J et al (2007). Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. *Biol Psychiatry* 62:970-976.

**Biederman J et. al (2007). Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a Phase III, multi-center, randomized, double-blind, forced-dose, parallel-group study. *Clin Therapeutics* 29: 450-463.

***Findling RL, el al. Long-term efficacy and safety of lisdexamfetamine in school-age children with attention-deficit/hyperactivity disorder. Poser presented at the annual meeting of the American Pscyhiatric Association; 2007 May 23; San Diego, CA.

****From Press Release, Results of VYVANSE pivotal trial in adult ADHD presented at major scientific meeting. At http://www.shire.com/shire/uploads/press/

REFERENCE 41

VYVANSE: Distinguishing Clinical Features

Ex. 6, Page 858

REFERENCE 41

The Prodrug Concept

- Lisdexamfetamine dimesylate is a therapeutically inactive prodrug
- The active ingredient d-amphetamine is covalently linked to the amino acid l-lyine
- The active ingredient d-amphetamine is released during the enzymatic breakdown of the prodrug in the gut and liver
- Saturation kinetics govern the breakdown into the active d-amphetamine form *(unlike other stimulants)*
- Pharmacokinetic properties associated with the prodrug mechanism of action confer unique clinical and safety properties
- First-in-class prodrug stimulant

Ex. 6, Page 859

REFERENCE 41

VYVANSE: Distinguishing Clinical Features

Does Vyvanse offer efficacy soon enough in the day? How does it measure up with other long-acting stimulants?

Ex. 6, Page 860

REFERENCE 41

VYVANSE: Time to Efficacy, Peak Levels

- How soon to work in the day? reach peak levels? (T-max = time to reach maximum drug concentration)
  - Likely fairly consistent given saturation kinetics
  - Significant improvement SKAMP-DS at 2 hours**
  - Mean T-max=3.7 hours*
  - Mean T-max=4.5 hours; Range of T-max=4.5-6 hours** (n=8 Vyvanse; 70 mg)
- How does this compare to Adderall XR?
  - Adderall XR carries higher variability; influenced by stomach pH/food content
  - Significant improvement of SKAMP-DS at 3 hours**
  - Mean T-max=6 hours; Range of T-max=3.00-12 hours** (n=9 Adderall XR; 30 mg)
- How might this compare to Concerta?
  - Mean T-max=6.8 hours***
- Clinical Practice
  - Good. In the range of other ER formulations
  - Booster IR-amphetamine can be used in the am if an issue
- Conclusions & Implications
  - Vyvanse works soon enough
  - May provide a more consistent T-max. More data needed
  - T-max may be between Adderall-IR and Adderall XR

*Krishnan S (2006): A multiple-dose single-arm pharmacokinetics study of oral lisdexamfetamine dimesylate (LDX; NRP-104) in healthy adult volunteers. Abstract presented at the New Clinical Drug Evaluation Unit 46th Annual Meeting; June 12-15, 2006; Boca Raton, Florida.

**Biederman J, et al (2007). Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 62:970-976.

***Concerta Package Insert. At: http://www.concerta.net/concerta/pages/full.jsp.

REFERENCE 41

VYVANSE: Distinguishing Clinical Features

What is Vyvanse's duration of effect in a given day? How does this compare to other ER stimulants? Implications, Pros & Cons?

Ex. 6, Page 862

REFERENCE 41

VYVANSE: Duration of Action

- Duration of Action
  - Efficacy on attention and deportment at 12 hours*
  - Efficacy on inattention and hyperactivity at 6 pm (dosed b/w 7:30-8:00 am)**
- Comparison to Adderall XR**
  - Small trial; not an active comparison trial
  - Vyvanse & Adderall XR both with significant effect on attention & deportment at 12 hours
  - Change in math scores (PERMP) most favorable for Vyvanse (49 for LDX; 22 for Adderall XR; -24 for placebo)
- Clinical Practice
- Conclusions & Implications
  - May offer greater efficacy in late afternoon/evening than other ER forms
  - Avoidance of booster doses
  - Mostly a positive
  - Possibly a negative
    - some patients prefer flexibility of dosing with other formulations
    - sleep

*Biederman J et al (2007). Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. *Biol Psychiatry* 62:970-976.

**Biederman J et. al (2007). Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a Phase III, multi-center, randomized, double-blind, forced-dose, parallel-group study. *Clin Therapeutics* 29: 450-463.

Ex. 6, Page 863

REFERENCE 41

VYVANSE: Distinguishing Clinical Features

Does Vyvanse offer more stable, consistent drug delivery than other (ER) stimulants? Implications for patients? Implications for clinicians?

Ex. 6, Page 864

REFERENCE 41

VYVANSE: A More Consistent Drug Delivery System?

- Phase II Trial with Vyvanse, Adderall XR, and placebo arms (n=52)*
- Coefficient of variance (%CV)
  - Measure of inter-patient variability of pharmacokinetic parameters
  - Lower numbers reflect less inter-patient variability
  - T-max (Time to max. concentration)
    - Vyvanse - 15.33
    - Adderall XR - 52.77
  - C-max (Max. observed concentration)
    - Vyvanse - 20.34
    - Aderrall XR - 43.96
- Clinical Practice
- Implications
  - Patients
  - Clinicians
  - Marketing

*Biederman J et al (2007). Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. *Biol Psychiatry* 62:970-976.

Ex. 6, Page 865

REFERENCE 41

VYVANSE: Distinguishing Clinical Features

Does Vyvanse offer a better safety profile among stimulants? Better alternative for patients at risk, or with a prior history of substance abuse? Other safety or side effect issues? How significant?

Ex. 6, Page 866

REFERENCE 41

VYVANSE: Safety Profile, Overdose Toxicity[1, 2]

- LD-50
  - Amount of drug expected to cause death of 50% of the animal population (ie, rats)
  - LD-50 of Vyvanse greater than 1000 mg/kg
  - LD-50 of amphetamine about 100 mg/kg
- Vyvanse carries significantly reduced toxicity compared with amphetamine
- Higher doses of Vyvanse lead to attenuated plasma concentrations (saturation kinetics) compared with amphetamine

[1]Krishnan S, et al. Determination of the acute oral toxicity of lisdexamfetamine dimesylate in rats [poster]. Presented at the 2007 Society of Biological Psychiatry; May 17-19, 2007; San Diego, California.

[2]Jasinski D, et al. Pharamacokinetics of oral lisdexamfetamine (LDXl NRP104) vs. d-amphetamine in healthy adults with a history of stimulant abuse [poster]. Presented at the 2006 U.S. Psychiatric & Mental Health Congress; November 17, 2006; New Orleans, LA.

REFERENCE 41

VYVANSE: Safety Profile, Misuse/Abuse Liabilities

- Schedule II: High Abuse Potential, Severe Dependence Liability
- Decreased Misuse/Abuse Liability?
  - IR formulations: greatest risk, recreational use/misuse on college campuses
  - ER formulations: less risk, can be crushed
  - Vyvanse - oral ingestion required; no crushing, sniffing, etc.…
  - Shire study: Vyvanse vs. amphetamine in patients with a history of drug abuse
    - Drug-liking events (DLE) significantly less than amphetamine
    - Implications
- Clinical Practice
- Marketing

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REFERENCE 41

VYVANSE: Safety Profile, Substance Abuse Comorbidities

- Comorbidity of ADHD & Substance Use Disorders (SUD)
  - Complicated & Extremely Signficant Clinical Area
  - 30% adults: ADHD-SUD comorbidity*
  - Stimulant treatment of ADHD reduces risk of SUD in adolescents** (contrary to what many may think)
- Clinical Practice
  - A role for Vyvanse? When?
  - "Wear-off" effects, drug re-enforcing behavior
- Clinical Trials
  - Pilot study of Vyvanse in ADHD Adolescents at Risk for Substance Abuse (at clinicaltrials.gov)
  - Sponsored by Columbia University; study start date January 2008

*Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. *Biol Psychiatry* 2005; 57:1215-1220.\

**Biederman J, et al. Pharmacotherapy of attention-deficit/hyperactivity disorder reduces risk of substance abuse disorder. *Pediatrics* 1999; 104:e20.

Ex. 6, Page 869

REFERENCE 41

VYVANSE: Safety Profile, Side Effects

- Cardiovascular Profile/Side Effects
  - Historical Background
    - Canada, 2005: Adderall XR pulled from market ~ 6 mos based on 20 int'l reports of sudden death
    - US FDA, 2006: Drug Safety/Risk Mgmt Comt. rec'd black box on CV risk; Pediatric Advisory Comt. against
  - Stimulants in General*
    - Retrospective cohort study (n=55,383; children/adolescents), ***Pediatrics, 12/07***
    - 20% increased hazard of cardiac ED/office visits, use v. non-use (low overall)
    - Rates of serious or fatal manifestations of heart disease small and comparable to national background rates
  - Vyvanse
  - FDA and Agency for Health Research and Quality (AHRQ) Study
    - most comprehensive study to date of potential CV risks and ADHD medications
    - Completion ~2009/2010, n=500,000 children and adults
- Other Side Effects/Issues
- Distinctions from other ER stimulants

*Winterstein AD, el al. Cardiac safety of central nervous system stimulants in children and adolescents with attention-deficit/hyperactivity disorder. *Pediatrics*. 2007; 120: 1494-1501

Ex. 6, Page 870

REFERENCE 41

VYVANSE: Current Clinical Trials*

- Clinicaltrials.gov (as of 1/2/08)
  - 9 registered clinical trials
  - mostly for trials completed, or nearing completion, as basis of Shire's FDA drug applications (children and adults)
- Shire sponsored trials (at clinicaltrials.gov)
  - Classroom study to assess time of onset in children ages 6-12 with ADHD *(study completed December 2007)*
  - Dose-optimization study in children ages 6-12 with ADHD
    - *study estimated close to completion*
    - dosing beginning with 20 mg, and up to 70 mg
- Columbia Study: Pilot Study of Vyvanse in ADHD Adolescents at Risk for Substance Abuse
  - Open-label feasibility study, estimated start January 2008
  - Aim: develop method to approach and treat high risk youth before they develop substance abuse
- Safety Studies Across ADHD Drug Treatments (AHRQ Study)
- Implications

*A listing currently registered Vyvanse clinical trials can be found at:http://clinicaltrials.gov by searching the term "Vyvanse"

Ex. 6, Page 871

Practice Patterns: What Am I Doing? Colleagues?

- History
  - IR Formulations
  - Concerta vs. Adderall XR, Canada
  - Vyvanse
- Initiating Stimulant Treatments
  - Favoring ER formulations
  - When Vyvanse? When Concerta or Adderall XR?
- Switching Stimulant Treatments
  - “if it ain’t broke, don’t fix it”, changing views?
  - Switching to Vyvanse
  - Switching off Vyvanse
- Future

REFERENCE 41

Other (Clinical & Non-Clinical) Factors that May Affect Stimulant Prescribing Patterns

Ex. 6, Page 873

Generic Incursion: The Landscape Ahead

- Adderall XR*
  - Shire Pharmaceuticals/Barr Laboratories patent litigation settled
  - Deal to allow Barr's launch of generic Adderall XR as early as April 1, 2009, followed by 180 days market exclusivity of the generic
  - Time delays?
- Concerta**
  - Concerta patent expired 2004
  - Two parties have filed generic ANDAs, pending approval
- Ritalin LA***
  - November 2007, Barr Pharmaceuticals filed ANDA with Paragraph IV certifications for generic Ritalin LA
  - Celgene & Novartis filed suit
  - 30 month stay before FDA will accept ANDA

*Shire/Barr: excitement levels rise on Adderall deal. At http://www.pharmaceutical-business-review.com/article_feature.asp?guid=28EC938C-683A-4E5F-90BC-770D38F4D471

**Johnson & Johnson 10-Q quarterly report, August 2007. At http://64.233.169.104/search?q=cache:-Q_PMr2NaFcJ:biz.yahoo.com/e/070808/jnj10-q.html+10-+and+Johnson+and+anda+and+concerta&hl=en&ct=clnk&cd=1&gl=us&ie=UTF-8

***Barr sued over Ritalin LA patent challenge. FDA-News. At http://fdanews.com/newsletter/article?issueId=10988&articleId=100965

REFERENCE 41

How Will the Use of Vyvanse Be Affected by a Generic Adderall XR?

- Adderall XR & its generic equivalent(s) will NOT be the generic equivalent of Vyvanse
- *Continuing Vyvanse Prescriptions.* Clinically (and in my view, from a managed care *quality of care* standpoint) it will be problematic for patients taking Vyvanse to be pressured to take a *"non-generic 'generic' alternative"* of Vyvanse
- *Initiating or Switching to Vyvanse Prescriptions.* Formularies may revise their step-therapy protocols for initiating or switching to new Vyvanse prescriptions once a generic version of Adderall XR or Concerta is out
  - Step-therapy may be bypassed by pre-certification
  - How willing would clinicians be to take on pre-certs, other advocacy roles?
  - Will Vyvanse be compelling enough clinically if such measures are required?
- When could a generic form of Vyvanse be available?

Ex. 6, Page 875

VYVANSE: Insurance Coverage, Pricing Structure, & Positioning for Formulary Coverage

REFERENCE 41

3-Tiered Formulary Models

- Three Tiers
  - Tier 1 - Generics, least expensive co-pay
  - Tier 2 - Preferred brand, middle co-pay
  - Tier 3 - Non-preferred brand or generic, highest co-pay
  - (Tiers 4, 5) – For self-injectables
- Step-Therapy Model
  - If step-therapy is not followed, then the drug claim may be rejected
  - Physician may bypass or override step-therapy by acquiring pre-certification ("medical exception") for the drug
    - Assessed on a case-by-case basis
    - Typically can be done prior to or after the prescription is filled
- Formularies are dynamically evolving based on economic and medical factors

Ex. 6, Page 877

REFERENCE 41

2008 Aetna Preferred Drug Guide, 3,4, & 5 Tier Open Formulary Plans*

DRUG	Co-Pay Tier	Pre-Certification	Step-Therapy
ADDERALL	3		
mixed amph salts	1		
ADDERALL XR	2		
VYVANSE	2		
CONCERTA	3		YES
FOCALIN, FOCALIN XR	3		YES
RITALIN, RITALIN LA, RITALIN SR	3		YES
methylphenidate, methylphenidate SR	1		
DAYTRANA	2		

* 2008 Aetna Preferred Drug Guide, 3,4 & 5 Tier Open Formulary Plans. At http://www.aetna.com/FSE/planType.do
Ex. 6, Page 878

VYVANSE: Insurance, Price Structure & Positioning

- Where does Vyvanse stand in other prescription formularies/plans?
  - Anthem
  - Medco
  - Others
- How will Shire's pricing structure of Vyvanse (vs. Adderall XR, Concerta) position it for inclusion and coverage?
  - Assumptions (wholesale, retail pricing)
  - Selected retail data

REFERENCE 41

PRICING: Vyvanse, Adderall XR, and Concerta

- Chain Pharmacy in CT, December 2007
- Vyvanse (#30 capsules/1 month supply)
  - 30 mg daily dose - $134.99
  - 50 mg daily dose - $134.99
  - 70 mg daily dose - $134.99
- Adderall XR (#30 capsules/1 month supply)
  - 10 mg daily dose - $167.99
  - 20 mg daily dose - $167.99
  - 30 mg daily dose - $167.99
- Concerta (#30/1 month supply)
  - 18 mg daily dose - $132.99
  - 27 mg daily dose - $140.99
  - 36 mg daily dose - $138.99
  - 54 mg daily dose - $157.99

Ex. 6, Page 880

REFERENCE 41

PRICING: Adderall, Branded & Generic

- Chain Pharmacy in CT, December 2007 (**con'd**)

- Amphetamine Line/Immediate Release Drugs
  - Adderall (Branded Version) - #60 tabs
    - 5 mg tabs - $86.99
    - 10 mg tabs - $77.99
    - 20 mg tabs - $77.99
  - Generic mixed amphetamine combo - #60 tabs
    - 5 mg tabs - $25.39
    - 10 mg tabs - $32.39
    - 20 mg tabs - $39.59

Ex. 6, Page 881

REFERENCE 41

PRICING: Vyvanse, Adderall XR, & Concerta

- HMO Pharmacy in CT, December 2007
- Vyvanse (#30 capsules/1 month supply)
  - 30 mg daily dose - $125.63
  - 50 mg daily dose - "
  - 70 mg daily dose - "
- Adderall XR (#30 capsules/1 month supply)
  - 5 mg daily dose - $125.63
  - 10 mg daily dose - $ "
  - 15 mg daily dose - $ "
  - 20 mg daily dose - $ "
  - 25 mg daily dose - $ "
  - 30 mg daily dose - $ "
- Concerta (#30/1 month supply)
  - 18 mg daily dose - $119.33
  - 27 mg daily dose - $121.68
  - 36 mg daily dose - $124.69
  - 54 mg daily dose - $142.38

Ex. 6, Page 882

REFERENCE 41

PRICING: Adderall & Ritalin, Branded & Generics

- HMO Pharmacy in CT, December 2007 (con'd)
- Amphetamine
  - Adderall (Branded Version)
    - 5 mg tabs (#30 - $90.27; #60 - $163.53)
    - 10 mg tabs (#30 - " ; #60 - $ ")
    - 20 mg tabs (#30 - " ; #60 - $ ")
  - Generic mixed amphetamine combo
    - 5 mg tabs (#30 - $19.93; #60 - $24.41)
    - 10 mg tabs (#30 - $24.69; #60 - $31.59)
    - 20 mg tabs (#30 - $19.93; #60 - $24.21)
- Methylphenidate
  - Ritalin
    - #30 10 mg tabs - $33.88
    - #30 20 mg tabs - $47.33
  - Generic methylphenidate
    - #30 10 mg tabs - $10.99
    - #30 20 mg tabs - $14.83

Ex. 6, Page 883

REFERENCE 41

Yet Other Factors that May Influence Rx Patterns….

- Clinician Factors
  - New clinical data, observable benefit, and tolerability
  - The New-Drug-On-The-Market Phenomenon
  - Who's treating the ADHD?
- Patient Factors
  - Perception of the drug
- Marketing & Public Awareness (ADHD, Vyvanse, Rx treatments)
- Adult ADHD Indication
- Greater Dosing Flexibility
- Will Novartis chose to market Focalin XR?
- New ADHD Drugs on the Market

Ex. 6, Page 884

REFERENCE 41

OVERVIEW: ADHD Drugs in The Pipeline

- The Problem with New Treatments
- Emerging Non-Stimulant Classes
  - Alpha-2 agonists
  - Neuronal Nicotinic Acetylcholine Receptor (NNR) agonists
- CV Safety
- The Adult ADHD Market
- Failures

Ex. 6, Page 885

REFERENCE 41

ADHD Drugs in the Pipeline

- **"APPROVABLE", now awaiting final FDA decisions**
  - SPD-465 (Shire)
    - "*Extended-release* Adderall XR", up to 16 hr effect
    - Shire's plans
  - INTUNIV (Shire)
    - Extended release guanfacine
    - Non-stimulant, alpha-2 agonist
    - Efficacy data & side effect profile
- **Phase III**
  - CLONICEL (Sciele Pharma/Addrenex)
    - First Phase III Trial, Children & Adolescents, initiated October 2007
    - Extended release clonidine
    - Non-stimulant, alpha-2 agonist

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REFERENCE 41

ADHD Drugs in the Pipeline

- Phase II
  - ABT-089 (Abbott Labs)
    - Children & Adults, ADHD
    - Neuronal Nicotinic Acetylcholine Receptor (NNR) partial agonist (alpha4beta2)
    - Published clinical data (n=11)
  - ABT-894 (Abbott Labs/Neurosearch)
    - Adult ADHD, initiated March 2007
    - Neuronal Nicotinic Acetylcholine Receptor (NNR) agonist (alpha4beta2)
  - MK0249 (Merck)
    - Adult ADHD, study start date July 2007
  - GTS21 (CoMentis)
    - Adult ADHD
    - ? Status (per CoMentis website, Phase II expected Q4 2007; per clinicaltrials.gov, Phase II/I "not yet open", last updated January 2007)
    - Neuronal Nicotinic Acetylcholine Receptor (NNR) agonist (alpha7)
  - PF-03654746 (Pfizer)
    - Adult ADHD (not yet enrolling, clinicaltrials.gov)
    - ? Novel Mechanism of Action (in a decongestant study)
  - JNJ-31001074 (Alza)
    - Adult ADHD (not yet open for recruitment)
    - Info last updated Dec 2007, clinicaltrials.gov
- Phase I & Pre-Clinical