Argument 1 (of 2) for Ground 1: Petitioner/Declarant grossly mischaracterize how a POSA at the time of the invention would have understood the term in the art known as "anti-obesity agent." Petitioner's/Declarant's argument is therefore illogically reasoned at its outset to a mistaken conclusion.

Summary. Petitioner grossly mischaracterizes Mickle's LDX-dimesylate as an "anti-obesity agent" by conflating the plainly understood and transparently disclosed meaning of the term as it would have been unambiguously used, and understood, in the art by a POSA "as of September 13, 2007," according to the art's standard for defining one at that time – and as it is self-evidently used in Appolinario. A POSA as of "September 13, 2007" would not have regarded LDX-dimesylate as an "anti-obesity agent," nor anything even modestly resembling one. Therefore, a POSA at the time of the invention would not have even been motivated from the outset to combine Mickle's art on LDX-dimesylate with Appolinario's teaching on the successful pharmacotherapy of BED with "anti-obesity agents," much less would a POSA have concluded a reasonable expectation of success for LDX-dimesylate to treat BED. A POSA, who by the Petitioner's standard "would be a medical doctor (M.D.) specializing in psychiatry" (p. 9) and "would have clinical experience in the diagnosis and psychopharmacology of eating disorders" (p. 9), would have regarded Mickle's teaching of amphetamine prodrugs, and LDX-dimesylate thereof, as merely speculative in nature, very far from satisfying the art's accepted standard of an "anti-obesity agent" as it would have been regarded at the time of '813's filing and as it is regarded by Appolinario and others, as disclosed in various of the Petitioner's prior art Exhibits. The Petitioner's Ground 1 line of reasoning ***relies*** *on LDX-dimesylate to empirically function like an "anti-obesity agent" -- as "d-fenfluramine" and "sibutramine" (in view of Appolinario) -- in order for the POSA to have been motivated to combine of Mickle and Appolinario to yield '813's independent claims with a reasonable expectation of success. But since a POSA would have understood at the time of the invention that LDX-dimesylate hadn't satisfied, nor even remotely approximated (simply based on the empirical evidence), the "burden of proof" required to establish it as an "anti-obesity agent," there would have been no reasonable expectation of success that the combination of Mickle and Appolinario could even produce '813's invention.*

The Petitioner's Ground 1 line of reasoning is derived from Appolinario's characterization of three different "classes" of drugs proven successful in the treatment of "Binge Eating Disorder as defined in the DSM-IV/DSM-IV-TR." The DSM-IV, published in 1994, and DSM-IV-TR, published in 2000 (and still in effect at the time of '813's filing), featured the same exact diagnostic criteria for BED in every respect (to the very word), which a POSA "as of September 13, 2007" would have understood as their "diagnostic equivalence" (i.e., "interchangeable" terms, without any differentiation/differences in their clinical criteria). (Exhibit 1026, p. 11 – DSM-IV; Exhibit 1010, p. 18 – DSM-IV-TR). The Petitioner, too, acknowledges this basic understanding of the art as well (Petition, p. 14). In this respect, a POSA "as of September 13, 2007" would have considered the "exact sameness" of BED's diagnostic criteria in the DSM-IV/IV-TR over the prior 13 years significant given the important pharmacologic teachings of its treatment in the art, as disclosed in

Appolinario's 2004 pharmacotherapy review (Exhibit 1020), as well as in the Petitioner's other Exhibits and '813's patent prosecution, among yet many other references in the art recognized for their teachings on the pharmacotherapy for, specifically, BED.

One of the three "classes" of drugs Appolinario identifies for its success in the treatment of "BED as defined in the DSM-IV/IV-TR" is the "class" of drugs well-recognized in the art as *"anti-obesity agents."* This particular "class" stands among two other "classes" of drugs, each also well-recognized in the art for their respective "class" designation -- *"anti-depressants"* and *"anticonvulsants." (Exhibit 1020, p. 2, Col. 1; p. 3, Cols. 1-2).* In particular, Appolinario identifies two specific drugs, d-fenfluramine and sibutramine, within the "class of anti-obesity agents" (Exhibit 1020, p. 3, Col. 1). The Petitioner's line of reasoning for its Ground 1 argument wholly relies on *"**LDX Dimesylate** [functioning] as a Centrally Acting **Anti-obesity Agent** Having Desirable Properties" (Petition, p. 15-16),* as the Petition's "Section IX.B.2" is called. After all, this would have been the primary motivation of a POSA at the time of the invention to combine Mickle with Appolinario and have a reasonable expectation of success it would produce '813's invention. In other words, a POSA at the time of the invention would have had to regard LDX-dimesylate as essentially the same as d-fenfluramine and sibutramine with respect to its therapeutic "anti-obesity function" in order to conclude a reasonable expectation for '813's claimed invention.

However, a POSA at the time of the invention would certainly not have regarded LDX-dimesylate as essentially the same as d-fenfluramine and sibutramine with respect to its "anti-obesity function" and thus would have recognized the Petitioner's characterization of LDX dimesylate as an "anti-obesity agent," vis-à-vis Mickle, as grossly misleading and even egregiously misrepresentative of Appolinario's teachings. This is simply because the meaning of the term "anti-obesity agent" would have been understood by those in the art to identify drugs that have been accepted in the art for their ***efficacy in the treatment of obesity*** on the basis of the art's standard for making such determinations, namely, through randomized placebo-controlled clinical trials and, optimally, from regulatory (i.e., FDA) approval. A POSA "as of September 13, 2007" would have simply known and recognized this most transparent and plainly stated feature of Appolinario's nomenclature and its implication for the treatment of BED, a condition long-associated with obesity from its earliest clinical characterizations going back to Stunkard's 1959 paper "Eating Patterns and Obesity" (Exhibit 1040). But if there would by any doubt about this, the context of Appolinario's use of the term "anti-obesity agent," in view of his other two clinical trials (Exhibits 1021, 1046), as well as in view of other art featured in Petitioner's prior art disclosures and further characterized below, quite clearly puts this all into perspective for even any reasonable person viewing the art to appreciate.

To begin with, its important to recognize that Appolinario characterizes his own line of reasoning to think about the "successful treatment of BED" by recognizing

"successful drugs" in its treatment according to their respective "class of therapeutic efficacy." This is why he writes, *"one could just as easily assume that antidepressants work for BED because of their anti-depressant action, anti-obesity agents because of their anti-obesity action, and anticonvulsants because of their anticonvulsant or mood-stabilizing properties." (Exhibit 1020, p. 5, Col. 1).* In other words, Appolinario teaches that a drug's observed therapeutic efficacy for BED could well be on account of its known "therapeutic efficacy" for the treatment of, respectively, "depression," "obesity" or "seizures." And, to be sure, a POSA at the time of the invention would simply not have regarded a drug as having "anti-depressant efficacy," "ant-obesity efficacy," or "anticonvulsant efficacy" unless it was empirically validated in the art for having such a clinical function. After all, the POSA, by the Petitioner's standard, *"would be a medical doctor (M.D.) specializing in psychiatry" (p. 9)* and would have practiced to the well-accepted standard of modern medicine, namely, on the basis of empirically validated methodologies. '813 was filed in 2007 and, as even any reasonable person would have appreciated at that time, this standard had long been accepted for determining a drug's efficacy in the treatment of disorders, diseases, etc…In view of Appolinario's line of reasoning, it goes without saying that a POSA at the time of the invention would have reasoned that if a given drug ***hadn't*** established a reasonable degree of efficacy (i.e., "success") for the treatment of "depression," "obesity," or seizures" by the standard with which such drugs are classified in the art for their "therapeutic efficacy" (i.e., controlled clinical trials), then the drug ***could not*** be reasonably expected to successfully treat BED.

With respect to the term "anti-obesity agent" as used in Appolinario, as its interpretation is central the Petitioner's Ground 1 argument even before it gets off the ground, a POSA at the time of the invention would have unmistakably understood that Appolinario was regarding "anti-obesity agents" as ***differentiated from other drugs*** (i.e., which might potentially cause weight loss in some way or another) ***on the basis of their established efficacy in controlled clinical trials for the <u>treatment of obesity</u>***. This, then, would serve as the basis for their regulatory (i.e., FDA) approval and their use in the community of POSAs for the treatment of obesity as an "on-label use" of the drug; or, in the instance that a given drug was not FDA-approved but validated for its effectiveness in controlled trials for the treatment of obesity by the standard of the art, then its "off-label use." Anyone who would not have understood this at the time of the invention, and its clear connection to Appolinario's nomenclature of "anti-obesity agent," would not have been practicing the art by Petitioner's standard of a POSA as one who *"would have clinical experience in the diagnosis and **psychopharmacology** of **eating disorders**, **specifically BED"** (p. 9).* The art could not be any clearer on its teaching here. And the best way to understand this is to see how, specifically, Appolinario uses the term "anti-obesity agent" to characterize d-fenfluramine and sibutramine in his 2004 pharmacotherapy review, how the term is used elsewhere in his own art, how the term is used among others who practice the art according to its most basic and essential distinctions (as featured in Petitioner's/Declarant's Exhibits), and then to return to the Petitioner's characterization of LDX-dimesylate as an "anti-obesity agent" in view of Mickle.

For one, Appolinario's 2004 pharmacotherapy review for BED, as cited in the Petitioner's Ground 1 argument, plainly discloses, "*the first report of an **anti-obesity** agent in the treatment of BED was a positive placebo controlled trial of d-fenfluramine. **D-fenfluramine** (**currently withdrawn from the market** for its association with cardiac valve lesions and pulmonary hypertension) was found to promote binge eating suppression in 22 patients with BED and **obesity**. Surprisingly, despite the **anti-obesity action** of **d-fenfluramine** and the high rate of remission of binge eating (80%) reported in this study, a **reduction in body weight was not observed."** (Exhibit 1020, p. 3, Col. 1).* A POSA at the time of the invention would have regarded it as common knowledge in the art that d-fenfluramine had been FDA-approved for the treatment of obesity based on randomized controlled trials, but which was withdrawn from the market for adverse events as Appolinario highlights (and as further characterized below in Petitioner's/Declarant's other prior art disclosures). Appolinario is "surprised" because here was an instance of a drug validated in the art for its ***treatment of obesity*** by controlled clinical trials, as well as by its FDA approval which had made it available for commercial use, that failed to reduce weight in "severely obese" BED patients even as it helped reduce binge eating, quite robustly no less. That these BED patients were *"severely obese"* and that d-fenfluramine had *"been recently approved by the Food and Drug Administration"* are both explicitly featured in 1996 clinical trial publication that Appolinario references, which is Stunkard's "d-fenfluramine Treatment of for Binge Eating Disorder." *(Exhibit 1044, p. 1, Col. 1; p. 1, "methods"; and p. 3, Col. 2).* Appolinario then goes on to characterize sibutramine and its place in the BED art, noting *"its efficacy for inducing initial weight loss and subsequent weight-loss **management in obesity** is **well-proven** in **short** and **long-term trials**." (Exhibit 1020, p. 3, Col. 1).* He identifies sibutramine as effective in BED in *"an open trial with 10 **obese** patients"* and, following evidence of benefit in that trial, he describes conducting a randomized controlled trial of sibutramine in *"60 **obese** patients with BED." (Exhibit 1020, p. 3, Col. 1).* Thus, he shows his motivation to use drugs validated for the treatment of obesity (with controlled clinical trials, both short and long term) in the treatment of BED.

If Appolinario's 2004 pharmacotherapy review leaves any question about what the term "anti-obesity agent" might have meant to one practicing the art with ordinary skill at the time of the invention, there is also Appolinario's characterization of sibutramine and d-fenluramine as ***effective agents*** in the ***treatment of obesity*** – ***i.e., "anti-obesity agents"*** -- featured in his 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge-Eating Disorder," also disclosed as prior art by the Petitioner. (Exhibit 1046). Therein Appolinario writes, *"**Sibutramine** hydrochloride is a serotonin and norepinephrine reuptake inhibitor and represents a new class of **agents** approved by the **US Food and Drug Administration** for the **treatment of obesity**. Its **efficacy** in **inducing weight loss** and **subsequent weight management** is **well-proved** in **short-term** and **long-term trials**. Sibutramine induces weight loss by affecting the physiological process of satiety and stimulating thermogenesis. Unlike fenfluramine and **d-fenfluramine**, it*

does not induce serotonin release and has not been implicated in the development of heart disease. Sibutramine is one of the few well established and ***well-proved agents*** *for the* ***treatment of obesity*** ***available*** *and* ***considered safe*** *in patients who require pharmacotherapy as part of the multimodal approach to weight loss." (Exhibit 1046, p. 3, Col. 1)* Here, Appolinario plainly and transparently communicates the meaning of the term "anti-obesity agent." And, as a POSA "as of September 13, 2007" would have particularly appreciated, he does so in view of his own randomized controlled trial that featured, not surprisingly, 60 comorbidly ***obese***/BED patients with a BMI 30-45 (Exhibit 1046; p. 2, "Methods"). A POSA would have surely recognized this clinical trial as the same one he identifies in his 2004 pharmacotherapy review for its teachings on the use of sibutramine in comorbidly obese/BED patients.

Appolinario's 2003 published clinical trial on sibutramine treatment of BED speaks to siburtamine's profile as an anti-obesity agent as it would have been expected in the art at the time of the invention. His art characterizes the drug's regulatory approval by the FDA ***for the treatment of obesity***, its validation across trials of different durations (i.e., "short" and "long") including for "weight management" after initial "weight loss," and its considered safety in view of these trials, all standard important features of a given drug's "anti-obesity agent therapeutic profile." Notably, and as a POSA would have appreciated at the time of the invention in relation to Appolinario's 2004 BED pharmacotherapy review, he again identifies sibutramine ***in view of*** d-fenfluramine when he writes, *"Unlike fenfluramine and* ***d-fenfluramine, it [sibutramine] does not induce*** *serotonin release and has not been implicated in the development of heart disease." (Exhibit 1046, p. 3. Col. 1).* The point, while it would have been assumed common knowledge to a POSA at the time of the invention, is that d-fenfluramine was "the other" centrall-acting anti-obesity drug which had similarly been approved by the FDA for the ***treatment of obesity*** on the basis of randomized controlled trials but which had been withdrawn from the market because of cardiac problems. In his 2003 publication, Appolinario again references d-fenfluramine with respect to its "class of therapeutic action" (i.e., "treatment of obesity"), just as he does in his 2004 pharmacotherapy review, and once again he regards the drug's regulatory status in view of its therapeutically recognized class (i.e., "anti-obesity agent"), *"the first report to use an* ***anti-obesity agent*** *to treat BED was published in 1996 by Stunkard et al, who showed that d-fenfluramine hydrochloride (****now withdrawn from the market)*** *was more effective than placebo for the treatment of BED." (Exhibit 1046, p. 3. Col. 1).*

A POSA at the time of the invention would have also understood that Appolinario, in both his 2004 pharmacotherapy review (Exhibit 1020) and his 2003 randomized controlled trial publication (Exhibit 1046), was teaching more than just "anti-obesity agents" as drugs which are differentiated from other drugs on the basis of their validated efficacy for the treatment of obesity in placebo-controlled clinical trials. He was also teaching that anti-obesity agents were ***differentiated from each other*** on the basis of their ***specific neurotransmitter ("NT") mechanism of action***. This was the "state of the art as of 2003," as plainly and transparently disclosed by Appolinario's own teachings. This can be seen when he characterizes the anti-

obesity agent sibutramine as a ***"a serotonin and norepinephrine reuptake inhibitor" (Exhibit 1046, p. 3, Col. 1)*** that *"does not induce serotonin release"* like the anti-obesity agent d-fenfluramine, in view of his *"randomized, double-blind, placebo-controlled trial of sibutramine in the treatment of Binge-Eating Disorder."* In this respect, Appolinario communicates important features of his art in the art's NT-specific language, as characterized in the Petitioner's and Declarant's "State of the Art." (Petition, pp. 5-8; Exhibit 1009, pp. 15-28). Specifically, as a POSA at the time of the invention would have unmistakably understood, Appolinario identifies sibutramine's potentiation of the specific NT's norepinephrine (NE) and serotonin (5-HT) through "reuptake inhibition," in contrast to d-fenfluramine's potentiation of serotonin (5-HT) through its "release." (Exhibit 1046, p. 3, Col. 1). He makes it a point to identify sibutramine's NT-specific mechanism of action on "serotonin and norepinephrine reuptake inhibition" in his 2004 pharmacotherapy as well, as the art regarded understanding a drug's given NT-specific mechanism of action ***in relation to its potential therapeutic efficacy*** in eating disorders as important, which the Petitioner's and Declarant's "State of the Art" highlights as well. (Exhibit 1020, p. 3. Col. 1; Petition, pp. 5-8; Exhibit 1009, pp. 15-28).

A POSA at the time of the invention would have appreciated Appolinario's repeated and plainly stated teachings about sibutramine's characteristics in two essential respects. The first of these relates to sibutramine's validated efficacy in the treatment of obesity in obese patients with, notably, regulatory approval that would enable clinicians to treat obesity in obese patients according to certain practice standards. Appolinario's 2003 randomized placebo-controlled trial itself only enrolled *"**obese outpatients** (**body mass index** [calculated as weight in kg divided by the square of the height in meters] **30-45**) who met DSM-IV criteria for BED" (Exhibit 1046, p. 2, "Methods")* and his earlier 2002 open-label trial of sibutramine in BED, briefly characterized in his 2004 pharmacotherapy review for its teachings and also disclosed in the Petitioner's prior art, similarly enrolled only "***obese patients*** *with DSM-IV binge eating disorder" (Exhibit 1020, p. 3, Col. 1; Exhibit 1021, p. 1, Col. 1, "Method").* In other words, Appolinario was clearly motivated to design his two clinical trial for sibutramine, an "anti-obesity agent," in the treatment of BED because there was a rational basis for doing so – ***his patients were obese***. This motivation was just like Stunkard's, which enrolled exclusively ***severely obese*** patients. But Appolinario had the benefit of a commercially available drug that had received regulatory approval for the treatment of obesity and had substantial data regarding its efficacy and safety in obesity treatment through both short and long term trials. By Appolinario's characterization of sibutramine, his motivation to use it seems also to have been motivated by its safety and that it worked by a different NT-specific mechanism of action than that of d-fenfluramine. And, of course and most relevantly, it was validated in the art as a successful treatment of obesity by the standard with which the art makes such determinations. The second essential aspect that a POSA at the time of the invention would have appreciated about sibutramine's "characteristics" in view of Appolinario's art would have been in relation to its NT-specific mechanism of action. This can be appreciated in the way Appolinario identifies sibutramine with a *"**new class of agents** approved by the US*

*Food and Drug Administration for the **treatment of obesity**" (Exhibit 1046, p. 3, Col. 1).* And, specifically, sibutramine's NT-specific actions would have been understood by a POSA as potentiating norepinephrine (NE) and serotonin (5-HT) through "reuptake inhibition." Here, Appolinario's is teaching about essential psychopharmacology distinctions in the art of treating obesity with respect to its NT-specific targets.

Appolinario's term "anti-obesity agent," as he intends it and as it would have been understood by a POSA "as of September 13, 2007," is also plainly seen for its for its meaning in his 2002 publication entitled "An Open-Label Trial of ***Sibutramine*** in ***Obese Patients*** with Binge Eating Disorder," also disclosed by the Petitioner as prior art. (Exhibit 1021). Again, Appolinario affords sibutramine and d-fenfluramine the same distinction as "anti-obesity agents," just as it would have been understood by the community of POSAs from the time of his 2002 publication to the time of 813's filing on September 13, 2007. He writes, *"The first report of the use of an **antiobesity agent** to treat binge-eating disorder was published in 1996. In a placebo-controlled clinical trial, Stunkard et. al. reported that **d-fenfluramine (recently withdrawn from the market)** was more effective than placebo in the treatment of binge-eating disorder." (Exhibit 1021, p. 2, Col. 2)* These repeated and consistent characterizations of sibutramine and d-fenfluramine as "anti-obesity agents" would have been familiar territory for a POSA diagnosing and treating of BED. More specifically, Appolinario's 2002 open-label clinical trial of sibutramine in BED was conducted in co-morbid BED and obesity (with a BMI >30) again speaking to his motivation to use the "anti-obesity agent" sibutramine in both his clinical trials – namely, that the patients he was treating in the trial (diagnosed with BED) ***were clinically obese.*** (Exhibit 1021, p. 2, Col. 1, "Methods").

It is not surprising, then, that the same characterization and reasoning by which the art identified "d-fenfluramine" and "sibutramine" as "anti-obesity agents" for ***the treatment of obesity***, on the basis of their validated efficacy in controlled clinical trials and ensuing regulatory approval, can be found repeatedly and consistently elsewhere within the disclosures of the Petitioner's cited prior art. For instance, the Petitioner's prior art disclosure of Ioannides-Demos entitled "Pharmacotherapy of Obesity" features d-fenfluramine's established efficacy in the treatment of obesity based on randomized placebo-controlled trials and also highlights its withdrawal from the market on account of valvular heart disease (Exhibit 1011, p. 8-9). Ioannides-Demos also provides an extensive characterization of sibutramine's anti-obesity efficacy based on numerous randomized controlled trials across varying doses and durations, the longest clinical trials of which are notably featured in a table (Exhibit 1011, pp. 9-12; Table of trials >/= 1 year on p. 10). The Petitioner's prior art disclosure of Blundell's "Serotonin and Appetite Regulation: Implications for the Pharmacological Treatment of Obesity" does the same (Exhibit 1015). Blundell highlights the withdrawal of d-fenfluramine from the market as a drug for the treatment of obesity due to valvular heart disease and primary pulmonary hypertension. (Exhibit 1015, p. 15, Col. 2). Blundell also characterizes sibutramine's regulatory approval, and features its NT-specific actions ***in view of*** d-fenfluramine,

yet further testimony that the art was focusing its attention on NT-specific targets, *"the action of the sibutramine, which has recently been approved by the US Food and Drug Administration is, at least in part,* ***mediated via serotonergic mechanisms****. Encouragingly, to date, sibutramine has not been associated with either pulmonary hypertension or valvular heart disease, but it has, as yet, been determined to a relatively small number of patients." (Exhibit 1015, p. 6).* Additionally, the Petitioner's prior art disclosure of Milano's 2005 "Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment of Binge Eating Disorder: A Placebo-Controlled Study," characterizes the drug sibutramine as an *"anti-obesity agent" (Exhibit 1022, p. 3)*, offers several references to other studies that speak to the drug's efficacy in the treatment of obesity, identifies its NT-specific mechanism of action in its title, and even identifies the physiologically-based mechanisms of action by which it is thought to induce weight loss, namely, *"through 2 metabolic processes (the supplementation of the physiologic process of satiation and the stimulation of thermogenesis)" (Exhibit 1022, p. 3).*

The Petitioner's declarant, Declarant, himself clearly acknowledges his understanding of d-fenfluramine and sibutramine as empirically validated and commercially approved drugs for the treatment of obesity, including that both drugs had received regulatory approval for such clinical use. He does this when he writes in his 1999 "Binge Eating Disorder: Diagnosis and Treatment Options,"

> *"dexfenfluramine, a pre-synaptic agonist of serotonin and a mild reuptake inhibitor, is* ***no longer an option for patients with obesity****...."* .... *"when it [dexfenfluramine] was discovered that it also induces valvular heart disease it was* ***taken off the international market****." (Exhibit 1037, p. 8. Col. 1; p. 8, Col. 2).*
>
> *"sibutramine, a serotonin and noradrenaline (norepinephrine) reuptake inhibitor without apparent antidepressant properties, has* ***just been released in the US*** *for the adjunctive* ***treatment of obesity*** *(along with behavior therapy). Results from a number of* ***double-blind, placebo-controlled studies*** *have demonstrated that this* ***new agent*** *is* ***effective in patients with obesity****." (Exhibit 1037, p. 8, Col. 2).*

Thus, Declarant plainly discloses his understanding of the successful pharmacotherapy of obesity with "anti-obesity agents" in the same way that it was consistently and transparently communicated in the art of Appolinario from 2002-2004 (Exhibits 1020, 1021, and 1046), Ioannides-Demos in 2005 (Exhibit 1011), Stunkard in 1996 (Exhibit 1044), Blundell in 1998 (Exhibit 1015) and Milano in 2005 (Exhibit 1015). In his 1999 BED review, Declarant considers d-fenfluramine with respect to each drugs' historical or potential application to BED and/or obesity, as d-fenflurmaine had been withdrawn from the market by 1999 when he published his art and sibutramine had yet to enter into Appolinario's clinical trial for BED but had been approved for use in the treatment of obesity in the US, just as he indicates. And, as a POSA "as of September 13, 2007" would have particularly appreciated,

Declarant differentiates each respective anti-obesity drug's NT-specific mechanism of action from the other, with d-fenfluramine a *"pre-synaptic agonist of serotonin and mild re-uptake inhibitor" (p. 8, Col. 1)* and *"sibutramine, a serotonin and noradrenaline (norepinephrine) reuptake inhibitor" (p. 8, Col. 2),* just as Appolinario would later do in his own teachings just a few years after Declarant's 1999 publication on BED.

Thus, Declarant's 1999 review of BED teaches openly on basic and essential distinctions that the art was making on BED psychopharmacology in view of the specific drugs shown to be successful for the treatment of obesity. As any POSA between 1999 and September 13, 2007 would have appreciated, Declarant was teaching on the kinds of psychopharmacologic distinctions a POSA would have considered in view of treating BED, in this instance that (broadly speaking):

a) ***anti-obesity agents are essentially the same*** on the basis of their therapeutic efficacy for the treatment of obesity in controlled trials (and regulatory approval) but ***essentially different than other drugs*** which have not been validated as such, and

b) ***ant-obesity agents are essentially different from each other*** on the basis of their different NT-specific mechanisms of action, with one drug featured for its exclusive serotonin target (i.e., d-fenfluramine) and the other drug (i.e., sibutramine) featured for its combination serotonin and norepinephrine targets.

Declarant's characterization of d-fenfluramine and sibutramine in these two essential respects, one having to do with their ***validated efficacy in the treatment of obesity*** and other with their respective ***NT-specific mechanism of action***, shares the same line of reasoning featured in Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge-Eating Disorder," as when Appolinario writes, *"Unlike fenfluramine and **d-fenfluramine**, it [sibutramine] **does not induce serotonin release** and has not been implicated in the development of heart disease." (Exhibit 1046, p. 3, Col. 1)*

A POSA seeking to apply Appolinario's teachings about "anti-obesity agents" to the treatment of "BED as defined in the DSM-IV/IV-TR" to another drug, such as Mickle's LDX-dimesylate, would have only been motivated to do so if such a drug were empirically validated in the ***treatment of obesity*** by the same standard applied to sibutramine and d-fenfluramine. As discussed, this was Appolinario's logic in view of his own controlled trials in comorbid BED and obese patients, and as established in his line of reasoning that *"one could easily assume…. anti-obesity agents [work for BED] because of their anti-obesity action" (Exhibit 1020. P. 5, Col. 1).* In other words, a POSA at the time of the invention would have first reasoned to determine whether a given drug satisfied the art's accepted standard as a ***"treatment of obesity" <u>before concluding (or assuming)</u>*** that the drug could reasonably enter into the line of reasoning that *"one could easily assume…. anti-obesity agents [work for BED] because*

of their anti-obesity action" (Exhibit 1020. P. 5, Col. 1). A POSA would have recognized that Appolinario was just as motivated to see the "obesity" of his patients successfully treated as he was to see the "binge eating" successfully treated, as all his patients were obese and sibutramine was already an empirically validated FDA-approved treatment of obesity.

While the Petitioner's prior art disclosures (i.e., Exhibits 1011, 1015, 1020, 1021, 1037, and 1046) repeatedly and consistently regard "anti-obesity agents" in terms of their efficacy in controlled clinical trials (and regulatory approval), a POSA "as of September 13, 2007" would have particularly appreciated the art's standard for an "anti-obesity efficacy" in view of one of its most essential and indispensable resources – the Physician's Desk Reference (i.e., "PDR"). The "PDR" features the many drugs that have received regulatory approval across different diseases and disorders. It provides important prescribing information for physicians who administer such drugs to their patients. Any drug that a POSA at the time of the invention would have been motivated to use for the treatment of BED, simply on the basis of its commercial availability for use and its consideration in view of Appolinario's basic line of reasoning, would have been characterized in the PDR according to its therapeutic efficacy as well as other clinical relevant properties. And if, for instance, such a "considered drug" for BED therapy just made it to the market and had yet to be included in that year's PDR, or had been discontinued as d-fenfluramine had been, a POSA could have easily accessed the drug's "package insert" or "drug label" (as it is called in the art) from any number of resources to investigate its features. This is how a POSA would have reasoned – in view of empirical data.

In this light, a POSA as of "anytime between d-fenfluramine's FDA-approval in 1996 and September 13, 2007" would have understood its characterization as an "anti-obesity agent" in its proper diagnostic, psychopharmacologic and regulatory (i.e., "labeled") context. For instance, the 1997 PDR provides the package insert for d-fenfuramine (trade name "Redux"). The "Clinical Studies" section of d-fenfluramine's package insert indicates that, *"Redux has been **effective** in **reducing excess body weight** in **obese patients**. In **16 of 17 double-blind, placebo-controlled trials, of varying treatment durations** and with different design features, where all patients were on reduced-calorie diets, Redux-treated patients lost significantly more weight on average than those treated with placebo….In the INDEX study, a **one-year, double-blind, placebo-controlled trial of obese patients**, Redux, in conjunction with a reduced calorie diet, produced a significant reduction in weight during the first 4 to 6 months. This response was maintained during continuation therapy (up to 12 months of treatment)." (Redux package insert, p. 2912, Cols. 1-2).* Further, d-fenfluramine demonstrated statistically significant efficacy as an "anti-obesity agent" in a one year randomized placebo-controlled trial of over 800 obese patients, as summarized in its package insert (p. 2912, Table entitled "Percentage of Patients Losing Weight at One Year"). D-fenluramine received FDA approval for its marketing as a drug treatment for obesity under the trade name "Redux," henceforth its ensuing classification in the art as an ***"anti-obesity agent."*** Its

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repeated and consistent characterization in the art as an "anti-obesity agent" and as a "treatment for obesity" that was "withdrawn from the market" by the likes of Appolinario (Exhibits 1020, 1021, 1046), Ioannides-Demos (Exhibit 1011), Blundell (Exhibit 1015), and Declarant himself (Exhibit 1037), is simply a function of its essentially distinctive clinical function "according to art" and "as transparently disclosed in the art" – a drug empirically validated for the treatment of obesity that was FDA-approved but then withdrawn from the market because of cardiac valve and primary pulmonary hypertension concerns. The drug's reasonable expectation of success in the treatment of obese patients would have derived, then, from its reasonable expectation of success in randomized placebo-controlled clinical trials ***for the treatment of obesity***.

A POSA "as of September 13, 2007" would have been particularly familiar with sibutramine as an "anti-obesity agent," one which was approved by the FDA and marketed under the trade name "Meridia," as the drug was still marketed for the ***treatment of obesity*** at that time though later withdrawn from the market due to safety concerns. The PDR's 2007 package insert of sibutramine (i.e., "Meridia") is attached. A POSA would have clearly appreciated that the data on which sibutramine established its "anti-obesity agent status" in the art was based on ***11 double-blind, placebo-controlled trials,*** with ***study durations of 12-52 weeks*** with varying dose ranges (PDR's 2007 Package insert, p. 489, Col. 3, "Clinical Studies" section). Notably, there were ***two one year studies*** that showed maximal weight loss on sibutramine was achieved in 6 months, with statistically significant weight loss maintained over 12 months (Meridia 2007 package insert, p. 489/Col. 1—p. 490/Col. 2), itself a finding similar to "Redux" (Redux package insert, p. 2912, Col. 2) wherein there was *"significant reduction in weight during the first 4 to 6 months. This response was maintained during continuation of therapy (up to 12 months of treatment)." (Redux package insert, p. 2912, Cols. 1-2).*

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The plain and transparent meaning of the term "anti-obesity agent," as it is used in Appolinario and as it would have been understood by a POSA at the time of the invention, is unmistakably clear. By the art's plainly stated and transparently disclosed teachings, such drugs (in view of Appolinario's line of reasoning) would have been ***validated for the treatment of obesity*** *(and thus would have received regulatory approval for treating obesity) and* ***shown evidence for successfully treating BED <u>in co-morbidly obese patients</u> (in view of their empirical validation and acceptance as "anti-obesity agents" according to the art).*** A POSA "as of September 13, 2007" would have particularly appreciated this aspect of the art since a POSA *"would have clinical experience in the diagnosis and* ***psychopharmacology*** *of eating disorders,* ***specifically BED"*** *(Petition, p. 9),* and especially as it is repeatedly featured in the art, as evidenced in the Petitioner's/Declarant's prior art disclosures of:

a) Stunkard's 1996 (Exhibit 1044) "d-fenfluramine Treatment of Binge Eating Disorder" which identifies that the 28 BED patients in the trial were also *"**severely obese**" (p. 2, "Methods")* with a *"mean body mass index > 36.7," (p. 3, Col. 1),* that ***d-fenfluramine*** *"has recently been* ***approved by the Food and***

Drug Administration*" (p. 3, Col. 1),* and that "*d-fenfluramine reduced the frequency of binge eating by* ***obese women*** *with binge eating disorder" (p. 2, "Conclusions"),*

b) Milano's 2005 (Exhibit 1022) "Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment of Binge Eating Disorder: A Placebo-Controlled Study" in which the *"efficacy, safety, tolerability of* ***sibutramine*** *were evaluated in the treatment of binge eating disorder* ***and obese patients****," (p. 1)* wherein sibutramine is explicitly characterized as an ***"antiobesity agent"*** *(p. 3)* and wherein the study found *"sibutramine was efficacious and well tolerated* ***in controlling both*** *binge eating disorder* ***and obesity****" (p. 6),*

c) Appolinario's 2004 (Exhibit 1020) pharmacotherapy review for BED identifying that the successful controlled clinical trials of both d-fenfluramine and sibutramine, both *"anti-obesity agents" (p. 3. Col. 1),* were conducted in patients who were comorbidly ***"obese,"*** as defined by a ***"BMI>30kg/m²"*** *(p. 5, Table 1, see "Diagnosis" Column),*

d) Appolinario's 2002 (Exhibit 2021) "An Open Label Trial of ***Sibutramine*** in ***Obese Patients*** with Binge Eating Disorder" identifying, in the very title of publication itself, that the BED subjects for which sibutramine, *"a new class of US Food and Drug Administration-agents for the treatment of obesity," (p. 2, Col. 1),* was being evaluated were also *"obese,"* the conclusion of which was *"sibutramine* ***might be an effective and well-tolerated treatment*** *of binge eating disorder* ***and obesity****" (p. 1, Col. 1),*

e) Appolinario's 2003 (Exhibit 1046) "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge Eating Disorder" identifying that the trial involved *"****60 obese outpatients (body mass index,*** *calculated as weight in kilograms divided by the square of height in meters,* ***30-35****), who met DSM-IV criteria for BED" (p. 2, "Methods")* wherein sibutramine, a *"new class of agents approved by the US Food and Drug Administration for the treatment of obesity," (p. 3. Co. 1),* was *"****found effective*** *and well tolerated in* ***the treatment of obese patients with BED****,"*

f) Brewerton's 1999 (Exhibit 1037) "Binge Eating Disorder: Diagnosis and Treatment Options" that identifies d-fenlfuramine as *"no longer a treatment option for obesity, bulimia nervosa, or BED" (p. 8, Col. 1)* on account of its being *"taken off the international market" (p. 8. Col. 1),* and also identifies sibutramine's recent *"release in the US for the adjunctive treatment of obesity (along with behaviour therapy)" (p. 8, Col. 2)* which *"holds promise [for BED] on theoretical grounds." (p. 8, Col. 2).*

The recognition of sibutramine and d-fenfluramine as empirically validated treatments for obesity (i.e., "anti-obesity agents") whose application to the treatment of BED was motivated by the strong association of obesity with BED could not have been in any plainer and clearer. All the clinical trials featuring their use exclusively involved BED subjects with comorbid obesity (i.e., Exhibits 1021, 1022, 1044, 1046). Notably, Declarant himself seems to have been quite clear on the same basic connection as well, writing in his Declaration, *"Many BED patients are obese*

(see Ex. 1043, Hudson, p. 4; see also Ex. 1044, Stunkard, p. 2), and the literature describes that anti-obesity agents were explored as potential treatments for BED (See Ex. 1020, Appolinario, p. 3). Anti-obesity agents have been successfully used for the treatment of BED, including d-fenfluramine and siburtamine. (Ex. 1020, Appolinario, p. 3; see also Ex. 1045, Wilfley, p. 1, Abstract)." (Exhibit 1009, p. 21).

In view of the unambiguous and consistently identified standard of the art for affording a drug its status as an "anti-obesity agent," a POSA "as of September 13, 2007" would have been perplexed as to how the Petitioner/Declarant could have regarded Mickle's LDX-dimesylate as an ***"Anti-obesity Agent"*** *(Petition, p. 15).* But needless to say, a POSA who *"would be a medical doctor (M.D.) specializing in psychiatry" (Petition, p. 9)* at the time of the invention would certainly have been curious as to how the Petitioner and its hypothetical POSA reasoned to this conclusion. For sure, accurately identifying LDX-dimesylate as an "anti-obesity agent" would have been the first and most critical first step for a POSA before arriving at a "reasonable expectation of success" of '813's independent claims in view of Appolinario and Mickle. With this in view and practicing the art with ordinary skill, a POSA would have looked to the art itself to evaluate whether any given drug's therapeutic efficacy ***in the treatment of obesity*** was essentially the same as d-fenfluramine and sibutramine – with an eye also toward safety considerations as d-fenfluramine had been withdrawn from the market because of safety issues. But is this what the Petitioner's hypothetical POSA did? Did the Petitioner's hypothetical POSA reason by the standard of the art as it would have been at the time of the invention, or did the Petitioner's hypothetical POSA reason arbitrarily and/or illogically?

Let's see. A competent POSA "as of September 13, 2007" would have understood that Mickle, as the Petition accurately writes (p. 16), *"**lists obesity** as a **preferred indication for treatment** with the amphetamine prodrugs of the invention, **e.g., LDX dimesylate**."* But a POSA would certainly not have assumed, nor concluded, that LDX dimesylate ***ought to be*** regarded as an "anti-obesity agent" by the art's standard of determining one just because Mickle ***listed*** "obesity" as a preferred indication for its use in his patent application. That would be an unskilled and reckless practice of the art. And, potentially, it could also be a highly dangerous one in the treatment of patients. To be sure, as a POSA at the time of the invention would have clearly recognized, when the clinical trials of Stunkard in 1996 (Exhibit 1044) and Appolinario in 2002, 2003 and 2004 (Exhibit 1021, 1046), for instance, were run in subjects with comorbid BED and obesity, they were not designed whimsically. Rather, they were designed rationally and with an understanding that the drugs d-fenfluramine and sibutramine had adequately met a basic standard --- *at the time of their use in such trials* – as drugs empirically validated and safe for the treatment of obesity in obese patients. Stunkard, in 1996, clearly recognized the use of d-fenfluramine in Europe for 10 years before its FDA approval in the US, which he mentions in his "Methods" section (Exhibit 1044, p. 3. Col. 1).

So when the Petitioner reasons (p. 16-17) that *"Appolinario teaches the diagnosis of BED as per criteria defined by the DSM-IV-TR, and the successful use of centrally acting **ant-obesity agents** in the treatment of BED,"* a POSA seeking to apply Appolinario's teaching in clinical practice would have unmistakably sought to understand the "considered drug intervention" in view of the art. Thus, the very first question a POSA "as of September 13, 2007" would have asked, if practicing the art of diagnosing and treating ***"specifically BED"*** with ordinary skill, would have simply been, *"has the drug been validated to the satisfaction of the art's standard for classifying it is as an empirically validated **treatment of obesity in obese patients**?"* Or, put another way, *"would my POSA colleagues consider this drug to be an 'anti-obesity agent'"?* Or, put yet another way, *"if I were asked to give a presentation to my POSA colleagues on current 'anti-obesity drugs' for the treatment of obesity, would I include this drug in my presentation, even as it might be for 'off-label use'?* To address these questions, a POSA at the time of the invention would have first asked these kinds of questions:

> *"Has the drug been investigated in the treatment of obesity in obese patients? If so, how? In randomized placebo-controlled trials, in open-label studies, in case reports? Has the drug been investigated in the treatment of obesity in obese patients for a sufficiently long period of time, with "shorter range trials" in the range of months and "longer term trials" in the range of a year or longer? If so, what does the data show? And what kind of safety issues were identified during the trials? As any reasonable person would appreciate, obesity (and therefore BED) is often associated with various medical conditions (i.e., HTN, lipid disorders, etc…), so were these kinds of things looked at in the trials?"*

A POSA at the time of the invention would have been particularly concerned about safety matters, in part given d-fenfluramine's withdrawal from the market on account of cardiac and pulmonary concerns but also because obesity is commonly associated BED and itself is commonly associated with various medical conditions like HTN, lipid disorders, and type 2 diabetes, among others. BED, in particular because of its strong association with obesity, is a serious condition with serious potential medical co-morbidities. And a POSA at the time of the invention would have understood that in view of its drug treatment implications. With the presence of already "successful" and commercially available drug therapies generally considered "safe" for the treatment of BED based on controlled trials, such as the SSRI anti-depressants disclosed in Appolinario's 2004 pharmacotherapy review, a POSA "as of September 13, 2007" would not have cavalierly regarded the psychopharmacology of BED on the basis of mere speculation. Rather, as a basic obligation of practicing the art with skill, a POSA would have considered therapeutic options for BED with respect to their limitations – limitations as defined by the art out of which the community of POSAs would have been practicing the art and communicating its practice. In this instance, the art had transparently made its position clear on a drug's limitation "on being an anti-obesity agent." It simply required empirically validated efficacy in the treatment of obesity in randomized

controlled trials and, to the degree that such efficacy would have been established with (preferably) regulatory approval, that the drug was considered safe for longer duration use. All very simple and basic teachings of the art. And all in transparent and clear view for a person practicing the art with ordinary skill – and also, for that matter, for a reasonable person in view of the art as seen in its proper clinical context.

With this in view, a POSA reading Mickle would have seen Mickle's ***disclosed list*** of diseases, conditions and disorders (Exhibit 1023, [0124]) for which LDX-dimesylate could potentially be used as a therapeutic agent and would have clearly determined that the list was, to be sure, quite extensive and broad. A bit too broad to be taken seriously. It would not have required a POSA to draw such a conclusion. Thus, a POSA would not have blindly accepted Mickle's therapeutic characterization of LDX-dimesylate as an "anti-obesity agent," especially in view of what the art had taught about the use of this particular class of drugs in both BED and obesity over the prior decade. POSA's consider things in view of the art within which they practice their skill and, indeed, a POSA who *would have clinical experience in the diagnosis and* ***psychopharmacology*** *of eating disorders,* ***specifically BED****" (Petition, p. 9)* would have regarded consideration of an "anti-obesity agent" as measured by its clinical properties and as measured against the standards of the art which would have distinguished such drugs as "anti-obesity agents" and, therefore, as "anti-obesity agents for the treatment of BED." For a POSA not to have practiced in this way would have been to practice the art without skill, unknowing of its important and basic teachings.

In this context, a POSA "as of September 13, 2007" reading Mickle would have appreciated Mickle's teaching on the human pharmacokinetics of LDX-dimesylate ([0333]-[0352]), notably in comparison to other stimulants commonly used to treat ADHD like Adderall XR and Dexedrine Spansules (i.e., Table 71). A POSA also would have recognized Mickle's teaching on LDX-dimesylate as a "successful" treatment for ADHD. In particular, a POSA would have identified the controlled clinical trial efficacy data in human subjects for the treatment of ADHD in children aged 6-12 years of age across two double-blind, randomized, placebo-controlled trials, one trial lasting 4 weeks ([0353]) and another trial lasting one week ([0354)]. But a POSA would have very soon recognized that there was absolutely nothing in Mickle's disclosures that would, or could, cause one of ordinary skill in the art to reasonably regard LDX-dimesylate as an "anti-obesity agent." The clinical profile characterized in Mickle's disclosures for LDX-dimesylate would have been unmistakably recognized by a POSA as ***highly different*** than the clinical profile characterized for the "anti-obesity agents" consistently and repeatedly characterized in the art for their efficacy in the ***treatment of obesity AND in the treatment of BED***, themselves based on randomized controlled trials for each respective clinical indication.

But a POSA at the time of the invention, perhaps wondering if there might be more to learn about this new drug featured in Mickle's patent application, would have

first determined to look at the PDR's package insert for LDX-dimesylate to understand the properties of the drug. After all, it does not require a POSA to understand that POSAs (as that characterized by Petitioner/Declarant), by their very training, are extraordinarily unlikely to draw their understanding of a drug's clinical properties from patent applications. POSAs who *"would have clinical experience in the diagnosis and* ***psychopharmacology*** *of* ***eating disorders, specifically BED****" (Petition, p. 9)* reason on the basis of the art's teachings, and particularly based on empirical data from sources known to communicate the art by its standard of practice. Thus, a POSA at the time of the invention would have found LDX-dimesylate's drug label in the PDR a much better starting place for understanding a given drug's therapeutic features – and clinical applications – and would not have relied on the disclosures from a relatively obscure patent application (as far as POSAs reason) that features "obesity" as a "preferred indication" among a list of many disorders that span, even, the territory of many different sub-specialties and body regions. Assuming that LDX-dimesylate featured some sliver of therapeutic efficacy in the treatment of obesity in Mickle's patent application, a POSA would have been motivated to consider its use in view of the art's standard for its application as one. And, therefore, a POSA would have investigated the PDR's drug label (or similar reference), mindful all the time that there were not a whole lot of "anti-obesity agents" flooding the market, so anything worthy of pursuit among the many other classes of drugs flooding the market might still be worthwhile exploring.

The "VYVANSE" package insert of February 2007 is featured in Exhibit 1002 (p. 756-772) and was submitted as prior art in the '813 patent prosecution (which is the basis for its inclusion in the Petition's Exhibit 1002). A POSA would have readily recognized that the only empirically-based therapeutic efficacy for LDX-dimesylate featured in the 2007 package insert is for ADHD in children aged 6-12 years old, with efficacy determined by two clinical trials each lasting only 4 weeks and involving a total of 342 patients (Exhibit 1002, p. 758). A POSA would have understood that this data would have been astronomically out of range of any reasonable standard for considering LDX-dimesylate as an "anti-obesity agent" the way Appolinario (Exhibits 1020, 1021, 1046), Stunkard (Exhibit 1044), Milano (Exhibit 1022), Ioannides-Demos (Exhibit 1011), Blundell (Exhibit 1015) and Brewerton (Exhibit 1037), among others in the art, would have considered it, if for no other reason than that its efficacy had not yet been established in the successful treatment of obesity by even the most minimal standard in the art – treating subjects who are obese. But beyond that, a POSA would have appreciated that the data was limited in other respects too, even if it were "imaginably applied" to the treatment obesity in these school-age children. For one, the period of evaluation of 4 weeks would have been an inexcusably short time-frame for the art to adequately regard a drug's efficacy and safety in treatment of obesity, and its application to "adults" would have been limited in view that the ADHD data was in children aged 6-12. All rather simple and ordinary teachings of the art to a POSA "as of September 13, 2007." Indeed, a POSA at the time of the invention would have seen hardly

anything in common between LDX-dimesylate and d-fenfluramine/sibutramine except, perhaps, that their generic names shared some similar letters.

In this context, a POSA might have wondered if anyone might be so disregarding of the art to consider references to "weight loss/weight reduction" in LDX-dimesylate's package insert as a basis for reasoning to LDX-dimesylate as an "anti-obesity agent" and then "therapeutically applying" such teachings to the treatment of BED. After all, there are references in the package insert to "weight loss/weight reduction." Of course, anyone reasoning along these lines would not be reasoning with any skill in the art because that is not what the art would have transparently disclosed in its most essential teachings on the treatment of BED with "anti-obesity agents" in particular, as repeatedly and consistently characterized in the same way over the prior decade. But moving along, a POSA, who *"would be a medical doctor (M.D.) specializing in psychiatry" (p. 9),* would have recognized that such references to "weight loss/weight reduction" are standard in the art of "stimulant treatment for ADHD." Stimulants, generally, can cause weight loss, and as with any stimulant FDA-approved for the treatment of ADHD, the LDX-dimesylate package insert features a section entitled ***"Long term growth suppression"*** (Exhibit 1002, p. 762). This particular section presents data from the stimulant methylphenidate in children 7-13 years age which suggests consistently medicated children have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development (Exhibit 1002, p. 762). This particular ***"Long term growth suppression"*** section can also be found in the Petitioner's Exhibits for the stimulant drugs Ritalin SR (Exhibit 1002, p. 925), Adderall XR (Exhibit 1002. P. 1060), and Ritalin LA (Exhibit 1002. P. 885), each reference of which was submitted as prior art in '813's patent prosecution. Additionally, a POSA would have identified in the LDX-dimesylate package insert other characterizations of "weight loss" and "weight reduction" in view of their studied clinical context for the use of LDX-dimesylate, which was a 4 week trial of LDX-dimesylate in children aged 6-12 years of age for the treatment of ADHD. Certainly, a POSA would have understood the importance of making inferences and drawing conclusions by first appreciating the clinical context of the featured data, itself important for practicing the art skillfully, competently and safely. After all, a POSA, by virtue of their ordinary skill, reasons rationally and in line with the basic distinctions in the art. This is what allows them to practice the art with ordinary skill.

Continuing with the 2007 LDX-dimesylate package insert, a POSA would have recognized that the package insert reports that among the 6-12 year old patients taking LDX-dimesylate, *"higher doses were associated with greater weight loss within the initial 4 weeks of treatment. In a controlled trial of lisdexamfetamine dimesylate in children ages 6-12 years, mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5, respectively, for patients receiving 30 mg, 50 mg, and 70 mg lisdexamfetamine, compared to 1 lb of weight gain for patients receiving placebo."* A POSA would have also recognized that among these 6-12 year old patients enrolled in the 4 week clinical trial, *"weight decreased" (Exhibit 1002, p. 762)* as a reported

adverse event in 9% of the patients. Clearly, after diligently reviewing LDX-dimesylate's February 2007 package insert, a POSA would have concluded the very same thing that they had concluded after reading Mickle, namely, that LDX-dimesylate could not reasonably regarded as an "anti-obesity agent" from its own "state of the art" characterization in its drug label. Thus, a POSA at the time of the invention would also have concluded that anyone claiming LDX-dimesylate "as an anti-obesity agent" in the way Appolinario had used the term in his 2004 pharmacotherapy review of BED would simply not be practicing the art like a POSA. Rather, they would be practicing the art like a person without skill. And, moreover, anyone applying LDX-dimesylate "as an anti-obesity agent" to Appolinario's teaching on the use of anti-obesity agents in BED ***as a basis for administering such treatment*** would be practicing the art ***very dangerously.***

At this point, a POSA "as of September 13, 2007" would have ended his/her consideration of LDX-dimesylate as an "anti-obesity agent," determining that there was simply no basis to logically conclude that LDX-dimesylate could even reasonably be identified as an "anti-obesity agent" in the first place, much less be combined with Appolinario's teachings to yield a reasonable expectation of success for "813's independent claims. And, to this effect, a POSA at the time of the invention would have read the Petitioner's and its hypothetical POSA's conclusion of (p. 17),

> *"As a result of the teachings and directives of Appolinario, in view of the disclosures in Mickle, a POSA would have used LDX dimesylate to treat BED with a reasonable expectation of success, making such a treatment obvious and unpatentable…,"*

to conclude that the only thing that was clear is how the Petitioner and its POSA reached their conclusion. And that would have been by making a highly inaccurate and even dangerous assumption that a Person with Ordinary Skill in the Art would simply never have made because, if they had, they would not have been practicing the art with ordinary skill.

But there is another thing that would have been most striking to a POSA at the time of the invention, ***as would be defined by Declarant himself at the time of the invention*** on the basis of his plainly stated and transparently disclosed research grants, publications both in peer and non-peer journals, and invitational talks ***according to his CV***. And it is this. Why would such a person, on the basis of their "composite POSA profile," have identified Mickle's "LDX-dimesylate" as an ***"anti-obesity agent"*** when the plainly stated and transparently disclosed standard of the art would have regarded it otherwise, ***particularly in view of:***

> a. *Invited Speaker, "**New Strategies** in the **Management of Obesity**," Laurens County Medical Society, Laurens, SC, August 28, **1996.** (Exhibit 1034, p. 31).*
> b. *Invited Speaker, "**New Approaches** in the **Diagnosis** and **Treatment of***

Obesity," *Psychiatry-Primary Care Grand Rounds, Veterans Administration Medical Center, Charleston, SC, February 28,* ***1997.*** *(Exhibit 1034, p. 31).*

c. *Invited Speaker, "****Psychopharmacology Update****: Eating Disorders and* ***Obesity****, Third Annual Baylor College of Medicine Psychopharmacology Update , Houston, TX, November 1-2,* ***1997.*** *(Exhibit 1034, p. 32).*

d. *Invited Speaker, "The* ***Four-Pronged Approach to Obesity Management****," MUSC CME presentation, Embassy Suites Hotel, Columbia, SC, April 3,* ***1997.*** *(Exhibit 1034, p. 31).*

e. *Invited Speaker, "****New Approaches*** *in the* ***Diagnosis*** *and* ***Treatment of Obesity****," Annual Meeting of the South Carolina Pharmacy Association, Hilton Head, SC, June 29,* ***1997.*** *(Exhibit 1034, p. 31).*

f. *BREWERTON TD:* ***Psychiatric Aspects of Obesity and Binge Eating Disorder****. Annual Postgraduate Course of the American Academy of Clinical Psychiatrists, Syllabus and Proceedings of the 49th Institute on Psychiatry Services. Washington, DC. October 24-25,* ***1997*** *(oral presentation),* ***page 3****. (Exhibit 1034, p. 21)*

Argument 2 (of 2) for Ground 1's Obviousness Position: The "State of the Art" Neurotransmitter ("NT") teachings of Serotonin (5-HT), Norepinephrine (NE) and Dopamine (DA) for BED Contradict Petitioner's/Declarant's own Line of Reasoning.

Summary. The Petitioner not only misleadingly misrepresents LDX dimesylate as an "anti-obesity agent" but also conflates the drug's neurotransmitter "NT" specific actions to suggest its centrally-acting mechanism of action is similar to Appolinario's sibutramine and d-fenfluramine, both of which were shown to have efficacy in treating BED. But this is not the case at all. The Petitioner/Declarant conflate their own "NT-based distinctions," the ones summarized in the "State of the Art" (Petition, p. 5-8), to illogically reason to a conclusion that LDX-dimesylate is pharmacologically ***essentially the same*** *in its NT-based mechanism of action to the drugs Appolinario teaches as having a "reasonable expectation of success" in treating BED when, to the contrary, a POSA "as of September 13, 2007" would have unambiguously reasoned to just the opposite conclusion based on Appolinario's teachings, namely, that LDX dimesylate is pharmacologically* ***essentially different*** *than these "successful BED drugs." In this respect, Appolinario – in view of a number of the Petition's/Declarant's disclosures and prior art submissions -- actually teaches that the NT-specific mechanism of action of drugs which have been proven effective for treating BED are* ***pharmacologically essentially different*** *than LDX-dimesylate. Completely setting aside the "anti-obesity agent argument" already presented, the* ***essentially dissimilar*** *NT-based mechanism of action of LDX-dimesylate as compared to sibutramine and d-fenfluramine,* ***as well as to the other drugs, and classes of drugs, Appolinario features*** *as having* ***efficacy in the treatment of BED****, only show that the "state of art" was suggesting/teaching away from drugs having an NT-based mechanism of action like LDX-dimesylate. Therefore, a POSA would not have been motivated to use LDX-dimesylate to treat BED, at least insofar as he/she was seeking a "reasonable expectation of success" for its use.*

"As of September 13, 2007," a POSA would have appreciated Appolinario's 2004 "Pharmacological Approaches in the Treatment of Binge Eating Disorder" as a "state of the art reference" in the "drug management of BED." In this respect, a POSA would have particularly appreciated that ***all 367 patients*** *(183 of whom received the "experimental drug" and the rest "placebo")* who participated in the seven randomized controlled trials between 1996-2003 upon which Appolinario drew his conclusions on "successful drug therapies for BED" were all diagnosed with the ***same disorder***, with the ***same exact diagnostic criteria*** – Binge Eating Disorder "as defined in the DSM-IV/IV-TR." This is because A POSA "as of September 13, 2007" would have recognized the DSM-IV and DSM-IV-TR diagnostic criteria to be ***perfectly identical*** down to the very word (and comma), as previously described, and simply understood that when Appolinario "differentiated" between "DSM-IV" and "DSM-IV-TR" in the "Diagnosis" column of his Table 1 "Randomized Controlled Trials with Pharmacological Agents for the Treatment of Binge Eating Disorder," his "differentiation" (i.e., 6/7 trials using DSM-IV criteria and 1/7 trials using DSM-IV-TR criteria) was simply a function of accurately reporting on the methodology of the trial according to its published art. (Exhibit 1020, p. 5, Table 1, see "Diagnosis"

column). And, thus, ***all 367 patients collectively*** *(183 of whom received the "experimental drug" and the rest "placebo" according to each trial's protocol)* were ***diagnosed*** with the ***same essential disorder*** by virtue of identical DSM-based criteria even as they were treated, across the seven clinical trials, with ***different specific drugs*** *which came from three* ***essentially different classes of drugs*** *(i.e., antidepressants, anti-obesity agents, and anticonvulsants),* something a POSA who,

a) *"at the time of the invention….would have regarded the* ***DSM-IV-TR*** *as the gold standard for* ***diagnosing*** *mental disorders, including* ***eating disorders****….." (Petition, p. 27),*
and
b) *"would have routinely relied on the* ***DSM-IV-TR****, the charter document of guidelines on mental disorders, for* ***diagnosing*** *a patient with* ***BED****" (Petition, p. 40),*
and
c) *"would have clinical experience in the* ***diagnosis*** *and* ***psychopharmacology*** *of eating disorders,* ***specifically BED"*** *(Petition, p. 9),*

would have particularly appreciated for its basic teachings. After all, at the time of Appolinario's 2004 pharmacotherapy review, the art of diagnosing and treating eating disorders, ***specifically BED***, had matured considerably over the prior decade since its debut DSM-IV diagnosis (and diagnostic criteria thereof) was accepted in the art (in 1994) as a basis for practicing and advancing the art. (Exhibit 1026, p. 11). Thus, Appolinario's art looks back, with hindsight, on hundreds of patients who participated in randomized controlled clinical trials to determine the successfulness of BED drug therapies on the basis of their shared DSM-IV/IV-TR diagnosis of BED. And such drug therapies, as Appolinario teaches, were tested in controlled clinical trials for BED which could then be considered, as Appolinario does, in view of ***differences <u>between</u> each respective "class"*** *(i.e., "anti-depressants" vs. "anti-obesity agents" vs. "anticonvulsants")* as well as in view ***differences <u>within</u> each respective class*** *(i.e., "anti-obesity agents" – d-fenfluramine vs. sibutramine).* As '813's three independent claims are directed to a specific drug therapy, LDX-dimesylate, for a specific eating disorder, BED as defined in the DSM-IV-TR (and thus, the DSM-IV), it is important to understand how a POSA at the time of the invention would have understood the art in view of important ***essential differences*** recognized in the art for their therapeutic applications to BED.

Appolinario's presentation of data regarding the pharmacotherapies proven successful in the treatment of BED is based on randomized placebo-controlled trials and is presented in view of both ***"class of drugs"*** (i.e., "antidepressants," "anti-obesity agents," and "anticonvulsants"; Exhibit 1020, pp. 2-4) as well as in view of ***"specific drugs"*** (Exhibit 1020, p. 5, Table 1). In this respect, Appolinario reasons like a POSA seeking to provide a meaningful framework for communicating his findings, particularly in view of his cautionary guidance that *"it is important to point out that the mechanism of action of pharmacological agents on BED is unknown." (Exhibit 1020, p. 5, Col. 1).* Thus, a POSA would have appreciated Appolinario's

approach to be founded on first determining which drugs have been empirically validated through randomized controlled trials for the treatment of "BED as defined in the DSM-IV/IV-TR" and, in view of those findings, then speaking the language of the art to communicate his observations about "successful drug therapies," which he self-evidently does by virtue of their respective "class of therapeutic efficacy" as well as by specific details of each particular drug's efficacy.

Appolinario's "therapeutic targets" for drugs proven successful in the treatment of BED are straightforward as a POSA would have appreciated at the time of the invention. They are ***depression, obesity, and seizures***. POSA's reason this way, namely, based on how the art has already been organized in its key distinctions. In particular, a POSA at the time of the invention who *"would be a medical doctor (M.D.) specializing in psychiatry" (Petition, p. 9)* would have had many ways to "classify" drugs, with quite a number of "therapeutic drug classes" beyond those featured in Appolinario (i.e., "anti-psychotics," "anxiolytics," "stimulants," "hypnotics," "mood stabilizers," among others), which themselves would have had their own differences within each specific class. The most straightforward example of these differences of classification, as it would have applied to Appolinario's teachings, would have been with respect to the ***"class of antidepressants"*** for BED. A POSA at the time of the invention would have known that the "class of antidepressants" featured its own essentially different ***"antidepressant classes of drugs,"*** such as the "SSRIs," "SNRIs," "TCAs," "MAOIs," and "DNRIs," for instance. But Appolinario, in his BED pharmacotherapy review, is clearly and plainly focused on the ***"antidepressant class of drugs"*** known as the ***"SSRIs"*** and, specifically, the SSRIs drugs of fluoxetine, citalopram, fluvoxamine, and sertraline, for their treatment success in BED. (Exhibit 1020, p. 2, Cols. 1-2)

But as the Petitioner and Declarant have highlighted in their statements, the state art of eating disorders had advanced remarkably in a rather short time. From an era when BED had yet to be recognized as its own "diagnostic entity" by the art's DSM-based criteria (i.e., pre-1994), Appolinario shows that by 2004 the art had already entered into a time of having validated, and continuing to validate, drug therapies based on their ***efficacy in randomized controlled trials for BED***, with observations being made ***between classes of drugs*** and ***within classes of drugs***. In particular, as the Petitioner and Declarant discuss regarding the "state of the art" of eating disorders, the art's attention was increasingly focused on centrally acting ***neurotransmitter "NT" targets*** in the brain. Nowhere is this basic concept better emphasized than in the Petition's characterization of the "State of the Art" wherein it writes that *"dysfunction of the **serotonin (5-HT)**, **dopamine (DA)**, and **norepinephrine (NE)** neurotransmitter systems in the brain have been implicated in the underlying cause of eating disorders." (Petition, p. 6).* To be sure, a POSA at the time of the invention would have been motivated to follow the direction of the art's advances regarding NTs in the treatment of BED, something that is featured in Declarant's Declaration wherein he even titles Section V.F of his characterization of the "State of the Art" "*"Neurochemical Bases for the Successful Treatment of Binge Eating with **Agents** that **Influence Neurotransmitters**" (Exhibit 1009, p. 23).*

Therein, Declarant echoes the Petition's characterization of the "state of the art," itself based on his own Declaration, writing, *"Eating disorders have been linked to the dysfunction of **three primary neurotransmitter (NT) systems** found in the brain, namely, serotonin (5-HT), dopamine (DA), and norepinephrine (NE). (Ex. 1011, Ioannides-Demos, p. 5). It is postulated that a major cause of binge eating is a decrease in NT levels in the synaptic cleft between neurons. (Ex. 1012, Jimerson, p. 5)." (Exhibit 1009, p. 23)*

Naturally, then, a POSA "as of September 13, 2007" would have been particularly motivated to understand what Appolinario taught on the successful treatment of BED in view of the Petition's, and Declarant's, "NT-specific" characterization of the "state of the art." After all, the Petition and Declarant regard a POSA as one who *"would have clinical experience in the **diagnosis** and **psychopharmacology** of eating disorders, **specifically BED"** (p. 9) -- **specifically** "BED as defined in the DSM-IV/IV-TR."* And with over a decade-long period of advances in the art of psychopharmacology for BED, a POSA at the time of the invention would have been particularly motivated to understand what Appolinario taught about the successful pharmacotherapy of BED in relation to each "successful drug's," and each "successful class of drug's," ***targeted action*** on the ***NTs*** of ***norepinephrine (NE)***, ***dopamine (DA),*** and ***serotonin (5-HT) –*** even beyond that already plainly and transparently disclosed in the teachings of the art regarding anti-obesity agents (as already discussed). After all, this was the "state of the art as of September 13, 2007" and certainly well before it. Nowhere is this better evidenced than when Declarant, in his 1999 "Binge Eating Disorder: Diagnosis and Treatment Options" (Exhibit 1037), characterizes the NT-specific mechanisms of action of drugs such as,

> ***d-fenfluramine*** [i.e. *"pre-synaptic agonist of serotonin and mild re-uptake inhibitor" (p. 8, Col. 1)*],
>
> ***fluoxetine*** [i.e., "*Selective Serotonin Reuptake Inhibitor," "SSRIs" (p. 6. Col. 2)],* and
>
> ***sibutramine*** [i.e., *"serotonin and noradrenaline (norepinephrine) reuptake inhibitor" (p. 8, Col. 2)*],

in view of their,

> ***prior*** [i.e., d-fenfluramine, *"no longer an option"* (p. 8. Col. 1)],
>
> ***present*** [i.e., "*it is generally advised that the initial psychopharmacological treatment strategy involves an SSRI"* (p. 7, col. 1-2) or
>
> ***future*** [i.e., *"holds promise on theoretical grounds" (*p. 2, Col.)]

application to the treatment of BED, among other drugs and classes of drugs.

At the time of the invention, a POSA would have reasoned along these lines, considering which NT-specific targets could prove valuable in predicting a "reasonable expectation of success" for, ***specifically***, BED as defined in the DSM-IV/IV-TR. As the art itself discloses, not only would the question have been *"which NT -- serotonin, dopamine and/or norepinephrine?"* but also *"by what mechanism of action?"* Self-evidently, the art did not want a repeat of d-fenfluramine's potent "serotonin ***release***" believed to be associated with cardiac valve problems and pulmonary hypertension. And, as Appolinario's 2004 pharmacotherapy review plainly and transparently highlighted, the art was clear on its guidance to its community of POSAs, namely, first diagnose the specific eating disorder recognized in the art as BED as defined in the DSM-IV/IV-TR and then consider targeted therapies for its treatment by "class of drugs" (i.e., anti-depressant, anti-obesity agent, and/or anticonvulsant). And, as already discussed, the unmistakably clear guidance was to be mindful of the comorbidity of obesity in the treatment of BED and to consider pharmacotherapy in view of the art's teachings therein. All of this would have been in plain and transparent view to a POSA at the time of the invention, though only reinforced by the 2006 American Psychiatric Association's Practice Guidelines for the treatment of BED (as defined in the DSM-IV/IV-TR), disclosed as prior art by the Petitioner/Declarant and further characterized below for its teachings (Exhibit 1031, p. 86-87, Section on "Medications" for the "Treatment of Binge Eating Disorder").

POSAs practice the art by making distinctions. And by this way, they also advance the art. This is their ordinary skill in the art and it is what makes them different than those without skill who might otherwise conflate distinctions and simply stop at the point of, in the instance of eating disorder pharmacotherapy, "it potentiates serotonin." By stopping at "it potentiates serotonin," for instance, the art and the POSAs who practice it would never have been able to understand the essential difference between SSRIs and d-fenfluramine, as both "potentiate serotonin." But, as the art disclosed, their mechanisms of action for "potentiating serotonin" are essentially different. And by the time of the '813's invention, the art of diagnosis and psychopharmacology of eating disorders, specifically BED, had indeed advanced considerably based on the kinds of critical distinctions Declarant taught in his 1999 review on BED and which are, not surprisingly, featured consistently and repeatedly throughout the Petitioner's many Exhibits, as will be further characterized below regarding their relevance to the Petitioner's/Declarant's Ground 1 argument. That Declarant was able to actually publish a paper on "Binge Eating Disorder: Diagnosis and Treatment Options," considering it in view of its "DSM-IV diagnostic criteria" and its "treatment options," itself is a testament to how the art had -- by that time in 1999 -- already differentiated it diagnostically from other disorders which might feature binge eating behavior, like Anorexia Nervosa and Bulimia Nervosa. (Exhibit 1037, p. 1, Col. 1). As Declarant teaches in his Declaration, there was a time when BED was yet undifferentiated from other eating disorders –yet to even be known or regarded in the art's teachings for its differential diagnosis in view of Anorexia Nervosa and Bulimia Nervosa, much less for its specific pharmacotherapy. (Exhibit

1009, p. 15-16). But the work of Declarant, among many others in the art, helped to clarify the art of diagnosing and treating BED. Which is why just five years after Declarant's 1999 BED review (when only two controlled clinical trials would have been published), there were by the time of Appolinario's 2004 pharmacotherapy review seven controlled clinical trials regarding effective drug therapies for BED, across ***seven different drugs*** (i.e., d-fenfluramine, fluvoxamine, sertraline, fluoxetine, citalopram, topiramate, and sibutramine), ***three different classes of drugs*** (i.e., antidepressants, anti-obesity agents, and anticonvulsants), and ***two different classes of anti-obesity agents*** (i.e., sibutramine – "SNRI", d-fenfluramine – "serotonin releaser."). (Exhibit 1020, p. 5, Table 1, Stunkard in 1996, Hudson in 1999; other trials 2000-2003).

Indeed, the art was teaching basic lessons to its community of POSAs who treat BED. One of these, among the most important, was that there could be two different drugs (i.e., fluoxetine – "Prozac"; d-fenfluramine – "Redux"), each of which could have ***essentially the same efficacy*** for the ***treatment of BED*** (i.e. statistically significant vs. placebo) but each of which could have ***essentially different safety profiles*** from each other. And also, that these two different drugs could each ***essentially potentiate the same NT of serotonin*** but do so through ***essentially different mechanisms of actions*** (i.e., fluoxetine – "selective serotonin reuptake inhibition" and d-fenfluramine – "serotonin release"). It was these distinctions (among others), plainly and transparently disclosed in the art itself, and their rational application to the successful pharmacotherapy of BED, that a POSA would have had in view at the time of the invention or, for that matter, a POSA would have had in view at any time since Declarant's 1999 BED review and "September 13, 2007" as the controlled clinical trials of d-fenlfuramine and the SSRI fluvoxamine would have been published and d-fenfluramine would have been withdrawn from the market. (Exhibit 1020, p. 5., Table 1). It is also with these ***essential NT-based differences*** in mind that a POSA, at the time of the invention, would have appreciated Appolinario for his pharmacotherapy teachings on the treatment of BED as defined in the DSM-IV/IV-TR.

So how would a POSA "as of September 13, 2007" have understood Appolinario's 2004 teaching on pharmacotherapy in view of the art as characterized in the Petitioner's/Declarant's NT-specific characterization of the state of the art – and, also, as plainly and transparently disclosed in the teachings themselves of the Petitioner's/Declarant's prior art submissions relating to, ***specifically, the pharmacotherapy of BED?*** And how would a POSA "as of September 13, 2007," practicing the art with ordinary skill, have understood Mickle's LDX-dimesylate in view of such NT-specific teachings? These are the kinds of questions, simple as they may have been, that would have been foremost in the mind of a POSA at the time of the invention. This is because these are the kinds of distinctions that the art had regarded as relevant to its understanding and practice of the psychopharmacology of eating disorders.

A POSA "as of September 13, 2007" who,

> *"would have clinical experience in the **diagnosis** and **psychopharmacology** of eating disorders, **specifically BED"** (Petition, p. 9)* and
>
> *"would have routinely relied on the **DSM-IV-TR**, the charter document of guidelines on mental disorders, for **diagnosing** a patient with **BED**" (Petition, p. 40),*

would have unmistakably regarded Appolinario's 2004 pharmacotherapy review as teaching the following about the ***"successful pharmacotherapy of BED,"*** simply because the teachings are all plainly stated and transparently disclosed in the Petitioner's/Declarant's prior art exhibits (as specified below):

NT-specific** [i.e., **serotonin (5-HT), norepinephrine (NE), and/or dopamine (DA)]** mechanisms of action in the **treatment of BED:

***1. Serotonin (5-HT) potentiation**. The NT-specific mechanism of action through which serotonin (5-HT) is potentiated is differentiated as follows:*

a. Mainly serotonin "release" with partial serotonin re-uptake inhibition. Specifically cited in Appolinario for its efficacy in BED as defined in the DSM-IV/IV-TR is the anti-obesity agent ***d-fenfluramine*** (p. 3, Col. 1; p. 5, Table 1). D-fenfluramine's NT-specific mechanism of action, as a POSA would have appreciated at the time of the invention, is featured in Declarant's 1999 "Binge Eating Disorder" review and characterized as a *"pre-synaptic agonist of serotonin and mild re-uptake inhibitor" (Exhibit 1037, p. 8, Col. 1).* In particular, Declarant's Declaration (Exhibit 1009, p. 27) highlights d-fenfluramine's robust serotonin potentiation in relation to its relevance to the successful treatment of BED, writing, *"As a **5-HT agonist** and a mild **5-HT reuptake inhibitor**, the likely mechanism of the anorectic action is to **increase the availability of 5-HT** at central synapses and indirectly stimulate postsynaptic receptors. (Ex. 1014, Samanin, p. 2). **These mechanisms** likely explain d-fenfluramine's **therapeutic efficacy** in the **treatment of BED**."*

Notably, Declarant writes in his 1999 reference that while d-fenfluramine is no longer available for use in patients at the time of his publication, *"its **efficacy** indicates a **specific mechanism of action** that is likely to be considered in the process of **future drug development**" [for BED]." (Exhibit 1037, p. 8. Col. 1).* Here, Declarant reasons like a POSA, mindful that *"in clinical practice, it is generally advised that the initial psychopharmacological treatment strategy involves an SSRI" (p. 7. Cols. 1-2)* because of their safety, but one need not forsake the teachings of Stunkard's study that had demonstrated d-fenfluramine's robust efficacy and its essentially different mechanism of action by which it potentiated serotonin (5-HT) as compared to other serotonergic drugs. As would be expected of a POSA, Declarant is seeking to differentiate his observations, the objective of which is to achieve a better expectation of success in treatments and also *"to*

*be considered in the process of future drug development." (*Exhibit 1037, p. 7, Cols. 1-2).

The NT-specific mechanism of action of d-fenfluramine in relation to its therapeutic role for the ***specific treatment*** *of* ***BED*** *is also transparently and plainly disclosed in the teachings of the Petitioner's/Declarant's cited prior art of*:

a) Stunkard's 1996 "d-Fenfluramine Treatment of Binge Eating Disorder," *"it [d-fenfluramine] acts primarily by* ***inhibiting the reuptake of serotonin*** *into presynaptic neurons, while its metabolite, d-norfenfluramine, acts by* ***increasing release of serotonin*** *into brain synapses and by direct action on post-synaptic neurons" (Exhibit 1044, p. 3, Col. 1),*

b) Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge Eating Disorder," writing to teach on the essentially different serotonin (5-HT)-potentiating mechanisms of action in view of sibutramine, *"unlike fenfluramine and d-fenfluramine, it [sibutramine] does not* ***induce serotonin release****…." (Exhibit 1046, p. 3, Col. 1).* A POSA between Brewerton's 1999 BED review and "September 13, 2007" would have understood Appolinario's comment the same way as both Declarant and Appolinario communicated it in plain language, namely, that "reuptake inhibition" is essentially different than "release" in a drug's the NT-specific mechanism of action, even as "serotonin potentiation" is essentially the same end-result.

b. ***Selective Serotonin "Reuptake Inhibition."*** Specifically cited in Appolinario for its therapeutic efficacy in BED as defined in the DSM-IV/IV-TR are the "class" of "antidepressants" known in the art as ***"SSRIs"*** (i.e., "Selective Serotonin Reuptake Inhibitors"). Particularly, he writes in his "Final Comments" *"at present, antidepressants are the best studied class of agents in* ***BED****, and* ***SSRIs*** *represent the* ***best studied class*** *of* ***antidepressants*** *in this condition." (Exhibit 1020, p. 6, Col. 1).* Here, as previously characterized, Appolinario is speaking to one of the most basic distinctions in the art, namely, that among essentially different classes of antidepressants (i.e., "SSRIs," SNRIs," "DNRIs," "TCAs," MAOIs") well-recognized in the art and commercially available for practice, the "class" of "antidepressant" that is favored for its use in the treatment of BED is the class having essentially the same NT-specific target, that of *"****serotonin (5-HT),"*** as well as essentially the same "mechanism of action" of ***"reuptake inhibition."*** Specifically cited in Appolinario for their efficacy in treatment of BED are the specific SSRI drugs of ***fluvoxamine***, ***sertraline***, ***fluoxetine***, and ***citalopram*** (Exhibit 1020, p. 2; and p. 5, Table 1).

As a POSA "of September 13, 2007" would have unmistakably appreciated and understood, the NT-specific mechanism of action of ***"selective serotonin (5-HT) reuptake inhibition"*** for the ***specific treatment*** *of* ***BED*** *is also transparently and plainly disclosed for its basic teachings in the Petitioner's prior art submissions of*:

a) Brewerton's 1999 "Binge Eating Disorder: Diagnosis and Treatment Options" (Exhibit 1037, p. 6, Col. 2; p. 7, Col. 2; p. 8, Col. 1; p. 9, Col. 2),

b) Malhorta's 2002 "Venlafaxine Treatment of Binge Eating Disorder Associated with Obesity: A Series of 35 Patients" (Exhibit 1049, p. 2. Col. 2; p. 3, Col. 1),

c) Arnold's 2002 "A Placebo-Controlled, Randomized Trial of Fluoxetine in the Treatment of Binge Eating Disorder" (Exhibit 1030, p. 2, Col. 2; p. 6, Col. 2),

d) Appolinario's 2002 "An Open-Label Trial of Sibutramine in Obese Patients with Binge Eating Disorder" (Exhibit 1021, p. 2. Col. 1),

e) Carter's 2003 "Pharmacological Treatment of Binge Eating Disorder" (Exhibit 1054, p. 3, 4, 5, 7, 9, 13),

f) Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge Eating Disorder" (Exhibit 1046, p. 2, Col. 2),

g) Milano's 2005 "Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment of Binge Eating Disorder: A Placebo-Controlled Study (Exhibit 1022, p. 3).

h) the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031, p. 86, Section on "Medications" for the "Treatment of Binge Eating Disorder"),

2. Serotonin (5-HT) norepinephrine (NE) potentiation. *The NT-specific mechanism of action through which serotonin and norepinephrine are potentiated is by* ***"reuptake inhibition"*** *(i.e., Serotonin and Norepinephrine Reuptake Inhibition, "SNRIs").*

Specifically cited in Appolinario for its efficacy in the treatment of BED as defined in the DSM-IV/IV-TR is the anti-obesity agent ***sibutramine***, as well as its NT-specific mechanism of action, *"Sibutramine is* ***a serotonin*** *and* ***noradrenaline reuptake inhibitor****" (Exhibit 1020, p. 3, col. 1; Table 1 on p. 5).* A POSA would have readily appreciated "noradrenaline" and "norepinephrine" are interchangeable, which Declarant's Declaration also affirms, *"Sibutramine is a mixed* ***5-HT*** *and* ***NE*** *reuptake inhibitor approved for the treatment of obesity,"* as does his 1999 review on "Binge Eating Disorder: Diagnosis and Treatment Options" wherein he writes that sibutramine is *"a* ***serotonin*** *and* ***noradrenaline (norepinephrine) reuptake inhibitor."*** *(Exhibit 1009, p. 27; Exhibit 1037, p. 8, Col. 2).* Thus, A POSA "as of September 13, 2007" would have readily identified sibutramine as potentiating the specific NTs of serotonin and norepinephrine through "reuptake inhibition." The NT-specific mechanism of action of sibutramine in relation to its therapeutic role for the ***specific treatment*** *of* ***BED*** *is also transparently and plainly disclosed for its teachings in the Petitioner's prior art submissions of*:

a) Appolinario's 2002 "An Open-Label Trial of Sibutramine in Obese Patients with Binge Eating Disorder," as already characterized (Exhibit 1021, "p. 2. Col. 1),

b) Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge Eating Disorder," as already characterized (Exhibit 1046, p. 2, Col. 2),

c) Milano's "Use of **Sibutramine**, an **Inhibitor of the Reuptake of Serotonin and Noradrenaline**, in the Treatment of Binge Eating Disorder: A Placebo-Controlled Study" (Exhibit 1022, p. 27).

Notably, Milano's art, published in 2005 (the year after Appolinario's 2004 review), features sibutramine's NT-specific mechanism of action in relation to successful treatment of ***Binge Eating Disorder*** in the title of the article itself. As a POSA at the time of the invention would have appreciated, this only highlights the weight given sibutramine's NT-specific mechanism of action in the art, as seen through the lens characterized by the Petitioner's and Declarant's respective "State of the Art" sections regarding specific-NT treatment targets in eating disorders, including ***BED*** *(as defined in the DSM-IV/IV-TR)*. (Petition, pp. 5-8; Exhibit 1009, pp. 15-28). Milano's study, a randomized, double-blind, placebo- controlled study in patients diagnosed with BED according to DSM-IV/IV-TR criteria found that the *inhibitor of the reuptake of serotonin and noradrenaline (as taken from the title) "sibutramine was **efficacious** and well tolerated in controlling both **binge-eating disorder** and obesity" (Exhibit 1022, p. 1, p. 3, p. 6).*

In this regard, a POSA "as of September 13, 2007" would have particularly appreciated how the art had evolved from 1999 when Declarant wrote, in his "Binge Eating Disorder: Diagnosis and Treatment Options," that sibutramine's *"usefulness in the treatment of BED per se has not yet been reported, even in open studies, but it nevertheless holds promise on theoretical grounds." (Exhibit 1037, p. 8, Col. 2)* A POSA at the time of the invention would have appreciated how Declarant reasoned to sibutramine's *"promise on theoretical grounds"* in view of Stunkard's 1996 trial (which came a few years before his 1999 BED paper) using the anti-obesity drug d-fenfluramine in BED in ***severely obese*** women had already been published – and its results were remarkably good for BED. Which would makes sense in view of the two sentences that precede Declarant's reasoning, which a POSA would have likened to Appolinario's, *"Finally, **sibutramine**, a serotonin and noradrenaline (norepinephrine) reuptake inhibitor without antidepressant properties, has just been released in the US for the adjunctive **treatment of obesity** (along with behavior therapy). Results from a number of double-blind, placebo-controlled studies have demonstrated that this new agent is **effective** in the **treatment of obesity."** (Exhibit 1037, p. 8, Col. 2).*

Non—NT-specific *mechanisms of action (i.e., drugs whose primary mechanism of action is **not** characterized in the art by their NT-specific actions on dopamine, norepinephrine and/or serotonin) for the treatment of BED.*

1. Anticonvulsants of Topiramate and Zonisamide. Appolinario identifies the anticonvulsant Topiramate as having therapeutic efficacy in the treatment of BED and characterizes its mechanism of action as *"known to enhance [gamma]-amino*

butyric acid [GABA] activity, block voltage-dependent Na channels, antagonize kainite/AMPA glutamate receptors, and to inhibit carbonic anhydrase." (Exhibit 1020, p. 4. Col. 1). While Appolinario also identifies the anticonvulsant Zonisamide as having been studied in BED, he does not identify its success in randomized controlled trials, nor does he highlight its therapeutic efficacy but rather speaks to its safety and tolerability generally. (Exhibit 1020, p. 4, Col. 1)

Topiramate. Topiramate as an effective drug therapy ***specifically*** *for the treatment of* ***BED*** *is also transparently and plainly disclosed for its teachings in Petitioner's prior art submissions of*:

a) Carter's 2003 "Pharmacological Treatment of Binge Eating Disorder" wherein its therapeutic action is regarded in view of its "anticonvulsant" properties and its specific mechanism of action is not identified, (Exhibit 1054, p. 4, 6, 8, 9, 11),

b) Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge Eating Disorder" wherein its efficacy is characterized in two clinical trials (i.e., one "open" and one "controlled") and it is identified as an "anticonvulsant" but its specific mechanism is not identified, (Exhibit 1046, p. 2, Col. 1),

c) the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders wherein its efficacy is characterized in three clinical trials (i.e., two "open" and one "controlled") and it is identified as an "anticonvulsant" but its specific mechanism is not identified, (Exhibit 1031, p. 86, Section on "Medications" for the "Treatment of Binge Eating Disorder").

Zonisamide. Appolinario's 2004 pharmacotherapy review also *"suggested the effectiveness of this agent [zonisamide] in BED,"* which is an "anticonvulsant," but he adds its data comes from an "open-label" (and not randomized, controlled) clinical trial. (Exhibit 1020, p. 3, Col. 1), Zonisamde's characterization as an "anticonvulsant" with *potential therapeutic application for BED is also transparently and plainly cited in the disclosures of the Petitioner's submitted prior art of*:

a) Carter's 2003 "Pharmacological Treatment of Binge Eating Disorder" (Exhibit 1054, p. 11), and

b) the American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031, p. 87).

2. "Opioid antagonists." Appolinario identifies "opioid antagonists" as a "class" of drugs that have been studied in the treatment of BED to a *"lesser extent"* than the classes of drugs he identifies as *"antidepressants, anti-obesity agents, and "anticonvulsants."* (Exhibit 1020, p. 2, Col. 1) Opioid antagonists, drugs of which a POSA at the time of the invention would have readily recognized in the art as naltrexone and naloxone, for the *specific treatment of* ***BED*** *are also transparently and plainly disclosed for their teachings in the Petition's cited prior art of:*

a) Brewerton's 1999 "Binge Eating Disorder: Diagnosis and Treatment Options" wherein he writes, notably, *"the* ***opioid receptor antagonists,***

*naltrexone and naloxone, have been reported to exhibit therapeutic effects in patients with **BED**…", (Exhibit 1037, p. 8, Col. 1),*

b) the 2006 "American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders" references *"naltrexone"* by name but adds, "*caution is required in evaluating the claims of effective treatments"* in relation to limitations in naltrexone's data (Exhibit 1031, p. 86, Section on "Medications" for the "Treatment of Binge Eating Disorder"), and

c) Marrazi's 1995 "Binge Eating Disorder: Response to Naltrexone" which (Exhibit 1024, p. 1, Col. 1).

Therefore, a POSA "as of September 13, 2007" in view of Appolinario and the ***NT-specific state of the art*** (i.e., putting aside consideration of non-NT-based drugs), reasoning according to the art's most basic psychopharmacology teachings as repeatedly and consistently characterized in the plainly stated and transparently disclosed art itself for over a decade prior to the invention, would have come to one unmistakable conclusion, namely, that the art was:

suggesting/teaching toward *the use of NT-based drugs that* ***specifically potentiate "serotonin (5-HT)."***

This is because ***every single NT-based drug, and class of drug,*** Appolinario identifies for its "success" in the treatment of "BED as defined in the DSM-IV/IV-TR" features ***serotonin (5-HT)*** as an NT-specific target in its mechanism of action. And there are two essentially different mechanisms of action for its potentiation that are identified, one of them ***"release"*** and the other ***"reuptake inhibition."*** The observation, "as of September 13, 2007," could not have been more evident to one practicing the art with ordinary skill. This same conclusion, curiously, is nearly identical to the kind of conclusion a POSA "as of 1999" would have also come to, as disclosed in Declarant's 1999 "Binge Eating Disorder: Diagnosis and Treatment Options" (Exhibit 1037). Therein, Declarant identifies ***"serotonin (5-hydroxytryptamine)"*** as an important NT-specific target for the treatment BED, further adds that *"it is generally advised that initial* ***psychopharmacological treatment strategy*** *involves an* ***SSRI,"*** and also provides guidance that *"more controlled studies in patients with BED using new generation antidepressants are definitely required, but* ***agents*** *which* ***inhibit serotonin reuptake*** *show some promise." (Exhibit 1037, p. 6, Col. 2; p. 7, col. 2; p. 7, Col. 1).* In addition, a POSA at the time of the invention would have appreciated that Declarant also identified in that publication the potential therapeutic application of the serotonin-potentiating drug nefazodone in the treatment of BED, particularly in relation to its NT-specific mechanism of action as a *"serotonin-antagonist/reuptake inhibitor." (Exhibit 1037; p. 8. Col. 1)* Herein, the art can be seen across time, from 1999 with Declarant highlighting ***essentially the same specific NT-target of serotonin*** along with different drugs/classes of drugs having ***essentially different mechanisms of action*** to potentiate it, to a point in the future wherein NT-specific drug targets have actually been more demonstrably ***identified*** in the art for their success in the

treatment of BED along with their essentially different mechanisms of action which increase the levels of the specific NTs.

Yet a POSA "as of September 13, 2007" would have appreciated that while ***every*** NT-specific "drug," and ***every*** NT-specific "class of drug," featured in Appolinario's 2004 pharmacotherapy review which was "successful" for BED ***necessarily potentiated serotonin***, there was a specific drug that could be considered in its ***essential "NT" difference*** from the four SSRIs of fluoxetine, sertraline, citalopram, and fluvoxamine. And that drug was ***sibutramine***, an ***"SNRI,"*** as it also potentiated norepinephrine. Thus, a POSA "as of September 13, 2007," in view of Appolinario and the specifically cited disclosers as referenced above, would have also appreciated that the art was,

> ***suggesting/teaching toward*** the use of NT-based drugs that ***specifically potentiated*** the NTs of ***serotonin (5-HT) and norepinephrine (NE) in combination.***

In this light, a POSA would have particularly appreciated that the 35 patients in Malhorta's 2002 open-label series of obese BED (as defined by the DSM-IV) patients were treated with the anti-depressant ***venlafaxine***, also an ***"SNRI,"*** and that the study concluded a therapeutic role for venlafaxine in the treatment of BED, its teachings plainly stated and transparently disclosed in the Petitioner's prior art submission having the title of "Venlafaxine Treatment of Binge Eating Disorder Associated with Obesity: A Series of 35 Patients" (Exhibit 1049, p. 2, Cols. 1 and 2). This is how a POSA reasons, based on distinctions taught in the art of psychopharmacology of eating disorders, specifically for BED.

Certainly, a POSA "as of September 13, 2007" would have not only understood but also would have applied the self-evident NT-specific teachings of the art for the treatment of BED (as defined in the DSM-IV/IV-TR), namely, by favoring drugs that ***specifically potentiated "serotonin (5-HT)"*** and/or ***"serotonin (5-HT) + norepinephrine (NE)."*** This is how the art is practiced by those of ordinary skill. The POSA is motivated to understand what the art teaches and then to apply its teaching to the treatment of patients with eating disorders, among them BED, with, hopefully, a reasonable expectation of success to help patients. In this respect, a POSA at the time of the invention would have been motivated to use drugs/classes of drugs that would ***essentially potentiate "5-HT" and/or "5-HT + NE,"*** at least insofar as a "reasonable expectation of success" was considered important or relevant. Or they might have been motivated to go outside of the NT-based art. But as Appolinario's review of controlled clinical trials for BED makes clear, NT-based drugs were, indeed, "state of the art." Thus, a POSA who *"would be a medical doctor (M.D.) specializing in psychiatry" (Petition, p. 9)* would been motivated to use the kinds of drugs, and/or classes of drugs, that are disclosed in '813 below (with respect to their NT-specific targets and their respective mechanisms of action to potentiate them):

a) ***selective serotonin reuptake inhibitors***, with exemplary drugs including citalopram, escitalopram, femoxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, and zimeldine, (Exhibit 1001; p. 9, Col. 2, line 13; p. 10, Col. 1, lines 5-8; p. 10, Col. 2, lines 27-28, lines 39-40),
b) ***serotonin partial agonists***, with exemplary drugs pindolol, gepirone, and flesinoxan, (p. 9, Col. 2, lines 13-14; p. 10, Col. 1, lines 8-9), also classified with respect to 5-HT1a and 5-HT1b partial agonist NT-specific targets (Exhibit 10001, p. 9, Col. 2, lines16-17),
c) ***serotonin norepinephrine reuptake inhibitors***, with exemplary drugs duloxetine, venlafaxine, desvenlafaxine, milnacipran, and clovoxamine (Exhibit 1001; p. 9, Col. 2, lines 10-12; p. 10, Col. 2, lines 19-20, lines 39-40),
d) ***serotonin-2 antagonist reuptake inhibitors***, with exemplary drug trazodone (Exhibit 1001; p. 9, Col. 2, line 18; p. 10, Col. 1, lines 15-16),
e) ***serotonin norepinephrine dopamine reuptake inhibitor*** (p. 9, Col. 2, lines 15-16),

A POSA "as of September 13, 2007" would have come to one other unmistakable conclusion in view of Appolinario and the art's plainly stated and transparently disclosed NT-specific teachings on "successful drug therapies for BED." That conclusion, of course, is that there was ***not one single drug*** that ***specifically potentiated*** the NT of ***dopamine (DA),*** including even among those drugs, and classes of drugs, featured in Appolinario with respect to their "ongoing limitations" (i.e., "opioid antagonists" and "zonisamide"). To this effect, a POSA would have understood Appolinario's teaching, in view of the NT-specific state of the art as well as in view of the many commercially available NT-based drugs for clinical use, as ***suggesting/teaching away*** from the use of NT-based drugs that ***specifically potentiated*** the NT of ***"dopamine (DA)"*** **--** or, as a POSA would put it because POSAs practice with ordinary skill and reason logically from one point to another,

> ***suggesting/teaching away*** from the use of NT-based drugs that ***specifically potentiated "dopamine (DA) in the absence of serotonin potentiation (5-HT)."***

Of course, this conclusion would have been obvious to a POSA at the time of the invention because it would have been plainly, repeatedly, consistently, unambiguously and transparently disclosed in the teachings of the Petitioner's prior art submissions of Appolinario (Exhibits 1020, 1021, 1046), Arnold (Exhibit 1030), the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031), Brewerton (Exhibit 1037), Stunkard (Exhibit 1044), Malhorta (Exhibit 1049), and Carter (Exhibit 1054).

Contrary to the Petitioner's Ground 1 argument, a POSA at the time of the invention -- who would have been logically reasoning in view of the art's most rudimentary distinctions -- would have only concluded that LDX-dimesylate simply did not have a "reasonable expectation of success" in the treatment of Binge Eating Disorder "as

defined in the DSM-IV/IV-TR". This is because its NT-specific mechanism of action would have been clearly understood by a POSA to ***specifically potentiate dopamine (DA) and norepinephrine (NE)*** *without any appreciable serotonergic (5-HT) potentiation*. Thus, there was no precedent whatsoever for its success in all the BED treatment art.

As the Petitioner accurately writes (p. 29) regarding Mickle's art, *"The preferred amphetamine prodrug disclosed is LDX dimesylate (see id; [0098]), which following oral administration releases d-amphetmaine (see id. [0085], [0358]). Like methylamphetamine,* ***d-amphetamine*** *is a known central nervous system stimulant (see id [0003], [0096]), and both methylamphetamine and d-amphetamine share similar neurobiological mechanisms of action and also affect the same neurotransmitters,* ***in particular dopamine****."* The Petition (p. 16) again emphasizes this basic NT-specific teaching, which would have been well-known in the art at the time of the invention, *"a POSA would have known that d-amphetamine* ***increases NE*** *and* ***DA*** *levels in the brain…." (Petition, p. 16).* And Declarant, in his Declaration, also writes, *"Because* ***amphetamine*** *has been researched and even studied clinically for decades, much is known about its biochemical* ***mechanism of action****, as well as the* ***mechanism of action*** *of various structurally related analogs.* ***Amphetamine*** *and* ***amphetamine-like analogs increase NE levels*** *in the* ***synapytic cleft****, resulting in the stimulation of post-synaptic receptors and the inhibition of feeding. (Ex. 1011, Ioannides-Demos, p. 6). Also, amphetamine* ***blocks DA reuptake*** *on post-synaptic receptors, which increases the levels of DA in the synaptic cleft and reinforces the suppression of hunger. (Ex. 1011, Ioannides-Demos, p. 6)."*

A POSA "as of September 13, 2007" would have seen d-amphetamine's NT-specific mechanism of action just the same. Thus, a POSA as of "September 13, 2007," who would have reasoned as one with ordinary skill to apply Appolinario's 2004 teachings to the successful pharmacotherapy of BED in view of the art's very basic NT-specific pharmacotherapy teachings as evidenced in Petitioner's/Declarant's prior art submissions of,

1. Appolinario (Exhibits 1021, 1046),
2. Arnold (Exhibit 1030),
3. the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031),
4. Milano (Exhibit 1022)
5. Brewerton (Exhibit 1037),
6. Stunkard (Exhibit 1044),
7. Malhorta (Exhibit 1049), and
8. Carter (Exhibit 1054),

would have concluded that LDX-dimesylate simply had no reasonable expectation of success in the treatment of BED. But if there would be any doubt about this new class of "ADHD stimulant d-amphetamine prodrug," a POSA would have found the February 2007 "package insert" for LDX-dimesylate ("Vyvanse") helpful for

clarifying the drug's NT-specific mechanism of action, as characterized in the *"Clinical Psychopharmacology: Mechanism of Action and Pharmacology."* Therein, the drug label identifies LDX dimesylate's NT-specific mechanism of action on the basis of its "amphetamine" active moiety, *"amphetamines are thought to **block the reuptake** of **norepinephrine** and **dopamine** into the presynaptic neuron and **increase the release** of these **monoamines** into the extraneuronal space." (Exhibit 1002, p. 756-57).*

In this respect, a POSA at the time of the invention would have also concluded that Mickle's "LDX-dymeslate" could not be any more ***essentially "NT" different*** than the NT-specific drugs cited in Appolinario for their successful treatment for "BED as defined in the DSM-IV/IV-TR." But a POSA at the time of the invention would have reasoned to another conclusion, in view of Appolinario and Mickle. And that conclusion would have been that "LDX-dimesylate" and "BED as defined in the DSM-IV-/IV-TR" could not be any more ***essentially the same*** for their teachings in view of '813's independent claims 1, 8 and 13. Yet a POSA at the time of the invention would have also made even another observation, which is that at least with respect to the successful NT-specific pharmacotherapies of BED, in view of Appolinario and the art of,

1. Appolinario (Exhibits 1021, 1046),
2. Milano (Exhibit 1022),
3. Arnold (Exhibit 1030),
4. the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031),
5. Brewerton (Exhibit 1037),
6. Stunkard (Exhibit 1044),
7. Malhorta (Exhibit 1049), and
8. Carter (Exhibit 1054),

the "NT-basis for success" could not be any more ***essentially the same*** than when Declarant published his singly-authored "Toward a Unified Theory of **Serotonin Dysregulation** in Eating and Related Disorders" in 1995. Therein, Declarant broadly investigates the pathophysiology of various eating disorders and concludes, *"As our knowledge about the **5-HT system** and its **receptor types** and **subtypes** in humans is increased, our understanding of the **role of 5-HT** in these disorders will be enhanced and further clarified, but **unique serotonergic mechanisms of action** are **likely to be responsible** for specific phenomenology across diagnoses."* Any POSA between "as of 1995" and "as of September 13, 2007" would have considered it similarly, at least with regard to BED. It is striking, therefore, that Declarant writes in his 1999 "Binge Eating Disorder: Diagnosis and Treatment Options," *"In my opinion, the **diagnostic recognition of BED** will allow this group of patients to be further studied from a clinical perspective, and it will allow them to get more accessible and **appropriate treatment**,"* since the entire line of reasoning of the Petitioner's/Declarant's Ground 1 argument is to do just the opposite. (Exhibit 1037, p. 2, Col. 2).

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Brewereton's "Toward a Unified Theory of Serotonin Dysregulation in Eating and Related Disorders"

But there is something else. What would have been most striking to a POSA at the time of the invention, ***as would be defined by the "composite POSA behavioral profile" of Declarant himself at the time of the invention*** on the basis of his plainly stated and transparently disclosed research grants, publications both in peer and non-peer journals, and invitational talks ***according to his CV***, is why:

1) Such a person would ***not*** have recognized ***at the time of the invention the most obvious thing of all*** about Appolinario's ***"successful NT-specific drugs for BED"*** (i.e., fluoxetine, citalopram, fluvoxamine, sertraline, d-fenfluramine, and sibutramine), namely, that they ***all potentiated serotonin (5-HT)*** -- especially in view that such a person's CV explicitly identifies ***"serotonin"*** or ***"5-HT"*** a total of ***73 times*** across titles of publications, titles of abstracts, titles of grants, titles of talks, etc… (per Word search in the CV for the two terms of "serotonin" and "5-HT")?

2) Such a person would ***not*** have submitted as prior art their own (and colleagues' art), as disclosed below, to highlight the art's ***NT-specific understanding of BED*** as well as its teachings on the ***successful pharmacotherapy*** of the ***specific DSM-IV-TR eating disorder of "Binge Eating Disorder"?***

    a. *BREWERTON TD:* ***Drug Therapy*** *for Patients with* ***Eating Disorders (Section on "Binge Eating Disorder****"). Psychiatric Times XXI (5): 59-68,* ***2004.*** *(Exhibit 1034, p. 46)*

    b. *BREWERTON TD, Steiger H:* ***Neurotransmitter Dysregulation*** *In Anorexia Nervosa, Bulimia Nervosa and* ***Binge Eating Disorder****. In BREWERTON TD (Ed.),* ***Clinical Handbook of Eating Disorders: An Integrated Approach.*** *New York: Marcel Dekker, Inc.,* ***2004****, pp. 257-281. (Exhibit 1034, p. 49)*

3) Such a person would ***not*** have recognized the ***"NT-specific serotonin-potentiation"*** pattern in Appolinario's "successful BED drugs" (i.e., d-***fenfluramine***, ***fluoxetine***, ***sertraline, citalopram, fluvoxamine, sibutramine***) in view of their ***pharmacotherapy drug trial research*** and pharmacotherapy publications on eating and/or other psychiatric disorders for the following ***specific serotonergic (5-HT)-potentiating drugs*** *(i.e., fenfluramine, fluoxetine, fluvoxamine, sertraline), as explicitly identified in their CV?*

    a. *MUSC IRB-Approved Research Protocols (PI or Co-PI)****: A*** ***double-blind controlled trial*** *of* ***fenfluramine*** *in* ***bulimia*** *(1989-1994). (Exhibit 1034, p. 7)*

    b. *Co-I: "****Fluoxetine*** *versus Placebo in* ***Posttraumatic Stress Disorder."***

Eli Lilly and Company ($117,804). (Exhibit 1034, p. 8)

c. *MUSC IRB-Approved Research Protocols (PI or Co-PI)**: Long-term effects of fluoxetine** in the **treatment of eating disorder patients** (1991-1995). (Exhibit 1034, p. 7)*

d. *Co-I: "**An International Multi-Center Trial** of Two Dose Ranges of **Nefazodone** and Placebo in the Treatment of Outpatients with **Posttraumatic Stress Disorder**." Bristol-Myers Squibb Pharmaceuticals, Inc. ($104,570). (Exhibit 1034, p. 8).*

e. *BREWERTON TD: **Fluoxetine**-induced Suicidality, Serotonin, and Seasonality. Biological Psychiatry 30:190-196, 1991. (Exhibit 1034, p. 42).*

f. *Markowitz JS, Gill HS, LaVia M, BREWERTON TD, DeVane CL: **Fluvoxamine**-Clozapine Dose Dependent Interaction. Canadian Journal of Psychiatry 41:670-671, 1996. (Exhibit 1034, p. 45).*

g. *BREWERTON TD, Markowitz JS, Keller SG, Cochrane CE: Stuttering and **sertraline**. Journal of Clinical Psychiatry 57:90, 1996. (Exhibit 1034, p. 44).*

h. *BREWERTON TD: Does **Fluoxetine** Induce Suicidality? Journal of Clinical Psychiatry 52:479, 1991. (Exhibit 1034, p. 42).*

i. *Deas-Nesmith D, BREWERTON TD: A Case of **Fluoxetine**-Responsive Psychogenic Polydipsia: A Variant of Obsessive Compulsive Disorder? Journal of Nervous and Mental Disease 180:338- 339, 1992. (Exhibit 1034, p. 43).*

j. *BREWERTON TD, Murphy DL, Mueller EA, and Jimerson DC: The Induction of Migraine-like Headaches by the **Serotonin Agonist m-Chlorophenylpiperazine**. Clinical Pharmacology and Therapeutics 43:605-609, 1988. (Exhibit 1034, p. 42).*

k. *Head LA, BREWERTON TD, Cochrane CE, Anton R: **Fluoxetine and Norfluoxetine** Levels in Eating Disorders. Abstracts of the Fifth International Conference on Eating Disorders. New York, NY. April 24-26, 1992 (oral presentation), Abstract #198. (Exhibit 1034, p. 16).*

l. *BREWERTON TD, Mueller EA, George DT, Brandt HA, Lesem MD, Narang PK, Jimerson DC, Murphy DL: Blunted Prolactin Response to the **Serotonin Agonist m-Chlorophenylpiperazine (m- CPP)** in Bulimia. Book of Abstracts and Poster Presentation Sessions. 15th Collegium Internationale Neuro- Psychomarmacologium Congress. San Juan,*

Puerto Rico, December 14-17, 1986 (poster presentation), Abstract #P-186, page 186. (Exhibit 1034, p. 11).

Further, the ***"composite POSA behavioral profile"*** of such a person would have testified to two (of five) ***"primary areas of interest"*** that relate to the ***specific "NT" neurotransmitter*** of ***"serotonin" (5-HT)***, thus emphasizing its importance in eating disorders. These two areas of "primary interest" are:

> *"**Serotonin:** its role in affective, anxiety, and eating disorders, migraine, **psychotropic drug action**, and **modulation** of neuroendocrine and other **neurochemical systems**.*
>
> *Chronobiology: **seasonal variations of psychiatric disorders** and related biochemical parameters, **particularly measures of serotonin function**." Exhibit 1034, p. 10)*

Therefore, such a person -- at the time of the invention – would surely have recognized that:

a) ***every drug NT-specific drug*** (i.e., d-fenfluramine, fluoxetine, fluvoxamine, citalopram, sertraline, sibutramine), and every single ***NT-specific "drug class"*** (i.e., "serotonin releasing," "SSRI," and "SNRI"), represented in Appolinario for the ***"successful" treatment of BED*** did, in fact, ***specifically "potentiate serotonin (5-HT)."***

b) there was ***not one single NT-specific drug*** *(*or ***NT-specific drug class****)* that ***specifically "potentiated dopaminergic" or dopaminergic/norepinephrine."***

c) ***LDX dimesylate*** is an amphetamine-based stimulant that ***specifically "potentiates dopamine/norepinephrine"*** and ***does not target serotonin in any appreciable way***,

Especially in view of their prior of:

PGY-2 Lecture Series on Psychopharmacology (Exhibit 1034, p. 9)

Invited Workshop Presenter, "***The Role of Psychopharmacology in the Treatment of Eating Disorders***," Eating Disorders Program, Menninger Foundation, Houston, TX, September 26, ***2005***. (Exhibit 1034, p. 33)

BREWERTON TD, Steiger H: ***Neurotransmitter Dysregulation*** In Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder. In BREWERTON TD (Ed.), Clinical Handbook of Eating Disorders: An Integrated Approach. New York: Marcel Dekker, Inc., 2004, pp. 257-281. (Exhibit 1034, p. 49)

1999: FDA Psychopharmacology Advisory Panel, Guest Expert: PTSD Indication for Sertraline (Zoloft) (Exhibit 1034, p. 8)

Invited Speaker, "***The Psychopharmacology of Eating Disorders and Obesity***," South Carolina Society of Health-System Pharmacists Psychopharmacy Seminar, Columbia, SC, September 13, ***1996***. (Exhibit 1034, p. 31)

BREWERTON TD: The ***Psychopharmacology of Eating Disorders***. Proceedings of the Sixth Annual International Eating Disorders Symposium. Long Beach, CA. August 14-18, ***1992*** (invited oral presentation). (Exhibit 1034, p. 17)

Jimerson DC, Lesem MD, BREWERTON TD, Hegg AP, Brandt HA: ***Neurotransmitter Function*** in Major Depression and Eating Disorders. Program and Abstracts: World Federation of Societies of Biological Psychiatry (WFSBP) Biological Aspects of Non-Psychotic Disorders Regional Congress. Jerusalem, Israel. April 2-7, ***1989*** (oral presentation), page 257. (Exhibit 1034, p. 27)

Jimerson DC, Lesem MD, Kaye WH, BREWERTON TD: Symptom Severity and ***Neurotransmitter Studies*** in Bulimia. XVIth Collegium Internationale Neuro-Psychopharmacologicum. Munich, Germany, August 15-19, ***1988*** (oral presentation). (Exhibit 1034, p. 12)

Ground 4 and 7 counter-argument: There would have been no reasonable expectation of success of '813 in View of the Ground 1 arguments already presented but also in view of further clarification of the basic teachings of the Petitioner's/Declarant's prior art disclosures, as featured below.

In view that the only reasonable conclusion a POSA "as of September 13, 2007" would have made, based on the plainly stated and transparently disclosed teachings of the art as characterized above, was that LDX-dimesylate had no reasonable expectation of success in the treatment of BED, the Petitioner's Ground 4/7 arguments are reasoned in error. In view of Appolinario and others featured in the Petitioner's disclosures (Exhibits 1021, 1030, 1031, 1037, 1044, 1046, 1049, 1054), the art actually would have suggested/taught against the use of LDX-dimesylate for the successful treatment of BED and dissuaded a POSA to even use it at all, insofar as a reasonable expectation of success was desired and the POSA was practicing the art in a way that would have been expected of one. With respect to Petitioner's/Declarant's Ground 4/7 arguments, ***all eight*** of Ong's bulimia nervosa patients (Ground 4) were administered a one time dose of methylamphetamine as the basis of their method of treatment and ***all six*** of Dukarm's bulimia nervosa patients were administered dextroamphetamine ("d-amphetamine") as the basis of their method of treatment (Ong, Exhibit 1017, p. 3, Col. 1; Exhibit 1019, p. 3, Col. 2; p. 3, Cols 1 and 2; p. 5, Col. 1). A POSA (as that characterized by Petitioner/Declarant) would simply not dismiss salient pharmacotherapy teachings ***for the specific treatment of BED*** in favor of drawing from the decades-long art of treating a different eating disorder like BN without first addressing any number of clinical distinctions (both in terms of diagnosis and treatment), though that is how Petitioner's/Declarant's Ground 4/7 arguments are reasoned. These distinctions are further clarified in what follows.

But if there would have been any doubt as to the art's plainly-stated and transparently-disclosed teachings on how it regarded the successful pharmacological treatment of, ***specifically, BED*** among the community of POSAs by its most basic standard for administering treatment (i.e., first diagnosing BED as defined by its DSM-IV/IV-TR criteria and then administering a therapeutically effective amount of drug for its treatment), as featured in the Petitioner's/Declarant's prior art disclosures below (from the years 1995-2005) of,

a) Marrazi's 1995 "**Binge Eating Disorder**: Response to Naltrexone" (Exhibit 1024),
b) Stunkard's 1996 "d-Fenfluramine **Treatment of Binge Eating Disorder**" (Exhibit 1044, p. 3, Col. 1),
c) Brewerton's 1999 "**Binge Eating Disorder**: Diagnosis and **Treatment Options**" (Exhibit 1037),
d) Arnold's 2002 "A Placebo-Controlled, Randomized Trial of Fluoxetine in the **Treatment of Binge Eating Disorder**" (Exhibit 1030),
e) Appolinario's 2002 "An Open-Label Trial of Sibutramine in Obese Patients with **Binge Eating Disorder**" (Exhibit 1021),

f) Malhorta's 2002 "Venlafaxine **Treatment of Binge Eating Disorder** Associated with Obesity: A Series of 35 Patients" (Exhibit 1049,
g) Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the **Treatment of Binge Eating Disorder"** (Exhibit 1046),
h) Carter's 2003 "Pharmacological **Treatment of Binge Eating Disorder**" (Exhibit 1054),
i) Milano's 2005 "Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the **Treatment of Binge Eating Disorder**: A Placebo-Controlled Study (Exhibit 1022), and
j) the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031, Section on "**Treatment of Binge Eating Disorder**," pp. 86-87),

then a POSA at the time of the invention might have considered re-reviewing the pharmacotherapy teachings outside their "NT-specific context" to see what had been taught for "successful pharmacotherapy in BED." After all, a POSA is someone who, "*would have clinical experience in the **diagnosis** and **psychopharmacology** of eating disorders, **specifically BED"** (Petition, p. 9)* and would have been motivated to practice the art as it had been taught, namely, by respecting basic distinctions and essential teachings in the art with an eye toward a "reasonable expectation of success." While Appolinario's 2004 pharmacotherapy review featured his own designation of identifying drugs by class, namely, *"anti-depressants, anti-obesity agents, and anticonvulsants,"* a POSA at the time of the invention would have considered other ways to apply the kinds of distinctions taught in the art. This is how a POSA reasons. They differentiate and build on the basis of the distinctions the art has already established for skillful practice – between and within disorders, between and within drugs classes, between and within NT-specific targets, among many other such examples.

So, regarding the ***specific treatment of BED,*** as it would be limited in '813's independent claims to the entity known as "BED as defined in the DSM-IV-TR" (and thus DSM-IV too), represented below is what the Petitioner's/Declarant's prior art submissions (as referenced therein) would have plainly stated and transparently disclosed to a POSA at the time of the invention regarding different kinds of ways to classify "drugs" and "classes of drugs" in view of their potential therapeutic application for ***specifically BED:***

"Antidepressants" -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Milano, Exhibit 1022, p. 27; Brewerton, Exhibit 1037, p. 7, Co. 1; Carter, Exhibit 1054, p. 3, 5.

1. **SSRIs** -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Milano, Exhibit 1022, p. 27; Malhorta, Exhibit 1049, p. 2; Appolinario "2002," Exhibit 2021, p. 2, Col. 2; Appolinario "2003", Exhibit 1046, p. 2, Col. 1; Brewerton, Exhibit 1037, p. 6, Col. 2 and p. 7, Cols. 1-2 and p. 9, Col 2; Carter, Exhibit 1054, p. 3.

a. **"Citalopram" --** APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Brewerton, Exhibit 1037, p. 8, Col.1 and p. 8, Table 3 "Recommended daily initiation doses and maintenance dosages of psychopharmacological agents for the treatment of binge eating disorder"; Carter, Exhibit 1054, p. 3.
b. **"Fluoxetine" --** APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Arnold, Exhibit 1030, p. 1, Col. 2; Brewerton, Exhibit 1037, p. 8, Col. 1 and p. 9. Col. 2, and p. 8, Table 3 "Recommended daily initiation doses and maintenance dosages of psychopharmacological agents for the treatment of binge eating disorder"; Carter, Exhibit 1054, p. 4.
c. **"Fluvoxamine" --** APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Arnold, Exhibit 1030, p. 3, Col. 3; Malhorta, Exhibit 1049, p. 2, Col. 2; Appolinario "2003", Exhibit 1046, p. 7. Col 1; Brewerton, Exhibit 1037, p. 8, Col. 1 and p. 9, Col. 2 and p. 8, Table 3 "Recommended daily initiation doses and maintenance dosages of psychopharmacological agents for the treatment of binge eating disorder"; Carter, Exhibit 1054, p. 4.
d. **"Sertraline" --** APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Arnold, Exhibit 1030, p. 3, Col. 2; Malhorta, Exhibit 1049, p. 2, Col. 1; Appolinario "2003", Exhibit 1046, p. 7, Col. 1; Brewerton, Exhibit 1037, p. 8, Col 1and p. 8, Table 3 "Recommended daily initiation doses and maintenance dosages of psychopharmacological agents for the treatment of binge eating disorder"; Carter, Exhibit 1054, p. 4.
e. **Paroxetine --** Brewerton, Exhibit 1037, p. 8, Col. 1 and p. 8, Table 3 "Recommended daily initiation doses and maintenance dosages of psychopharmacological agents for the treatment of binge eating disorder"

2. **"TCA's"** (or older generation antidepressants as a POSA would have appreciated to characterize their "classification" in the art) -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Milano, Exhibit 1022, p. 27; Malhorta, Exhibit 1049, p. 2; Appolinario "2002," Exhibit 2021, p. 2; Brewerton, Exhibit 1037, p. 8, Cols 1 and 2; Carter, Exhibit 1054, p. 5.
   a. **"Desipramine"** -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Milano, Exhibit 1022, p. 27; Malhorta, Exhibit 1049, p. 2, Col. 2; Appolinario "2003", Exhibit 1046, p. 7, Col. 1; Brewerton, Exhibit 1037, p. 7, Col. 1 and p. 8, Col. 1 and p. 9, Col. 2 and p. 8, Table 3 "Recommended daily initiation doses and maintenance dosages of psychopharmacological agents for the treatment of binge eating disorder"; Carter, Exhibit 1054, p. 3.
   b. **"Imipramine"** -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Malhorta, Exhibit 1049, p. 2; Brewerton, Exhibit 1037, p. 8, Table 3 "Recommended daily initiation doses and maintenance dosages of psychopharmacological agents for the treatment of binge eating disorder."
   c. **"Clomipramine"** -- Brewerton, Exhibit 1037, p. 8.

3. **"SNRIs" (Serotonin Norepinephrine Reuptake Inhibitors) --** APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Carter, Exhibit 1054, p. 19.
    a. **Venlafaxine** -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Malhorta, Exhibit 1049, p. 3, Col. 1.

4. **"Serotonin antagonist/reuptake inhibitor"** -- Brewerton, Exhibit 1037, p. 8, Col. 1.
        i. **Nefazodone** -- Brewerton, Exhibit 1037, p. 8, Table 3 "Recommended daily initiation doses and maintenance dosages of psychopharmacological agents for the treatment of binge eating disorder."

"Anti-obesity agent" (or "treatment of obesity") -- Milano, Exhibit 1022, p. 27; Appolinario "2002," Exhibit 2021, p. 2; Appolinario "2003", Exhibit 1046, p. 1, Col. 1; Brewerton, Exhibit 1037, p. 8, Col. 2.

1. **"Sibutramine"** -- Milano, Exhibit 1022, p. 27; Appolinario "2002," Exhibit 2021, p. 2; Appolinario "2003", Exhibit 1046, p. 2, Col. 1; Brewerton, Exhibit 1037, p. 8, Co. 2.
2. **"D-fenfluramine" -** Appolinario "2002," Exhibit 2021, p. 2. Appolinario "2003", Exhibit 1046, p. 2, Col. 1; Brewerton, Exhibit 1037, p. 8, Col. .

"Appetite-Suppressants" -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Stunkard, Exhibit 1021, p. 3, Col. 1; Carter, Exhibit 1054, p. 4.

1. **"Sibutramine"** -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Milano, Exhibit 1022, p. 27; Carter, Exhibit 1054, p. 4, 10.
2. **"D-fenfluramine/fenfluramine"** -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Stunkard, Exhibit 1021, p. 3. Col. 1; Carter, Exhibit 1054, p. 4, 10.

"Anticonvulsants" -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Carter, Exhibit 1054, p. 4, 10; Appolinario "2003", Exhibit 1046, p. 2, Col. 1.

1. **"Topiramate" --** APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Carter, Exhibit 1054, p. 4; Appolinario "2003", Exhibit 1046, p. 2, Col. 1.
2. **"Zonisamide" --** APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Carter, Exhibit 1054, p. 11.

"Opioid Antagonists" -- Brewerton, Exhibit 1037, p. 8. Col. 2, Col. 2; Marrazzi, Exhibit 1024, p. 1, summary.

1. **"Naltrexone"** -- APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Brewerton, Exhibit 1037, p. 8, Col. 2; Marazzi, Exhibit1024, p. 1, summary.
2. **"Naloxone" --** Brewerton, Exhibit 1037, p. 8, Col. 2.

"SNRI" (i.e., serotonin norepinephrine reuptake inhibition) Mechanism of Action (highlighted, irrespective of its therapeutic classification, i.e., as an "antidepressant" or "anti-obesity agent")

1. **"Sibutramine"** -- Milano, Exhibit 1022, p. 27; APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Appolinario "2002," Exhibit 2021, p. 2; Appolinario "2002," Exhibit 2021, p. 1, Col. 1; Brewerton, Exhibit 1037, p. 8, Col. 1;
2. **"Venlafaxine"** -- Milano, Exhibit 1022, p. 27; APA Guidelines for Eating Disorders, Exhibit 1031, p. 86; Malhorta, Exhibit 1049, p. 3 Col. 1; Carter, Exhibit 1054, p. 10.

"Serotonin-Releasing Agent"/ Presynaptic Agonist of Serotonin – Stunkard, Exhibit 1044, p. 3, Col. 1; Brewerton, Exhibit 1037, p. 8, Col. 1.

1. **"d-fenfluramine"** - Stunkard, Exhibit 1044, p. 3, Col. 1; Brewerton, Exhibit 1037, p. 8, Col. 1.

Thus, a POSA "as of September 13, 2007" who,

a) *"would have clinical experience in the **diagnosis** and **psychopharmacology** of eating disorders, **specifically BED"*** (*Petition, p. 9), and,*

b) *"would have routinely relied on the **DSM-IV-TR**, the charter document of guidelines on mental disorders, for **diagnosing** a patient with **BED"** (Petition, p. 40), and,*

c) *"at the time of the invention, [a POSA] would have regarded **the DSM-IV-TR** as the gold standard for diagnosing mental disorders, including **eating disorders**….." (Petition, p. 27).*

would surely have come to one unmistakably conclusion in view of the Petitioner's/Declarant's prior art submissions regarding the ***specific treatment of "BED as defined in the DSM-IV/IV-TR,"*** which is the key claim limitation of "813's independent claims 1, 8 and 3. That conclusion, of course, is that ***there is not one drug*** among these many teachings of different specific drugs across different specific classes of drugs, which features a "stimulant drug" of the kind that a POSA would have been very familiar with at the time of the invention as "commonly used to treat ADHD." After all, a POSA, who *"would be a medical doctor (M.D.) specializing in psychiatry" (Petition p. 9),* would have recognized that stimulant drugs at the time of the invention were widely used for the treatment of ADHD for decades, in both children and adults, and were also commercially available in many different kinds of preparations tailored to meet patient needs, from short acting stimulants to long acting stimulants to even intermediate acting stimulants. So putting aside even any NT-specific characterization and/or its therapeutic implications, the art of treating ***specifically BED*** was certainly not favoring "stimulant drugs" like those used to treat ADHD, at least not among the community of POSAs who practice the art with

ordinary skill and who respect the art's basic teachings and rudimentary distinctions, beginning first with an accurate diagnosis. And, of course, a POSA "as of September 13, 2007" would also have recognized that ***the most salient feature of Mickle's LDX-dimesylate*** is that it is, indeed, a "stimulant drug" whose active ingredient is "d-amphetamine" -- of the kind that has been used for decades to treat ADHD, in both children and adults, and for which there are many different commercially available forms tailored to meet patient needs, from short acting stimulants to long acting stimulants to even intermediate acting stimulants. At the time of the invention, a POSA would have recognized LDX-dimesylate as a d-amphetamine-based stimulant differentiated by its "prodrug mechanism of action," approved by the FDA for the treatment of ADHD in children 6-12 years of age as its February 2007 package insert plainly states and transparent discloses (Exhibit 1002; p. 759). Thus, a POSA at the time of the invention would have understood LDX-dimesylate to be ***specifically different*** than many of the other stimulants by virtue of its "prodrug mechanism of action" but ***essentially the same*** as many of the other stimulants by virtue of its therapeutic application for the treatment of ADHD and its d-amphetamine active moiety, in particular the class of stimulants known as "long-acting stimulants."

In this light, a POSA would surely not have been motivated to even consider LDX-dimesylate as a treatment of BED, much less consider it to have a reasonable expectation of success for its treatment. But, a POSA at the time of the invention would have been very motivated to understand why a person claiming to be a POSA was not reasoning as one and coming to a very different conclusion. In this respect, the Declarant's Declaration would have been particularly striking to a POSA at the time of the invention. In *"Section 5.G -- The State of the Art as of September 13, 2007: The Biochemical Mechanism of Action of Certain Agents Explains Their Usefulness in the Treatment of BED" (Exhibit 1009, p. 26-28),* the Declarant explains that there are three ***"biochemical mechanism[s] of action of certain agents"*** for their ***"usefulness*** *in the* ***treatment of BED."*** Declarant classifies these ***"biochemical mechanisms of action"*** according to the ***three classes:***

1) ***"Amphetamine and Amphetamine Analogs"*** *(p. 26),*

2) *"Anti-obesity agents," (p. 26-27) and*

3) *"Antidepressants" (p. 28).*

A POSA "as of September 13, 2007" would have wondered how the Declarant had reasoned to this kind of classification. After all, a person practicing the art with ordinary skill at the time of the invention would have seen the art, well, essentially very differently, notably in view that "stimulants as a class of agents" were not recognized in the art for their "usefulness in the treatment of BED."
But there is more. A POSA at the time of the invention would have found it odd that the Declarant treats two essentially different concepts in the art as essentially the same. For instance, *"amphetamine and amphetamine analogs"* represents a "specific

class of stimulants" within a "broader class of stimulants" which all ***essentially share the same general "biochemical mechanism of action"*** – potentiation of the NTs dopamine/norepinephrine. But *"anti-obesity agents"* and *"antidepressants"* represent an ***essentially different class*** altogether as their respective "class" is reasoned on the basis of its having ***essentially the same "therapeutic efficacy" for its respective therapeutic target*** – obesity and depression, respectively (as Appolinario reasoned). The concepts of "biochemical mechanism of action" (i.e., amphetamines and amphetamine analogs) and "therapeutic efficacy" (i.e., anti-obesity agents, antidepressants) are thus conflated.

A POSA in view of the Declarant's reasoning would have wondered, *"what went wrong here?"* How did *'amphetamine and amphetamine analogs'* get juxtaposed next to *'anti-obesity agents'* and *'antidepressants'*? And why would the heading of *"The **Biochemical Mechanism of Action** of Certain Agents Explains Their **Usefulness in the Treatment of BED**'* not feature the NT-specific targets of 5-HT/NE/DA (i.e., "biochemical mechanism of action") of "successful drugs in BED treatment" (i.e., sibutramine, fluoxetine, fluvoxamine, sertraline, citalopram, d-fenflurmaine). A POSA at the time of the invention would have been particularly motivated to understand "the Biochemical Mechanism of Action of Certain Agents Explains Their Usefulness in the Treatment of BED' as a basis for treating BED pharmacologically. A POSA at the time of the invention would have likely answered those questions in view of identifying "the Biochemical Mechanism of Action of Certain Agents Explains Their Usefulness in the Treatment of BED," which would have looked like this:

1) *Serotonin release*

2) *Selective serotonin reuptake inhibition*

3) *Serotonin and norepinephrine reuptake inhibition*

For any POSA over the last couple decades, the Declarant's line of reasoning would have been considered remarkably illogical, representative of someone without any knowledge or understanding whatsoever in the psychopharmacology of eating disorders and, moreover, without any ability to apply basic concepts of drug classification by way of what would be regarded as "therapeutic efficacy," "biochemical mechanism of action," etc…, among other features. But what is even more extraordinary is that the Declarant comes to his three-item conclusion (i.e., *"amphetamines/analogs," "anti-obesity agents,"* and *"antidepressants")* on "The Biochemical Mechanism of Action of Certain Agents Explains Their Usefulness in the Treatment of BED" after a three page NT-specific characterization of the *"Neurochemical Bases for the Successful Treatment of Binge Eating with Agents that Influence Neurotransmitters."* This particular section even begins with, *"Eating disorders have been linked to the dysfunction of the three primary **neurotransmitter (NT) systems** found in the brain, namely **serotonin (5-HT)**, **dopamine (DA),** and **norepinephrine (NE)."** (Exhibit 1009; p. 23-25).* So how, specifically, did the Declarant's line of reasoning get from the ***three specific NTs of 5-HT, DA, and NE***

for "binge eating" to a illogical listing of "classes" that conflate "therapeutic efficacy" and "biochemical mechanism of action"? Or, conversely, how did the Declarant, specifically, arrive at the "classes" of ***"amphetamines/analogs,"*** *"anti-obesity agents,"* and *"antidepressants"* for their ***usefulness in the treatment of BED*** from the three specific NTs of 5-HT, DA, and NE for binge eating in view of Appolinario's ***"anticonvulsants,"*** *"anti-obesity agents" and "antidepressants" for* their ***usefulness in the treatment of BED***? Surely, a POSA practicing the art with skill anytime in the history of anticonvulsants and stimulants couldn't have seen two more essentially different types of drugs in terms of their respective "biochemical mechanisms of action" or their respective "therapeutic efficacy."

Declarant's Declaration makes the answer clear. It is reasoned without skill or knowledge of the art. Declarant's knowledge of the art and his line of reasoning through which it is expressed reveals that he does not understand the art at all, even its most essential diagnostic distinction between "binge eating" and "Binge Eating Disorder," one that has been recognized and practiced in the art since as far back as 1959, but notably since 1994, and upon which his 1999 BED review is based. And also upon which randomized controlled and open label trials have been run, APA treatment guidelines have been issued, and patients have been treated. And the Declarant's failure to recognize this most essential diagnostic distinction between "binge eating" and "Binge Eating Disorder" occurs because he conflates the two terms to mean essentially the same thing. Declarant reasons completely unaware that there is, and has been for some time, an ***important and critical diagnostic teaching*** of the art which has been practiced by the community of POSAs, including by himself when he chose to title his 1999 publication "Binge Eating Disorder: Diagnosis and Treatment Options" and not, instead, "Binge Eating: Treatment Options." Of course, that important diagnostic teaching is that "binge eating" can occur in any of three major eating disorders of 1) Anorexia Nervosa, 2) Bulimia Nervosa, and 3) BED (though necessarily occurs in BED AND BN). And the ***most basic and rudimentary skill*** of a POSA, at any time between 1994 and the time of the invention who *"would have clinical experience in the* ***diagnosis*** *and* ***psychopharmacology*** *of* ***eating disorders, specifically BED"*** (*Petition, p. 9),* would have been to ***clinically differentiate "binge eating in AN"*** from ***"binge eating in BN"*** from ***"binge eating BED"*** as a basis for treatment. That is because the DSM-IV/IV-TR plainly states and transparently discloses that "binge eating" can occur any of these three major eating disorders and, therefore, it is the very skill of the POSA to apply their skill to differentiate these disorders according to the standard of the art for making an accurate diagnosis. As any POSA between 1994 to the time of the invention would have recognized, Anorexia Nervosa (as defined in the DSM-IV/IV-TR criteria) featured a specific type known in the art as "***binge-eating****/purging type."*

A POSA "between 1994-2007" would never have reasoned from the

> *"****Neurochemical Bases*** *for the Successful* ***Treatment of Binge Eating*** *with Agents that Influence Neurotransmitters," (Exhibit 1009, p. 23),*

as it relates to the NTs of dopamine, norepinephrine and serotonin in "binge eating" very generally and non-specifically to,

> "***Biochemical Mechanism*** *of Action of Certain Agents* ***Explains*** *Their Usefulness in the* ***Treatment of BED****" (Exhibit 1009, p. 26-28)*

without first having recognized the distinction between the two terms of "binge eating" and "BED," and then looking to the art's teachings regarding the essential distinction in view of "binge eating in BN," "binge eating in AN," and "binge eating in BED" --- and, of course, "binge eating in obesity." POSAs reason through differences, not on the basis of conflating those differences. Declarant's logic is analogous to a person reasoning to treat a patient's depression without consideration whatsoever to what the art teaches about what differentiates bipolar disorder, which also involves depression and mania, and major depressive disorder, which involves depression but not mania.

The only way that the Declarant can reason from the non-specific NT-based treatments of "binge eating" generally (as a non-specific symptom) to the final destination of "The Biochemical Mechanism of Action of Certain Agents Explains Their **Usefulness in the Treatment of BED**" that features "*amphetamines/analogs*," *"anti-obesity agents,"* and *"antidepressants"* is
to completely ignore, as if it never existed, the most basic and rudimentary teachings of diagnosing eating disorders, specifically BED, over decades of history but also to ignore the same for BN and AN. And then, on that foundation, to completely ignore the art's most basic and rudimentary teachings since 1995 for the treatment of ***specifically BED*** whose pharmacotherapy teachings include, but are not limited to, Declarant's/Petitioner's prior art submissions of,

a) Marrazi's 1995 "**Binge Eating Disorder**: Response to Naltrexone" (Exhibit 1024),
b) Stunkard's 1996 "d-Fenfluramine **Treatment of Binge Eating Disorder**" (Exhibit 1044, p. 3, Col. 1),
c) Brewerton's 1999 "**Binge Eating Disorder**: Diagnosis and **Treatment Options**" (Exhibit 1037),
d) Arnold's 2002 "A Placebo-Controlled, Randomized Trial of Fluoxetine in the **Treatment of Binge Eating Disorder**" (Exhibit 1030),
e) Appolinario's 2002 "An Open-Label Trial of Sibutramine in Obese Patients with **Binge Eating Disorder**" (Exhibit 1021),
f) Malhorta's 2002 "Venlafaxine **Treatment of Binge Eating Disorder** Associated with Obesity: A Series of 35 Patients" (Exhibit 1049,
g) Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the **Treatment of Binge Eating Disorder"** (Exhibit 1046),
h) Carter's 2003 "Pharmacological **Treatment of Binge Eating Disorder**" (Exhibit 1054),

i) Milano's 2005 "Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the **Treatment of Binge Eating Disorder**: A Placebo-Controlled Study (Exhibit 1022), and
j) the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031, Section on "**Treatment of Binge Eating Disorder**," pp. 86-87),

Declarant's line of reasoning in his Declaration is plainly stated and transparently disclosed, as are the teachings references above regarding ***useful agents in the treatment of BED***. And taken collectively, they reveal how Declarant got from the ***"three NTs of 5-HT, DA,*** *and* ***NE*** in ***binge eating"*** to, specifically, the class of stimulants known as ***"amphetamines/amphetamine analogs"*** for their usefulness in ***"BED."*** A POSA at the time of the invention would have recognized how Declarant arrived at "anti-obesity agents" and "anti-depressants" in view of Appolinario's pharmacotherapy teachings. But there is still the mystery of how Declarant specifically reasoned to the ***usefulness of amphetamine/analogs in the treatment of BED*** when the prior art submissions referenced above for the useful treatments in BED do not disclose any such things whatsoever and speak to the contrary.

This is how, as a POSA at the time of the invention would have appreciated. In particular, Declarant's "run-up" to his ***"amphetamine/analogs' usefulness in BED"*** cites the work of Ioannides-Demos and Blundell, both of which are ***exclusively*** related to ***"obesity"*** and its aberrant feeding behaviors, itself reflected in their respective titles, "The ***Pharmacotherapy of Obesity***" and "Serotonin and Appetite Regulation: Implications for the ***Pharmacological Treatment of Obesity***." (Exhibit 1011; 1015). But neither of these teach on the topic of Declarant's 1999 publication called "***Binge Eating Disorder: Diagnosis and Treatment Options,***" or on the claim limitation in '813's independent claims that teaches on ***Binge Eating Disorder,*** or on ***"usefulness in BED"*** as in the heading "The Biochemical Mechanism of Action of Certain Agents Explains Their Usefulness in the Treatment of **BED."** In his "run-up" to ***"amphetamine/analogs' usefulness in BED,"*** Declarant also cites Jimerson, a publication he himself co-authored ***in 1992*** – a time even before BED was "officially recognized" in the art as different than BN (via its 1994 inclusion in the DSM-IV). Jimerson features low "serotonin and ***dopamine*** metabolite concentrations" in the cerebrospinal fluid of patients with ***Bulimia Nervosa***. (Exhibit 1012). Thus far, Declarant's line of reasoning features obesity, eating behavior related to obesity, serotonin, "dopamine and serotonin" in BN-binging patients. Declarant also cites Samanin's ***1993*** "***Neurochemical mechanism of action of anorectic drugs***" from 1994. The title speaks for itself and any POSA between "1994 and September 13, 2007" would have reasonably either assumed, or concluded, that "amphetamines" and/or "amphetamine analogs" were somewhere therein but also, of course, that "BED" was nowhere therein since the reference was published before the DSM-IV. And, not surprisingly, Declarant's line of reasoning continues with a citation of Drimmer, which features three BN patients treated with ***stimulants***. (Exhibit 1016). Yet perhaps most remarkably, Declarant returns to the more recent era drawing on

Epstein's 2002 "Dopamine Transporter Genotype as a Risk Factor for Obesity in African-American Smokers," a study that investigated dopamine receptor variants in smokers to conclude that *"the likelihood of obesity in African Americans (n=90) with the 10/10 SLC6A3 [dopamine transporter] was 5.16 times that of African Americans with 9/9 or 9/10 SLC6A3 genotypes." (Exhibit 1013, p. 1, Col. 1, "Results").*

In this way, the Declarant traverses fifteen years of art, between 1992 and September 13, 2007, in just 2 2/3 pages to provide a declaration on *"The Biochemical Mechanism of Action of Certain Agents Explains Their* ***Usefulness in the Treatment of BED****"* that begins with none other than, *"amphetamine and amphetamine analogs." (Exhibit 1009, p. 31).* In so doing, Declarant renders his own distinguishing work from 1999, "Binge Eating Disorder: Diagnosis and Treatment Options," irrelevant and unnecessary, since the only distinction that is relevant and necessary to this line of reasoning is "binge eating" and anything that can be associated with it by what is known in the art as "free association." In this line of reasoning, it's all "essentially the same," whether binge eating, DA, 5-HT, NE, BN, BED, obesity, AN, stimulants, anti-obesity agents, etc….There are no distinctions. There are no essential differences to speak of, much less specific differences based upon the essential ones -- even the most obvious one of all, the one featured in the title of Declarant's 1999 publication. Not only does Declarant consistently and repeatedly reason on the assumption that there is ***no essential difference between BN and BED***, he also reasons on the assumption that there is no essential difference in "binge eating" at all because all the art he draws from, in his line of reasoning to end up at *"amphetamine and amphetamine analogs,"* is random and undifferentiated in its consideration of diagnostic context and therapeutic application. There is no evidence in Declarant's line of reasoning that he is even understands what "BED" means when he features it in his Declaration, *"The Biochemical Mechanism of Action of Certain Agents Explains Their* ***Usefulness in the Treatment of BED****" (Exhibit 1009, p. 31).*

It is not hard to see how Declarant arrived at his conclusion that ***"amphetamine/amphetamine analogs are useful agents in the treatment of BED."*** He reasons without any skill in the art, taking essentially different ideas, terms and nomenclature, across essentially different diagnoses and essentially different drugs and classes of drugs, to illogically and arbitrarily arrive at a conclusion. But worse, from a POSA's perspective, Declarant does so in view that a POSA is supposed to be someone who:

a) *at the time of the invention….would have regarded the DSM-IV-TR as the gold standard for* ***diagnosing*** *mental disorders, including* ***eating disorders****….." (Petition, p. 27)*

b) *"would have routinely relied on the* ***DSM-IV-TR****, the charter document of guidelines on mental disorders, for* ***diagnosing a patient with BED****" (Petition, p. 40),*

c) *"would have clinical experience in the **diagnosis** and **psychopharmacology** of **eating disorders**, **specifically BED"** (Petition, p. 9).*

POSAs do not reason the way Declarant reasons. If they did, they would be putting patients in harm's way by ignoring of the art's most basic teachings on diagnosis and pharmacotherapy. There are yet other basic and essential teachings of the art, recognized by the art for their plainly stated and transparently disclosed teachings. They are applied below more specifically to the Petitioner's Ground 4 and 7 arguments to further demonstrate that '813's independent claims would not have been obvious "as of September 13, 2007" and that they are, therefore, patentable over the Petitioner's/Declarant's objections.

A POSA "as of September 13, 2007" would never have assumed, as the Petitioner/Declarant does in its Ground 4 and 7 arguments, an equivalent "reasonable expectation of success" for the same drug (and/or class of drugs) between one specific eating disorder, BN, and another specific eating disorder, BED. This is because a POSA at the time of the invention would have understood the clinical dangers of doing so from the plainly stated and transparently disclosed teachings of the art itself.

The line of reasoning in the Petitioner's Ground 4 and 7 arguments assumes that ***essentially the same drug*** (i.e., "d-amphetamine" or "d-amphetamine prodrugs") can be reasonably applied to ***essentially different disorders*** (i.e., BED and BN) with a reasonable expectation of success. ***All eight patients in Ong (Ground 4)*** and ***all the six patients in Dukarm (Ground 7)*** that received the "amphetamine-based" intervention were all, also, ***actively symptomatic BN subjects***. *(Exhibit 1017, p. 1, Col. 2; Exhibit 1019, p. 2, Abstract).* They are characterized in further detail in each respective section's counter-arguments, but are mentioned here for establishing a proper diagnostic clinical context.

A POSA at the time of the invention would have clearly regarded BN and BED as ***essentially different disorders***, simply because that was one of the most rudimentary skills required for them to practice the art with ordinary skill. After all, *"at the time of the invention, a POSA would have regarded the **DSM-IV-TR** as the gold standard for **diagnosing** mental disorders, including **eating disorders**....." (p. 27)* and, therefore, would have understood that in BED as defined in the DSM-IV-TR (and DSM-IV that came before it) ***required*** that *"the **binge eating [in BED]** is **not associated** with the regular use of **inappropriate compensatory behaviors** (e.g., purging, fasting, excessive exercise) and **does not occur exclusively during** the course of Anorexia Nervosa or **Bulimia Nervosa."** (Exhibit 1010, p. 18; Exhibit 1026, p. 11).* The DSM-IV/IV-TR could not be any clearer about its teachings. The POSAs skill was to practice the art of diagnosis according to the DSM-IV/IV-TR in order to not only differentiate these three eating disorders in terms of their "textbook definitions" but also to identify ***one of them*** diagnostically as a basis for administering drug treatment, conducting a study, and/or recommending non-

pharmacologic therapy, etc… If "binge eating" were present in a patient, a POSA's very ordinary skill, naturally, would have been to determine whether they were "AN-binge eating/purging type," "BN," or "BED."

At the time of the invention, a POSA would have particularly regarded BED and BN as ***so essentially different*** that, since 1994, each disorder had its own ***essentially different DSM-IV/IV-TR criteria*** which itself required the POSA to use his/her ordinary skill to ***differentiate BED from BN*** as ***the most basic and elementary practice of the art***, namely, to properly practice the diagnosis and psychopharmacology of eating disorders according to the standard of the art. Nowhere is the basic skill of accurately diagnosing "BED as defined in the DSM-IV/IV-TR" according to the standard of the art and its application to the treatment of "BED as defined DSM-IV/IV-TR" better evidenced than in the plainly stated and transparently disclosed teachings of the Petitioner's/Declarant's prior art submissions of Appolinario (Exhibits 1020, 1021, 1046), Arnold (Exhibit 1030), the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031), Milano (Exhibit 1022), Brewerton (Exhibit 1037), Stunkard (Exhibit 1044), Malhorta (Exhibit 1049), and Carter (Exhibit 1054). After all, it was these publications in the art that, among many others in the art, allowed the art to even produce the pharmacotherapy findings that came before '813's filing. Without a diagnostic recognition of BED as defined in the DSM-IV/IV-TR, the community of POSA's would never have been able to accurately diagnose the disorder. And without an ability to accurately diagnose the disorder according to the standard of the art, the community of POSAs would have never have produced the likes of people such as the Declarant who brought attention to BED and urged the art to respect its classification, to apply its "diagnostic differentiation from BN" to clinical practice, and to seek better and more targeted therapies for its treatment. This is evidenced in Declarant's 1999 "Binge Eating Disorder: Diagnosis and Treatment Options,"

> *"As psychiatric knowledge as accumulated and evolved over time, so our **diagnostic nomenclature** has evolved to reflect this knowledge and to more precisely describe psychiatric disease states. As part of this process, the eating disorders have only recently received serious research attention compared with other disorders. The inclusion of **binge eating without compensatory behaviours as an illness** is a natural extension of this evolving process of understanding the bulimic disorders spectrum. **BED is in fact a serious behavioral health problem** that appears to have been **underrecognized** and **undertreated**. **In my opinion**, the **diagnostic recognition of BED** will allow this group of patients to be further **studied from a clinical research perspective**, and it will allow them to get **more accessible and appropriate treatment**." (Exhibit 1037, p. 2. Cols. 1-2)."*

And, of course, without people like the Declarant who can be seen here respecting the art's basic and essential teachings, there would never have been the seven randomized controlled clinical trials between 1996-2003 for the treatment of BED

as defined by the DSM-IV/IV-TR, as plainly stated and transparently disclosed in the 2004 teachings of Appolinario (Exhibit 1020). But there were. And the teachings of those who conducted these trials and the teachings of those who spoke to the findings of these trials, much as Declarant did in 1999, taught very clearly and plainly on the diagnosis and pharmacotherapy of, ***specifically, "BED as defined in the DSM-IV/IV-TR."*** In this regard, it does not take a POSA to understand that if the art did not recognize and accept ***BED and BN*** as ***essentially different disorders***, and treat them differently on the basis of their ***essential (diagnostic) difference,*** then the Petitioner/Declarant would have made no prior art disclosures regarding the treatment of, ***specifically, BED –*** and, of course, there would have been no Inter Partes review of '813's patent claims. But the Petitioner/Declarant have made such disclosures and there is, of course, an Inter Partes review of '813's patent claims, itself its own validating testimony to the clear recognition of BED as defined in the DSM-IV/IV-TR.

There are other important teachings that would have been recognized by a POSA at the time of the invention for their significance in view of '813's independent claims, especially in view of the Petitioner's/Declarant's Ground 4/7 arguments, ones that the Petitioner/Declarant has failed to disclose. Among these is one of the art's most essential teachings, namely, about the ***danger of assuming that (essentially) the same drug has a reasonable expectation of success for essentially different eating disorders, specifically BED and BN.***

Nowhere is this teaching in the art more saliently revealed than with the specific drug ***d-fenfluramine*** and its therapeutic application to BED and BN. As already characterized, d-fenfluramine proved highly effective for the treatment of ***BED*** *as defined in the DSM-IV/IV-TR.* Particularly, Appolinario's 2004 "Pharmacological Approaches in the Treatment of Binge Eating Disorder" highlights d-fenfluramine's robust remission rate in its disclosures, writing that the drug produced a *"high rate of remission (80%) in this study." (Exhibit 1020, p. 3, Col. 1)* Appolinario's citation is from Stunkard's 1996 "d-fenfluramine Treatment of Binge Eating Disorder" and, not surprisingly, its robust 80% remission rate is featured in the plainly stated language of the Petitioner's Exhibit 1044 (Stunkard's original work), *"the statistical significance [of reduction in binge eating in BED subjects] was matched by the clinically significant finding that 80% (eight of 10) of the patients stopped binge eating completely." (Exhibit 1044, p. 4. Col. 2).* A POSA, whether in view of Stunkard's original art in 1996 (Exhibit 1044) or Appolinario's 2004 review of BED pharmacotherapy (Exhibit 1020) that features Stunkard's data, would have appreciated Stunkard's study as a double-blind, placebo-controlled trial of 28 patients who met full criteria for BED ("as defined in the DSM-IV") and designed to specifically determine the efficacy (i.e., reduction of binge eating) and practice measures (i.e., duration of treatment, dose of drug) for administering d-fenfluramine to patients with, ***specifically, BED***. Notably – and in view of Appolinario's comparative efficacy findings for all the "successful drugs" for the treatment of BED, a POSA would have appreciated just how "robust" d-fenfluramine was in ***inducing remission*** in BED subjects. In particular, Appolinario's 2004

characterization of d-fenfluramine as having a statistically significant ***80% remission rate*** on binge eating behavior versus placebo's 33% can be appreciated in view that it was the highest among the NT-specific drugs featured for their "success," albeit a comparison a POSA would have made with caution (i.e., other NT-specific drugs were fluvoxamine, sertraline, fluoxetine, cilatolpram, and sibutramine; comparative efficacy data featured on Table 1, Exhibit 1046, p. 5). Needless to say, d-fenfluramine worked very well in BED.

Three years before 1996 Stunkard's clinical trial, the art of diagnosing and treating eating disorders featured another double-blind, placebo-controlled trial involving d-fenlfuramine in patients with, ***specifically, BN***. In Fahy's 1993 "A Placebo-Controlled Trial of d-fenfluramine in Bulimia Nervosa," 43 patients were randomized to placebo or d-fenfluramine and treated for 8 weeks, the very same duration as Stunkard's trial, to assess the therapeutic efficacy of d-fenfluramine on ***binge eating***, ***self-induced vomiting*** and ***purging behaviors*** (Fahy, p. 599, Col. 2). All of Fahy's patients also received cognitive-behavioral therapy in the trial so that it would not be a confounding variable in determining the efficacy of d-fenfluramine on the core symptoms of BN, as defined and measured by the art's standard for doing so (i.e., binge eating, self-induced vomiting and purging behaviors). (p. 598, Col. 1). Fahy's randomized controlled clinical trial investigating the use of d-fenflurmaine in BN yielded dramatically ***different*** results from Stunkard's trial in d-fenfluramine trial in BED to come just three years later.

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Fahy 1993 "A Placebo-Controlled Trial of d-fenfluramine in Bulimia Nervosa,"

A POSA at the time of the invention would have certainly understood what Fahy meant in his findings when he wrote, *"the drug [d-fenfluramine] is **not an effective treatment for bulimia nervosa**" (p. 597, summary)* as *"there was **no difference** between treatment groups **[placebo/d-fenfluramine]** in frequency of **binge eating**, self-induced vomiting, and laxative abuse. (p. 599, Col. 1)."* Or, as Fahy later writes in his discussion section, *"this study **failed to detect any clinically significant difference** in treatment response between the d-fenfluramine and placebo groups….there was no difference in the improvement of psychiatric symptoms as measured by questionnaires or interviews, and there was no difference in outcome at the end of drug treatment, after a further eight weeks, or after one year. (p. 602, Col. 1)"* Despite the ***essential success of d-fenfluramine in "binge eating <u>in BED</u>,"*** the same exact drug could only be considered in the art as ***an essential failure in "binge eating <u>in BN</u>,"*** not to mention an essential failure also in "vomiting in BN" and "purging in BN." After all, a POSA at the time of the invention would have understood that both "vomiting" and "purging" could also be a symptom of Anorexia Nervosa, as plainly stated and transparently disclosed in the DSM-IV/IV-TR criteria for Anorexia Nervosa (which are identical, to the word, across both versions) and which feature a specific type of Anorexia Nervosa characterized in the plain text of the DSM-IV/IV-TR criteria itself called ***"Binge-Eating/Purging Type,"***

> *"during the current episode of Anorexia Nervosa, the person has **regularly engaged in binge-eating** or **purging behavior** (i.e., **self-induced vomiting***

> *or the **misuse of laxatives**, diuretics, or enemas." (Exhibit 1026, p. 3; Exhibit 1010, p. 9)."*

Returning to Fahy, his findings could not be any clearer to one of ordinary skill. Thus, the same exact drug, investigated across two placebo-controlled clinical trials of essentially the same design but with essentially different disorders, could not be more essentially different in their outcome. A POSA "as of September 13, 2007," much as a POSA "as of 1996," would have understood the significance, namely, it would be unwise and reckless, even dangerous in the care of patients, to assume that the same drug administered for the treatment of two essentially different eating disorders would have essentially the same reasonable expectations of success for the treatment of essentially the same non-specific behavior (i.e., binge eating) shared by both of them. The teaching could not be more obvious to one skilled in the art of diagnosing and treating eating disorders. It is not surprising, then, that Stunkard's 1996 study, one that features patients with "BED as defined in the DSM-IV," does not even mention Fahy's 1993 trial in its introduction, nor is Fahy's 1993 clinical trial even cited as a reference in Stunkard's work. A POSA "as of 1996" would have understood why, just as a POSA at the time of the invention would have understood why. The reason is that a POSA would have understood that the art diagnosing eating disorders had already embarked on its "differentiation," both in the DSM-IV and in the practice of the skill of "diagnosing and treating disorders." To see the disorders as essentially the same, or to see their non-specific symptom as essentially representative of the same disorder, meant to step back in time well before 1994, or step randomly into disparate areas loosely associating their connection as the Declarant does in his line of reasoning on pp. 23-26 of his Declaration. But Stunkard was living in 1996. And respecting the art's criteria for BED as defined by the DSM-IV, he and his team diagnosed his patients as such and ran his clinical trial to demonstrate the efficacy of d-fenfluramine for, specifically, BED. Thus, Stunkard already was on the path to treating an essentially different disorder, BED, recognized in the art for its being an essentially different disorder than BN and AN – and, as the story goes, obtaining essentially different results than Fahy who treated, specifically, BN.

A POSA, who *"would have clinical experience in the **diagnosis** and **psychopharmacology** of **eating disorders**, **specifically BED"** (Petition, p. 9),* would have understood the teachings of Stunkard and Fahy in several important respects. The most conspicuous teaching is that these two studies, each published in close proximity to each other as the DSM-III-TR (1987; Exhibit 1026) transitioned to the DSM-IV (1994; Exhibit 1010), quite dramatically highlighted the importance of considering the ***essential sameness(es)*** and ***essential difference(s)*** of diagnoses (and their respective symptoms), their drug interventions, their treatment outcomes, and their clinical trial designs. For instance, here were two different clinical studies similarly designed to assess the efficacy of the same drug, d-fenfluramine, on certain symptoms, some of which were the essentially the same (i.e., binge eating) and some of which were essentially different (i.e., vomiting, laxative abuse), between the two essentially different disorders of BN and BED.

Specifically, these two studies were essentially the same in duration (i.e., 8 weeks), number of patients enrolled/completed (i.e., 24/28 in Stunkard, p. 1044, Col. 2; and 39/43 in Fahy, p. 597, summary), and trial design (i.e., randomized, double-blind, placebo-controlled).

But they were essentially different in that Fahy's study was directed to the ***treatment BN patients*** *(as defined in the DSM-III-TR and per Russell)* and Stunkard's study was directed to the ***treatment of BED patients*** *(as defined in the DSM-IV).* And, importantly, they were also fundamentally different in yet another very significant way, namely, that d-fenfluramine was found to be ***essentially different in its efficacy*** for ***essentially the same symptom of "binge eating."*** Fahy's BN trial showed *"**no difference** between treatment groups in frequency of **binge eating**, self-induced vomiting, and laxative abuse" (Fahy, p. 599, Col. 2)* while Stunkard's BED patients showed d-fenfluramine ***"significantly reduced the frequency of binge eating** in women suffering from binge eating disorder"* and "***80%*** (eight of 10) of the patients with adequate plasma levels of d-fenfluramine ***stopped binge eating completely***, compared to 33% who stopped binge eating in the placebo group *(Exhibit 1044, p. 4, Col. 2)."* Simply put: essentially different disorders (BED and BN), treated with the same drug (d-fenfluramine), had essentially different results (success and failure) in treating the essentially same symptom (binge eating). This was a point of differentiation in the art's knowledge – and a POSA would have reasoned on that assumption.
In this respect, Stunkard's study defined a temporal juncture after which a POSA would not have cavalierly operated on the dangerous assumption that because ***the essential diagnostic criteria of Binge Eating for BN and BED are the same*** it would be reasonable to conclude ***"binge eating in BN"*** and ***"binge eating in BED"*** are essentially the same and can also be treated as essentially the same. POSA's don't reason that way. If they did, they wouldn't be POSAs but only "persons without skill in the art" (i.e., "PWSAs"). As a POSA at the time of the invention would have understood, Declarant's Declaration is reasoned like a "PWSA" since its fundamental assumption, as represented in the title of SectionV.A.B (Exhibit 1009, p. 23) (i.e., "***the essential diagnostic criteria of Binge Eating for BN and BED are the same***") is that the ***"binge eating in BN"*** and ***"binge eating in BED"*** are essentially the same and so are there treatments. Therefore, by the Declarant's logic, Ong's and Dukarm's BN patients can be reasonably applied to '813's independent claims that feature "binge eating in BED" with a "reasonable expectation of success" to render them obvious. Self-evidently, there would have been no art for BED, at all and in any form, if the community of POSAs reasoned this way. But, fortunately, the community has POSAs who reason like the Declarant along the lines of his 1999 BED review, wherein he respectfully acknowledges the art's most basic diagnostic distinctions, writing,

> *The inclusion of **binge eating without compensatory behaviours as an illness** is a natural extension of this evolving process of understanding the bulimic disorders spectrum. **BED is in fact a serious behavioral health problem**....**In my opinion**, the **diagnostic recognition of BED** will allow this*

> *group of patients to be further studied from a clinical research perspective, and it will allow them to get **more accessible and appropriate treatment**." (Exhibit 1037, p. 2. Cols. 1-2).*

A POSA reasons like the Declarant does here in his 1999 BED review, seeking to differentiate disorders on the basis of their ***essential core features*** which, in the instance of ***BED*** as Declarant accurately writes, is, ***"binge eating without compensatory behaviours."*** This is in contrast to BN, which features the ***essential core feature*** of ***binge eating with compensatory behavior.*** The concepts are simple – basic to the art, plainly stated and transparently disclosed in the DSM-IV-IV/IV-TR criteria for BED and BN since 1994 (as they are identical). In his 1999 art on BED, Declarant recognizes how the art has evolved, beyond the point of Ong' 1983 BN study (Exhibit 1017) to now require its community of POSAs to differentiate, which meant that the art of making an accurate diagnosis ***necessarily required a POSA to diagnose*** in:

BN (among the five core criteria):

> *"B. **Recurrent inappropriate compensatory behavior** in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications, fasting; or excessive exercise."*
>
> *"C. The **binge eating** and **inappropriate compensatory behaviors both occur**, on average, at least twice a week for 3 months." (Exhibits 1010, p. 14; Exhibit 1026, p. 7-8)*

BED (among the five core criteria):

> *"E. The **binge eating** is **not associated** with the **regular use of inappropriate compensatory behaviors** (e.g., purging, fasting, excessive exercise) and **does not occur** exclusively during the course of Anorexia Nervosa or Bulimia Nervosa" (Exhibit 1026, 11; Exhibit 1010, p. 18)*

A POSA "as of 1996" (in the time of Stunkard) or at the time of the invention on September 13, 2007" would have recognized that Fahy's BN patients, who were diagnosed by DSM-III-TR and Russell criteria (as further characterized below), exhibited ***the core essential feature of BN*** -- binge eating behavior ***inextricably linked*** with regular inappropriate compensatory behavior such as "self-induced vomiting" and "laxative abuse/purge." For one, it is plainly stated and transparently disclosed in Fahy's art. Specifically, Fahy quantifies the ***"binge frequency," "vomit frequency" and "purge frequency"*** in his subjects (p. 599, Table 1). He adds, *"in an attempt to bring the **binge—vomit cycle** under control, the patient was first asked to monitor **food intake**, **self-induced vomiting**, and **laxative abuse** using numbered food diaries which were supplied at weekly intervals beginning one week before drug treatment." (p. 598, Col. 2).* Moreover, Fahy reports that *"subjects meeting the inclusion criteria for the trial were female out-patients aged 18-45 years, satisfying*

DSM-III-TR *(American Psychiatric Association, 1987) and* ***Russell's (1979)*** *criteria for* ***bulimia nervosa****…." (p. 598, Col. 2).* The DSM-III-TR criteria for BN are featured in the Petitioner's prior art disclosures and clearly indicate that there are ***both*** *"recurrent episodes of* ***binge eating*** *(rapid consumption of a large amount of food in a discrete period of time"* ("Criteria A") ***and*** *"the person regularly engages in either* ***self-induced vomiting, use of laxatives or diuretics****, strict dieting or fasting, or vigorous exercise in order to prevent weight gain."* ("Criteria C")*(Exhibit 1038, pp. 7-8).* Russell's diagnostic criteria for BN, also disclosed as prior art by the Petitioner/Declarant, also emphasizes the ***core essential feature*** of ***BN***, namely, the inextricable link of binge eating and inappropriate compensatory behaviors. Russell quite succinctly characterizes this in the very first line of his two-line *"two criteria: (i)* ***an irresistible urge to overeat (bulimia nervosa), followed by self-induced vomiting or purging****; (ii) a morbid fear of becoming fat." (Exhibit 1039, p. 2, first sentence of "synopsis").* Therefore, ***even before the DSM-IV in*** 1994, which itself served to diagnose the patients in Stunkard's clinical trial with BED, a POSA would have understood that one of the art's most basic teachings was that ***the core essential feature*** of BN is that the binge eating is ***inextricably linked*** to inappropriate compensatory behaviors like vomiting and purging --- or, ***in view of BED***, that BN's ***core essential feature*** is ***inappropriate compensatory behaviors***.

This is in contrast to Stunkard's BED patients whose binge eating behavior was, as Declarant would have characterized it in his 1999 BED review, "***binge eating without compensatory behaviours."*** *(Exhibit 1037, p. 2. Cols. 1-2)."* After all, the art's ***"diagnostic recognition of BED"*** as defined in the DSM-IV (as Stunkard practiced in his study or as practiced in the art with exactly the same criteria at/after 2000 with the DSM-IV-TR), ***necessarily required*** that *"the binge eating is not associated with the regular use of inappropriate compensatory behaviors (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of Anorexia Nervosa or Bulimia Nervosa." (Exhibit 1026, BED, "Criteria E," p. 11; Exhibit 1010, BED, "Criteria E," p. 18).*

In this respect, a POSA "as of 1994-1996 (or thereabouts)" would have surely appreciated that the art of diagnosing BED or BN in a particular patient ***necessarily required*** that he/she differentiate between these two disorders on the basis of their skill and on the basis of ***the essential difference*** of each respective disorder's ***core essential feature.*** In BN (as defined in the DSM-IV/IV-TR), the ***core essential feature*** is that,

> *"the* ***binge eating*** *and* ***inappropriate compensatory behaviors both occur****, on average, at least twice a week for 3 months" (Exhibit 1026, BN, "Criteria C," pp. 7-8; Exhibit 1010, BN, "Criteria C," p 14).*

In BED (as defined in the DSM-IV/IV-TR), the ***core essential feature*** is that***,***

> ***"****the* ***binge eating*** *is* ***not associated*** *with* ***the regular use of inappropriate compensatory behaviors*** *(e.g., purging, fasting, excessive exercise) and* ***does***

> ***not occur*** *exclusively during the course of Anorexia Nervosa or* ***Bulimia Nervosa****." (Exhibit 1026, BED, "Criteria E," p. 11; Exhibit 1010, BED, "Criteria E," p 18).*

In other words, a POSA "as of 1996 (or thereabouts)," just as a POSA "as of September 13, 2007," would have clearly appreciated that Stunkard's patients, all of whom were diagnosed with BED according to the basic teachings of the art, were ***essentially different*** than Fahy's patients who were diagnosed with BN – essentially different in their ***most essential core feature.*** This, now, can be seen in view of Declarant writing in his Declaration as the heading of Section V.B,

> "*The* ***Essential Diagnostic Criteria*** *of* ***Binge Eating*** *for* ***BN*** *and* ***BED*** *are the* ***Same****." (Exhibit 1009; p. 18)."*

Of course, anyone could see that the DSM definition of a "binge eating episode" was the "textually the same" between BN and BED, but the POSA's skill since 1994 to the time of the invention would have been to understand *"binge eating without compensatory behaviours as an illness,"* as the Declarant adeptly wrote in his "BED: Diagnosis and Treatment Options." (Exhibit 1037, p. 2. Cols. 1-2).

Between 1994 and September 13, 2007 – in view of the transparently disclosed and plainly stated teachings of the art of DSM-based diagnosed – the most basic and rudimentary knowledge of a POSA would have been to understand this ***essential difference diagnostically*** between ***BED*** *from* ***BN,*** the one Declarant highlights in his 1999 BED review because, to quote Declarant once again, *"****BED is in fact a serious behavioral health problem****...[and]...****diagnostic recognition of BED*** *will allow this group of patients to be further studied from a clinical research perspective, and it will allow them to get* ***more accessible and appropriate treatment****." (Exhibit 1037, p. 2. Cols. 1-2).*

And, therefore, the most basic and rudimentary skill of a POSA would have been to diagnose BED or BN in a given patient based on applying this most basic and rudimentary distinction. And last, but not least, the most basic and rudimentary skill of a POSA would have been to treat patients based on their diagnosis. After all, a POSA *"would have clinical experience in the* ***diagnosis*** *and* ***psychopharmacology*** *of eating disorders,* ***specifically BED"*** *(p. 9)* and would have appreciated the art for its plainly stated and transparently disclosed teachings on the diagnosis and psychopharmacology of BED in view of what the art taught on them, as specifically evidenced in Declarant's/Petitioner's prior art submissions of,

a) Stunkard's "d-fenfluramine Treatment of Binge Eating Disorder" (Exhibit 1044),

b) Brewerton's 1999 "Binge Eating Disorder: Diagnosis and Treatment Options" (Exhibit 1037),

c) Arnold's 2002 "A Placebo-Controlled, Randomized Trial of Fluoxetine in the Treatment of Binge Eating Disorder" (Exhibit 1030),

d) Appolinario's 2002 "An Open-Label Trial of Sibutramine in Obese Patients with Binge Eating Disorder" (Exhibit 1021)

e) Malhorta's 2002 "Venlafaxine Treatment of Binge Eating Disorder Associated with Obesity: A Series of 35 Patients" (Exhibit 1049),

f) Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge Eating Disorder" (Exhibit 1046),

g) Carter's 2003 "Pharmacological Treatment of Binge Eating Disorder" (Exhibit 1054),

h) Appolinario's 2004 "Pharmacocological Approaches in the Treatment of Binge Eating Disorder" (Exhibit 1020),

i) Milano's 2005 "Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment of Binge Eating Disorder: A Placebo-Controlled Study (Exhibit 1022),

j) the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031).

It is through this lens that a POSA "as of September 13, 2007" would have appreciated the teachings of the art. And it is through this lens that the Petitioner's Ground 4 and 7 arguments can be clearly seen for, well, their still ongoing egregious mischaracterizations and errors in reasoning – all in plainly stated and transparently disclosed view.

Ground 4: The Petitioner Mischaracterizes Ong's Art. The Petitioner's line of reasoning is illogical and misrepresents that of a Person of Ordinary Skill.

Before examining Ong's art more carefully for its limitations for '813's independent claims, it is important once again to bear in mind who the Petitioner/Declarant characterize as a POSA, namely, one who,

a) "*would be a medical doctor (M.D.) specializing in psychiatry" (Petition p.* 9)

b) *would regard the DSM as "psychiatry's preeminent diagnostic manual of mental disorders" (Petition, p. 6)*

c) *"at the time of the invention….would have regarded the DSM-IV-TR as the gold standard for diagnosing mental disorders, including* ***eating disorders****….." (Petition, p. 27)*

d) *"would have routinely relied on the* ***DSM-IV-TR****, the charter document of guidelines on mental disorders, for diagnosing a patient with BED" (Petition, p. 40),*

e) *"would have clinical experience in the* ***diagnosis*** *and psychopharmacology of eating disorders,* ***specifically BED"*** *(Petition, p. 9).*

With this in view, to better understand why the Petitioner's Ground 4 argument is completely illogical and only, at best, representative of a person without skill in the art (i.e., "PWSA") it is important to understand what the art actually taught and how a Person of Ordinary Skill in the Art would have understood and practiced these teachings during the decade-plus time frame preceding '813's filing. In other words, understanding a POSA's most essential skills helps even "any reasonable person" put in perspective how the Petitioner and its hypothetical POSA go wrong in their Ground 4 line of reasoning. To again emphasize a most essential distinction in the art of eating disorders, once "binge eating" would have been identified in a patient, the POSA's skill would have been to determine its diagnostic context. This meant determining whether this was "binge eating-AN," "binge eating-BN," or "binge eating-BED." After all, any POSA between 1994 and the time of the invention would have been clear that BED and BN required "binge eating" and AN could indeed manifest it in its "binge-eating/purging" type. In this respect, a POSA would have kept in mind, as woven deep within the fabric of their reasoning, the ***essentially differences between*** each of the three major eating disorders, as defined by each specific eating disorder's core essential feature according to its DSM-IV/IV-TR language (as taken from the introduction of the DSM-IV/IV-TR "Eating Disorder Section"),

1) ***Anorexia Nervosa*** *– "Anorexia Nervosa is characterized by a* ***refusal to maintain a minimally normal body weight****." (DSM-IV, second sentence of*

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DSM-IV intro in eating disorders (part missing from Exhibit 1023).

introductory paragraph of "Eating Disorders," p. 539; DSM-IV-TR, Exhibit 1010, p. 3).

*2) **Bulimia Nervosa** – "Bulimia Nervosa is characterized by repeated episodes of **binge eating followed by inappropriate compensatory behaviors** such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise" ((DSM-IV, second sentence of introductory paragraph of "Eating Disorders," p. 539; Exhibit 1010, p. 3)*

*3) **Binge Eating Disorder** – "The **binge eating is not associated with the regular use of inappropriate compensatory behaviors** (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of Anorexia Nervosa or Bulimia Nervosa. (Exhibit 1010, p. 16; Exhibit 1026, p. 9)*

In this diagnostic context, as it would have been the most basic of all contexts for practicing the art with ordinary skill, a POSA between 1994 and September 13, 2007 would have unmistakably understood that "binge eating" is a non-specific symptom that can occur in any of the three eating disorders of AN, BN and BED. And the POSA's ordinary but very essential skill was to differentiate which specific eating disorder it was that its presence was associated. And then, after making an accurate diagnosis, to practice the skill of treating the disorder according to the teachings of the art. In particular, the DSM-IV/IV-TR provided the art's basic instruction on how to do this, as the DSM-based criteria could not be any clearer about the specific diagnostic criteria. For instance, even the ***"Binge-Eating/Purging Type"*** of Anorexia Nervosa is plainly and transparently characterized in the very criteria of DSM-IV/IV-TR for AN itself, *"**during the current episode of Anorexia Nervosa**, the person has **regularly engaged** in **binge eating** or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)." (Exhibit 1026, p. 3; Exhibit 1010, p. 9).* But, as a POSA would have understood, "binge eating" could also occur in BN and BED. And here was art's role in teaching skill of diagnosis, namely, to provide the pathway wherein a POSA could identify the non-specific symptom "binge eating" and consider it in view of the DSM-IV/IV-TR criteria as "binge eating" could signify AN, BN, or BED – and then to accurately diagnose the disorder wherein it was present. And, as the art of Stunkard and Fahy taught, it would be reckless and even dangerous to blindly assume that because the ***essential diagnostic criteria of binge eating for BN and BED are the same*** it was reasonable to treat them the same. So the art taught differential diagnosis to its community of POSA's so they could practice the skill of differentiating eating disorders with "binge eating" based on the art's accepted standard for making such clinical differentiations (i.e., the DSM-IV/IV-TR criteria for each of the three eating disorders of AN, BN or BED). After all, if there was no basic teaching, or skill thereof, to diagnose BED, BN and AN, then self-evidently there would have been no art on any of these disorders since such specific diagnoses could never be made to give rise to the art that did, in fact, emerge from their initial diagnoses. But there is art including art on pharmacotherapy, and as it relates to '813's independent claims (i.e., "BED as defined in the DSM-IV-TR"), such art can be found in the Petitioner's/Declarant's

Exhibits of Appolinario (Exhibits 1020, 1021, 1046), Arnold (Exhibit 1030), the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031), Milano (Exhibit 1022), Brewerton (Exhibit 1037), Stunkard (Exhibit 1044), Malhorta (Exhibit 1049), and Carter (Exhibit 1054).

Consider, then, the "real state of art" in view of the Petition's/Declarant's Ground 4 reasoning. The Petitioner writes (p. 26) that, *"Ong reports on the effects of stimulant methylamphetamine on patients diagnosed with BN, and focuses on the* ***symptom of "bulimia."*** *(See. Ex. 1017, Ong, p. 1, Abstract). Ong defines an episode as* ***'overeating,'*** *(id. at p. 1), and characterizes it as 'rapid, excessive and distressing eating' (id. at Abstract)."* Here, the Petitioner identifies the non-specific symptom of "binge eating" in a specific diagnostic context, namely, in patients with BN. This is how POSA's reason. They identify the symptoms but, always, they have in mind the broader diagnostic context since that is their ordinary skill. And for a POSA with ordinary skill in the diagnosis and treatment of eating disorders, the broader diagnostic context necessarily always involves consideration of the three specific disorders of AN, BN, and BD, on the basis of both their essential and specific differences. This is simply because that is what the art had taught between 1994-September 13, 2007, all in plainly stated and transparently disclosed view through its DSM-IV/IV-TR criteria of each respective eating disorder.

The Petitioner continues the line of reasoning (p. 27), *"At the time of the invention, a POSA would have regarded the* ***DSM-IV-TR*** *as the gold standard for* ***diagnosing*** *mental disorders, including* ***eating disorders*** *(see supra Section IV; see also Ex. 1009, Brewerton Dec, p. 30), and would have recognized the* ***symptom of bulimia*** *defined in Ong displays* ***many overlapping characteristics*** *with the* ***criteria*** *for* ***binge eating*** *in the DSM-IV-TR for both BN and BED. For example, DSM-IV-TR teaches that an* ***essential diagnostic feature*** *of* ***BN*** *and* ***BED*** *is recurrent episodes of* ***binge eating*** *(definitely a large amount of food in a short period of time) associated with indicators of impaired control, and significant distress about, binge eating.(Ex. 1010, DSM-IV-TR, pp. 14, 18; see also Ex. 1009, Brewerton Dec., p. 99)."* Here, any POSA between 1994-2007, practicing the art with ordinary skill, would have clearly recognized that this is not how POSA's reason. POSA's practice the art through their understanding of the ***essential and specific differences of disorders.*** Their skill, thus, is aimed at making important distinctions clinically that serve better, more predictable treatment responses. They do not practice the art by focusing on the essential similarity of symptoms. Obviously, there would be no art to practice if they reasoned this way, just as there would be no art in oncology if oncologists reasoned by way of the essential sameness of weight loss and cachexia in patients, or the essential sameness of all brain cancers. There would be no art in neurology if neurologists reasoned by way of the essential sameness of cognitive deterioration, to use one example. It is the differences that define the skill of a POSA, and why the first thing any POSA learns on their way to becoming a POSA is something called a "differential diagnosis." And, of course, it would not require any skill at all to see the "essential sameness of binge eating" in BN and BED, as all one would need to do is simply spend 3 minutes comparing the textbook (i.e., DSM-based) diagnostic criteria

of the two disorders, as perhaps a college student might do under time pressure to write a 2 page paper about the essential sameness of binge eating in BED and BN. Fortunately, for the advancement of the art, POSA's don't practice this way. If they did, they wouldn't be regarded as POSAs but, rather, PWSAs.

A POSA "with ordinary skill" anytime between 1994-September 13, 2007 would have appreciated Ong in its entire clinical context as understood in the art, not in its exclusively narrow range of "binge eating" as it is quite revealingly featured in Petitioner's line of reasoning following the clinical characterization of *"bulimia"* as *'overeating'* and as a *'rapid, excessive and distressing eating,'*

> *"The most important finding reported in the study was that the symptom of bulimia was suppressed by methylamphetamine." (Petition, p. 27).*

A POSA "as of September 13, 2007" reading Ong's 1983 publication would have appreciated that every patient in the study was diagnosed with BN and, not surprisingly, clinically exhibited its ***core essential feature (in view of BED)***, namely, ***regular inappropriate compensatory behavior***. The observation would have been simple and straightforward enough, simply on the basis that Ong writes that each of the patients *"satisfied criteria for the diagnosis of bulimia nervosa (Russell, 1979)" (Exhibit 1017, p. 1, Col. 2).* Thus, they all would have necessarily had "*an irresistible urge to overeat (bulimia nervosa), followed by self-induced vomiting or purging,"* as Russell's BN diagnostic criteria require. *(Russell, p. 429, first sentence of "synopsis").* But also, a POSA would have also readily appreciated from Ong's study that each patient's ***recurrent inappropriate compensatory behavior,*** as associated with their "bulimia" (i.e., overeating, binge eating), was important, which is why Ong's art recognizes these particular behaviors in Table I's "Summary of principal clinical data" as itemized below for each specific patient, (Exhibit 1017, p. 2):

1) Patient 1 – vomiting, laxatives
2) Patient 2 – vomiting, laxatives, excessive exercise
3) Patient 3 – food abstinence (i.e., fasting)
4) Patient 4 – vomiting, laxatives
5) Patient 5 – vomiting, excessive exercise, food abstinence
6) Patient 6 – vomiting, laxatives
7) Patient 7 – vomiting
8) Patient 8 – vomiting, laxatives

And, moreover, any POSA between 1994-2007 would have also appreciated Ong's explicit identification of *"**Previous** Anorexia Nervosa"* in Table 1 as well. In other words, while BED may not have been an explicitly recognized diagnostic category in the days of Ong, which was published more than a decade before the DSM-IV, a POSA between 1994-2007 would have appreciated that none of Ong's patients were actively symptomatic with AN. In fact, Ong reports that 6 of 8 of them would have never satisfied the diagnostic criteria for AN and, while 2 of 8 of the patients would have had a diagnosis of AN in the past, their inclusion in the current study is ***on the***

basis of their BN diagnosis. And, therefore, on the basis of BN's essential core feature as Russell put so well, "*an irresistible urge to overeat (bulimia nervosa), followed by self-induced vomiting or purging." (Russell, p. 429, first sentence of "synopsis").* So even in 1983, the community of POSAs was reasoning on the basis of essential and specific distinctions, seeking to logically differentiate patients on the basis of their essential and specific differences – not, self-evidently, on the basis of their essentially similarities. Simply because this is how POSA's reason, at least insofar as they are persons of ordinary skill in the art and are practicing the art as it is accepted in the community of those who practice it with skill.

In this light, the Petitioner's line of reasoning can be seen for its limitations, formidable ones at that, particularly when it writes (p. 27), *"Therefore, in light of the teachings in the DSM-IV-TR, a POSA would have understood the characteristics of **'bulimia'** of the patients of Ong **closely resemble the symptom of binge eating** for **BED**. (See Ex. 1009, Brewerton Dec, p. 99). Since Ong discloses that methylamphetamine administered to these patients resulted in **suppression of the bulimic or binge eating symptoms**, a POSA would have had a **reasonable expectation of success** in **treating BED** with methylamphetamine. (See id pp. 100)."* This is not how POSAs would reason, ever. They do not go from "binge eating--BN" directly to " ? drug success (more forthcoming)" directly to "reasonable expectation of success in binge eating—BED" in one straight 5-line shot without any consideration of 24 years of art between 1983 to 2007, and the hard work of patients and professionals during that time including, even, lives gained and lost from eating disorders. Putting aside the dangers taught by Fahy and Stunkard, namely, that the same drug could not reasonably be considered to have the same efficacy for the essentially different eating disorders of BN and BED (much less their non-specific symptom of binge eating), a POSA would simply not have taken a textbook definition of a symptom like "binge eating" and blindly apply its characterization to whatever they arbitrarily choose to see, making inferences and drawing conclusions along the way. A POSA would not have reasoned like the Petitioner's POSA, anymore than they would have read Appolinario's 2004 pharmacotherapy review, for instance, and come to the conclusion that Appolinario was teaching on the use of amphetamines and amphetamine analogs as a useful treatment in BED. Surely, anyone can make random and arbitrary inferences/conclusions simply by stringing the text of some shared language together from a bunch of sources, in particular a college student who has, for instance, 2 hours to write a 5 page paper on the essential sameness of BED and BN. But a POSA reasons about a symptom in view of its clinical context. And the POSA's skill is to consider the clinical context in view of what the art teaches about the symptom and, very importantly, the essentially different disorders in which that symptom can exist. And then, on the basis of clarifying those diagnostic distinctions, administer treatment accordingly to what the art teaches about treatment. This is how a POSA reasons. And, herein, a POSA "as of September 13, 2007" would have understood Ong as an experimental intervention for ***BN,*** an ***essentially different disorder than BED*** for which, already, the art taught on a number of essentially

different drug treatments as featured in the prior art submissions of the Petitioner's Exhibits of,

> Appolinario (Exhibits 1020, 1021, 1046), Arnold (Exhibit 1030), the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031), Milano (Exhibit 1022), Brewerton (Exhibit 1037), Stunkard (Exhibit 1044), Malhorta (Exhibit 1049), and Carter (Exhibit 1054),

among others, some of which were disclosed in '813's patent prosecution and a great many others which were not as they were not relevant to 813's independent claims that are limited to, ***specifically, a pharmacologic method of treating BED as defined in the DSM-IV-TR (and thus, DSM-IV, as they are the same).***

The Petitioner's line of reasoning, which goes from "binge eating in BN" to "binge eating in BED" and even assumes a reasonable expectation of success in doing so, would itself have been striking to a POSA "as of September 13, 2007" for its brazen disregard of ***nearly everything taught and practiced*** in the art of eating disorders between Ong's 1983 publication and '813's filing in 2007, that is, nearly everything taught to how the POSA ought to practice differentiating BED from BN – and AN – with respect to the non-specific symptom of binge eating. And, of course, how to then practice differentiating the treatment of BED from BN – and AN – with respect to making a specific diagnosis of BED, BN, or AN. After all, "as of September 13, 2007" the art taught that BED required a POSA to differentiate from BN and AN by virtue of its diagnostic criteria that required, in BED, that the binge eating "*….does not occur exclusively during the course of Anorexia Nervosa or Bulimia Nervosa. (Exhibit 1010, "Criteria E." p. 16).*

This kind of POSA reasoning could be seen in Ong's art too, wherein Ong differentiates his BN patients from being characterized in the art as AN. This is how a POSA reasons and how the art, as characterized above and featured in the Petitioner's/Declarants Exhibits (as previously referenced), repeatedly and consistently teaches. Nowhere is this better featured than in Appolinario's 2004 pharmacotherapy review wherein 367 patients, across seven randomized controlled trials, were treated for essentially the same disorder, ***BED as defined in the DSM-IV/IV-TR***, so that the community of POSAs could make inferences and conclusions regarding essentially different treatments for essentially the same disorder, BED. This is how POSA's think. By the Petitioner's line of reasoning, the prior art submissions it has disclosed regarding the specific treatment of BED (as referenced above) are not only irrelevant, but also meaningless in view of Ong, because a reasonable expectation of success can simply be assumed for use of any essentially same drug for essentially different disorders. Fahy and Stunkard had shown otherwise. By the Petitioner's line of reasoning, why differentiate when everything can be seen through the lens of the non-specific symptom of "binge eating." But POSAs do not reason this way because if they did, they wouldn't be POSAs. And, as it applies to '813's independent claims, they wouldn't be making the important

differentiations taught in '813's independent claims, as highlighted in the art of Appolinario (Exhibits 1020, 1021, 1046), Arnold (Exhibit 1030), the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031), Milano (Exhibit 1022), Brewerton (Exhibit 1037), Stunkard (Exhibit 1044), Malhorta (Exhibit 1049), and Carter (Exhibit 1054).

The Petitioner continues (p. 28), *"Further, at the time of the invention numerous studies had already shown that stimulants as a class were effective at suppressing binge eating. (See supra Section VI; see also Ex. 1009, Brewerton Dec. 39-45, 100). Hence, from Ong and DSM-IV-TR, a POSA would have learned to treat BED by diagnosing the patient based upon DSM-IV-TR and administering methylamphetamine to the patient. (See Ex. 1009, Brewerton Dec, 100)."* Here, any POSA between 1994-2007 would have recognized what the Petitioner was doing, namely, conflating "binge eating-BN" with "binge eating-BED," one of the most ***basic things not to conflate*** as taught in the plainly stated and transparently disclosed criteria of the DSM-IV/IV-TR. And, of course, as plainly stated and transparently disclosed in '813's independent claims. In this respect, any POSA between 1994-2007 would have recognized the Petitioner was not reasoning like a POSA at all but actually quite the opposite, reasoning without any skill and oblivious to the most essential and basic distinctions in the art of diagnosis – the art of differentiating binge eating among the three major eating disorders. To be sure, stimulants (i.e., amphetamines/amphetamine analogs) were not represented in the state of the art characterization for the treatment of, specifically, BED, in any of the Petitioner's prior art submissions (i.e., Exhibits 1020, 1021, 1022, 1030, 1031, 1037, 1044, 1046, 1049, 1054), nor did any of the Petitioner's prior art disclosures teach to favoring them as a class for their usefulness in the treatment of BED. Though it might be understandable how a college student under time pressure might conflated "amphetamine-like drugs in obesity" with "binge eating in BED," a "POSA as of September 13, 2007" would have concluded that there couldn't be a more likely NT-specific candidate for failure in the treatment of BED than LDX-dimesylate simply because it had no serotonergic potentiation and all the NT-specific drugs that worked in BED potentiated serotonin.

So how does the Petitioner conclude, *"numerous studies had already shown that **stimulants as a class** were **effective** at suppressing **binge eating**….**Hence**, from Ong and DSM-IV-TR, a **POSA** would have learned to **treat BED** by **diagnosing** the patient based upon **DSM-IV-TR** and administering methylamphetamine to the patient."* The answer itself is obvious based on just a small sampling of the art itself. The Petitioner/Declarant conclude this by treating the art of diagnosing and treating eating disorders with willful disregard of its most basic and essential teachings, as transparently disclosed and plainly stated in their own prior art submissions. The Petitioner/Declarant conclude this because of their inability to see the essential differences between disorders that defined the art for the more than two decades between Ong and September 13, 2007. The Petitioner/Declarant conclude this because they reason recklessly and dangerously. They reason that the essential sameness of a non-specific symptom like binge eating is the main reason to conclude

a reasonable expectation of success of methylamphetamine between disorders (BED and BN) when the art teaches the essential difference of disorders (BED and BN) in which binge eating is present is the basis for considering differential treatments which may have a reasonable expectation of success. The Petitioner and its hypothetical POSA reason backward and, by the standard of the art, would not even be qualified to treat an eating disorder patient because their reasoning clearly demonstrates their inability to even accurately diagnose one. The danger of their reasoning, as any reasonable person would have recognized at the time of the invention and in view of the art, is that one cannot administer adequate treatment to effectively treat a disorder if they don't know what they are treating. And by the Petitioner's reasoning, they don't know what they are treating in view of '813's claims because they consider BED and BN as essentially the same.

Consider if a patient diagnosed with breast cancer were treated without regard to the essential differences between the different types of breast cancer and their respective essentially different treatments. The answer is clear: women would be dying at a much faster pace. But fortunately, POSAs who practice the art of medicine do not reason like the Petitioner and its hypothetical POSA. They reason on the basis of distinctions recognized and practiced in the art, and base their treatment decisions based on what the art teaches them to do. Had the art collectively reasoned in the way the Petitioner and its POSA reason, Stunkard would likely never have even run his d-fenfluramine/BED-specific study in view of Fahy's conclusion that d-fenfluramine proved ineffective for, specifically, binge eating behavior in, specifically, BN. But POSAs differentiate, for that is the basis of their ordinary skill in the art.

Moving along and putting aside even this most fundamental distinction of "understanding" what disorder is being treated and what the art may have taught about its accepted standard of treatment, a POSA at the time of the invention would have understood the Petitioner and its hypothetical POSA to miss another most remarkable thing about Ong's art. So remarkable that it warrants consideration as to whether the Petitioner and its hypothetical POSA are even reasoning rationally outside the art. And the best way to appreciate this is to understand what the art taught about a "reasonable expectation of success" in the treatment of BED and what "813's disclosures teach, in the broadest reasonably light in view of the specification, about administering a therapeutically effect amount of drug for the treatment of BED "as defined in the DSM-IV/IV-TR." So, assuming all of Ong's patients were diagnosed with essentially the same disorder, specifically BED, then how would Ong have been read by a POSA in view of '813's independent claims, which themselves could not be more plainly stated and transparently disclosed for their teaching? For one, administering a therapeutically effective amount to treat the disorder known as "BED as defined in the DSM-IV/IV-TR" would have been understood by a POSA to be adequately treating a disorder wherein the binge eating symptoms occur in the context of BED, and wherein the *"binge eating occurs, on average, at least 2 days a week for 6 months." (Exhibit 1026, p. 11; Exhibit 1010, p, 18).* '813's independent claims clearly teach on the treatment of a disorder, BED, not on a

specific symptom even as that symptom may be the essential feature of the disorder. In other words, a psychiatrist would not advise a patient with major depression to smoke crack even if it might make the patient feel better because the psychiatrist would be focused on treating the disorder in which depression is the core feature. Specifically, '813's independent claims feature three patients who were treated between 5-11 weeks (Exhibit 1001; p. 12, Col. 1-2; p. 13, Col. 1; and p. 14, Col. 1-2). This is the duration of time a POSA would have treated a patient with BED at the time of the invention to determine whether a given drug demonstrated success, as taught in the BED pharmacotherapy art submitted as prior art by the Petitioner/Declarant (i.e., Exhibits (1020, 1021, 1022, 1030, 1044, 1046, 1049, 1054). Particularly, a POSA at the time of the invention, in view of Appolinario "2004," would have recognized that the art taught toward administering a therapeutically effective amount of drug for 6-14 weeks before concluding "success," with 6-8 weeks representative of the majority of controlled clinical trials evaluating the efficacy of drug therapies for "BED as defined in the DSM-IV/IV-TR." (Exhibit 1020, p. 5, Col. 1).

With this in view, a POSA at the time of the invention would have been astonished as to what Ong actually disclosed and how the Petitioner and its hypothetical POSA reasoned to the reasonable expectation of methylamphetamine in BN, or BED – again, putting aside the matter of understanding the art on the basis of its proper diagnostic context. As plainly stated and transparently disclosed, Ong's method of treatment involved a ***one-time dose*** of methylamphetamine. This ***one-time dose*** of methylamphetamine was administered ***intravenously "IV"*** over 60 seconds. To determine therapeutic efficacy of the IV methlamphetamine, "bulimia" (i.e., "binge eating") was observed during a ***30-minute interval*** two hours following the administration of the "therapeutically effective amount" of IV drug. As Ong writes, charactering these rather salient methodological details, *"all patients received methylamphetamine on one day and placebo an another, with an interval of a week and in random order….At **9 am a cannula was inserted** into a **forearm vein** and no observations were made for 30 minutes. Baseline observations on 10 self-ratings were made and repeated at fifteen minute intervals for the next 30 minutes using visual analogue scales. Methylamphetamine (15 mgm/75 kg body weight) or placebo was then **infused intravenously** through the **cannula over 60 seconds**. Further self-ratings were made at fifteen-minute intervals for a further 120 minutes….Observer ratings were made at 0, 7 ½, 15, 30, 45, 60 and 90 minutes after injection….**At 120 minutes after receiving methylamphetamine** or placebo, **each patient** was **left alone** with a **large supply of food** which she had selected for the test….The caloric content of the **food consumed over 30 minutes** was calculated for each test." (Exhibit 1017, p. 3, Col. 1).*

A POSA between 1994-2007 would have wondered how the Petitioner, or its " POSA," could claim success for the treatment of any eating disorder as represented by its plainly stated and transparently disclosed criteria in the DSM-IV/IV-TR with symptoms of "binge eating and inappropriate compensatory behaviors" ongoing for *"at least twice a week for 3 months"* (as in BN) or "binge eating behavior" ongoing for

"at least 2 days a week for 6 months" (as in BED), on the basis of Ong's art. After all, the period of observation was for but 30 minutes on one day, coming just 2 hours after the IV "hit" of methylamphetamine. A POSA would have first reasoned to ask, *"what about the rest of the 21 ½ hours that day?"* and *"what about the rest of the days that week?"* And, "*with such a fast onset of action, unlike say LDX-dimesylate, what about a late day rebound with binge eating getting worse?*" Of course, a POSA reasoning as POSA would have been expected to reason "between 1994-2007"– and also long before then – would have had many more questions to resolve before coming to the conclusion that that the Petitioner and its hypothetical POSA do, namely, that *"since Ong discloses that methylamphetamine administered to these patients resulted in suppression of bulimic or binge eating symptoms, a POSA would have had a reasonable expectation of success in treating BED with methylamphetamine" (Petition, p. 26).* Indeed, a POSA between 1994-2007 might well have wondered if the Petitioner, and its hypothetical POSA, had mistakenly been among those enrolled on Ong's study who received the IV infusion of methyamphetamine, albeit at too high a dose. That is because this is how POSA's reason. They make distinctions based on what they see and what the art teaches them, in view the distinctions they make. And, to be sure, a POSA by the Petitioner's standard, who *"would be a medical doctor (M.D.) specializing in **psychiatry**" (Petition, p. 9),* would have therefore been familiar with the effects of drugs like stimulants when administered IV, as even Ong characterizes for their limitations when he writes, *"drugs with stimulant and euphoric effects carry the dangers of dependence and drug induced psychosis." (Exhibit 1017, p. 5, Col. 2).*

But a POSA "as of September 13, 2007," in view of Mickle and Ong and the Petitioner's line of reasoning to a "reasonable expectation of success" of LDX dimesylate in BED, would have found the Petitioner's line of reasoning even more remarkably perplexing in yet another respect. Ong plainly states that one very possible reason for the patients' short-lived 30-minute treatment success might well be that *"**bulimic overeating** is triggered by a dysphoric mood which is **reversed** by the stimulant or **euphoriant effects** of **methylamphetamine"** (Exhibit 1017, p. 5, Col. 2).* A POSA at the time of the invention reading the Petitioner's argument even on the fly would have found this remarkable in view that the Petitioner writes, *"Mickle provides the solution…Specifically, Mickle discloses **amphetamine prodrugs** that **reduce the euphoric effects** associated with amphetamine abuse" (Petition, p. 28).* Here Ong is teaching that his "30 minute success" may well be due to the euphoriant effects of IV methylamphetamine and, moreover, that "*the findings of the present study are also compatible with this observation" (Exhibit 1017, p. 5. Col. 2)* while the Petitioner and its hypothetical POSA are reasoning to a *"reasonable expectation of success*" for LDX-dimesylate in BED on the basis that LDX-dimesylate can *"reduce euphoric effects."* The Petitioner's and its hypothetical POSA's reasoning is self-contradictory.

Fortunately, POSAs do not reason like the Petitioner and its hypothetical POSA, who could not have a more self-contradictory position. POSA's reason logically, respecting the art's important distinctions and teachings. They pay careful attention

to both essential and specific teachings of their art. That is why they are persons of skill. And that is why the Petitioner's argument is reasoned without skill and, as a POSA "between 1983-2007" would have concluded, reasoned with reckless disregard for the art of diagnosing and treating eating disorders. Indeed, the Petitioner and its POSA are reasoning on the basis of an entirely different skill than that characterized by the Petitioner for someone who *"would have clinical experience in the **diagnosis** and **psychopharmacology** of **eating disorders**, **specifically BED"*** and *"would be a medical doctor (M.D.) specializing in psychiatry" (p. 9).* That is because their reasoning then arrives at the paired conclusions of,

> *"Therefore, because of the teachings of Ong, DSM-IV-TR, and Mickle, it would have been obvious at the time of the invention for a POSA to diagnose BED based on the DSM-IV-TR and treat BED with the stimulant LDX dimesylate"*
> and

> *"The combination of Ong, DSM-IV-TR, and Mickle claims 1-5, 8-10, and 13 of the '813 obvious under 35 USC 103a" (Petition, p. 30),*

when it only would have been understood by a rationally-minded POSA that their reasoning to get there could not have been any more irrational. And, after all, POSA's are trained to practice the art with rationality. That is central to their skill.

Yet there is something else that would have struck a POSA at the time of the invention, ***as would have been understood by someone with the "composite POSA behavioral profile" of the Declarant himself at the time of the invention*** on the basis of his experience as *"Part II Adult **Psychiatry Board Examiner**, **American Board of Psychiatry and Neurology**, New York, NY, May 4-6, 1997" (Exhibit 1034, p. 9).* A POSA by such a standard would have recognized that in the example below there is ***no differential diagnosis considered by the "POSA."*** Therefore, the POSA the Petitioner characterizes is not a POSA:

> *"At the time of the invention, a POSA would have regarded DSM-IV-TR as the gold standard for diagnosing mental disorders, including eating disorders…., and would have recognized that the symptom of bulimia defined in Ong displays many overlapping characteristics with the criteria for binge eating in DSM-IV-TR for both BN and BED….For example, DSM-IV-TR teaches that an essential diagnostic feature of BN and BED is recurrent episodes of binge eating (eating a definitely large amount of food in a short period of time) associated with indicators of impaired control over, and significant distress about, the binge eating….Therefore, in light of the teachings in DSM-IV-TR, a POSA would have understood that the characteristics of 'bulimia' of the patients treated in Ong closely resemble the symptom of binge eating for BED….Since Ong discloses that methylamphetamine administered to these patients resulted in suppression of the bulimic or binge eating symptoms, a POSA would have had a reasonable expectation of success in treating BED with methylamphetamine. (Petition, pp. 27-28).*

Ground 7: The Petitioner mischaracterizes Dukarm's art with respect to its limitations on '813's independent claims. The Petitioner's line of reasoning is illogical and misrepresents that of a Person of Ordinary Skill.

The Petitioner's Ground 7 argument follows the same basic line of reasoning that its Ground 4 argument does. It also makes the same erroneous assumptions repeatedly and consistently recognized in the art for their error, as previously discussed. A POSA at the time of the invention would have applied the teachings already characterized in the Grounds 1 and 4 counter-arguments and similarly concluded that there would have been no reasonable expectation of success for LDX-dimesylate in the treatment of BED, much less even a motivation to combine the art of Dukarm, Mickle and the DSM-IV-TR in the first place, simply because of its limitations in view of '813's independent claims.

But for the purpose of clarifying the plainly stated and transparently disclosed essential teachings of the art in service of teaching the art, as the Petitioner and its hypothetical POSA have repeatedly and consistently disregarded them, it is worth highlighting the Petitioner's and its hypothetical POSA's line of reasoning for its Ground 7 argument. In particular, the Petitioner's Ground 7 line of reasoning provides the perfect lens through which the art can be appreciated for its most essential teachings, as practiced rightly with those with ordinary skill and as practiced wrongly by those without skill. Indeed, the essential difference between a POSA practicing the art and a PWSA failing to understand it.

For instance, the Petitioner begins its line of reasoning by characterizing Dukarm's art are as follows (Petition p. 39-41),

> *"Dukarm presents case reports on the use of the stimulant dextroamphetamine (commonly referred to as d-amphetamine) on six patients diagnosed with BN and comorbid ADHD,* ***who experienced recurrent binge eating****" (p. 39-40),*
>
> *"After administration of d-amphetamine 'all the 6 patients described reported* ***complete abstinence from binge eating****…'" (p. 40),*
>
> *"Dukarm thus concluded that, 'these cases suggest the potential role of psychostimulants in the management of BN because of the* ***high rate of abstinence from bulimic symptoms*** *and the low rate of adverse side effects' " (Petition's bold) (p. 40),*

A POSA "as of September 13, 2007," in view of the Petitioner's characterization of Dukarm, would have appreciated that the Petitioner is identifying the "'binge eating--BN" in Dukarm. A POSA at the time of the invention would have understood that Dukarm ***had already applied her understanding of the art*** to make a critical essential distinction in these 6 patients, namely, to differentiate their binge eating from the "binge eating in AN" and the "binge eating in BED" so that they could be diagnosed with "BN." After all, Dukarm makes it clear that these patients were

being *"treated in an outpatient interdisciplinary eating disorder program"* and thus a POSA at the time of the invention would have simply assumed Dukarm would have practiced the art with skill by respecting the art's essential distinctions of "binge eating – BN," "binge eating – BED," and "binge eating – AN." A POSA at the time of the invention would have also appreciated for its therapeutic implications that Dukarm had gone one step further, which was the further differentiate these "binge eating – BN" patients on the basis of their comorbid ADHD. That is because this is how POSAs think. They appreciate the clinical context and consider it in view how they would practice the art according to its recognized and accepted teachings.

But, curiously, a POSA would have also recognized that the Petitioner, in its characterization of Dukarm's art, fails to characterize any aspect of the BN patients' ***regular inappropriate compensatory behavior,*** as if it may not even be relevant or worthy of consideration for its diagnostic and treatment implications. After all, this is ***the essential difference between BED and BN***. And it is the key differentiating feature on which the ***art of BN***, and its treatment considerations, is based. Assumed in a POSA's line of reasoning at the time of the invention, that is a POSA who *"would have clinical experience in the **diagnosis** and **psychopharmacology** of **eating disorders**, specifically BED" (Petition, p. 9),* would have been what the DSM-IV-TR very specifically characterized in its very first paragraph (third sentence) of each of its respective "Eating Disorders" introductory sections, "*Bulimia Nervosa is characterized by repeated episodes of binge eating **followed by inappropriate compensatory behaviors** such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise." (DSM-IV**, p. 539; Exhibit 1010, p. 3).*** After all, a POSA at the time of the invention would have understood that this inextricable link of "binge eating and inappropriate compensatory behavior," ***absent its presence in Anorexia Nervosa*** wherein ***the core essential feature*** is *"the patient's refusal to maintain a minimally normal body weight,"* is the core essential distinction a POSA would have had to make to reason clearly toward the kinds of ***differential treatments*** taught in the art about how to treat each respective disorder, BN vs. BED, based on its ***differential diagnosis*** in a given patient.

A POSA at the time of the invention would have established their line of reasoning regarding Dukarm's patients ***in view of the art of BN.*** Thus, a POSA at the time of the invention would have established their line of reasoning regarding Dukarm's patients ***in view of their essential difference from BED,*** which would have included the ***art of BED and its treatment considerations*** as reflected in works of Appolinario (Exhibits 1020, 1021, 1046), Brewerton (Exhibit 1037), Marrazi (Exhibit 1024), Grilo (Exhibits 1025, 1029), Arnold (Exhibit 1030), Milano (Exhibit 1022), Stunkard (Exhibit 1044), Malhorta (Exhibit 1049), and Carter (Exhibit 1054), and the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031), not to mention the art of BN and its treatment considerations. As far back as 1979, in Russell's work (Exhibit 1039), the art had characterized BN as featuring the inextricable link of ***both*** "binge eating" ***and*** "inappropriate compensatory behaviors" like self-induced vomiting and laxative abuse. And a POSA reasoning to determine its proper treatment would

have had that distinction squarely in view from the outset and regarded treatment considerations in view of the art's teachings cumulatively built over thousands and thousands of publication, and over decades of research and clinical practice. And, similarly, a POSA would have reasoned on the assumed knowledge of its essential difference with BED.

It is essential to understand that built into a POSA's reasoning, since it would have been necessary to practice the art with ordinary skill, was that treating BN was essentially different than treating BED because BED and BN were essentially different diagnostically. Each disorder had its own specific diagnostic features, its own more common comorbidities, its own lessons from past treatment successes and failures. And built into a POSA's reasoning, then, would have been the teachings of Fahy and Stunkard wherein the same drug could have essentially opposite outcomes in these two essentially different disorders. Built into a POSA's reasoning, then, would have been Stunkard's own observations in the ***art of obesity*** characterized in his 1959 publication entitled "Eating Patterns and Obesity," "*binge eating disorder is a newly delineated syndrome characterized by the consumption of a large amount of food in a short period of time accompanied by a subjective sense of loss of control." (Exhibit 1044, p. 2).* And also, Declarant's when he wrote,

> *The inclusion of **binge eating without compensatory behaviours as an illness** is a natural extension of this evolving process of understanding the bulimic disorders spectrum. **BED is in fact a serious behavioral health problem**....**In my opinion**, the **diagnostic recognition of BED** will allow this group of patients to be further studied from a clinical research perspective, and it will allow them to get **more accessible and appropriate treatment**." (Exhibit 1037, p. 2. Cols. 1-2).*

Built into a POSA's line of reasoning would have been the DSM-IV/IV-TR's criteria for BN that *"self-evaluation is **unduly influenced by body shape and weight"** (Exhibit 1026, p. 7-8; Exhibit 1010, p. 14)* ***in view of*** Stunkard's and Appolinario's clinical trials featuring *"severely obese"* and *"obese"* patients, respectively, and Declarant's comment from his Declaration that *"many BED patients are obese."* (Exhibit 1044, 1021, 1046; Exhibit 1009, p. 21). Built into a POSA's line of reasoning at the time of the invention, as plainly stated and transparently disclosed in teachings of the art as far back as Stunkard in 1959, would have been that there were two ***essentially different populations*** whose essential difference could be understood as one group trying to be thin by engaging in inappropriate compensatory behavior and another group actually being obese and behaving very differently to compensate for it. This is how POSAs reason. And how a POSA at the time of the invention would have reasoned, simply because of the plainly stated and transparently disclosed teachings of the art over the decades preceding '813's filing. It was on this line of reasoning that Stunkard chose to run his 1996 trial in comorbid severely obese/BED patients with d-fenflurmaine, an anti-obesity agent, and why Appolinario used the anti-obesity drug sibutramine in his 2002 and 2003 clinical trials of obese/BED, and why Milano replicated Appolinario's work in 2005, and

why the Declarant was motivated to make the comment in 1999 in his BED review, *"[sibutramine's] usefulness in the treatment per se has not yet been reported [in BED], even in open studies, but it nevertheless holds promise on **theoretical grounds**."* And it was on this line of reasoning that Stunkard did not forego a trial of d-fenfluramine in BED just because it failed to successfully treat the "binge eating in BN."

But the Petitioner and its hypothetical POSA reason differently. They reason as those without skill who neither know the art, nor rationally apply any of its most basic teachings. This can be seen in the Petitioner's and its hypothetical POSA's ensuing line of reasoning,

> *"At the time of the invention, and as described above, a POSA would have routinely relied on the DSM-IV-TR, the charter document of the guidelines on mental disorders, for diagnosing a patient with BED." (p. 40)*
>
> *"DSM-IV-TR teaches that **an essential feature** of both **BN** and **BED** is 'recurrent episodes of **binge eating**' …and provides the **same** characterization of a **binge eating episode** with respect to the diagnosis of **both BN and BED."** (p. 40)*
>
> *"In fact, in the discussion of the 'Diagnostic Features' of **BED**, DSM-IV-TR refers the reader to the section on **BN**: 'the characteristics of a **binge episode** are discussed in the text for **Bulimia Nervosa**…' (p. 40)*
>
> *"Given the teachings of the DSM-IV-TR, a POSA would have understood the characteristics of **binge eating episodes** in **BN** and **BED** are **essentially the same."** (p. 40)*

At this juncture in the Petitioner's and its hypothetical POSA's line of reasoning, a POSA at the time of the invention would have unmistakably recognized that the Petitioner and its hypothetical POSA simply do not understand anything about the art, as their thinking had become unrelentingly motivated to see the essential sameness of "binge eating" in BN and BED ***to the exclusion*** of all the art that has collectively taught of their essential difference, from diagnosis, to comorbidities, to prognosis, to treatment. To be sure, a POSA at the time of the invention would have recognized that there could be no worse way to practice the art. But fortunately, the art weeds out such who practice it without skill, as do the patients who receive treatment from such people. And so the art builds, on the knowledge and distinctions of its community who practice the art with skill. And such knowledge and distinctions would have never motivated a "real POSA" at the time of the invention to reason on the basis of "essential sameness." Rather, a POSA would have been motivated to reason on the basis of the essential difference of BN and BED, in view of "BED as defined in the DSM-IV/IV-TR" and in view of the plainly stated and transparently disclosed teachings of Brewerton (Exhibit 1037), Appolinario (Exhibits 1020, 1021, 1046), Carter (Exhibit 1054), Grilo (Exhibit 1029), Grilo (Exhibit 1025), Malhorta (Exhibit 1049), 2006 APA Guidelines on Eating Disorders

(Exhibit 1031), Arnold (Exhibit 1030), and Milano (Exhibit 1022) -- among many others featured in '813's patent prosecution and, of course, among and a great many more others in the art recognized for its contribution to better understanding, specifically, BED, as well as, ***specifically, BN.*** And, thus, a POSA at the time of the invention would have understood the claim limitations of "813's independent claims in the broadest light of the specification (and the art itself) just as they are plainly stated and transparently disclosed in its three independent claims, as "BED as defined in the DSM-IV-TR."

So considering Dukarm, a POSA "as of September 13, 2007" would have ***assumed*** that Dukarm's art ***relies on the assumption*** that the community of POSAs who practice the art of diagnosis and psychopharmacology of eating disorders understand the ***essential distinction*** between BED, BN and AN and, to be sure, that they also practice it and communicate it to others who practice the art according to its accepted standard. Dukarm's art would not be informative in its "eating disorder teachings" if, for instance, she did not differentiate BN from BED on the basis of its essential difference(s), which she makes a point of doing not only by identifying them as "BN" patients but also by explicitly identifying in each of her six patients the inextricably linked ***inappropriate compensatory behavior*** that is associated with the binge eating behavior:

1) Case 1 -- *"obsessive exercise, purging" (Exhibit 1019, p. 3, Col. 2),*
2) Case 2 -- *"restrictive intake, laxative use, and obsessive exercise (p. 3, Col. 2),*
3) Case 3 -- *"purging" (Exhibit 1019, p. 4, Col. 1),*
4) Case 4 -- *"purging" (Exhibit 1019, p. 4, Col. 2),*
5) Case 5 – *"restrictive intake and significant weight loss" (Exhibit 1019, p. 4, Col. 2),*
6) Case 6 -- *"purging, excessive exercise" (Exhibit 1019, p. 5, Col. 1).*

Dukarm practices the art as it would have been expected of a POSA. She behaves showing an understanding of key assumptions central to the art. She recognizes important distinctions, both implicitly and explicitly, in just the way that Stunkard did in 1996, and many others who preceded and followed. She recognizes, as her communications reveal, that her art would be meaningless if she did not practice it with skill according to its standard, if she did not accurately differentiate BN from BED, and if she did not consider "stimulant treatment" in BN with respect to its ***clinical context with comorbid ADHD.*** POSAs reason this way, because if they didn't there would be no art – and no skill. But there is an art and a skill, one that speaks to differential diagnosis and differential treatment including, in view of the Petitioner's/Declarant's Ground 7 argument, a comorbidity of BN and ADHD. Nowhere is this kind of reasoning better evidenced than in Declarant's 1999 "Binge Eating Disorder: Diagnosis and Treatment Options" which teaches on differential diagnosis, comorbidities specific to BED (both medical and psychiatric), and treatment options specific to BED. And nowhere is the art of BED, with respect to these same features, better evidenced than in the Petitioner's/Declarant's prior art

disclosures of Appolinario (Exhibits 1020, 1021, 1046), Carter (Exhibit 1054), Grilo (Exhibit 1029), Grilo (Exhibit 1025), Malhorta (Exhibit 1049), 2006 APA Guidelines on Eating Disorders (Exhibit 1031), Arnold (Exhibit 1030), and Milano (Exhibit 1022).

In this respect, a POSA "as of September 13, 2007" would have recognized that the most rudimentary understanding of ***eating disorder diagnosis*** could have been reached by the Petitioner and its hypothetical POSA if only they completed their last line of reasoning (as represented below in blue) to accurately reflect a ***competent*** POSA's understanding of the art as it would have been practiced at the time of the invention (as represented below in red),

> *Given the teachings of the DSM-IV-TR, a POSA would have understood the characteristics of **binge eating episodes** in **BN** and **BED** are **essentially the** same but would have also understood the disorders of **BN** and **BED** are **essentially different.***

And a POSA "as of September 13, 2007" would have recognized that the most essential understanding of ***eating disorder psychopharmacology*** could have been reached by the Petitioner and its hypothetical POSA if only they completed their line of reasoning (as represented below in blud/red) even further to accurately reflect a ***competent*** POSA's understanding of the art as it would have been practiced at the time of the invention (as represented below in green):

> *Given the teachings of the DSM-IV-TR, a POSA would have understood the characteristics of **binge eating episodes** in **BN** and **BED** are **essentially the same** but would have also understood the disorders of **BN** and **BED** are **essentially different,** which therefore requires a thoughtful consideration of what the art teaches about specific pharmacotherapies for each specific disorder.*

In this regard, a POSA "as of September 13, 2007" -- who *"would have clinical experience in the **diagnosis** and **psychopharmacology** of **eating disorders**, specifically BED" (Petition, p. 9)* and who *"would have routinely relied on the **DSM-IV-TR**, the charter document of guidelines on mental disorders, for diagnosing a patient with BED" (Petition, p. 40)* – would have understood Dukarm and her teachings on the treatment of BN, and its "binge eating behavior," in view the art's teachings on ***essential diagnostic differences between*** BN and BED, the ***essential psychopharmacologic differences between*** BN and BED – and, very importantly, the ***essential diagnostic and psychopharmacologic differences within*** BN (i.e., BN with ADHD; BN without ADHD). Thus, a POSA at the time of the invention, even if entertaining the idea of Mickle's teaching in relation to the treatment of BED, would have already accounted for, by virtue of their basic skill in the art, the foundational teachings of
Stunkard and Fahy (which warned against assuming comparative success of any given drug across BN and BED), the art of BN and BED (the latter as already

characterized, and the art of ADHD treatment across its many stimulant drugs. This is how POSAs reason. There is an art – a consciously reasoned context based on countless publications and shared experiences – through which the POSA arrives at their conclusions. That is how POSA's reason and why they are POSAs in contrast to PWSAs. They consider the treatment of their patients in view of the art's teaching about what they determined to diagnose in their patients and how to best treat them based on the art's teachings for that diagnosis.

So even after reading Dukarm, if a POSA at the time of the invention somehow considered the idea of Mickle's LDX-dimesylate ***in relation to the treatment of BED***, he/she would never have ***assumed*** – or ***concluded*** - a reasonable expectation of success for a d-amphetamine drug that had only months earlier been approved for ADHD in children aged 6-12 years of age, without any evidence to support the ***usefulness of a stimulant in the treatment of BED (as it would have been recognized in the art by its DSM-IV-TR criteria)***. And, the same POSA would have also first considered, reflected on, even further investigated, the consistently represented teachings in the prior art of ***BED (as defined in the DSM-IV/IV-TR)*** as featured in the Petitioner's prior art disclosures of:

a) Fahy's 1993 "A Placebo-Controlled Trial of d-fenfluramine in Bulimia Nervosa"

b) Stunarkd's 1996 "d-fenfluramine Treatment of Binge Eating Disorder (Exhibit 1044)

c) Brewerton's 1999 "Binge Eating Disorder: Diagnosis and Treatment Options" (Exhibit 1037),

d) Arnold's 2002 "A Placebo-Controlled, Randomized Trial of Fluoxetine in the Treatment of Binge Eating Disorder" (Exhibit 1030),

e) Appolinario's 2002 "An Open-Label Trial of Sibutramine in Obese Patients with Binge Eating Disorder" (Exhibit 1021)

f) Malhorta's 2002 "Venlafaxine Treatment of Binge Eating Disorder Associated with Obesity: A Series of 35 Patients" (Exhibit 1049),

g) Appolinario's 2003 "A Randomized, Double-Blind, Placebo-Controlled Study of Sibutramine in the Treatment of Binge Eating Disorder" (Exhibit 1046),

h) Carter's 2003 "Pharmacological Treatment of Binge Eating Disorder" (Exhibit 1054),

i) Appolinario's 2004 "Pharmacological Approaches in the Treatment of Binge Eating Disorder" (Exhibit 1020),

j) Milano's 2005 "Use of Sibutramine, an Inhibitor of the Reuptake of Serotonin and Noradrenaline, in the Treatment of Binge Eating Disorder: A Placebo-Controlled Study (Exhibit 1022),

k) the 2006 American Psychiatric Association's Practice Guidelines for the Treatment of Eating Disorders (Exhibit 1031),

before concluding that there would be "reasonable expectation of success" of a stimulant for the treatment of BED. But the Petitioner and its hypothetical POSA do not reason this way. They reason like a college student who has a term paper due in

five hours – or perhaps half-an-hour -- and decides their conclusion in advance of its writing by making it an assumption. And once they have established that conclusion/assumption in their line of reasoning, then they are motivated to find whatever random scattering of references they can to prove the conclusion/assumption while disregarding ***everything*** that has actually been done over many years so that they can even articulate that conclusion in real life.

It is not surprising, then, how the Petitioner and its hypothetical POSA reason to their conclusion of the obviousness of '813's independent claims. Picking up where the Petitioner and its hypothetical POSA left off at *"binge eating episodes in BN and BED are essentially the same," (Petition, p. 40),* they write,

> *"Further, Dukarm discloses that **d-amphetamine** administered to patients with **BN** resulted in **abstinence from binge eating**, a **POSA** would have had a **reasonable expectation of success** in **treating BED** with **d- amphetamine.***
>
> *Further, Dukarm highlights numerous studies that had already shown **stimulants as a class** to be **effective** in suppressing **binge eating**.*
>
> *Thus, from Dukarm and DSM-IV-TR, a POSA would have learned to **treat BED** by **diagnosing** the patient according to **the DSM-IV-TR** and **administering d-amphetamine** to the patient." (pp. 40-41).*
>
> *"Since Dukarm teaches that **d-amphetamine** successfully treated **binge eating of BN**, and the DSM-IV-TR provides that **BN and BED share the common essential feature of binge eating**, a POSA would have had a **reasonable expectation of success** in treating **BED** with **d-amphetamine."** (p. 42)*

The Petitioner's and its hypothetical POSA's ***consistent and repeated disregard*** to reason as the art teaches, to reason based on the distinctions that have been taught in the art and also integrated into the shared understanding of the art by, for instance,

a) Stunkard's (Exhibit 1044) paper about ***obesity*** and ***eating disorders*** followed by his 1996 ***successful d-fenfluramine*** trial in ***severely obese BED*** patients in view of Fahy's ***failed d-fenfluramine trial in BN*** patients, or
b) Appolinario's (Exhibits 1021, 1046) 2002 and 2003 trials using the ***anti-obesity drug sibutramine for, specifically, BED***, in view of Fahy's and Stunkard's work;
c) Milano's (Exhibit 1022) 2005 replicating trial using the ***anti-obesity drug sibutramine for BED/obese patients*** in view of Appolinario's favorably results ***BED/obesity-sibutramine***, and in view of Stunkard's work on ***BED/obesity-d-fenfluramine***, and in view of Fahy's ***failed d-fenfluramine/BN trial.***

d) Brewerton's (Exhibit 1037) taking notice that ***sibutramine, an effective FDA-approved anti-obesity drug, could be promising for BED***, in clear view of the success that the once ***FDA-approved, but afterward withdrawn from the market, anti-obesity drug d-fenfluramine*** had for BED in Stunkard's 1996 trial, in view of Fahy's ***failed d-fenfluramine trial in BN*** patients,

is extraordinary. Neither Stunkard, nor Fahy nor Appolinario, nor Milano, nor Brewerton, nor the 2006 APA Treatment Guidelines (Exhibit 1031), among the many other references submitted as prior art by the Petitioner and its Declarant, are ever considered by the Petitioner and its hypothetical POSA ***with respect to their limitations –*** the most obvious one of all being that nowhere does the art teach toward using a stimulant drug, much less "***stimulants as a class"*** or NT-specific dopamine/norepinephrine potentiating agents like stimulants.

So why, then, does the Petitioner and its hypothetical POSA reason as follows,

> *"Further, Dukarm highlights numerous studies that had already shown* ***stimulants as a class*** *to be* ***effective*** *in suppressing* ***binge eating****.*
>
> *Thus, from Dukarm and DSM-IV-TR, a POSA would have learned to* ***treat BED*** *by* ***diagnosing*** *the patient according to* ***the DSM-IV-TR*** *and* ***administering d-amphetamine*** *to the patient." (pp. 40-41)."*

Because the Petitioner and its hypothetical POSA reason without skill in the art and, by their very reasoning, give testimony that they do not know the art. Or worse, that they know the art and willfully misrepresent its teaching, its most basic teachings about differentiating "binge eating-BN" from "binge eating-BED" from "binge eating-AN," as well as its prognostic and treatment implications for the care of patients, for some arbitrary or self-serving purpose.

A POSA "as of today" would clearly see that the Petitioner and its hypothetical POSA do a remarkably thorough job of actually proving the ***non-obviousness*** of '813's independent claims that feature the treatment of a ***specific DSM-IV-TR based eating disorder*** well-recognized in the art as ***"Binge Eating Disorder"*** (as Declarant's 1999 publication was entitled) with the specific drug well-recognized in the art as ***"lisdexamfetamine dimesylate"*** (as featured in its 2007 drug label). This is, essentially, for two reasons. The first reason is that their line of reasoning relies ***exclusively*** on conflating basic distinctions recognized and accepted in the art, in terms of both diagnosis and psychopharmacology, to reason to their obviousness position – and their reasoning on how this happens is in full view for its errors and irrationality, much as any POSA over the last decade would appreciate with those in the past seeing it in view of their foresight of today. The second reason, related to the first ***as a function of time***, is that their line of reasoning relies ***exclusively*** on a knowledge and understanding of the "art of diagnosing and treating eating disorders" that came ***even before specifically BED (as defined in the DSM-IV/IV-***

TR) even came into the art – to a time ***even before*** it made any difference to a POSA within which diagnostic context the "binge eating" existed (i.e., BN, AN, BED), simply because the diagnostic context of BED (as defined by the DSM-IV/IV-TR) had still yet to be defined by the art vis-a-vis its DSM-based criteria.

In other words, the Petitioner's and its hypothetical POSA's line of reasoning ***exclusively relies*** on understanding and practicing the art at a time ***even before*** it would have even been possible for '813's claims to have been written as they are, and to be understood in view of the limitations they hold as the are written.
This is because to have even written '813's claims, as they are explicitly written ***in their DSM-based context*** in independent claims 1, 8 and 13, would have first required the art recognize and accept the essential and specific differences of BED and BN with respect to ***both their essential and specific differences***. Thus, the art first had to recognize and accept the essential and specific difference ***between "binge eating-***BN" and "***binge eating***-BED" in order for them to be characterized in their proper diagnostic setting and, then, for their proper diagnostic setting to guide specific treatment. But the line of reasoning of the Petitioner and its hypothetical POSA completely fail to recognize the essential and specific difference ***between*** "***binge eating-BN"*** and ***"binge eating-BED"*** when they argue,

> *"Further, Dukarm highlights numerous studies that had already shown* ***stimulants as a class*** *to be* ***effective*** *in suppressing* ***binge eating****.*
>
> *Thus, from Dukarm and DSM-IV-TR, a* ***POSA*** *would have learned to* ***treat BED*** *by* ***diagnosing*** *the patient according to the* ***DSM-IV-TR*** *and* ***administering d-amphetamine*** *to the patient." (pp. 40-41).*

Here, the Petitioner and its hypothetical POSA ***ignore and disregard everything*** that the art has taught about the essential and specific differences between BED and BN for over a decade and longer, including by Declarant himself, in both its diagnostic and pharmacologic dimensions. And they do it in plain and transparent view, visible to a POSA or a PWSA or any reasonable person having a basic understanding of the art. The irony, of course, is that the very disclosures submitted by the Petitioner/Declarant as prior art reveal the true story of how BED did come to be accepted and recognized in the art, by way of the art's very standard of essentially differentiating BED from BN through both their essential and specific differences. And the other irony, of course, is that the Petitioner and its hypothetical POSA had to use the very art which established the essential and specific differences between BED and BN to actually communicate its ***very specific conclusion,*** namely, that what is plainly stated and transparently disclosed in '813's independent claims is "obvious." This, of course, is made possible because the Petitioner and its hypothetical POSA view the art backward through time with a line of reasoning that ignores and disregards all the essential and specific distinctions of the art that speak to the uniqueness, and limitations, of '813's claimed invention (i.e., "LDX-dimesylate" treatment for "BED as defined in the DSM-IV-TR"). And they do it ***in the***

context of the art in which it was practiced and characterized by its inventor until '813's filing on September 13, 2007. But then, remarkably, the Petitioner and its hypothetical POSA in the end validate the most essential and specific difference of all by claiming it to have been "obvious" at the time of the invention (i.e., "lisdexamfetamine dimesylate" treatment for "BED as defined in the DSM-IV-TR"). This is how hindsight works. And also how it is revealed for its limitations. It allows one to organize, with specificity, what has happened at different points in the past by what is known, with specificity, to have come at a point in the future, and knowing all the time the specificity of what comes in the future as it reasons its way back through the past, picking and choosing whatever it needs to make that final and very specific claim of "obviousness," however irrational its reasoning is. This is how the Petitioner and its hypothetical POSA have argued their position. And their line of reasoning, in the very end, only shows just how obviously incoherent it has been, and therefore, just how "non-obvious" '813's independent claims are in view of their own plainly stated and transparently disclosed representations of the art. In other words, the very line of reasoning the Petitioner and its PWSA enjoin to reach the conclusion of "obviousness" only goes to prove the diametric opposite -- the non-obviousness of 813's independent claims as it would have been understood by a POSA "as of September 13, 2007."

To this effect, a POSA "as of September 13, 2007" -- who *"would have clinical experience in the **diagnosis** and **psychopharmacology** of **eating disorders**, **specifically BED"** (Petition, p. 9)* and who *"would have routinely relied on the **DSM-IV-TR**, the charter document of guidelines on mental disorders, for diagnosing a patient with **BED**" (Petition, p. 40) –* would have understood the Petitioner's conclusion below for its limitations, ***limitations based on reasoning illogically, ignoring essential and specific distinctions in the art, and conflating fundamental teachings plainly stated and transparently disclosed in the art over and over:***

> *"In light of the teachings of Dukharm, DSM-IV-TR, and Mickle, it would have been obvious at the time of the invention for a POSA to diagnose BED according to the DSM-IV- and treat BED with LDX dimesylate." (Petition, p. 42).*

And, similarly, a POSA "as of September 13, 2007" - who *"would have clinical experience in the **diagnosis** and **psychopharmacology** of **eating disorders**, **specifically BED"** (Petition, p. 9)* and who *"would have routinely relied on the **DSM-IV-TR**, the charter document of guidelines on mental disorders, for diagnosing a patient with **BED**" (Petition, p. 40) –* would have understood '813's independent claims below in their broadest reasonable interpretation in light of the specification and with respect to their limitations, ***limitations based on reasoning logically, respecting essential and specific distinctions in the art, and skillfully differentiating fundamental teachings plainly stated and transparently disclosed in the art over and over:***

> ***Claim 1:***

*A method of **treating Binge Eating Disorder**, comprising diagnosing a patient as having Binge Eating Disorder, wherein the patient exhibits **Binge Eating Disorder as defined in the DSM-IV-TR** and **administering** a therapeutically effective amount of **lisdexamfetamine dimesylate** to the patient, wherein the **lisdexamfetamine dimesylate** is the only active agent administered or administered with **one or more active agents**.*

Claim 8:
*A method of **treating Binge Eating Disorder**, comprising diagnosing a patient as having Binge Eating Disorder, wherein the patient exhibits **Binge Eating Disorder as defined in the DSM-IV-TR** and **administering** a therapeutically effective amount of **lisdexamfetamine dimesylate** to the patient wherein the **lisdexamfetamine dimesylate** is the **only active agent** administered.*

Claim 13.
*A method of **treating Binge Eating Disorder as defined in the DSM-IV-TR**, comprising **administering** a therapeutically effective amount of **lisdexamfetamine dimesylate** to a patient in need thereof, wherein the **lisdexamfetamine dimesylate** is the **only active agent** administered **or** is administered together **with one or more additional agents**.*

A Person with Ordinary Skill in the Art practices the art on the basis of its accepted distinctions. After all, this is the very basis of the art and the skill. '813's independent claims could not be any clearer for their limitations, limitations that are themselves unambiguously disclosed in '813's specifications (i.e., "BED as defined in the DSM-IV-TR," Exhibit 1001, p. 8, Col. 2, lines 46-66; "LDX-dimesylate," Exhibit 1001, p. 6, Col. 1, lines 3-26) and based on the well-accepted and recognized limitations of the art itself which would have defined them and which includes, but is not limited to, the art of Brewerton (Exhibit 1037), Mickle (Exhibit 1023), Appolinario (Exhibits 1020, 1021, 1046), Carter (Exhibit 1054), Grilo (Exhibit 1029), Grilo (Exhibit 1025), Malhorta (Exhibit 1049), 2006 APA Guidelines on Eating Disorders (Exhibit 1031), Arnold (Exhibit 1030), and Milano (Exhibit 1022). Self-evidently, there is neither art, nor skill, when things all look the same. But to a POSA, things all look different. And when they look the same, the POSA's skill is to further differentiate them. A POSA at the time of the invention would have understood '813's independent claims as non-obvious on account of their skill and knowledge of the art, though a PWSA might have not understood '813s independent claims at all because of their having no skill or knowledge of the art. But someone who, by definition, can't "see and understand" what is being taught can't be considered to "see and understand" the "obvious." A POSA at the time of the invention would have understood '813's independent claims in the broadest reasonable interpretation in light of the specification, namely***, in light of the broadest reasonable interpretation of the art in view of its limitations*** -- as defined by the art's distinctions which, importantly, features in independent claims 1, 8 and 13***"BED as defined in the DSM-IV-TR."*** On the other hand, a PWSA at the time of the invention would have understood nothing all, simply because they would

not have had the skill to understand it. It will have looked the same as anything else in the art.

A POSA's line of reasoning, then, is always and necessarily premised on the distinctions and differentiations that the art teaches, simply because the art – and the communications of its POSAs -- is always and necessarily defined by the distinctions and differentiations it has accepted for its practice of the skill. This is what makes the art "art," and what makes a POSA a "Person of Ordinary Skill in the Art." Nowhere is this better evidenced in the "art of eating disorders" than in the eating disorder art of the Declarant himself. For instance, the Declarant co-authored a paper in 2000 entitled "Comorbidity of Bulimia Nervosa and Alcohol Use Disorders: Results from the National Women's Study." Declarant's co-authored publication discloses that (Danksy, p. 181), *"Researchers also have begun to examine **characteristics** which may **differentiate** women **with BN and substance use disorders (SUDs)**, women **with BN–SUDs [BN without SUDs]**, and **"controls."*** Here, Declarant and his co-authors are communicating their art to the community of POSAs in a way that they can understand, based on the shared and accepted language of the art which, in this instance, regards "BN" and "SUDs" and would be appreciated by a POSA in view of DSM-based criteria. The assumption is built into the communication, for that is the standard of the art. Further, Declarant and his colleagues are letting the community of POSAs know that they are seeking to understand on how "BN" patients may be ***essentially different between each*** other based on whether their BN is "with SUDs" (i.e., BN+SUDs) or "without SUDs" (i.e., BN-SUDs). In other words, Declarant and his colleagues are reasoning like POSAs, motivated to understand how BN itself, even as it may be "one diagnosis" with its own specific features (i.e., binge eating, inappropriate compensatory behavior, and self-evaluation unduly influenced by body shape/weight) according to its DSM-based criteria, may itself have ***essentially different characteristics within its "classification" -- depending on its clinical context***. In this instance, the ***essentially different characteristic*** Declarant and his colleagues are focused on is "Substance Abuse Disorders" (i.e., SUDs). And Declarant even provide the nomenclature to represent these essentially different characteristics with "BN patients with SUDs" as "BN+SUDs" and "BN patients without SUDs" as "BN-SUDs." They do this because they reason like POSAs who are seeking to further differentiate BN patients on the basis of a Substance Abuse Disorder.

It is not surprising, then, that Declarant and his co-authors write in the next sentence that follows (Dansky, p. 181), *"It is believed that by identifying **characteristics specific** to women with **comorbid BN** and **AUDs [Alcohol Use Disorders], therapeutic interventions** can be **tailored** to meet their needs and **more accurate predictions regarding therapy prognosis** can be made."* Here, Declarant and his colleagues are doing several important things very familiar to a POSA, simply because that his how POSA's reason. Declarant and his colleagues are communicating to the community of POSAs why they think it is important to ***specifically differentiate between "substance abuse" characteristics*** of BN patients, in this instance the focus on "alcohol." The reason they think it important

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Comment [6]:

Reference 6

Dansky "Comorbidity of Bulimia Nervosa and Alcohol Use Disorders: Results from the National Women's Study."

is simple: it could help provide different, better treatments for essentially the same disorder, BN, based on its specifically different features. But a POSAs understanding of the art and its teachings herein assumes, of course, he/she understands and recognizes the ***essential distinction between BN*** and ***Substance Abuse Disorders*** (i.e., "BN + SUDs") and, even more fundamental, that the POSA understands and recognizes the essential features that comprise its diagnosis (i.e., binge eating, inappropriate compensatory behavior, and self-evaluation unduly influenced by body shape/weight, temporal duration of symptoms).

This is how POSA's reason: logically, based on accepted distinctions in the art, and considered in the proper clinical context. The line of reasoning of Declarant and his co-authors is further extended in the next sentence that follows (Dansky, p. 181), "*In general, researchers have documented higher rates of psychiatric comorbidity, impulsivity and Axis II pathology among the women with comorbid **BN+SUD** than in woman **with BN-SUD**."* Here, Declarant and his colleagues are communicating to the community of POSAs that ***based on empirical evidence in BN patients***, which shows that "BN+SUD" patients have essentially higher rates of "other psychiatric problems" than "BN-SUD," it is reasonable to further specifically differentiate "BN+SUD" on the basis of whether their "SUD" ***specifically*** involves ***"alcohol"*** (i.e., "AUD" – "Alcohol Use Disorder."). This line of reasoning, of course, is that by specifically differentiating BN patients with "BN+SUD that is ***specifically*** for alcohol'" from "BN-SUD that is ***specifically*** for alcohol'" or "BN-SUDs" (i.e., no SUD at all), the art can develop more targeted therapies with more predictable expectations of success in their administration– or in the words of three POSAs "as of 2000," *"therapeutic interventions can be tailored to meet their needs and more accurate predictions regarding therapy prognosis can be made." (Dansky, p. 181).*

This is how POSAs in the "art of eating disorders" reason. They work within the accepted standard of the art and its nomenclature to make distinctions, ones that are assumed to be understood among the community of POSAs who, by their very role, do not conflate distinctions simply because their practice of the art relies that they understand and apply them. Then, POSAs are motivated to clarify those distinctions and, when they are better clarified, they seek to further differentiate and further clarify. And this is how the art matures. The "foundation" of Declarant's co-authored paper on BN and "AUDs", of course, requires that the community of POSA's be clear on what is meant when terms like "BN" and "AUDs," for instance, are used. The art practices with respect to its limitations, for the art at any given time only knows so much and has only characterized so much, and the POSA's obligation is to communicate those limitations as clearly as possible and, when possible, even seek to overcome them with advancements in both diagnosis and treatment, among other things. But a POSA necessarily must communicate these limitations based on the art's accepted standard of communication. Otherwise, they are not a POSA. As it relates to the art of treating the specific eating disorder known as "Binge Eating Disorder," for instance, the limitation is communicated by the very criteria established by the art through its DSM criteria so that the community of POSAs understand the essential and specific differences between "binge eating-BN" and

"binge eating-BED," which they then can apply in their practice of the art. It is this limitation, ***built into the diagnostic criteria itself*** and accepted in the "art of diagnosing and treating eating disorders" according to their DSM-based criteria, that enables the art to advance and to "*be tailored to meet their [patient's] needs and more accurate predictions regarding therapy prognosis can be made." (Dansky, p. 181).* And it is this limitation, ***built into the very diagnostic criteria itself of "BED as defined in the DSM-IV/IV-TR,"*** that even made it possible in the first place for the art of BED psychopharmacology to advance through the seven randomized controlled clinical trials Appolinario characterizes for their "success" in – specifically, "BED as defined in the DSM-IV/IV-TR." (Exhibit 1020, p. 5, Table 1).

Nowhere is line of reasoning, which involves respecting the art's essential and specific distinctions and then building on them to advance the art's understanding, better evidenced than in the same 2000 paper co-authored by the Declarant. As he and his colleagues describe in their "Methods" section (Danksy, p. 182), a sample of 3006 women were interviewed by telephone. In order to identify women with "BN" for the study, *"participants who endorsed a screening question pertaining to **binge eating** were **asked additional questions**, including those **necessary** to **diagnose BN according the criteria** defined in the 3rd Rev. ed. of the Diagnostic and Statistical Manual of Mental Disorders **(DSM-III-R**; American Psychiatric Association, 1987) **and binge eating disorder (BED) according to the criteria** in the 4th ed. **(DSM-IV;** APA, 1994; see Danksy, et. al., 1997, for details)."* Here, Declarant and his colleagues are reasoning like POSAs since the ***very first*** thing they identify in their "method" of further studying BN patients is to ***specifically differentiate "binge eating--BN"*** *(as defined in the DSM-III-TR)* from ***"binge eating--BED" (as defined in the DSM-IV)*** on the basis of the essential difference between these two recognized eating disorders***.*** As Declarant and his colleagues well-knew back in 2000, it would have been impossible from them to even identify *"characteristics specific to women with comorbid BN and AUDs [Alcohol Use Disorders]*," much less develop *"therapeutic interventions [which] can be tailored to meet their needs and [make] more accurate predictions regarding therapy prognosis…." (Dansky, p. 181),* if they couldn't first specifically differentiate between BED and BN. ***Specifically differentiating between BED and BN*** was itself necessary – completely foundational – to their study, which is why Declarant and his colleagues list "BN" first on the list of what they plan to screen for among the disorders they are diagnosing for their phone-based study. Declarant and his colleagues practice the art of "diagnosing eating disorders" like POSA's, beginning by practicing one of the art's most basic and essential distinctions, namely***, specifically differentiating between BN from BED***. And, not surprisingly, Declarant and his colleagues practice the art with skill. This is because their method is to specifically differentiate their "binge eating" phone subjects based on whether they satisfy criteria for ***either*** BN ***or*** BED (or neither at all). A POSA would have understood at the time of this publication or as of September 13, 2007, it would have been necessary for the patient/subject be given a specific diagnosis of one disorder, or the other, or neither at all. This was a most basic feature of the art of diagnosing eating disorders – and it was reasoned and practiced like a POSA here.

With respect to "AUDs" ("Alcohol Use Disorders"), Declarant and his colleagues write (Danksy, p. 183), *"To diagnose lifetime **AA [Alcohol Abuse]** and **AD [Alcohol Dependence]**, participants were asked frequency, age of onset, and recency of use of alcohol. In addition, they were assessed for alcohol-related difficulties at home, work, or in the community. Although the NWS survey instrument was designed prior to publication of the DSM-IV, the questions probed for symptoms of both abuse and dependence and **close approximations of these diagnoses were made**."* Here, Declarant and his colleagues are letting the community of POSAs know that ***within the "class" of "Substance Use Disorders" (i.e., SUDs),*** which a POSA would have understood to exist among other "classes" of DSM-based "disorders" (i.e., "mood," "anxiety," "eating," "psychotic," etc…), their study is premised on ***specifically differentiating their BN patients*** on how much alcohol they are using and how problematic their use is. A POSA would have understood this because within the "essential class" of "Alcohol Use Disorders," there are the "specific classes" of "Alcohol Abuse" (AA) and "Alcohol Dependence" (AD). Declarant and his colleagues are interested in what they can learn about this specific difference in their sampled BN patients who are identified with, first, a "SUD," and then second, an "AUD." This is how POSA's reason. They need to in order to practice the art skillfully. They seek clarification in diagnosis based on the accepted diagnostic distinctions taught in the art. And when there are limitations, as even Declarant and his colleagues identify above based on their outdated screening instrument (i.e., before the DSM-IV), they communicate them based on the shared language of POSAs. The objective, of course, is to develop better treatments based on the distinctions which they observe and which they communicate to the community of POSAs.

In this light, then, it is not surprising how Declarant and his colleagues begin their "Results" section as featured in the opening "Abstract" of this same 2000 paper, *"**AA [Alcohol Abuse]** was higher in women **with BN compared to** women **without BN** or **binge eating disorder**, only when the influence of major depressive disorder (MDD) and posttraumatic (PTSD) was controlled."* This is how a POSA reasons. They draw conclusions based on the very distinctions that define the art. And the conclusion that Declarant and his colleagues arrive at based on their study is that when ***controlling for sameness*** *(as in the presence of MDD and PTSD),* ***women with BN*** are ***specifically different*** than women ***with BED*** (or without BN) with respect to, specifically, the AUD known in the art as Alcohol Abuse ("AA"), itself specifically differentiated from Alcohol Dependence ("AD"). Of course, as a POSA at the time of this this 2000 study would have recognized, it would have been assumed that BN and BED were essentially different disorders and that Declarant and his colleagues properly practiced the art according to its accepted standard, which they did and even qualified their "diagnosis" of BN to its "DSM-III-TR diagnostic criteria." In other words, Declarant and his colleagues were already making progress back in 2000 on ***specifically differentiating between BED from BN on the basis of their specific differences***. After all, they did not have to waste any POSA's time to teach on the essential differences between BED and BN simply because those essential differences had already been accepted and recognized in the art -- through the very DSM-based criteria of BN and BED themselves. The task for Declarant and his

colleagues, back in 2000, was to specifically differentiate within the accepted framework of the art – in this instance "within BN" and "between BN and BED."

A POSA "as of September 13, 2007" reasoning like Declarant and his colleagues do in this 2000 reference would have read Dukarm ***in view of its teachings on BN*** and with an assumed understanding of BN's essential difference with BED (across the many basic teachings the art provided up through that time, including from Declarant himself). Specifically, a POSA would have been motivated to read Dukarm ***in view of its teachings on the comorbidity of BN and ADHD*** (i.e., "BN+ADHD") in just the way Declarant and his colleagues were motivated to understand the comorbidity of BN and Alcohol Use Disorders ("BN+AUD"), which itself was further differentiated into "BN+(AUD)AA" and "BN+(AUD)AD." The same reasoning can be seen in Stunkard (Exhibit 1044), Appolinario (Exhibits 1020, 1021, and 1046), and Milano (Exhibit 1022) who were drawn to the comorbidity of BED and obesity as well as treatments based on validated "anti-obesity agents," as would be considered with the designation of "O+BED" with the "O" coming first in the sequence since it was "obesity" that, from a POSAs real-time evolving view of the art, set the "frame" out of which, then, BED derived. In this light, BED can be seen as set apart from BN at the outset because it existed outside of its 1979 Russell criteria of "BN" as defined by *"two criteria: (i)* ***an irresistible urge to overeat (bulimia nervosa), followed by self-induced vomiting or purging****; (ii) a morbid fear of becoming fat." (Exhibit 1039, p. 2, first sentence of "synopsis").* This in contrast to Stunkard's 1959 paper "Eating Patters and Obesity" that focused on binge eating behavior without compensatory behaviors and its link to obesity (Exhibit 1040). The motivation for this reasoning "by way of essential and specific differences," of course, is so that *"therapeutic interventions can be tailored to meet their [patients] needs and more accurate predictions regarding therapy prognosis can be made." (Danksy, p. 181).*

In this respect, then, it is not surprising that two of three of Dukarm's explanations regarding why the six d-amphetamine-treated "BN+ADHD" patients in her study had a favorable response are reasoned along the lines of their "potential link" between, specifically, BN and ADHD:

1) *"A possible explanation for the effectiveness of* ***psychostimulants*** *in* ***BN*** *is the hypothesis that* ***BN and ADHD share a common causal factor*** *or* ***several common factors****" (Exhibit 1019, p. 5, Col. 2, parag. 3).*

2) *"An alternative explanation may be that symptoms of* ***BN*** *are the* ***result*** *of* ***untreated ADHD****. Specifically, the impulsivity may result in* ***binge eating followed by compensatory purging****. Therefore, decreasing impulsivity through use of a stimulant medication may decrease the desire to* ***binge eat****." (Exhibit 1019, p. 5, Col. 2, parag. 3)*

A POSA reasons on the basis of the art's distinctions and, to be sure, reasoning coherently to essentially ***and specifically*** differentiate between BN and BED in patients/subjects is a most ordinary and basic skill. As Declarant and his colleagues

clearly recognized and appreciated in their 2000 reference for its diagnostic limitations, "binge eating" is a non-specific symptom. No POSA would or could leave it unattended, or they wouldn't be behaving and reasoning like a POSA. Their skill is to probe further and, in knowing conscious consideration of the art's standard, to practice the art's skills. The reasoning of Declarant and his colleagues ***necessarily required*** differentiating "BED--binge eating" from "BN--binge eating" from "AN-binge eating." After all, they needed to make a firm diagnosis of BN in BN subjects and they needed to make a firm diagnosis of BED in BED subjects to even report the more specific comorbidity data that they that did in their study which, mainly, featured BN patients.

Nowhere is this kind of "POSA reasoning" better evidenced than in a publication by Declarant and his colleagues from 1997 entitled, "The National Women's Study: Relationship of Victimization and Posttraumatic Stress Disorder." The "Method" of the study, succinctly described in the opening summary of the article (Danksy, p. 213), writes, *"To examine the relationship among assault,* ***bulimia nervosa****, and* ***binge eating disorder****, a national representative sample of 3,006 women completed structured telephone interviews."* Here, Declarant and his colleagues are letting the community of POSAs know that they are curious about whether BN and BED can be more specifically differentiated with respect to "assault" (i.e., crime victimization). Again, it is simply assumed here that Declarant and his colleagues accept the essential difference between BN and BED. After all, that essential difference is the basis of their study and they wouldn't want to waste their time, or any other POSAs time for that matter, researching something that hadn't been accepted in the art (lest they be PWSAs and informing the community of POSAs that they were practicing without skill).

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Reference 8

Danksy, "The National Women's Study: Relationship of Victimization and Posttraumatic Stress Disorder."

As Declarant and his colleagues were particularly interested in drawing comparisons between BN and BED, it is not surprising that in their "Survey Instrument" section (Danksy, p. 216) they explain specifically how they differentiated these two disorders based on their telephone interview. Since their study is based on a pool of patients that a POSA (at the time of its publication in 1997) would have understood identified the same non-specific symptom of "binge eating," they provide specific details on their methodology regarding how they diagnoses either BED, or BN, or neither. After all, they necessarily had to arrive at a specific diagnosis of ***either*** BED ***or*** BN in this pool of patients to report their findings. Needless to say, once "binge eating episodes" were identified in the phone subject and characterized according to their "essential sameness," as explained in detail over two paragraphs in the way that would have been expected by a POSA at that time, they do the next logical thing a POSA would have been expected to do. They specifically differentiate between the eating disorder known as BN and the eating disorder known as BED. And the way they do this, as it would have been expected of a POSA at that time or at anytime between then and September 13, 2007," is to make the diagnosis on the basis of DSM-based criteria. This is evidenced when, upon first determining "binge eating episodes" in the phone subject, Declarant and his colleagues write,

> ***"A diagnosis of BN was assigned to respondents who met the following criteria:***
> *1)Episodes of eating large amounts of food in a brief time period;*
> *2) During their period, the episodes occurred at least several times each week;*
> *3) Worst period lasted at least 3 months;*
> *4) Engaged in at least two types of binge eating behaviors which are indicators of a loss of control as outlined in the proposed DSM-IV criteria for BED;*
> *5)* ***Compensation for a binge by excessive exercise, vomiting, and laxative, or diuretic use.***
>
> ***A diagnosis of BED was given to respondents*** *who met all the criteria for BN indicated that* ***they did not engage in compensatory behaviors and the their period of binging last for at least 6 months."*** *(Danksy, p. 216-217)*

Declarant and his colleagues practice the art perfectly in their study – all in plainly stated and transparently disclosed view, a whole decade before '813's filing. That is, the art of diagnosing eating disorders and specifically differentiating the "binge eating" in BN for the "binge eating" in BED. And they communicate the limitation of their methods of diagnosis by virtue of its DSM-based diagnostic criteria. They do all of this in plainly stated and transparently disclosed view, just as '813's independent claims 1, 8 and 13 do.

Yet what is, perhaps, most striking is what Declarant and his colleagues learned in their 1997 study, namely, "*Even when PTSD [Post-Traumatic Stress Disorder] was controlled, a higher prevalence of sexual molestation was found among respondents* ***with BN as compared with*** *those without BN or* ***BED****. In contrast, respondents* ***with BED did not differ*** *from* ***NonBN/NonBED*** *respondents for these types of assaults. These findings suggest women* ***diagnosed with BN*** *and women* ***diagnosed with BED differ on important variables*** *such as a history of sexual assault or aggravated assault and lend support for further investigation of BED as a diagnostic category." (p. 225).* Here, a whole decade before '813's filing of September 13, 2007, Declarant and his colleagues are reasoning like POSA's and, thus, they are specifically differentiating BED and BN. The essential difference between BED and BN has already been built into the frame of their research. The task is to do what POSAs do – to further clarify and differentiate, and to further clarify again and further differentiate again. It is not surprising, then, that Declarant and his colleagues further characterize their findings as such (Dansky, p. 225), *"Specifically, it appears that* ***purging****, rather than binging, may be the* ***central component*** *connected with a history of* ***sexual assault****. Since* ***purging*** *is the* ***central difference*** *between* ***BN*** *and* ***BED****, and* ***only BN*** *was* ***significantly associated*** *with a* ***history of sexual assault****, it can be hypothesized that the* ***purging or compensatory behavior*** *exhibited by women* ***with BN*** *(or a combination of binging with purging) may be* ***the critical aspect*** *associated with* ***past victimization****."*

Here, Declarant and his colleagues – reasoning as POSAs would have been expected to reason at that time – are letting the community of POSA's know that it appears as if they may have identified a ***specific difference*** ***between BED and BN*** (i.e., sexual assault) ***based on the essential difference between BED and BN*** (i.e., BED's lack of compensatory behaviors). But Declarant and his colleagues can only report this because they rely on the essential and specific differences between BED and BN that the art teaches. And they ***respect it***, ***at its most basic level – at its most rudimentary level of diagnosis*** according to the art of DSM-based diagnosis. Declarant and his colleagues respected the essential and specific differences between BED and BN back in 1997 and 2000 just as, of course, a POSA who *"would have routinely relied on the **DSM-IV-TR**, the charter document of guidelines on mental disorders, for diagnosing a patient with **BED**" (p. 40),* would have respected them "as of September 13, 2007." Simply because this is how a POSA reasons. In this light, then, it is not surprising that the third of three of Dukarm's explanations as to why the six d-amphetamine-treated "BN+ADHD" may have benefited from stimulant treatment is reasoned along the lines of the inextricably link of "binge eating ***and inappropriate compensatory behaviors,***"

> *"An additional explanation for the effectiveness of psychostimulants on bulimic symptoms in these 6 patients may be that the appetite-suppressing effects of stimulants resulted in a **decreased desire to binge eating and, therefore, a decrease in compensatory purging**." (Exhibit 1019, p. 5, Col. 2, parag. 3)*

A POSA at the time of the invention, practicing the art rationally and competently as a POSA, would never have reasoned the way the Petitioner and its hypothetical POSA reason in their Ground 7 (and 4 arguments) to conclude the obviousness of the'813's independent claims, simply because it is purely irrational to one of ordinary skill in the art. The Petitioner's line of reasoning and that of its hypothetical POSA is akin to someone reasoning without the most essential and basic distinctions of the art in conscious view (or even in the "unconscious" to borrow nomenclature from the art) -- but then, unexpectedly, coming to the conclusion that one of the most specific and unique distinctions of the art had been in plain and transparent view all the time. For that is the only way anyone in ***the daily and ordinary practice of the art*** could reason ***from a place of:***

> 3006 non-differentiated women by phone, to further differentiate them into "binge eaters" and "non-binge eaters," to then further differentiate "binge eaters" to give them with a diagnosis of ***either*** BED ***or*** BN (or none), to then further differentiate each of BN and BED to give a diagnosis of PTSD (or none), MDD (or none), SUD (or none), to then further differentiate BN and BED into +/-SUD which then would be further differentiated into +/-AA or +/-AD,
>
> ***to a place of,***

> *"Because of the overlapping of binge eating between BN and BED, in my clinical practice I have determined and opined that the two disorders tend not to be distinct but rather on a continuum, and that patients move in and out of specific disorders over time. (Exhibit 1009, Declarant Declaration, p. 19).*

And that is also why the only way anyone in ***the daily and ordinary practice of the art*** could reason ***from a place of,***

> "binge eating--BN" and d-amphetamine in Dukarm,
>
> then to "binge eating—BED" in the DSM-IV-TR,
>
> then to LDX-dimesylate in Mickle, and then finally
>
> ***to a place of,***
>
> LDX-dimesylate and BED in '813's independent claims is obvious.

A POSA reasons on the basis of distinctions made in the art, essential and specific ones, and considers them in the context of the art – its teachings, its community of POSAs, and its ongoing research, among many other variables. And a POSA's reasoning begins with the most fundamental distinction of all in the art of medicine – the ***differential diagnosis***, as reasoned by Declarant and his colleagues in his 1997 and 2000 research studies, as well as reasoned by POSAs in their own respective research at the time of their work and within the limitations of their time of practicing the art, as evidenced in art of Jimmerson (Exhibit 1012), Drimmer (Exhibit 1016), Brewerton (Exhibit 1037), Ong (Exhibit 1017), Dukarm (Exhibit 1019), Appolinario (Exhibits 1020, 1021, 1046), Marrazi (Exhibit 1024), Fairburn (Exhibit 1027), Grilo (Exhibits 1025, 1029), McCann (Exhibit 1048), Arnold (Exhibit 1030), Milano (Exhibit 1022), Russell (Exhibit 1039), Stunkard (Exhibit 1044), Malhorta (Exhibit 1049), and Carter (Exhibit 1054). And on the foundation of these essential differentiations, specific differentiations are reasoned and practiced by the POSA in a process that itself models the art and its natural growth through its differentiation. And for the POSA, the foundation begins with their reasoning ***"the differential diagnosis,"*** which then becomes the ***diagnosis,*** which is the ***basis for "therapeutic interventions*** *[which] can be tailored to meet their [patients] needs and more accurate predictions regarding therapy prognosis can be made." (Danksy, p. 181).*

A POSA understands essential and specific differences since that is their skill in the art. And that understanding is inherent in the reasoning with which they can even make a diagnosis and see the possibilities of what can even be diagnosed. The POSA's motivation is to accurately diagnose patients based on these essential and specific differences that the art teaches for doing so and to then reason toward treatments that may have a reasonable expectation of success. This is how the art is practiced, how it recognizes its limitations, how it matures past them, and how it

protects itself from regression in view of its maturation. This is how the Declarant practiced the art with his colleagues in 1997 and 2000, and how the POSAs referenced above practiced the art with their colleagues, and how countless other POSAs have practiced the art over recent decades, accepting and respectful of the distinctions made in the art within their time of practice but, always, seeking further and further differentiation and clarification to advance the knowledge and practice of the art in view of its step-wise advancement.

Nowhere is this better evidenced than in the Declarant's "Pharmacotherapy of Eating Disorders," published in 2004 – the same year as Appolinario's 2004 "Pharmacological Approaches in the Treatment of Binge Eating Disorders." This is because the Declarant's brief but very detailed pharmacotherapy review underscores his understanding of the:

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Reference 8

Brewerton, 2004 "Pharmacotherapy of Eating Disorders" – Psychiatric Times

a) ***essential and specific differences between*** and ***within the diagnoses of each of AN, BN and BED*** and the
b) ***essential and specific differences*** regarding the ***psychopharmacology of eating disorders between*** and ***within different classes of drugs,*** their ***NT-targets***, and their ***NT-specific mechanisms of action*** as they apply to "(a)" above and also with respect to their therapeutic implications, as further characterized below.

At the outset of his 2004 pharmacotherapy review, Declarant ***differentiates between*** the ***pharmacotherapy of the three eating disorders*** of ***AN***, ***BN*** and ***BED.*** He does so on the basis the art's standard of randomized controlled trials. These are the guidelines that have been accepted in the art and Declarant regards them for their teaching to a reasonable expectation of success for each respective eating disorder. But even in his introduction, even before setting out to specifically characterize the pharmacotherapy of each specific eating disorder, Declarant discusses the limitations of such controlled trials,

> *"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**. 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."*

Declarant lets the community of POSAs know that the reasoning behind his 2004 pharmacotherapy review assumes the ***well-accepted essential and specific***

diagnostic differences of AN, BN, and BED. He is not presenting his findings on the basis of the "essential sameness of non-specific symptoms" like "binge eating" and "inappropriate compensatory behavior." That is because it would not have been helpful to a POSA whose reasoning is based on differentiating these three specific eating disorders according to their patient-specific diagnostic context in AN, BN or BED, and then determining treatment for the patient based on an accurate diagnosis. After all, "binge eating behavior" can exist all three disorders and "inappropriate compensatory behavior" can be seen in AN and BN. POSA's are always motivated to understand what they are trying to treat before prescribing a drug for its treatment. And they look to the art's teachings for guidance of how to best treat that disorder. This is what Declarant does in his 2004 pharmacotherapy review, which itself is logically divided into three sections with each particular section providing ***the art's specific pharmacotherapy guidelines*** for ***the specific eating disorder (i.e., AN, BN and BED, respectively)***. This is how POSAs reason. Declarant is careful not to conflate distinctions in his classification, with respect to symptom(s) or diagnosis (es). He reasons as a POSA would have been expected to in the diagnosis and treatment of AN, BN and BED at the time of the invention, namely, in view of each specific disorder's "diagnostic frame" and the art's guidance on its pharmacotherapy including with respect to its limitations. These are Declarant's 2004 pharmacotherapy teachings, as a POSA at the time of the invention would have understood and applied them to the specific treatment of patients having ***one of either AN, BN or BED***:

IN ANOREXIA NERVOSA:

1) Declarant emphasizes the importance of reasoning to a drug's "reasonable expectation of success" on the basis of randomized controlled trials ***as well as*** in view of the clinical context,

> *"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****.*

2) Declarant ***differentiates between drugs*** in view of their efficacy ***for different specific symptoms*** *(i.e., "bulimia/binge eating" and restriction") of the* ***same essential disorder*** *(i.e., AN)****,***

> *"Another study found* ***amitriptyline (Elavil)*** *statistically* ***better than placebo*** *for patients who are* ***both bulimic ["binge eaters"] and***

> ***anorexic**, while **cyproheptadine (Periactin)** was better for **restricting anorexia.** (Halmi et al., 1986)."*

Declarant is careful not to conflate important distinctions such as "binge eating" and "fasting/restriction" which may be seen in other eating disorders. He does this, as POSA would appreciate, by focusing on the ***differential treatment*** (i.e. amitriptyline; cyproheptadine) *of the **same eating disorder (i.e., AN)*** and, for cross-reference, he cites another POSA's publication for its empirical evidence. In this instance, he draws from Halmi's "***Anorexia Nervosa:*** Treatment ***efficacy*** *of **cyproheptadine** and **amitriptyline***." And Declarant also speaks to his mindfulness that *"other studies have mixed results."*

3) Declarant warns about the ***dangers of making pharmacotherapy assumptions without empirical evidence***, particularly in view of ***safety concerns***. A POSA at the time of the invention would have appreciated how he thus extends this basic line of reasoning from "Fahy/Stunkard—BN/BED" into the realm of AN,

> *"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**."*

4) Declarant teaches on one way to consider a ***drug's prospect for usefulness for, specifically, AN*** -- namely, in terms of its ***"therapeutic efficacy"*** and its ***"NT-specific target."*** He reasons along the lines of Appolinario and others in the art (as previously characterized) without conflating important NT-specific psychopharmacologic distinctions. In particular, he even cites his own research on the important role of ***5-HT (serotonin)*** in, ***specifically, AN:***

> *"**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)."*

5) Declarant emphasizes ***important NT-specific distinctions***, ones that he himself researched and which he also references in his article in case POSA's seek to expand and further differentiate their understanding. In particular, he highlights the importance of not only the ***specific NT (i.e., 5-HT)*** that it ***"depleted"*** (i.e., "low") ***in AN*** patients but also further differentiates other important clinical factors related to a given ***"5-HT drug's"*** reasonable expectation of success in ***AN-specific treatment***,

*"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."*

Declarant has researched serotonin dysregulation in, ***specifically, AN.*** In a 1996 study published in Psychiatry Research, entitled ***Studies of Serotonin Function in Anorexia Nervosa***, Declarant and colleagues investigated the mediating effects of serotonin on the hypothalamic-pituitary circuit in ***AN patients*** by testing the ***serotonin partial agonist drug m-CPP*** and ***L-tryptophan.*** Particularly, he and his colleagues were focused on the different effects of ***mCPP*** *and* ***L-tryptophan*** on the various ***neuroendocrine functions*** to understand how 5-HT may work in different centrally-acting pathways. He and his colleagues write in the opening abstract, "*Neuroendocrine, temperature, test-meal, and psychometric responses are reviewed following challenges with the **post-synaptic 5-HT receptor agonist m-chlorophenylpiperazine (m-CPP)**, the **5-HT precursor L-tryptophan (L-TRP)**, and placebo in **12 patients with anorexia nervosa (AN)** and **16 healthy controls**. A subset of the AN patients (n = 8) were rechallenged 3-4 weeks after attaining a predetermined goal weight. **AN patients had blunted prolactin (PRL)** responses to both m-CPP and L-TRP at low-weight and at goal-weight in comparison to controls, although there was a tendency toward normalization with weight gain. **.....Cortisol (CORT) responses** following m-CPP and L-TRP **were not significantly different** among any of the groups. Temperature and test-meal measures were largely unaffected by serotonergic agents in the patients, although **m-CPP decreased meal size in the controls**.....Taken together, these findings indicate that responsiveness in **post-synaptic hypothalamic-pituitary serotonergic pathways is altered in AN patients**. ....These may represent changes in **serotonergic function** at levels **in the CNS "above" the hypothalamus**." (p. 31).*

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Brewerton, "Studies of Serotonin Function in Anorexia Nervosa, " -1996

6) Declarant demonstrates his knowledge and understanding of not only differentiating between the ***three NTs*** of ***5-HT, DA,*** *and* ***NE*** as an ***NT-specific drug target*** but he also teaches on ***specific differences within the NT-specific drug target by sub-receptor type (i.e., 5-HT2, serotonin).*** He considers the ***"NT-super-specific distinction"*** in view of its pharmacological application for the specific treatment of AN,

*"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**.*

7) Declarant reasons as a POSA would have been expected at the time of the invention when he teaches on the "therapeutic properties" (i.e., "anti-anxiety," "anti-obsessional," "anti-depressant") of a drug in view of its potential application to a ***specific sub-type of AN*** -- its ***"restricting subtype."*** He differentiates his teachings between "speculation," "data with limitations" (i.e., open trials and case reports) and "validated controlled trials," as would be expected of a POSA,

*"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."*

8) Declarant teaches on the ***use of certain specific drugs, and a certain specific "class of drugs" (i.e., anti-psychotics), for the treatment of, specifically, AN.*** In particular, he does so in view of AN-specific clinical considerations and ***comorbidities***. He is careful not to conflate their use for other conditions wherein non-specific symptoms such as "binge eating" may be present (i.e., BN, BED) and/or "inappropriate compensatory behaviors" (i.e., BN), which is made self-evident in that he is teaching on AN and about its "weight implications." He is careful to acknowledge the limitations of data that are not empirically validated,

*"**Open trials and case reports are promising** [for **Olanzapine]** (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****."*

IN BULIMIA NERVOSA:

1) Declarant, as a POSA at the time of the invention would have appreciated, teaches on the importance of reasoning to a reasonable expectation of treatment success in view of validated methodologies along with their limitations (i.e., trial length, comorbidities) and also in view of ***treating both binge and purge symptoms*** – the core essential feature of BN. He even differentiates the potential effectiveness of "antidepressants" in, ***specifically, BN*** *outside* their "antidepressants effects." Thus, Declarant shows a degree of knowledge even beyond that of Appolinario's characterization for the treatment of BED on the basis of classifying drugs by their "therapeutic class" (i.e., *"antidepressants work for BED because they are antidepressants"*),

   *"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."*

2) Declarant teaches on the ***dangers of assuming a reasonable expectation of success for different drugs even within the same sub-class*** (i.e., "SSRIs") of the "class of antidepressant drugs" because data shows that ***different specific SSRI drugs (i.e., fluoxetine, fluvoxamine) "are not equally effective,"***

   "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)."*

   Declarant himself researched serotonin dysgregulation in, ***specifically, Bulimia Nervosa***. In a 1994 article published in the journal Neuropsychopharmacology, ***"Testmeal Responses Following m-Chlorophenylpiperazine and L-Tryptophan in Bulimics and Controls,"*** he

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Brewerton, "Testmeal Responses Following m-Chlorophenylpiperazine and L-Tryptophan in Bulimics and Controls,"

and his colleagues investigated different serotonin mechanisms of action of the ***serotonergic agonist drug "m-cpp"*** and the ***serotonin precursor "l-tryptophan."*** They concluded ***m-cPP*** and ***L-TRP*** may ***exert differential effects on food intake*** because of ***different serotonergic mechanisms of actions.*** The opening summary of their article writes, *"A wealth of data support a role for **serotonin (5-HT) function** in the **mediation of satiety responses**, that are **impaired in patients with bulimia nervosa.** Testmeal results are presented in which 26 bulimic patients and 17 normal controls were given in **randomized, double-blind-fashion, placebo**, and the **5-HT agents m-chlorophenylpiperazine** (m-CPP, 0.5 mglkg p.o.) and **L-tryptophan** (L-TRP, 100 mglkg I. V.)…… **M-CPP, but not L-TRP, significantly decreased meal size in the combined group, the controls, and to a lesser extent, the bulimics**…. Following **m-CPP, there were significant decreases in carbohydrate, protein, and fat in**take in the total group of subjects. There were also trends for decreased carbohydrate and protein intake in the bulimics following m-CPP…..**Differences in the effects between m-CPP and L-TRP are likely due to differential involvement of 5-HT receptor subtypes at presynaptic and postsynaptic sites."** (p. 63).* In this respect, Declarant was even able to differentiate between AN and BN in terms of key serotonergic actions, even as both disorders may share the same non-specific symptoms (i.e., binge eating, purging).

3) Declarant teaches on the importance of ***specific dose ranges*** *(i.e., 40-80 mg/day)* of a ***specific drug*** *(i.e., fluoxetine)* for the treatment of ***specifically BN*** because empirical evidence shows that one cannot assume a reasonable expectation of success in treatment ***even with the same drug unless it is dosed properly.*** And again Declarant teaches on the treatment of ***both*** bulimic ("binge") ***and*** purge frequencies, recognizing that the disorder is recognized in the art in view of its "whole" and not, for instance, in view of its "half" (i.e., "binge eating" or "purging"),

   *"**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).*

4) Declarant teaches on the limitations of the pharmacotherapy of BN (and even AN), specifically with regard to drugs characterized in the art for their "antidepressant actions." A POSA would appreciate his teaching in view of the history of eating disorders, that being --- don't over generalize, even if there is some data to suggest one drug in the class (i.e., "antidepressants") works (i.e., fluoxetine, as above) because other drugs may not work (i.e., fluvoxamine) and still other drugs might be contraindicated (i.e., bupropion):

*"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."***

5) Declarant teaches on a ***specific drug*** with respect to its ***highly-specific "5-HT sub-type" (i.e., "5-HT3")*** in view of its ***validated efficacy*** for ***both*** binge eating ***and*** purging in BN. He does so in relation to controlled clinical trial data since this is what the art teaches for making such claims on the "effectiveness of a drug", and he even teaches on "ideal clinical scenarios,"

*"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."*

6) Declarant teaches on another drug (i.e., topiramate) in view of its "therapeutic class" (i.e., "anticonvulsant") and once again in view of its ***BN-specific efficacy*** on ***both binge and purge behaviors,*** as this is the core essential feature of BN. He speaks to the drug's potential side effects (i.e., impaired mentation, metabolic disturbances) as certain drugs can prove difficult for patients and limit their success. And he also teaches to its potential efficacy on ***BN-specific comorbidities,*** as he recognizes a more targeted drug-treatment may prove helpful in a ***clinically differentiated sub-set of BN patients (i.e., BN+obesity; BN+bipolar; BN+migraine)***,

*"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 parasthesias, 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**."*

7) Declarant teaches on the use of a specific drug (i.e., "naltrexone") on a ***specific subset of BN patients*** (i.e., refractory to SSRIs), and in even a ***more specific subset therein*** who have a ***comorbid condition (i.e., alcoholism,***

self-injurious behaviors). He teaches on a failed trial in view of a positive trial, the latter of which he is ***careful to specifically comment*** ***that the study included "binge/purging behaviors" in both AN and BN.*** The reason, of course, is to avoid conflating non-specific symptoms (i.e., "binge eating" and/or "purging") since he understands that the community of POSAs always views any non-specific symptom in its proper diagnostic framework. The trial he cites was a mixed pool of "binge eating/purging" ***AN or BN*** patients, the "or" signifying that each had ***either*** one diagnosis ***or*** another in the trial. This mirrors how a POSA would reason to make the specific determination, which is their ordinary skill.

> *"**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 binging and purging** (Marrazzi et al., 1995)."*

IN BINGE EATING DISORDER:

1) Declarant teaches on the ***specific treatment of BED*** with respect to ***empirically-based data.*** He highlights ***"CBT" as the treatment of choice according to randomized controlled trials.*** He also teaches on pharmacologic treatments and the combination of both CBT and medications (i.e., fluoxetine, fluvoxamine).

> *"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).*

2) Declarant teaches on a "***specific class of antidepressants"*** (i.e., the SSRIs) for the ***treatment of specifically BED*** in view of its ***NT-specific target (i.e., 5-HT)*** and its ***specific mechanism of action by which 5-HT is potentiated*** (i.e., ***"reuptake inhibition").*** He identifies different specific drugs by name (i.e, fluoxetine, sertraline, and fluvoxamine). His teaching, as a POSA at the time of the invention would have appreciated, warns broadly against making dangerous assumptions (i.e., *"although the use of antidepressant medications **in AN** seems theoretically sound, the results from randomized controlled trials have been dismal"* and "***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"*), and is rooted in the empirical evidence:

*"**Nevertheless, randomized controlled trials suggest that binging [in BED] 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)."*

Here, Declarant is careful not to conflate the non-specific symptom of "binge eating" that may be present in AN or BN. He does this by clearly identifying randomized controlled trials for the ***specific treatment of Binge Eating Disorder (as defined by the DSM-IV/IV-TR)*** and making sure that under the heading "Binge Eating Disorder" (in his article) that he is ***accurately representing the teachings of the art for BED***. Thus, he shows himself to be reasoning like another POSA in the art – Appolinario, who cited the same studies in his own "2004 pharmacotherapy review" of, specifically, BED, and was careful to accurately represent categories according to "therapeutic class" (i.e., "antidepressants," "anticonvulsants," and "anti-obesity agents" or "biochemical mechanism of action" (i.e., SSRIs).

3) Declarant teaches on two other drugs in view of ***their efficacy in treating both "binge eating behavior" and "obesity"*** in, ***specifically,*** **BED.** The data is based from controlled clinical trials which shows reduction of ***both "binge eating" and "weight"*** in these ***co-morbid patients***. Both Appolinario's and McElroy's studies, which as cites, are also cited in Appolinario's "2004 pharmacotherapy review" where they are identified for their comorbid BED-obesity patients also. Declarant's identification of sibutramine's brand name "Meridia" is, as a POSA would have appreciated at the time of the invention, based on its being FDA-approved for the management of obesity. Thus, Declarant speaks to POSAs "like a POSA,"

*"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)."*

Declarant is careful to regard the art in view of its plainly stated and transparently disclosed teachings ***for the treatment of BED***, as would be expected of a Person with Ordinary Skill in the Art. He does not conflate diagnoses or psychopharmacologic principles, as that would be practicing the art without skill. And this publication is in the "Psychiatric Times," which reads widely among "psychiatrists."

CONCLUSION:

Declarant's conclusion speaks for itself, reasoned as a POSA would have expected at the time of the invention, establishing essential and specific differences and making sure to conflate nothing,

"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."*

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A POSA is always interested in a publication's reference. This is to understand where the author is getting his/her information. While it is assumed that the references speak to the art according to its standard, a POSA is always mindful that there are those without skill who try to claim themselves as having skill and use references misleadingly, perhaps by taking material out of its proper context. And, not surprisingly, Declarant's references as listed below are ***all specific to the treatment*** of ***specific eating disorders (i.e., AN, BN, and/or BED)*** and, when they are not, the context of the reference is made self-evident. No conflation. Rational-thinking. The standard of the art to communicate the teachings of the art.

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A POSA at the time of the invention would have recognized Declarant's reasoning, in his 2004 "Pharmacotherapy of Eating Disorders," as essentially and specifically different than ***that of his Declaration***. This is because in his Declaration (Exhibit 1009), ***he declares*** *(pages cited accordingly)*,

1) *"Because of the **overlapping symptom of binge eating** between **BN** and **BED**, in **my clinical practice** I have **determined and opined that the two disorders tend not to be distinct disorders** but rather exist on a continuum….." (p. 19)*

2) *"G. Biochemical Mechanism of Action of Certain **Agents** Explains their **Usefulness in the treatment of BED**.*

   1. ***Amphetamine and Amphetamine Analogs***

      *"**Amphetamine and amphetamine-like analogs** increase **NE levels** in the synaptic cleft, resulting in the stimulation of post-synaptic receptors and inhibition of feeding. (Ex. 1011, Ioannides-Demos). Also, amphetamine **blocks the DA reuptake** on post-synaptic receptors, which increases the levels of DA in the synaptic cleft and reinforces the suppression of hunger. (Ex. 1011, Ioannides-Demos). **Stimulants** that can increase the **dopaminergic and noradrenergic tone** in the brain may help reduce food cravings. (Ex. 1016, Drimmer, p. 3). **Because all these mechanisms address what is believed to be a main dysfunction in BED**, namely, **abnormally low levels of NTs** in the brain, a **POSA would expect** that **amphetamine and amphetamine analogs** would be **successful….**" (p. 26)*

3) *Re: Claims Construction, "it therefore follows that **the broadest reasonable interpretation of 'therapeutically effective amount'** is an amount effective to decrease the symptoms of BED **or an amount sufficient to significantly reduce the frequency and severity of binge eating behavior [i.e., as in BN and/or AN]**." (p. 32)*

4) *"**It has been explained to me** by my counsel that once prior art is identified, an **obviousness analysis** involves **comparing** a **properly constructed claim** to the **prior art** to determine **whether the claimed invention would have been obvious to a POSA in light of the art**, and in light of the **general knowledge of the art**. I also understand that in order to assess whether a claim is obvious in light of the prior art, I must **step backward in time and***

***into the shoes worn by the hypothetical POSA at the time of the invention**, which I understand is September 13, 2007 with respect to the '813 patent." (p. 33).*

5) *"**It is my understanding** that where there is a **reason to modify** or combine the prior art to achieve a claimed invention, **there must also be a reasonable expectation of success** for a finding of obviousness." (p. 34).*

REGARDING GROUND 1:

1) *"Because of the success of these [d-fenfluramine and sibutramine] centrally acting anti-obesity agents in the treatment of BED, a POSA would have had a **reasonable expectation of success that other centrally acting anti-obesity agents** would similarly reduce binge eating behavior." (p. 36)*

2) *"Mickle teaches amphetamine prodrugs, such as **LDX-dimesylate**, that are **indicated for the treatment of certain disorders**, including **obesity**. In fact, **obesity is identified as a preferred indication**…..*

3) *"In light of the teachings of Appolinario together with Mickle, a **POSA would have diagnosed BED according to the DSM-IV-TR** and would have had a **reasonable expectation of success** in **treating BED** with **LDX-dimesylate**.*

4) *"Thus, it is **my opinion** that….*

    a. ***claim 1** would have been **obvious** over **the combination of Appolinario and Mickle.** (p. 37)*
    b. *claim 8 would have been **obvious** over the **combination of Appolinario and Mickle** for the same reasons that Claim 1 would have been obvious…" (p. 40)*
    c. *claim 13 would have been obvious over the combination of Appolinario and Mickle for the same reasons that claim 1 would have been obvious over the combination of Appolinario and Mickle." (p. 42)*

REGARDING GROUND 4:

1) *"**A POSA** would have known that the **symptom of bulimia** as studied in Ong **closely resembles the symptom of binge eating** described in the **DSM-IV-TR** for **both BN** and **BED."** (p. 45).*

2) *"**Therefore**, a **POSA** reading Ong and the DSM-IV-TR would have **learned to treat BED** by **diagnosing the patient** and **administering methyamphetamine** to the patient. And based upon the teachings of Ong and*

*the DSM-IV-TR, a POSA would have had a **reasonable expectation of success of treating BED** with methylamphetamine used in Ong." (p. 47)*

3) *"Yet, a **POSA** would have also recognized from Ong that 'drugs with **stimulant** and **euphoric effects** carry the dangers of drug dependence and drug induced psychosis…' Such a warning would have led and motivated the POSA to seek an alternative stimulant that could provide similar properties as **methylamphetamine given its success as a treatment** in Ong." (p. 47-48)*

4) *"A **POSA would have been motivated** to **replace methyamphetamin**e as disclosed in Ong with **LDX dimesylate** of Mickle. As noted above, **Ong cautions** about the dangers of dependence and drug-induced psychosis for drugs with stimulant and **euphoric effects**, **with LDX dimesylate designed to exhibit reduced euphoric effects** associated with abuse. Further, a POSA would have expected that LDX dimesylate would have the **same pharmacological effects** as methylamphetamine…."*

5) *"**Therefore,** based on the disclosures of Mickle, a **POSA** would have had a **reasonable expectation of successfully treating BED** by **replacing methylamphetamine** with **LDX dimesylate…."** (p. 50)*

6) *"**In light of the teachings** of **Ong t**ogether with **DSM-IV-TR** and **Mickle**, a **POSA** would have **diagnosed BED according to the DSM-IV-TR** and would have had a **reasonable expectation of success** of **treating BED** with **LDX dimesylate**." (p. 50)*

7) *Thus, … "it is **my opinion** that….*

    a. *claim 1 would have been **obvious** over the **combination of Ong together with DSM-IV-TR and Mickle."** (p. 50)*
    b. *claim 8 would have been **obvious** over the **combination of Ong, DSM-IV-TR, and Mickle** for the same reasons that Claim 1 would have been obvious…" (p. 53)*
    c. *claim 13 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle for the same reasons that claim 1 would have been obvious…." (p. 55).*

REGARDING GROUND 7:

1) *"As previously discussed, an **essential feature** of **both BN** and **BED in DSM-IV-TR** is **'recurrent episodes of binge eating'**….According to the DSM-IV-TR a **'recurrent episode of binge eating' in BED is the same** as a **'recurrent episode of binge eating in BN**." (p. 58)*

2) *"Thus, it **would have been clear** to a **POSA** that the **characteristics of the binge eating episodes in BED** are **essentially the same** as **those in BN**." (p.*

59)

3) ***"Based on the teachings** of the **DSM-IV-TR**, it is **my opinion** that **the binge eating of BN** is **the same** as the **binge eating of BED**." (p. 60)*

4) *"....**given the evidence** of Dukharm demonstrating that **d-amphetamine** was **successful** in eliminating the binge eating **in patients with BN**, a **POSA** would have had a **reasonable expectation of success** in **treating with BED** with **d-amphetamine." (p, 60)***

5) *"**A POSA** would have been **motivated** to replace d-amphetamine as disclosed in Dukarm with LDX dimesylate for the treatment of BED" (p. 61).*

6) *"**In light of the teachings** of **Dukarm** together with the **DSM-IV-TR** and **Mickle**, a **POSA** would have **diagnosed BED according to the DSM-IV-TR** and would have had a **reasonable expectation of success** of **treating BED** with **LDX dimesylate**." (p. 61-62).*

8) *Thus, ... "it is **my opinion** that....*

   a. *claim 1 would have been **obvious** over the **combination of Dukarm** together with **DSM-IV-TR and Mickle."** (p. 62)*
   b. *claim 8 would have been **obvious** over the **combination of Dukarn, DSM-IV-TR, and Mickle** for the same reasons that Claim 1 would have been obvious..." (p. 64-65)*
   c. *claim 13 would have been obvious over the combination of Ong, DSM-IV-TR, and Mickle for the same reasons that claim 1 would have been obvious...." (p. 67).*

REGARDING WHAT REMAINS IN Declarant's DECLARATION

1) *"While it is **not disputed that BN and BED are separate disorders**, it is the fact that **they share the same symptom of binge eating** that is **relevant to this analysis**. As discussed in detail above, one need only look to the DSM-IV-TR to recognize that the **binge eating episodes required for a diagnosis of BN** are **the same** as the **binge eating episodes required for a diagnosis of BED."** (p. 71)*

2) *"Regarding their classification, Fairburn 2000 considered **BN and BED** as **separate disorders**....Yet, it was known by **POSAs,** and recognized by Fairburn, that the **binge eating symptom**, an "objective bulimic episode," is the **essential feature of both disorders."** (p. 72-73).*

3) *"**With respect to treatment**, he [Fairburn] ultimately concludes that **'the patient's specific eating disorder is not of relevance to the treatment**." (p. 74).*

4) *"Providing hypotheses, in my view, is standard practice when authoring a scientific publication, particularly in a 'Discussion' section. The Applicant suggests that hypotheses would somehow derail a POSA from applying* ***the unequivocal results*** *of* ***Dukarm ['s comorbid BN+ADHD]*** *to the* ***treatment of BED. I disagree*** *because a* ***POSA*** *would have made a* ***determination on scientific data*** *and* ***not on hypothetical explanations"*** *(p. 76).*

5) *"****Specifically****, they [Cortese] noted, '****ADHD medications*** *might act both on the* ***brain pathways*** ***involved in ADHD*** *and on those that* ***mediate abnormal eating behaviors****....Thus, the fact that the patients in Dukarn had* ***comorbid ADHD and BN*** *and were* ***successfully treated*** *with the psychostimulant d-amphetamine, may provide* ***further support for the successful use*** *of* ***psychostimulants in BED*** *whether or not the patient satisfies the diagnostic criteria for ADHD.* ***It is my opinion*** *that****....a POSA would have had a reasonable expectation of success*** *in treating BED with the psychostimulant d-amphetamine...."*

6) *"....the result of Dukarm that the stimulant* ***d-amphetamine is useful*** *in treating* ***binge eating symptoms in BN*** *patients* ***comorbid with ADHD****,* ***would not be read in a vacuum."*** *(p. 79).*

7) *"****It is my opinion*** *that given the overlapping symptom of binge eating in BN and BED described in the DSM-IV-TR, together with* ***the extensive data*** *demonstrating the* ***successful use of psychostimulants*** *in the* ***treatment of binge eating described in Dukarm****,* ***POSA*** *would have had a* ***reasonable expectation of success*** *in extending the teachings of Dukarm to the* ***treatment of BED****." (p. 79).*

8) *"It was* ***well understood in 2007*** *that* ***centrally acting psychostimulants*** *can* ***successfully*** *treat binge eating as evidenced, for instance, by* ***Ong*** *(reduction in overeating* ***[for 30 minutes] after administering [IV] methylamphetamine****), Schweickert* ***[in BN with comorbid ADHD]*** *(reduction in binge eating after administration of methyphenidate), Sokol (reduction in binge eating and impulsivity* ***[in BN associated with Cluster B Personality Disorder]*** *after administering methylphenidate), Drimmer (reduction in binge eating* ***[in BN with and without ADHD]*** *after administering methylphenidate, mixed amphetamine salts, and d-amphetamine), and* ***Dukarm [in BN comorbid ADHD]*** *(reduction in binge eating after administering d-amphetamine.....*

Notably, the psychostimulants involved in these studies – methylamphetamine, methyphenidate, and d-amphetamine – ***all increase levels of DA levels [in the absence of any appreciable serotonin/5-HT potentiation]*** which as decribed above *'is one of the most important neurotransmitters involved in reinforcing value of food and regulation of food intake.' (p. 87-88)*

*In turn, a **POSA would have expected** that **psychostimulants as a class**, and **especially those that affect DA level**, would be effective for **treating BED**.*

*It follows that a **POSA would have expected LDX dimesylate** to **effectively treat binge eating** and **thereby treat BED**, since LDX dimesylate is a centrally acting amphetamine prodrug that releases d-amphetamine." (p. 87-88).*

7) *"As I have discussed at length above, it would have been **obvious to use psychostimulants** to **treat binge eating and therefore BED**."*

8) *"…during prosecution when discussing the use of LDX dimesylate for the treatment of BED, **the Applicant stated** that 'the **only known medications are only partially effective (anti-depressants)** or **have serious side effects (topiramate)'** and concluded that **LDX dimesylate 'thus fulfills a long felt unmet need.'**…The **Applicant ignored** the **extensive body of published literature** that **identifies the many classes** of **active agents** that were **used for the treatment** of binge eating**, including BED**."*

9) *"I hereby declare that **all statements made herein are** of my own knowledge are **true** and that **all statements made** on **information** and **belief are believed to be true**; and further that these statements were made with the knowledge that **willful false statement and the like** so made are **punishable by fine or imprisonment, or both**, under Section 1001 of Title of the United States Code."*

In this respect, a POSA "at the time of the invention" (with foresight) or a POSA "as of today" (with hindsight) would have recognized that nowhere is there a better example of a ***diametrically opposite line of reasoning*** than that of Declarant (***as plainly stated and transparently disclosed in his Declaration)*** than in the example of the Petitioner's randomized, placebo-controlled, double-blind clinical trial for the treatment of BED "as defined in the DSM-IV-TR" with the drug LDX-dimesylate. (See attached). The Petitioner's BED/LDX-dimesylate clinical trial, according to the attached Phase III clinical trial protocol (from clinicaltrials.gov) was reported to have begun in November 2012, the very same month '813 was issued. The Petitioner's BED/LDX-dimesylate clinical trial requires that each subject, in order to be included in the trial, satisfy the DSM-IV-TR criteria for a diagnosis of BED and also have a diagnosis of BED. Here, the Petitioner reasons like a POSA. The Petitioner reasons like Declarant in his 2004 "Pharmacotherapy of Eating Disorders." This is because the Petitioner seeks an accurate diagnosis according to the standards of the art, the same standard practiced by many POSAs for nearly two decades since the DSM-IV had been published in 1994 regarding, specifically, BED as defined in the DSM-IV/IV-TR.

Macowner 8/10/14 10:44 PM
Comment [11]:

Reference 11

Shire Pharmaceutical Development Phase III protocol -- clinicaltrials.gov

As the clinical trial protocol reveals, the Petitioner recognizes the limitations of the diagnosis and communicates it to the community of POSAs by the shared language

of the art – the DSM-IV-TR criteria of BED. The Petitioner teaches to making a specific diagnosis of BED by virtue of its essential and specific criteria. And thus, the Petitioner teaches on differentiating BED diagnostically from BN and AN in order to conduct its trial for LDX dimesylate in BED. Here, the Petitioner reasons like a POSA, motivated to treat the same essential disorder in view of its essential and specific differences with other eating disorders that may share certain non-specific symptoms (i.e., binge eating). The Petitioner even makes it a point to remind the community of the trial's ***exclusion criteria – NO patients with "concurrent symptoms of bulimia nervosa or anorexia nervosa."***

The Petitioner's trial is with the same drug (randomized with placebo) for essentially the same duration of time (up to 12 weeks) with specifically different doses (50-70 mg). Here, the Petitioner is reasoning with ordinary skill in the art. The Petitioner is making essential and specific distinctions about how to best provide a "therapeutically effective amount" of LDX-dimesylate to the treated subjects so that they may be treated for their particular disorder (i.e., BED as defined in the DSM-IV-TR). And the Petitioner is doing so in view of the plainly stated and transparently disclosed teachings of the art, including with respect to the limitations of diagnosis (i.e., ***no binge eating-BN patients***; ***no binge eating-AN patients***). And, of course, the Petitioner is showing that it respects the art's basic teachings and essential distinctions because it is investigating the ***same one drug***, ***LDX-dimesylate***, in ***essentially the same one disorder, BED as defined in the DSM-IV-TR,*** in order to evaluate the efficacy of the drug for the treatment of the one specific disorder***.*** The Petitioner is not conflating the art's essential teachings, nor its specific ones. But, rather, the Petitioner clarifies them in open view. The Petitioner is drawing on the art's teachings to establish practice measures for LDX-dimesylate's treatment in view of an adequate duration, an adequate dose, and a proper efficacy measure (i.e., number of "binge days/week") for the treatment of the ***DSM-IV-TR-based eating disorder known as BED***. Indeed, the Petitioner is ***very closely guided*** by the ***plainly stated*** and ***transparently disclosed teachings of the art*** that came before its very Phase III trial protocol. The reason for this is so that the trial could, naturally, be run according to the teachings of the art for diagnosing Binge Eating Disorder and successfully treating it with LDX-dimesylate.

In this respect, a POSA at the time of the invention (with foresight) or a POSA "as of today" (with hindsight) would readily identify ***diametrically opposite lines of reasoning*** that the Petitioner applies to the ***same exact one thing***, namely, ***LDX-dimesylate as a method of treatment for BED as defined in the DSM-IV-TR***. This is because the Petitioner reasons one way with respect to '813's independent claims but reasons in a way diametrically opposite for its Phase III clinical trial protocol. But a POSA, at the time of the invention (with foresight) or "as of today" (with hindsight), would readily have come to ***one other specific conclusion by essentially one line of reasoning in view of this.*** That conclusion is that the Petitioner's "big three" (Grounds 1, 4, and 7) arguments are ***patently wrong*** because they are ***completely reasoned by a person without ordinary skill in the art.*** The Petitioner's "big three arguments" repeatedly and consistently conflate, ignore,

disregard -- ***in view of their own Phase III trial protocol*** -- the most basic distinctions and rudimentary teachings of the art of diagnosis and psychopharmacology of eating disorders. And the Petitioner does so in view of the teachings plainly stated and transparent disclosed teachings ***in its own prior art Exhibits***. This would have all been obvious to a person of ordinary skill in the art "as of September 13, 2007" who could see into the future. Just as it would all be obvious to a person of ordinary skill in the art "as of today" who sees into the past.

And, conversely, a POSA "as of September 13, 2007" would have necessarily come to another unmistakable and very specific conclusion its diametric opposite - ***in view of the Petitioner's "big three" arguments.*** That conclusion is that '813's "big three" independent claims would not have been obvious. This is because a person with ordinary skill in the art, reasoning rationally and with respect to the art's most ordinary distinctions and basic teachings, as they are plainly stated and transparently disclosed in the art, would never have reasoned to "813's independent claims. And, surely, they would never have considered them to have a reasonable expectations of success.

And here is the lesson as "any reasonable person" would see it from a place of hindsight today. There is indeed an essential and specific difference in those that practice the art with ordinary skill and those who don't. But even so, they can end up at exactly the same place:

> ***'813's Claim 1:***
> *A method of treating Binge Eating Disorder, comprising diagnosing a patient as having Binge Eating Disorder, wherein the patient exhibits Binge Eating Disorder as defined in the DSM-IV-TR and administering a therapeutically effective amount of lisdexamfetamine dimesylate to the patient, wherein the lisdexamfetamine dimesylate is the only active agent administered or administered with one or more active agents.*
>
> ***'813's Claim 8:***
> *A method of treating Binge Eating Disorder, comprising diagnosing a patient as having Binge Eating Disorder, wherein the patient exhibits Binge Eating Disorder as defined in the DSM-IV-TR and administering a therapeutically effective amount of lisdexamfetamine dimesylate to the patient wherein the lisdexamfetamine dimesylate is the only active agent administered.*
>
> ***'813's Claim 13:***
> *A method of treating Binge Eating Disorder as defined in the DSM-IV-TR, comprising administering a therapeutically effective amount of lisdexamfetamine to a patient in need thereof, wherein the lisdexamfetamine dimesylate is the only active agent administered or is administered together with one or more additional agents.*

dosage of 1 to 2 g intravenously followed by increments of 250 mg every five minutes.

HOW SUPPLIED

NDC 0046-0374-06—*Hospital Package:* This contains six 20 mL vials of 1 g each of sterile Protopam Chloride (pralidoxime chloride) white to off-white porous cake*, without diluent or syringe. Solution may be prepared by adding 20 mL of Sterile Water for Injection, USP. These are single-dose vials for intravenous injection or for intravenous infusion after further dilution with physiologic saline. Intramuscular or subcutaneous injection may be used when intravenous injection is not feasible.

*When necessary, sodium hydroxide is added during processing to adjust the pH.

Store at room temperature (approximately 25°C).

ANIMAL PHARMACOLOGY AND TOXICOLOGY

The following table lists chemical and trade or generic names of pesticides, chemicals, and drugs against which Protopam (usually administered in conjunction with atropine) has been found to have antidotal activity on the basis of animal experiments. All compounds listed are organophosphates having anticholinesterase activity. A great many additional substances are in industrial use but have been omitted because of lack of special information.

AAT—see PARATHION

AFLIX®—see FORMOTHION

ALKRON®—See PARATHION

AMERICAN CYANAMID 3422—see PARATHION

AMITON—diethyl-S-(2-diethylaminoethyl)phosphorothiolate

ANTHIO®—see FORMOTHION

APHAMITE—see PARATHION

ARMIN—ethyl-4-nitrophenylethylphosphonate

AZINPHOS-METHYL—dimethyl-S-(4-oxo-1,2,3,-benzotriazin-3 (4H)-ylmethyl) phosphorodithioate

MORPHOTHION—dimethyl-S-2-keto-2-(N-morpholyl)ethylphosphorodithioate

NEGUVON®—see TRICHLOROFON

NIRAN®—see PARATHION

NITROSTIGMINE—see PARATHION

O,O-DIETHYL-O-p-NITROPHENYL PHOSPHOROTHIOATE—see PARATHION

O,O-DIETHYL-O-p-NITROPHENYLTHIO PHOSPHATE—see PARATHION

OR 1191—see PHOSPHAMIDON

OS 1836—see VINYLPHOS

OXYDEMETONMETHYL—dimethyl-S-2-(ethylsulfinyl) ethyl phosphorothiolate

PARAOXON—diethyl (4-nitrophenyl) phosphate

PARATHION—diethyl (4-nitrophenyl) phosphorothionate

PENPHOS—see PARATHION

PHENCAPTON—diethyl-S-(2,5-dichlorophenylmercaptomethyl) phosphorodithioate

PHOSDRIN®—see MEVINPHOS

PHOS-KIL—see PARATHION

PHOSPHAMIDON—1-chloro-1-diethylcarbamoyl-1-propen-2-yl-dimethylphosphate

PHOSPHOLINE IODIDE®—see echothiophate iodide

PHOSPHOROTHIOIC ACID, O,O-DIETHYL-O-p-NITROPHENYL ESTER—see PARATHION

PLANTHION—see PARATHION

QUELETOX—see FENTHION

RHODIATOX®—see PARATHION

RUELENE®—4-tert-butyl-2-chlorophenylmethyl-N-methylphosphoroamidate

SARIN—isopropyl-methylphosphonofluoridate

SHELL OS 1836—see VINYLPHOS

SHELL 2046—see MEVINPHOS

SNP—see PARATHION

SOMAN—pinacolyl-methylphosphonofluoridate

SYSTOX®—diethyl-(2-ethylmercaptoethyl) phosphorothionate

TEP—see TEPP

TEPP—tetraethylpyro phosphate

THIOPHOS®—see PARATHION

TIGUVON—see FENTHION

TRICHLOROFON—dimethyl-1-hydroxy-2,2,2-trichloroethylphosphonate

VAPONA®—see DICHLORVOS

VAPOPHOS—see PARATHION

VINYLPHOS—diethyl-2-chloro-vinylphosphate

PROTOPAM appears to be ineffective, or marginally effective, against poisoning by:
CIODRIN® (alpha-methylbenzyl-3[dimethoxyphosphinyloxy]-ciscrotonate)
DIMEFOX (tetramethylphosphorodiamidic fluoride)
DIMETHOATE (dimethyl-S-[N-methylcarbamoylmethyl]-phosphorodithioate)
METHYL DIAZINON (dimethyl-[2-isopropyl-4-methylpyrimidyl]-phosphorothionate)
METHYL PHENCAPTON (dimethyl-S-[2,5-dichlorophenylmercaptomethyl]phosphorodithioate)
PHORATE (diethyl-S-ethylmercaptomethylphosphorodithioate)
SCHRADAN (octamethylpyrophosphoramide)
WEPSYN® (5-amino-1-[bis-(dimethylamino) phosphinyl]-3-phenyl-1,2,4-triazole).

The use of Protopam should, nevertheless, be considered in any life-threatening situation resulting from poisoning by these compounds, since the limited and arbitrary conditions of pharmacologic screening do not always accurately reflect the usefulness of Protopam in the clinical situation.

CLINICAL STUDIES

The use of Protopam (pralidoxime) has been reported in the treatment of human cases of poisoning by the following substances:
Azodrin
Diazinon
Dichlorvos (DDVP) with chlordane
Disulfoton
EPN
Isoflurophate
Malathion
Metasystox I® and Fenthion
Methyldemeton
Methylparathion
Mevinphos
Parathion
Parathion and Mevinphos
Phosphamidon
Sarin
Systox®
TEPP

Of these cases, over 100 were due to parathion, about a dozen each to malathion, diazinon, and mevinphos, and a few to each of the other compounds.

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REDUX™ ℞

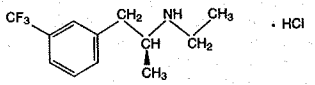
[*ree'duks*]

(dexfenfluramine hydrochloride capsules)

DESCRIPTION

Redux (dexfenfluramine hydrochloride capsules), an anti-obesity drug, is a serotonin reuptake inhibitor and releasing agent. Redux is available for oral administration in white, opaque, hard-gelatin capsules. The active ingredient is dexfenfluramine hydrochloride. Each capsule contains 15 mg dexfenfluramine hydrochloride. Inactive ingredients include: lactose, gelatin capsule, corn starch, microcrystalline cellulose, talc, titanium dioxide, magnesium stearate, colloidal silicon dioxide, and edible ink.

Dexfenfluramine hydrochloride, a white to off-white crystalline powder, is designated chemically as (S)-N-ethyl-α-methyl-3-(trifluoromethyl) benzene-ethanamine hydrochloride and has a molecular weight of 267.7. Its empirical formula is $C_{12}H_{16}F_3N \bullet HCl$ and its structural formula is:



Dexfenfluramine hydrochloride is freely soluble in water, alcohol, chloroform, and methanol. The pK_a of dexfenfluramine hydrochloride is 10.

CLINICAL PHARMACOLOGY

Pharmacologic Actions

The action of Redux in treating obesity is primarily via decreased caloric intake associated with increased serotonin levels in brain synapses. Redux is a serotonin reuptake inhibitor and releasing agent. *In vitro* studies have confirmed the dual serotoninergic mechanism of action of dexfenfluramine by demonstrating that the drug inhibits serotonin reuptake by axon terminals and causes the release of serotonin from synaptosomes. In animals, the reduced caloric intake and the loss in body weight elicited by dexfenfluramine is associated with release of serotonin from presynaptic axon terminals in the brain, inhibition of neuronal serotonin reuptake, and, therefore, an increase of serotonin receptor activation. This results in an enhancement of serotoninergic transmission in the centers of feeding behavior, located in the ventromedial nucleus of the hypothalamus. In rats, enhanced serotoninergic transmission induced by dexfenfluramine selectively suppressed appetite for carbohydrates which resulted in reduction of food consumption when the dietary carbohydrate to protein ratio was high. Unlike amphetamines and other serotonin-active agonists and antagonists, dexfenfluramine neither enhances nor suppresses dopamine-mediated neurotransmission.

In clinical trials, Redux treatment in conjunction with a reduced-calorie diet is associated with a reduction in appetite and may slow gastric emptying. These and other actions may contribute to the reduction in caloric consumption associated with Redux. In one clinical trial, Redux was shown to preferentially decrease carbohydrate consumption at meals and to manage carbohydrate craving between meals by decreasing the consumption of snack foods with a high carbohydrate content in patients who frequently snack on such foods.

Pharmacokinetics and Metabolism

Systemic Bioavailability

Dexfenfluramine is completely absorbed after oral dosing, with a systemic bioavailability of about 68% because of first pass metabolism by the liver. In studies in which patients received a single 30-mg oral dose of dexfenfluramine, mean peak plasma concentrations of dexfenfluramine ranged between 11 and 41 ng/mL in individual patients after 1.5 to 8.0 hours. The average terminal elimination half-life of plasma dexfenfluramine ranged from 17 to 20 hours, and the average total body clearance of dexfenfluramine was 691.9 mL/min. In man, following doses of 15 mg Redux twice a day for 15 days, mean maximal plasma dexfenfluramine concentrations ranging from 15 to 92 ng/mL were observed, and steady-state plasma levels were achieved 8 days after the initial dose. The average steady-state plasma concentrations were somewhat lower than predicted by single-dose pharmacokinetics and the average time to steady-state was longer

Continued on next page

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than the predicted 4 to 5 days. The major active metabolite, *d*-norfenfluramine, accumulated to maximal plasma concentrations of about 26 ng/mL, with steady-state plasma levels occurring at about 9 days. The *d*-norfenfluramine plasma half-life is estimated to be 32 hours. After reaching steady-state levels, there was no evidence of increasing concentrations of dexfenfluramine or *d*-norfenfluramine in plasma during 12 months of dosing. Following administration of single 30-mg, 40-mg, and 60-mg doses of dexfenfluramine to healthy volunteers, dexfenfluramine C_{max} values of 25 ng/mL, 33 ng/mL, and 51 ng/mL and area-under-the-curve$_{0-t}$ values of 144 ng·hr/mL, 191 ng·hr/mL, and 275 ng·hr/mL, respectively, were found. In a dose response study of Redux involving obese patients treated for 12 weeks, dexfenfluramine C_{min} values of 24 ng/mL at a dose of 15 mg twice daily and 58 ng/mL at a dose of 30 mg twice daily were observed. These data suggest that plasma concentrations of dexfenfluramine increase in proportion to the administered dose.

Protein Binding and Distribution

At a dexfenfluramine plasma concentration of 100 ng/mL, 36% is bound to plasma proteins. Dexfenfluramine is distributed into body tissue in non-obese subjects, with a volume of distribution of 839 L.

Metabolism

Dexfenfluramine is metabolized in the liver. The first steps in the metabolism of dexfenfluramine are dealkylation, resulting in formation of the active metabolite, *d*-norfenfluramine and deamination to an inactive *d*-hydroxy derivative. In a study of drug metabolism using radiolabeled dexfenfluramine, levofenfluramine and *d,l*-fenfluramine in two healthy subjects, 92% of the administered radioactivity was found in urine and 1% in feces over 6 days. Fenfluramine accounted for 7% to 19% and norfenfluramine accounted for 4% to 11% of the urine radioactivity. Other metabolites (inactive) included 1-(m-trifluoromethylphenyl)-1,2-propane diol (21 to 38%), m-trifluoromethyl benzoic acid (7 to 22%), m-trifluoromethyl hippuric acid (<1 to 11%), and 1-(m-trifluoromethylphenyl)-propan-2-ol (2 to 4%).

Renal Disease and Liver Disease

Specific studies in patients with renal and hepatic impairment have not been conducted.

Obese Patients

In obese patients who received a single 30-mg dose, a mean peak plasma dexfenfluramine concentration of about 22.3 ng/mL is reached after about 5.2 hours. In a parallel-group, multiple-dose pharmacokinetic study of dexfenfluramine (15 mg twice daily) there were no significant differences in steady-state pharmacokinetic parameters between obese and non-obese subjects.

Age

The pharmacokinetics of a single 30-mg dose of Redux in eight elderly patients, ranging from 66 to 83 years of age, have been examined in one study. The mean maximal plasma concentration was 21.8 ng/mL, and ranged from 9.7 to 33.0 ng/mL in individual patients. Time to maximal plasma concentration was about 5 hours and ranged from 3 hours to 10 hours. Area-under-the-curve to infinity was 615 ng·hr/mL and ranged from 16 to 1205 ng·hr/mL. Mean (±SD) steady-state plasma concentrations of dexfenfluramine and *d*-norfenfluramine after six months of treatment (15 mg twice daily) in 18 obese patients over 60 years old were 27.3 (±16.3) ng/mL and 14.0 (±7.4) ng/mL, respectively, compared to values of 24.1 (±15.9) and 15.6 (±11.2), respectively, in 268 patients under 60 years old. In a cohort of these patients followed through 12 months of treatment (15 mg twice daily) mean (±SD) steady-state plasma concentrations of dexfenfluramine and *d*-norfenfluramine in 17 obese patients over 60 years old were 32.9 (±16.8) ng/mL and 18.0 (±8.0) ng/mL, respectively, compared to values of 23.9 (±12.9) and 14.4 (±8.2), respectively, in 186 obese patients under 60 years old.

Clinical Studies

Observational epidemiologic studies have established a relationship between obesity and the risks for cardiovascular disease, non-insulin dependent diabetes mellitus (NIDDM), certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for some patients with chronic obesity who may also be at risk for other diseases.

The long-term effects of Redux on the morbidity and mortality associated with obesity have not been established. Short-term (<4 months), placebo-controlled, double-blind studies have provided evidence that Redux does not adversely affect glycemia, lipid profile, or blood pressure control in obese patients. Some short-term studies have suggested that weight loss with Redux may be associated with a reduction in hyperglycemia in obese diabetic patients, a reduction in blood pressure in obese hypertensive patients, and improvement in the lipid profile in obese hyperlipidemic patients.

Redux has been shown to be effective in reducing excess body weight in obese patients. In 16 of 17 double-blind, placebo-controlled trials, of various treatment durations and with different design features, where all patients were on reduced-calorie diets, Redux-treated patients lost statistically significantly more weight on average than those treated with placebo. In these studies, weight loss was evident within 4 weeks of initiating treatment, even in some patients where reduced-calorie diet alone had failed to induce a significant weight loss.

In the INDEX study, a one-year, double-blind, placebo-controlled trial of obese patients, Redux, in conjunction with a reduced-calorie diet, produced a significant reduction in weight during the first 4 to 6 months. This response was maintained during continuation of therapy (up to 12 months of treatment). The percentage of patients who achieved various levels of weight loss at 1 year are shown below:

Percentage of Patients Losing Weight at One Year

	≥15% loss		≥10% loss		≥5% loss	
	Redux	Pbo	Redux	Pbo	Redux	Pbo
Completers* (Redux n=297/ Placebo n=262)	29%	16%	52%	30%	72%	50%
All patients ** (Redux n=463/ Placebo n=467)	21%	10%	40%	21%	64%	43%

* Data for patients who completed the entire 12-month period of the trial.

** Data for all patients who received study drug and who had any post-baseline measurement; for those patients who discontinued treatment before 12 months, the last observed data is carried-forward through the end of the study and analyzed with data from those patients who completed the trial.

Based on another analysis of the INDEX study, among all patients who were treated with Redux and identified as initial responders (*i.e.*, lost at least 4 pounds in the first 4 weeks of therapy), 60% went on to lose ≥10% of their initial body weight by the end of 1 year of treatment. Among Redux-treated patients, 78% were identified as initial responders. At the end of 1 year, the mean weight loss for the initial responders was 22 pounds, while the non-responders had a mean weight loss of 6 pounds.

Among obese patients who had been successful in losing weight by dieting alone (*i.e.*, lost at least 10 pounds in the prior year), the addition of Redux to the regimen resulted in the further loss of 26% of initial excess weight, while successful dieters who received placebo lost only 7% of initial excess weight.

INDICATIONS AND USAGE

Redux is indicated for the management of obesity including weight loss and maintenance of weight loss in patients on a reduced calorie diet. Redux is recommended for obese patients with an initial body mass index ≥30 kg/m², or ≥27 kg/m² in the presence of other risk factors (*e.g.*, hypertension, diabetes, hyperlipidemia).

The safety and effectiveness of Redux beyond 1 year have not been determined at this time.

Below is a chart of Body Mass Index (BMI) based on various heights and weights.

BMI is calculated by taking the patient's weight, in kg, divided by the patient's height, in meters, squared. Metric conversions are as follows: pounds ÷ 2.2 = kg; inches × 0.0254 = meters.

BODY MASS INDEX (BMI), kg/m²

	Height (feet, inches)					
Weight (pounds)	5'0"	5'3"	5'6"	5'9"	6'0"	6'3"
140	27	25	23	21	19	18
150	29	27	24	22	20	19
160	31	28	26	24	22	20
170	33	30	28	25	23	21
180	35	32	29	27	25	23
190	37	34	31	28	26	24
200	39	36	32	30	27	25
210	41	37	34	31	29	26
220	43	39	36	33	30	28
230	45	41	37	34	31	29
240	47	43	39	36	33	30
250	49	44	40	37	34	31

Patients with BMI values ≥30 may be candidates for Redux therapy.

Patients with BMI values of 27-29 may be candidates for Redux therapy if they also have a concomitant risk factor (*e.g.*, hypertension, diabetes, hyperlipidemia).

CONTRAINDICATIONS

Redux is contraindicated in patients with diagnosed pulmonary hypertension (see **WARNINGS**).

Redux is contraindicated in patients receiving monoamine oxidase inhibitors (see **PRECAUTIONS**—*Drug Interactions*).

Redux is contraindicated in patients with hypersensitivity to dexfenfluramine, fenfluramine, or related compounds.

WARNINGS

Primary Pulmonary Hypertension

A 2-year, international (5 country), case-control (epidemiological) study identified 95 primary pulmonary hypertension (PPH) cases; 20 of these had been exposed to anorexigens in the past, and 9 of the 20 had been exposed to anorexigens for longer than three months. In this study, the use of anorexigens for longer than 3 months was associated with an increase in the risk of developing PPH (odds ratio = 9.1, 95% confidence interval = 2.6–31.5). This increased risk of PPH was concentrated in persons who had used the drugs within the preceding year; there was no significant increase in risk for persons who had taken the drugs more than 1 year ago or for persons who had used these agents for 3 months or less. In the general population, the yearly occurrence of PPH is estimated to be about 1–2 cases per 1,000,000 persons. Therefore, the case-control study indicated an estimated risk associated with the long-term use of anorexigen drugs of about 18 cases per million persons exposed per year. According to the case-control study, obesity itself (body mass index ≥30 kg/m²) was also associated with an increase of about two-fold in the risk of developing PPH.

PPH is a serious condition; the 4-year survival rate has been reported to be 55%.

The initial symptom of pulmonary hypertension is generally dyspnea. Other initial symptoms include: angina pectoris, syncope, or lower extremity edema. *Patients should be advised to report immediately any deterioration in exercise tolerance. Treatment should be discontinued in patients who develop new, unexplained symptoms of dyspnea, angina pectoris, syncope, or lower extremity edema. These patients should be evaluated for the etiology of these symptoms and the possible presence of pulmonary hypertension.*

Neurochemical Findings in Animals

Dexfenfluramine and its active metabolite *d*-norfenfluramine are believed to reduce food intake through interactions with the serotoninergic neurotransmitter system. In animals, doses of dexfenfluramine that result in brain concentrations approximately 10 times those observed in humans produce prolonged reductions (weeks to months) in brain serotonin concentrations following cessation of dexfenfluramine treatment. These reductions in brain serotonin concentrations are accompanied by correlate observations of diminished visualization of serotoninergic neurons by immunohistochemical techniques and decreased numbers of serotonin transporters. Some investigators have interpreted these results as surrogate indicators of neurotoxicity; others have interpreted these results as an extension of the pharmacology of serotonin reuptake inhibitors. Resolution of differences in the interpretation of the animal findings may occur with further research.

Changes in brain serotonin concentrations following acute, high-dose dexfenfluramine administration have been noted in all animal species and with all routes of drug administration tested. Prolonged reductions in brain serotonin concentrations in rats have been observed following acute, but not escalating, dose regimens. In mice, 2 years of drug administration at a dose producing at least 12 times the human brain level of dexfenfluramine produced no change in brain serotonin concentrations or serotonin transporter number. Changes in brain serotonin concentrations generally have been found to be reversible; however, the dose and brain concentration of dexfenfluramine and *d*-norfenfluramine may affect reversibility. Persistent reductions in brain serotonin concentrations and neuronal serotonin immunoreactivity were observed in three squirrel monkeys 14–17 months after a 4-day, 10 mg/kg/day subcutaneous dose regimen of dexfenfluramine; the effects of lower doses or different dose regimens were not reported in this study. In a separate study, other squirrel monkeys given this high-dose regimen achieved brain concentrations of dexfenfluramine approximately 35 times those of obese patients taking normal therapeutic doses.

Studies employing experimental techniques that are independent of serotonin content (*e.g.*, retrograde transport, silver staining, glial fibrillary acidic protein content) could not detect neuronal damage at doses of dexfenfluramine in animals producing decreased brain serotonin concentrations. The observed neurochemical changes were not associated with persistent changes in animal behavior.

The relevance of the animal findings to humans is not known.

Miscellaneous

Organic causes of obesity (*e.g.*, hypothyroidism) should be excluded before prescribing Redux.

Redux should be used with caution in patients with glaucoma.

PRECAUTIONS

General

Because of Redux's potential to produce mild-to-moderate drowsiness, the patient's individual response should be assessed before engaging in activities requiring alertness. Redux may potentiate the sedative effects of alcohol or other drugs with CNS action.

If the patient develops any symptoms of intolerance, *e.g.*, nausea and vomiting, the dosage should be reduced, or the drug discontinued.

Misuse Potential

As with any weight-loss agent, the potential exists for misuse of Redux in inappropriate patient populations (*e.g.*, patients with anorexia nervosa or bulimia). See **INDICATIONS AND USAGE** for recommended prescribing guidelines.

Information for Patients

Patients should be informed that false-positive urine drug tests for amphetamines have been observed for up to 24 hours following a 30-mg dose (2 capsules) of Redux. See ***Drug/Laboratory Test Interactions.***

Combination Therapy

The safety and efficacy of dexfenfluramine in combination with other weight-loss agents have not been studied; therefore, concomitant use is not recommended.

Use in Patients with Concomitant Illness

Weight loss has been associated with a reduction in hyperglycemia in obese diabetic patients, a reduction of blood pressure in obese hypertensive patients, and an improvement in the lipid profile in obese hyperlipidemic patients. Therefore, when Redux™ (dexfenfluramine hydrochloride capsules) is used for the management of obesity associated with hypertension, diabetes, or dyslipidemia, there may be changes in these conditions and the medications used to treat them should be monitored, and adjusted, if necessary.

Drug Interactions

In patients receiving nonselective monoamine oxidase inhibitors (MAOIs) (*e.g.*, selegiline hydrochloride) in combination with serotoninergic agents (*e.g.*, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), there have been reports of serious, sometimes fatal, reactions. Because Redux is a serotonin releaser and reuptake inhibitor, Redux should not be used concomitantly with a MAO inhibitor (see **CONTRAINDICATIONS**).

At least 14 days should elapse between discontinuation of a MAO inhibitor and initiation of treatment with Redux. At least 3 weeks should elapse between discontinuation of Redux and initiation of treatment with a MAO inhibitor.

A rare, but serious, constellation of symptoms, termed "serotonin syndrome," has been reported with the concomitant use of selective serotonin reuptake inhibitors (SSRIs) and agents for migraine therapy, such as Imitrex® (sumatriptan succinate) and dihydroergotamine. The syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.

Redux should not be administered with other serotoninergic agents. The appropriate interval between administration of these agents and Redux has not been established.

The use of dexfenfluramine with other CNS-active drugs has not been systematically evaluated; consequently, caution is advised if dexfenfluramine and such drugs are prescribed concurrently.

Drug/Laboratory Test Interactions

False-positive urine drug tests for amphetamines by ELISA have been observed for up to 24 hours following a 30-mg dose (2 capsules) of Redux. Patients should be informed of this possible false-positive laboratory finding when undergoing urine drug screenings. Gas chromatography/mass spectroscopy can distinguish false-positive urine drug tests caused by dexfenfluramine from true-positive drug tests. See ***Information for Patients.***

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies in rats and mice have not shown a carcinogenic potential for dexfenfluramine at doses up to 12 mg/kg and 27 mg/kg, respectively. These doses are 4.8 and 5.8 times the daily human dose (calculated on a body surface area [mg/m^2] basis). When given to pregnant rats, dexfenfluramine caused a significant reduction in the number of fetuses and live young.

Dexfenfluramine has no detectable mutagenic activity as determined by the Ames test, gene conversion-DNA repair test, evaluation of the clastogenic effect on cultures of human lymphocytes, mouse lymphoma cell mutation test, and the micronucleus test in the mouse.

Pregnancy

Teratogenic Effects—Pregnancy Category C

Dexfenfluramine produced dose-related effects on reproduction and fertility in rats. In a three-generation fertility and reproduction study, administration of dexfenfluramine to female rats at 2.5 and 5 times the human daily dose (calculated on a body surface area [mg/m^2] basis) caused significant reductions in body weight and weight gain throughout pregnancy; the number of placental implantations and fetuses was reduced, there was a reduced number of live young, and delayed ossification was seen in the fetuses. No significant treatment-related adverse effects or abnormalities were observed in second- and third-generation rats.

Teratogenicity studies were conducted in rats and rabbits. Neither study showed any treatment-related embryotoxicity or teratogenicity at doses up to 10 times the daily human dose (calculated on a body surface area [mg/m^2] basis).

There are no adequate and well-controlled studies of Redux in pregnant women. Redux is not recommended for pregnant women.

Nursing Mothers

Dexfenfluramine is excreted in rat milk. It is not known whether dexfenfluramine is excreted in human milk. Therefore, dexfenfluramine should not be administered to a nursing woman.

Use in Other Populations

Pediatric Use

Safety and effectiveness of Redux in pediatric patients have not been established.

Geriatric Use

As with all CNS-active medications, caution should be exercised in treating elderly patients with Redux. Clinical studies of Redux did not include sufficient numbers of patients aged 65 or older to determine whether they respond differently than younger patients. Pharmacokinetics in elderly patients are discussed in **CLINICAL PHARMACOLOGY.**

TREATMENT-EMERGENT ADVERSE EVENTS FROM PLACEBO-CONTROLLED CLINICAL TRIALS

ADVERSE EVENT	PERCENT OF REDUX-TREATED PATIENTS (15 mg twice daily) (n=1159)	PERCENT OF PLACEBO-TREATED PATIENTS (n=1138)
BODY AS A WHOLE		
Headache	16.1	15.5
Asthenia	15.8	10.7
Abdominal Pain	6.7	6.0
Chills	2.9	1.2
Accidental Injury	2.8	2.3
GASTROINTESTINAL SYSTEM		
Diarrhea	17.5	7.3
Vomiting	3.2	2.9
METABOLIC/NUTRITIONAL SYSTEM		
Thirst	2.8	1.1
NERVOUS SYSTEM		
Insomnia	19.9	18.6
Dry Mouth	12.5	5.0
Somnolence	7.1	3.4
Dizziness	5.5	4.0
Depression	4.7	3.6
Vertigo	3.1	1.7
Emotional Lability	3.1	2.7
Abnormal Dreams	2.0	1.4
Thinking Abnormal	2.0	1.1
RESPIRATORY SYSTEM		
Pharyngitis	6.1	5.6
Cough Increased	3.6	3.0
Bronchitis	3.4	1.8
SKIN/APPENDAGES		
Rash	2.3	2.2
UROGENITAL SYSTEM		
Urinary Frequency	2.8	1.1
Polyuria	2.1	1.0

ADVERSE REACTIONS

Commonly Observed

The most commonly observed, treatment-emergent adverse events associated with the use of Redux in double-blind, placebo-controlled clinical trials were diarrhea (17.5%), dry mouth (12.5%), and somnolence (7.1%). These and other commonly observed adverse reactions were generally mild and transient. (Commonly observed is defined as incidence of 5% or greater and incidence in dexfenfluramine group at least twice that of placebo group, as derived from the table below.)

Associated with Discontinuation of Treatment

Seven percent of the 1159 patients who received dexfenfluramine in double-blind, placebo-controlled clinical trials discontinued treatment because of an adverse event. The most common adverse events resulting in discontinuation included asthenia, insomnia, headache, and depression. Five percent of the 1138 placebo-treated patients discontinued because of an adverse event.

Incidence in Controlled Clinical Trials

The following table lists treatment-emergent adverse events from several double-blind, placebo-controlled trials that occurred at a frequency of 2% or more among patients treated with Redux and occurred at least as frequently as the placebo group, regardless of relationship to study medication. [See table above.]

Patients may experience more than one type of adverse event. Only events that occurred at a frequency of 2% or more in dexfenfluramine-treated patients and were at least as frequent as in placebo-treated patients are included.

Other Events Observed in Controlled Clinical Trials

The events below are classified within body system categories and enumerated in order of decreasing frequency using the following definitions. Frequent adverse events are those occurring in more than 1/100 patients but were not described above because the frequency in dexfenfluramine-treated patients was less than that in placebo-treated patients or they occurred at a rate less than 2%. Infrequent adverse events are those occurring in 1/100 to 1/1000 patients, while rare adverse events are those occurring in only one patient during placebo-controlled clinical trials.

Body as a whole—Frequent: infection, flu syndrome, pain, back pain, fever, allergic reaction. *Infrequent:* malaise, neck pain, chest pain, generalized edema, stress, face edema, neoplasm, pelvic pain. *Rare:* adenoma, immune system disorder, neck rigidity, suicide attempt.

Cardiovascular system—Frequent: hypertension, angina pectoris, palpitation, vasodilation, migraine. *Infrequent:* cardiovascular disorder, tachycardia, postural hypotension, hypotension, peripheral vascular disorder, syncope, arrhythmia, extrasystoles, hemorrhage, thrombophlebitis, varicose vein. *Rare:* heart block, pulmonary embolus, thrombosis.

Gastrointestinal system—Frequent: constipation, nausea, dyspepsia, increased appetite, rectal disorder, gastritis, gastroenteritis, flatulence. *Infrequent:* colitis, eructation, gastrointestinal hemorrhage, enteritis, peptic ulcer, hepatitis, hepatomegaly. *Rare:* appendicitis, cholelithiasis, fecal incontinence, melena, mouth ulceration, pancreatitis, rectal hemorrhage, sialoadenitis.

Endocrine—Infrequent: goiter, diabetes mellitus, thyroid disorder. *Rare:* hypothyroidism.

Hemic and lymphatic system—Infrequent: anemia, lymphedema. *Rare:* coagulation disorder, lymphadenopathy, polycythemia, thrombocythemia.

Metabolic and nutritional—Infrequent: edema, gout, hypoglycemia, hypokalemia. *Rare:* hyperglycemia, hyperkalemia, hyperlipemia, hyperuricemia.

Musculoskeletal system—Frequent: arthralgia, myalgia, arthritis. *Infrequent:* leg cramps, joint disorder, bone disorder, tenosynovitis, myasthenia, rheumatoid arthritis. *Rare:* bursitis, tetany.

Nervous system—Frequent: nervousness, anxiety, increased libido, hypertonia, paresthesia. *Infrequent:* tremor, amnesia, euphoria, decreased libido, incoordination, neuralgia, speech disorder, ataxia, hypokinesia, sleep disorder, abnormal gait, agitation, confusion, depersonalization, diplopia, hostility, hyperesthesia, hyperkinesia, peripheral neuritis. *Rare:* apathy, dementia, hallucinations, hypotonia, neuritis, neurosis, paralysis.

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Respiratory system—Frequent: rhinitis, sinusitis. *Infrequent:* asthma, dyspnea, epistaxis, laryngitis. *Rare:* apnea, hyperventilation.

Skin and appendages—Frequent: sweating, alopecia, urticaria, pruritus. *Infrequent:* skin disorder, fungal dermatitis, hirsutism, eczema, psoriasis. *Rare:* skin hypertrophy.

Special senses—Frequent: taste perversion, amblyopia. *Infrequent:* abnormal vision, conjunctivitis, eye disorder, glaucoma, tinnitus, vestibular disorder, dry eyes, mydriasis. *Rare:* abnormality of accommodation, anisocoria, lacrimation disorder, miosis, parosmia, retinal disorder.

Urogenital system—Frequent: menstrual disorder, urinary tract infection, nocturia, dysmenorrhea. *Infrequent:* amenorrhea, dysuria, oliguria, albuminuria, breast pain, kidney calculus, kidney pain. *Rare:* spontaneous abortion, threatened abortion, breast neoplasm, endometrial disorder, female lactation, hematuria, impotence, mastitis, nephritis, prostatic disorder, testis disorder, urinary incontinence, urinary retention, uterine hemorrhage.

In controlled clinical trials, there has been no consistent pattern of laboratory abnormalities in patients treated with dexfenfluramine.

Post-introduction Reports

Voluntary reports of adverse events temporally associated with dexfenfluramine that have been received since market introduction in countries other than the US, for which the association with the drug is unknown, and which are not included in descriptions of adverse events elsewhere in this labeling, include the following:

Body as a whole—anaphylaxis, congenital anomaly, eventration, hypothermia, laryngeal edema, peritonitis, reaction aggravation, retroperitoneal fibrosis, scleroderma, sudden death.

Cardiovascular system—pulmonary hypertension (see **WARNINGS**), atrial fibrillation, cardiomyopathy, cerebral vasculitis, ECG abnormal, heart arrest, heart failure, myocardial infarction, myocarditis, shock, tachycardia, ventricular fibrillation, ventricular tachycardia.

Digestive system—dysphagia, gastrointestinal disorder, tongue disorder.

Endocrine system—diabetic coma.

Gastrointestinal system—hepatic failure, jaundice, liver damage.

Hemic and lymphatic system—agranulocytosis, antinuclear antibody present, bone marrow depression, ecchymosis, hemolytic anemia, pancytopenia.

Metabolic and nutritional—dehydration, elevated lipases, increased prolactin, thyroid disease, weight increase.

Musculoskeletal—myopathy.

Nervous system—antisocial reaction, apathy, cerebellar ataxia, cerebrovascular accident (including cerebral hemorrhage, cerebral infarction, cerebral ischemia and cochlear infarction), choreoathetosis, convulsions, decreased reflexes, delirium, drug dependence, dyslexia, encephalopathy, grand mal convulsions, Guillain-Barré syndrome, hemiplegia, hypoesthesia, manic-depressive psychosis, manic reaction, memory loss, meningism, meningitis, neuropathy, papilledema, paraplegia, personality disorder, reflexes increased, retrobulbar neuritis, schizophrenic reaction, stupor, subdural hematoma, twitch, withdrawal syndrome.

Respiratory system—pulmonary hypertension (see **WARNINGS**), diffuse interstitial pneumonitis, dyspnea, hiccup, lung edema.

Skin and appendages—angioedema, bullous eruption, erythema multiforme, lower extremity purpura, purpura annularis telangiectodes, Stevens-Johnson syndrome (erythema multiforme major).

Special senses—ophthalmoplegia, photophobia, transitory deafness, visual field defects.

Urogenital system—breast enlargement, carcinoma (breast), carcinoma (cervix), ejaculation abnormal, gynecomastia, hypomenorrhea, kidney failure, placenta previa, urinary tract disorder.

Adverse Events Occurring After Discontinuation

In controlled clinical trials and/or in post-marketing reports, symptoms have been reported within a few days after discontinuation of Redux. These include one or more of the following: abdominal pain, anxiety, asthenia, delusion, depression, diarrhea, dizziness, hypertension, insomnia, nausea and vomiting.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Dexfenfluramine is a controlled substance in Schedule IV.

Abuse and Physical and Psychological Dependence

Dexfenfluramine is not an amphetamine or a stimulant. There is no evidence of addictive or drug-seeking behavior in pre-marketing clinical studies. Dexfenfluramine was inactive in rat and monkey self-administration, drug-discrimination, and place-preference models of abuse potential.

OVERDOSAGE

Human Experience

Post-marketing experience in Europe over 10 years (August 1984 through December 1994) in an estimated 10 million patients provided reports of 66 instances of overdose (maximum dose per body mass of 54 mg/kg, maximum total dose of 1800 mg), including eight children 6 years of age or under. Three deaths have occurred in association with dexfenfluramine overdosage. One patient with a history of suicide attempts ingested 1800 mg dexfenfluramine and 20 to 30 capsules of Tranxene (clorazepate), one patient was found dead, assumed to have consumed approximately 1500 mg of dexfenfluramine, and the third patient consumed dexfenfluramine (quantity unknown) and several other drugs in an apparent suicide. The second patient had post-mortem levels of dexfenfluramine of 3300 ng/mL, and positive levels for amphetamines and cannabinoids. The exact causes of death were unknown. In 23 other cases of dexfenfluramine overdose, plasma drug levels were determined; the maximum reported plasma drug level for dexfenfluramine was 778 ng/mL (with *d*-norfenfluramine 37 ng/mL); the maximum *d*-norfenfluramine level was 371 ng/mL (with dexfenfluramine 483 ng/mL).

Symptoms associated with overdosage consisted mainly of agitation, drowsiness, mydriasis, sweating, shivering, nausea, and vomiting.

Other symptoms observed with dexfenfluramine overdose and not noted under **ADVERSE REACTIONS** include cold sensation, excitation, nystagmus, garrulousness, delusions, bladder tenesmus, chattering teeth, abnormal reflexes, facial myoclonus, trismus, tonic-clonic seizures, impairment of consciousness, coma (stage 2–4), sinus bradycardia, repolarization abnormalities, right anterior hemiblock, polypnea, diffuse bronchial rales, and flushing.

Animal Experience

Significant acute toxicity occurred at oral doses greater than 40, 70, and 75 mg/kg in rats, mice, and guinea pigs, respectively. A dose of 40 mg/kg is approximately 31 times greater than the effective anorectic dose in rats.

Management of Overdose

General supportive measures for oral drug overdose should be instituted. Measures that have been used in dexfenfluramine overdose cases include aspiration of gastric contents, gastric lavage with activated charcoal, osmotic diuresis, forced acid diuresis, and careful monitoring of CNS or repiratory depression. The effectiveness of dialysis is not known. Patients should be followed closely until there is no further evidence of drug-related CNS effects. No specific therapy for dexfenfluramine overdose is known.

DOSAGE AND ADMINISTRATION

The usual dosage is one 15-mg capsule twice daily, with meals. Doses above 30 mg per day are not recommended.

Analysis of numerous variables has indicated that about 60% of patients who lose at least 4 pounds in the first 4 weeks of treatment with Redux in combination with a reduced-calorie diet lose at least 10% of their initial body weight by the end of 1 year of treatment. If a patient has not lost at least 4 pounds in the first 4 weeks of treatment, the physician should consider reevaluation of therapy which may include discontinuation of Redux.

The safety and effectiveness of Redux beyond 1 year have not been determined at this time.

Infrequently, symptoms (*e.g.*, abdominal pain, anxiety, asthenia, delusion, depression, diarrhea, dizziness, hypertension, insomnia, nausea and vomiting) have occurred within several days following cessation of Redux. If the physician notes such symptoms, clinical judgment should guide the treatment, which may include tapering the dose (15 mg once daily) for 2 weeks prior to complete discontinuation.

HOW SUPPLIED

Redux™ (dexfenfluramine hydrochloride capsules) 15 mg, is supplied in number 3, white, opaque, hard-gelatin capsules. Each capsule is marked with "REDUX" and three black vertical bands. Redux is provided as follows:

HDPE bottles containing:

60 capsules per package (NDC 0008-0904-01)

Store at room temperature, between 15°C and 30°C (59°F and 86°F).

CAUTION: Federal law prohibits dispensing without prescription.

Address medical inquiries to:
Wyeth-Ayerst Laboratories
1-610-688-4400

Redux™ is a trademark of ORSEM (SERVIER).

Manufactured for and distributed by:
Wyeth Laboratories Inc.
A Wyeth-Ayerst Company
Philadelphia, PA 19101

Under license from:
Interneuron Pharmaceuticals, Inc.
Lexington, MA 02173

8A0551

Shown in Product Identification Guide, page 341

SECTRAL® ℞

[*sek'tral*]

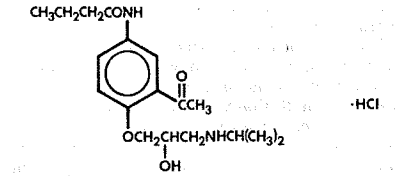
(acebutolol hydrochloride)

Capsules

DESCRIPTION

Sectral (acebutolol HCl) is a selective, hydrophilic beta-adrenoreceptor blocking agent with mild intrinsic sympathomimetic activity for use in treating patients with hypertension and ventricular arrhythmias. It is marketed in capsule form for oral administration. Sectral capsules are provided in two dosage strengths which contain 200 or 400 mg of acebutolol as the hydrochloride salt. The inactive ingredients present are D&C Red 22, FD&C Blue 1, FD&C Yellow 6, gelatin, povidone, starch, stearic acid, and titanium dioxide. The 200 mg dosage strength also contains D&C Red 28 and the 400 mg dosage strength also contains FD&C Red 40.

Acebutolol HCl has the following structural formula:



$C_{18}H_{28}N_2O_4 \cdot HCl$ M.W. 372.9

Acebutolol HCl is a white or slightly off-white powder freely soluble in water, and less soluble in alcohol. Chemically it is defined as the hydrochloride salt of Butanamide, N-[3-acetyl-4-[2-hydroxy-3-[(1-methylethyl)amino]propoxy]phenyl]-, (±)- or (±)-3′-Acetyl-4′-[2-hydroxy -3- (isopropylamino) propoxy] butyranilide.

CLINICAL PHARMACOLOGY

Sectral is a cardioselective, β-adrenoreceptor blocking agent, which possesses mild intrinsic sympathomimetic activity (ISA) in its therapeutically effective dose range.

PHARMACODYNAMICS

β_1-cardioselectivity has been demonstrated in experimental animal studies. In anesthetized dogs and cats, Sectral is more potent in antagonizing isoproterenol-induced tachycardia (β_1) than in antagonizing isoproterenol-induced vasodilatation (β_2). In guinea pigs and cats, it is more potent in antagonizing this tachycardia than in antagonizing isoproterenol-induced bronchodilatation (β_2). ISA of Sectral has been demonstrated in catecholamine-depleted rats by tachycardia induced by intravenous administration of this agent. A membrane-stabilizing effect has been detected in animals, but only with high concentrations of Sectral.

Clinical studies have demonstrated β_1-blocking activity at the recommended doses by: a) reduction in the resting heart rate and decrease in exercise-induced tachycardia; b) reduction in cardiac output at rest and after exercise; c) reduction of systolic and diastolic blood pressures at rest and postexercise; d) inhibition of isoproterenol-induced tachycardia.

The β_1-selectivity of Sectral has also been demonstrated on the basis of the following vascular and bronchial effects:

Vascular Effects: Sectral has less antagonistic effects on peripheral vascular β_2-receptors at rest and after epinephrine stimulation than nonselective β-antagonists.

Bronchial Effects: In single-dose studies in asthmatics examining effects of various beta-blockers on pulmonary function, low doses of acebutolol produce less evidence of bronchoconstriction and less reduction of beta$_2$ agonist, bronchodilating effects, than nonselective agents like propranolol but more than atenolol.

ISA has been observed with Sectral in man, as shown by a slightly smaller (about 3 beats per minute) decrease in resting heart rate when compared to equivalent β-blocking doses of propranolol, metoprolol or atenolol. Chronic therapy with Sectral induced no significant alteration in the blood lipid profile.

Sectral has been shown to delay AV conduction time and to increase the refractoriness of the AV node without significantly affecting sinus node recovery time, atrial refractory period, or the HV conduction time. The membrane-stabilizing effect of Sectral is not manifest at the doses used clinically.

Significant reductions in resting and exercise heart rates and systolic blood pressures have been observed 1.5 hours after Sectral administration with maximal effects occurring between 3 and 8 hours postdosing in normal volunteers. Sectral has demonstrated a significant effect on exercise-induced tachycardia 24 to 30 hours after drug administration.

There are significant correlations between plasma levels of acebutolol and both the reduction in resting heart rate and the percent of β-blockade of exercise-induced tachycardia.

The antihypertensive effect of Sectral has been shown in double-blind controlled studies to be superior to placebo and similar to propranolol and hydrochlorothiazide. In addition, patients responding to Sectral administered twice daily had

Concomitant administration of MAVIK with potassium supplements, potassium salt substitutes, or potassium sparing diuretics can lead to increases of serum potassium. (See **PRECAUTIONS.**)

Heart Failure Post Myocardial Infarction or Left-Ventricular Dysfunction Post Myocardial Infarction:
The recommended starting dose is 1 mg, once daily. Following the initial dose, all patients should be titrated (as tolerated) toward a target dose of 4 mg, once daily. If a 4 mg dose is not tolerated, patients can continue therapy with the greatest tolerated dose.

Dosage Adjustment in Renal Impairment or Hepatic Cirrhosis:
For patients with a creatinine clearance <30 mL/min. or with hepatic cirrhosis, the recommended starting dose, based on clinical and pharmacokinetic data, is 0.5 mg daily. Patients should subsequently have their dosage titrated (as described above) to the optimal response.

HOW SUPPLIED

MAVIK® (trandolapril tablets) are supplied as follows:

1 mg tablet – salmon colored, round shaped, scored, compressed tablets, with ⊟ on one side and Abbo-Code identification letters FT on the other side.
NDC 0074-2278-13 - bottles of 100
NDC 0074-2278-11 - unit dose packs of 100

2 mg tablet – yellow colored, round shaped, compressed tablets with ⊟ on one side and Abbo-Code identification letters FX on the other side.
NDC 0074-2279-13 - bottles of 100
NDC 0074-2279-11 - unit dose packs of 100

4 mg tablet – rose colored, round shaped, compressed tablets, with ⊟ on one side and Abbo-Code identification letters FZ on the other side.
NDC 0074-2280-13 - bottles of 100
NDC 0074-2280-11 - unit dose packs of 100

Dispense in well-closed container with safety closure.

Storage: Store at controlled room temperature: 20–25°C (68–77°F) see USP.

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Ref.: 03-5264-R2

Abbott Laboratories
North Chicago, IL 60064, U.S.A. PRINTED IN U.S.A.

Shown in Product Identification Guide, page 303

MERIDIA® ℞

[*mer-ID-dee-uh*]

(sibutramine hydrochloride monohydrate) Capsules

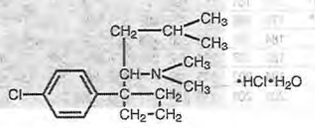
Tear at Perforation to dispense Patient Information.

℞ only

DESCRIPTION

MERIDIA® (sibutramine hydrochloride monohydrate) is an orally administered agent for the treatment of obesity. Chemically, the active ingredient is a racemic mixture of the (+) and (–) enantiomers of cyclobutanemethanamine, 1-(4-chlorophenyl)-*N,N*-dimethyl-α-(2-methylpropyl)-, hydrochloride, monohydrate, and has an empirical formula of $C_{17}H_{29}Cl_2NO$. Its molecular weight is 334.33.

The structural formula is shown below:



Sibutramine hydrochloride monohydrate is a white to cream crystalline powder with a solubility of 2.9 mg/mL in pH 5.2 water. Its octanol: water partition coefficient is 30.9 at pH 5.0.

Each MERIDIA capsule contains 5 mg, 10 mg, and 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains titanium dioxide, USP; gelatin; FD&C Blue No. 2 (5- and 10-mg capsules only); D&C Yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].

CLINICAL PHARMACOLOGY

Mode of Action

Sibutramine produces its therapeutic effects by norepinephrine, serotonin and dopamine reuptake inhibition. Sibutramine and its major pharmacologically active metabolites (M_1 and M_2) do not act via release of monoamines.

Pharmacodynamics

Sibutramine exerts its pharmacological actions predominantly via its secondary (M_1) and primary (M_2) amine metabolites. The parent compound, sibutramine, is a potent inhibitor of serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine reuptake *in vivo*, but not *in vitro*. However, metabolites M_1 and M_2 inhibit the reuptake of these neurotransmitters both *in vitro* and *in vivo*.

In human brain tissue, M_1 and M_2 also inhibit dopamine reuptake *in vitro*, but with ~3-fold lower potency than for the reuptake inhibition of serotonin or norepinephrine.

Potencies of Sibutramine, M_1 and M_2 as *In Vitro* Inhibitors of Monoamine Reuptake in Human Brain Potency to Inhibit Monoamine Reuptake (K_i; nM)

	Serotonin	Norepinephrine	Dopamine
Sibutramine	298	5451	943
M_1	15	20	49
M_2	20	15	45

A study using plasma samples taken from sibutramine-treated volunteers showed monoamine reuptake inhibition of norepinephrine > serotonin > dopamine; maximum inhibitions were norepinephrine = 73%, serotonin = 54% and dopamine = 16%.

Sibutramine and its metabolites (M_1 and M_2) are not serotonin, norepinephrine or dopamine releasing agents. Following chronic administration of sibutramine to rats, no depletion of brain monoamines has been observed.

Sibutramine, M_1 and M_2 exhibit no evidence of anticholinergic or antihistaminergic actions. In addition, receptor binding profiles show that sibutramine, M_1 and M_2 have low affinity for serotonin (5-HT_1, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2C}), norepinephrine (β, β_1, β_3, α_1 and α_2), dopamine (D_1 and D_2), benzodiazepine, and glutamate (NMDA) receptors. These compounds also lack monoamine oxidase inhibitory activity *in vitro* and *in vivo*.

Pharmacokinetics

Absorption

Sibutramine is rapidly absorbed from the GI tract (T_{max} of 1.2 hours) following oral administration and undergoes extensive first-pass metabolism in the liver (oral clearance of 1750 L/h and half-life of 1.1 h) to form the pharmacologically active mono- and di-desmethyl metabolites M_1 and M_2. Peak plasma concentrations of M_1 and M_2 are reached within 3 to 4 hours. On the basis of mass balance studies, on average, at least 77% of a single oral dose of sibutramine is absorbed. The absolute bioavailability of sibutramine has not been determined.

Distribution

Radiolabeled studies in animals indicated rapid and extensive distribution into tissues: highest concentrations of radiolabeled material were found in the eliminating organs, liver and kidney. *In vitro*, sibutramine, M_1 and M_2 are extensively bound (97%, 94% and 94%, respectively) to human plasma proteins at plasma concentrations seen following therapeutic doses.

Metabolism

Sibutramine is metabolized in the liver principally by the cytochrome P450 ($3A_4$) isoenzyme, to desmethyl metabolites, M_1 and M_2. These active metabolites are further metabolized by hydroxylation and conjugation to pharmacologically inactive metabolites, M_5 and M_6. Following oral administration of radiolabeled sibutramine, essentially all of the peak radiolabeled material in plasma was accounted for by unchanged sibutramine (3%), M_1 (6%), M_2 (12%), M_5 (52%), and M_6 (27%).

M_1 and M_2 plasma concentrations reached steady-state within four days of dosing and were approximately two-fold higher than following a single dose. The elimination half-lives of M_1 and M_2, 14 and 16 hours, respectively, were unchanged following repeated dosing.

Excretion

Approximately 85% (range 68–95%) of a single orally administered radiolabeled dose was excreted in urine and feces over a 15-day collection period with the majority of the dose (77%) excreted in the urine. Major metabolites in urine were M_5 and M_6; unchanged sibutramine, M_1, and M_2 were not detected. The primary route of excretion for M_1 and M_2 is hepatic metabolism and for M_5 and M_6 is renal excretion.

Summary of Pharmacokinetic Parameters

[See table below]

Effect of Food

Administration of a single 20 mg dose of sibutramine with a standard breakfast resulted in reduced peak M_1 and M_2 concentrations (by 27% and 32%, respectively) and delayed the time to peak by approximately three hours. However, the AUCs of M_1 and M_2 were not significantly altered.

Special Populations

Geriatric: Plasma concentrations of M_1 and M_2 were similar between elderly (ages 61 to 77 yr) and young (ages 19 to 30 yr) subjects following a single 15-mg oral sibutramine dose. Plasma concentrations of the inactive metabolites M_5 and M_6 were higher in the elderly; these differences are not likely to be of clinical significance. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Pediatric: The safety and effectiveness of sibutramine in pediatric patients under 16 years old have not been established.

Gender: Pooled pharmacokinetic parameters from 54 young, healthy volunteers (37 males and 17 females) receiving a 15-mg oral dose of sibutramine showed the mean C_{max} and AUC of M_1 and M_2 to be slightly (≤19% and ≤36%, respectively) higher in females than males. Somewhat higher steady-state trough plasma levels were observed in female obese patients from a large clinical efficacy trial. However, these differences are not likely to be of clinical significance. Dosage adjustment based upon the gender of a patient is not necessary (see **"DOSAGE AND ADMINISTRATION"**).

Race: The relationship between race and steady-state trough M_1 and M_2 plasma concentrations was examined in a clinical trial in obese patients. A trend towards higher concentrations in Black patients over Caucasian patients was noted for M_1 and M_2. However, these differences are not considered to be of clinical significance.

Renal Insufficiency: The disposition of sibutramine metabolites (M_1, M_2, M_5 and M_6) following a single oral dose of sibutramine was studied in patients with varying degrees of renal function. Sibutramine itself was not measurable.

In patients with moderate and severe renal impairment, the AUC values of the active metabolite M_1 were 24 to 46% higher and the AUC values of M_2 were similar as compared to healthy subjects. Cross-study comparison showed that the patients with end-stage renal disease on dialysis had similar AUC values of M_1 but approximately half of the AUC values of M_2 measured in healthy subjects (CLcr ≥ 80 mL/min). The AUC values of inactive metabolites M_5 and M_6 increased 2–3 fold (range 1- to 7-fold) in patients with moderate impairment (30 mL/min < CLcr = 60 mL/min) and 8–11 fold (range 5- to 15-fold) in patients with severe impairment (CLcr ≤ 30 mL/min) as compared to healthy subjects. Cross-study comparison showed that the AUC values of M_5 and M_6 increased 22–33 fold in patients with end-stage renal disease on dialysis as compared to healthy subjects. Approximately 1% of the oral dose was recovered in the dialysate as a combination of M_5 and M_6 during the hemodialysis process, while M_1 and M_2 were not measurable in the dialysate.

Sibutramine should not be used in patients with severe renal impairment, including those with end-stage renal disease on dialysis.

Hepatic Insufficiency: In 12 patients with moderate hepatic impairment receiving a single 15-mg oral dose of sibutramine, the combined AUCs of M_1 and M_2 were increased by 24% compared to healthy subjects while M_5 and M_6 plasma concentrations were unchanged. The observed differences in M_1 and M_2 concentrations do not warrant dosage adjustment in patients with mild to moderate hepatic impairment. Sibutramine should not be used in patients with severe hepatic dysfunction.

CLINICAL STUDIES

Observational epidemiologic studies have established a relationship between obesity and the risks for cardiovascular disease, non-insulin dependent diabetes mellitus (NIDDM), certain forms of cancer, gallstones, certain respiratory disorders, and an increase in overall mortality. These studies suggest that weight loss, if maintained, may produce health benefits for some patients with chronic obesity who may also be at risk for other diseases.

The long-term effects of sibutramine on the morbidity and mortality associated with obesity have not been established. Weight loss was examined in 11 double-blind, placebo-controlled obesity trials (BMI range across all studies 27–43) with study durations of 12 to 52 weeks and doses ranging from 1 to 30 mg once daily. Weight was significantly reduced in a dose-related manner in sibutramine-treated patients compared to placebo over the dose range of 5 to 20 mg once daily. In two 12-month stud-

Continued on next page

Mean (% CV) and 95% Confidence Intervals of Pharmacokinetic Parameters (Dose = 15 mg)

Study Population	C_{max} (ng/mL)	T_{max} (h)	AUC† (ng*h/mL)	T½ (h)
Metabolite M_1				
Target Population:				
Obese Subjects	4.0 (42)	3.6 (28)	25.5 (63)	—
(n = 18)	3.2-4.8	3.1-4.1	18.1-32.9	
Special Population:				
Moderate Hepatic	2.2 (36)	3.3 (33)	18.7 (65)	—
Impairment (n = 12)	1.8-2.7	2.7-3.9	11.9-25.5	
Metabolite M_2				
Target Population:				
Obese Subjects	6.4 (28)	3.5 (17)	92.1 (26)	17.2 (58)
(n = 18)	5.6-7.2	3.2-3.8	81.2-103	12.5-21.8
Special Population:				
Moderate Hepatic	4.3 (37)	3.8 (34)	90.5 (27)	22.7 (30)
Impairment (n = 12)	3.4-5.2	3.1-4.5	76.9-104	18.9-26.5

† Calculated only up to 24 hr for M_1

Meridia—Cont.

ies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months. The amount of placebo-subtracted weight loss achieved on sibutramine was consistent across studies.

Analysis of the data in three long-term (≥6 months) obesity trials indicates that patients who lose at least 4 pounds in the first 4 weeks of therapy with a given dose of sibutramine are most likely to achieve significant long-term weight loss on that dose of sibutramine. Approximately 60% of such patients went on to achieve a placebo-subtracted weight loss of ≥5% of their initial body weight by month 6. Conversely, of those patients on a given dose of sibutramine who did not lose at least 4 pounds in the first 4 weeks of therapy, approximately 80% did not go on to achieve a placebo-subtracted weight loss of ≥5% of their initial body weight on that dose by month 6.

Significant dose-related reductions in waist circumference, an indicator of intra-abdominal fat, have also been observed over 6 and 12 months in placebo-controlled clinical trials. In a 12-week placebo-controlled study of non-insulin dependent diabetes mellitus patients randomized to placebo or 15 mg per day of sibutramine, Dual Energy X-Ray Absorptiometry (DEXA) assessment of changes in body composition showed that total body fat mass decreased by 1.8 kg in the sibutramine group versus 0.2 kg in the placebo group ($p<0.001$). Similarly, truncal (android) fat mass decreased by 0.6 kg in the sibutramine group versus 0.1 kg in the placebo group ($p<0.01$). The changes in lean mass, fasting blood sugar, and HbA_1 were not statistically significantly different between the two groups.

Eleven double-blind, placebo-controlled obesity trials with study durations of 12 to 52 weeks have provided evidence that sibutramine does not adversely affect glycemia, serum lipid profiles, or serum uric acid in obese patients. Treatment with sibutramine (5 to 20 mg once daily) is associated with mean increases in blood pressure of 1 to 3 mm Hg and with mean increases in pulse rate of 4 to 5 beats per minute relative to placebo. These findings are similar in normotensives and in patients with hypertension controlled with medication. Those patients who lose significant (≥ 5% weight loss) amounts of weight on sibutramine tend to have smaller increases in blood pressure and pulse rate (see **"WARNINGS"**).

In Study 1, a 6-month, double-blind, placebo-controlled study in obese patients, Study 2, a 1-year, double-blind, placebo-controlled study in obese patients, and Study 3, a 1-year, double-blind, placebo-controlled study in obese patients who lost at least 6 kg on a 4-week very low calorie diet (VLCD), sibutramine produced significant reductions in weight, as shown below. In the two 1-year studies, maximal weight loss was achieved by 6 months and statistically significant weight loss was maintained over 12 months.

[See first table below]

Maintenance of weight loss with sibutramine was examined in a 2-year, double-blind, placebo-controlled trial. After a 6-month run-in phase in which all patients received sibutramine 10 mg (mean weight loss, 26 lbs.), patients were randomized to sibutramine (10 to 20 mg, 352 patients) or placebo (115 patients). The mean weight loss from initial body weight to endpoint was 21 lbs. and 12 lbs. for sibutramine and placebo patients, respectively. A statistically significantly ($p<0.001$) greater proportion of sibutramine treated patients, 75%, 62%, and 43%, maintained at least 80% of their initial weight loss at 12, 18, and 24 months, respectively, compared with the placebo group (38%, 23%, and 16%). Also 67%, 37%, 17%, and 9% of sibutramine treated patients compared with 49%, 19%, 5%, and 3% of placebo patients lost ≥5%, ≥10%, ≥15%, and ≥20%, respectively, of their initial body weight at endpoint. From endpoint to the post-study follow-up visit (about 1 month), weight regain was approximately 4 lbs for the sibutramine patients and approximately 2 lbs for the placebo patients.

Sibutramine induced weight loss has been accompanied by beneficial changes in serum lipids that are similar to those seen with nonpharmacologically-mediated weight loss. A combined, weighted analysis of the changes in serum lipids in 11 placebo-controlled obesity studies ranging in length from 12 to 52 weeks is shown below for the last observation carried forward (LOCF) analysis.

[See second table below]

Sibutramine induced weight loss has been accompanied by reductions in serum uric acid.

Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with cardiac valve dysfunction. The possible occurrence of cardiac valve disease was specifically investigated in two studies. In one study 2-D and color Doppler echocardiography were performed on 210 patients (mean age, 54 years) receiving sibutramine 15 mg or placebo daily for periods of 2 weeks to 16 months (mean duration of treatment, 7.6 months). In patients without a prior history of valvular heart disease, the incidence of valvular heart disease was 3/132 (2.3%) in the sibutramine treatment group (all three cases were mild aortic insufficiency) and 2/77 (2.6%) in the placebo treatment group (one case of mild aortic insufficiency and one case of severe aortic insufficiency). In another study, 25 patients underwent 2-D and color Doppler echocardiography before treatment with sibutramine and again after treatment with sibutramine 5 to 30 mg daily for three months; there were no cases of valvular heart disease.

The effect of sibutramine 15 mg once daily on measures of 24-hour blood pressure was evaluated in a 12-week placebo-controlled study. Twenty-six male and female, primarily Caucasian individuals with an average BMI of 34 kg/m^2 and an average age of 39 years underwent 24-hour ambulatory blood pressure monitoring (ABPM). The mean changes from baseline to Week 12 in various measures of ABPM are shown in the following table.

Parameter	Systolic			Diastolic		
mm Hg	Placebo n=12	Sibutramine 15 mg n=14	Sibutramine 20 mg n=16	Placebo	Sibutramine 15 mg n=12	Sibutramine 20 mg n=16
Daytime	0.2	3.9	4.4	0.5	5.0	5.7
Nighttime	–0.3	4.1	6.4	–1.0	4.3	5.4
Early am	–0.9	9.4	5.3	–3.0	6.7	5.8
24-hour mean	–0.1	4.0	4.7	0.1	5.0	5.6

Normal diurnal variation of blood pressure was maintained.

Mean Weight Loss (lbs) in the Six-Month and One-Year Trials

Study/Patient Group	Placebo (n)	Sibutramine (mg) 5 (n)	10 (n)	15 (n)	20 (n)
Study 1					
All patients*	2.0 (142)	6.6 (148)	9.7 (148)	12.1 (150)	13.6 (145)
Completers**	2.9 (84)	8.1 (103)	12.1 (95)	15.4 (94)	18.0 (89)
Early responders***	8.5 (17)	13.0 (60)	16.0 (64)	18.2 (73)	20.1 (76)
Study 2					
All patients*	3.5 (157)		9.8 (154)	14.0 (152)	
Completers**	4.8 (76)		13.6 (80)	15.2 (93)	
Early responders***	10.7 (24)		18.2 (57)	18.8 (76)	
Study 3****					
All patients*	15.2 (78)		28.4 (81)		
Completers**	16.7 (48)		29.7 (60)		
Early responders***	21.5 (22)		33.0 (46)		

* Data for all patients who received study drug and who had any post-baseline measurement (last observation carried forward analysis).

** Data for patients who completed the entire 6-month (Study 1) or one-year period of dosing and have data recorded for the month 6 (Study 1) or month 12 visit.

*** Data for patients who lost at least 4 lbs in the first 4 weeks of treatment and completed the study.

**** Weight loss data shown describe changes in weight from the pre-VLCD; mean weight loss during the 4-week VLCD was 16.9 lbs for sibutramine and 16.3 lbs for placebo.

Combined Analysis (11 Studies) of Changes in Serum Lipids – LOCF

Category	TG % (n)	CHOL % (n)	LDL-C % (n)	HDL-C % (n)
All Placebo	0.53 (475)	–1.53 (475)	–0.09 (233)	–0.56 (248)
<5% Weight Loss	4.52 (382)	–0.42 (382)	–0.70 (205)	–0.71 (217)
≥5% Weight Loss	–15.30 (92)	–6.23 (92)	–6.19 (27)	0.94 (30)
All Sibutramine	–8.75 (1164)	–2.21 (1165)	–1.85 (642)	4.13 (664)
<5% Weight Loss	–0.54 (547)	0.17 (548)	–0.37 (320)	3.19 (331)
≥5% Weight Loss	–16.59 (612)	–4.87 (612)	–4.56 (317)	4.68 (328)

Baseline mean values:
Placebo: TG 187 mg/dL; CHOL 221 mg/dL; LDL-C 140 mg/dL; HDL-C 47 mg/dL
Sibutramine: TG 172 mg/dL; CHOL 215 mg/dL; LDL-C 140 mg/dL; HDL-C 47 mg/dL
TG: Triglycerides, CHOL: Cholesterol, LDL-C Low Density Lipoprotein-Cholesterol, HDL-C: High Density Lipoprotein-Cholesterol

INDICATIONS AND USAGE

MERIDIA® (sibutramine hydrochloride monohydrate) 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. MERIDIA is recommended for obese patients with an initial body mass index ≥30 kg/m^2, or ≥27 kg/m^2 in the presence of other risk factors (e.g., diabetes, dyslipidemia, controlled hypertension).

Below is a chart of Body Mass Index (BMI) based on various heights and weights.

BMI is calculated by taking the patient's weight, in kg, and dividing by the patient's height, in meters, squared. Metric conversions are as follows: pounds ÷ 2.2 = kg; inches × 0.0254 = meters.

BMI		25	26	27	28	29	30	31	32	33	34	35	40
		WEIGHT (lbs)											
	4'10"	119	124	129	134	138	143	149	153	158	163	167	191
	4'11"	124	128	133	138	143	148	154	158	164	169	173	198
	5'	128	133	138	143	148	153	159	164	169	175	179	204
	5'1"	132	137	143	148	153	158	165	169	175	180	185	211
	5'2"	136	142	147	153	158	164	170	175	181	186	191	218
H	5'3"	141	146	152	158	163	169	175	181	187	192	197	225
	5'4"	145	151	157	163	169	174	181	187	193	199	204	232
E	5'5"	150	156	162	168	174	180	187	193	199	205	210	240
	5'6"	155	161	167	173	179	186	192	199	205	211	216	247
I	5'7"	159	166	172	178	185	191	198	205	211	218	223	255
	5'8"	164	171	177	184	190	197	204	211	218	224	230	262
G	5'9"	169	176	182	189	196	203	210	217	224	231	236	270
	5'10"	174	181	188	195	202	207	216	223	230	237	243	278
H	5'11"	179	186	193	200	208	215	222	230	237	244	250	286
	6'	184	191	199	206	213	221	228	236	244	251	258	294
T	6'1"	189	197	204	212	219	227	236	243	251	258	265	302
	6'2"	194	202	210	218	225	233	241	250	258	265	272	311
	6'3"	200	208	216	224	232	240	248	256	264	272	279	319

CONTRAINDICATIONS

MERIDIA is contraindicated in patients receiving monoamine oxidase inhibitors (MAOIs) (see **"WARNINGS"**).

MERIDIA is contraindicated in patients with hypersensitivity to sibutramine or any of the inactive ingredients of MERIDIA.

MERIDIA is contraindicated in patients who have a major eating disorder (anorexia nervosa or bulimia nervosa).

MERIDIA is contraindicated in patients taking other centrally acting weight loss drugs.

WARNINGS

Blood Pressure and Pulse

MERIDIA SUBSTANTIALLY INCREASES BLOOD PRESSURE AND/OR PULSE RATE IN SOME PATIENTS. REGULAR MONITORING OF BLOOD PRESSURE AND PULSE RATE IS REQUIRED WHEN PRESCRIBING MERIDIA.

In placebo-controlled obesity studies, sibutramine 5 to 20 mg once daily was associated with mean increases in systolic and diastolic blood pressure of approximately 1 to 3 mm Hg relative to placebo, and with mean increases in pulse rate relative to placebo of approximately 4 to 5 beats per minute. Larger increases were seen in some patients, particularly when therapy with sibutramine was initiated at the higher doses (see table below). In pre-marketing placebo-controlled obesity studies, 0.4% of patients treated with sibutramine were discontinued for hypertension (SBP ≥ 160 mm Hg or DBP ≥ 95 mm Hg), compared with 0.4% in the placebo group, and 0.4% of patients treated with sibutramine were discontinued for tachycardia (pulse rate ≥ 100 bpm), compared with 0.1% in the placebo group. **Blood pressure and pulse should be measured prior to start-**

ing therapy with MERIDIA and should be monitored at regular intervals thereafter. For patients who experience a sustained increase in blood pressure or pulse rate while receiving MERIDIA, either dose reduction or discontinuation should be considered. MERIDIA should be given with caution to those patients with a history of hypertension (see **"DOSAGE AND ADMINISTRATION"**), and should not be given to patients with uncontrolled or poorly controlled hypertension.

Percent Outliers in Studies 1 and 2

	% Outliers*		
Dose (mg)	SBP	DBP	Pulse
Placebo	9	7	12
5	6	20	16
10	12	15	28
15	13	17	24
20	14	22	37

* Outlier defined as increase from baseline of ≥15 mm Hg for three consecutive visits (SBP), ≥10 mm Hg for three consecutive visits (DBP), or pulse ≥10 bpm for three consecutive visits.

Potential Interaction With Monoamine Oxidase Inhibitors
MERIDIA is a norepinephrine, serotonin and dopamine reuptake inhibitor and should not be used concomitantly with MAOIs (see **"PRECAUTIONS"**, Drug Interactions subsection). There should be at least a 2-week interval after stopping MAOIs before commencing treatment with MERIDIA. Similarly, there should be at least a 2-week interval after stopping MERIDIA before starting treatment with MAOIs.

Concomitant Cardiovascular Disease
MERIDIA substantially increases blood pressure and/or pulse rate in some patients. Therefore, MERIDIA should not be used in patients with a history of coronary artery disease, congestive heart failure, arrhythmias, or stroke.

Glaucoma
Because MERIDIA can cause mydriasis, it should be used with caution in patients with narrow angle glaucoma.

Miscellaneous
Organic causes of obesity (e.g., untreated hypothyroidism) should be excluded before prescribing MERIDIA.

PRECAUTIONS

Pulmonary Hypertension
Certain centrally-acting weight loss agents that cause release of serotonin from nerve terminals have been associated with pulmonary hypertension (PPH), a rare but lethal disease. In pre-marketing clinical studies, no cases of PPH have been reported with sibutramine capsules. Because of the low incidence of this disease in the underlying population, however, it is not known whether or not MERIDIA may cause this disease.

Seizures
During premarketing testing, seizures were reported in <0.1% of sibutramine treated patients. MERIDIA should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Bleeding
There have been reports of bleeding in patients taking sibutramine. While a causal relationship is unclear, caution is advised in patients predisposed to bleeding events and those taking concomitant medications known to affect hemostasis or platelet function.

Gallstones
Weight loss can precipitate or exacerbate gallstone formation.

Renal Impairment
MERIDIA should be used with caution in patients with mild to moderate renal impairment. MERIDIA should not be used in patients with severe renal impairment, including those with end stage renal disease on dialysis (see **Pharmacokinetics-*Special Populations***-Renal Insufficiency).

Hepatic Dysfunction
Patients with severe hepatic dysfunction have not been systematically studied; MERIDIA should therefore not be used in such patients.

Interference With Cognitive and Motor Performance
Although sibutramine did not affect psychomotor or cognitive performance in healthy volunteers, any CNS active drug has the potential to impair judgment, thinking or motor skills.

Information For Patients
Physicians should instruct their patients to read the patient package insert before starting therapy with MERIDIA and to reread it each time the prescription is renewed.
Physicians should also discuss with their patients any part of the package insert that is relevant to them. In particular, the importance of keeping appointments for follow-up visits should be emphasized.
Patients should be advised to notify their physician if they develop a rash, hives, or other allergic reactions.
Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, especially weight-reducing agents, decongestants, antidepressants, cough suppressants, lithium, dihydroergotamine, sumatriptan (Imitrex®), or tryptophan, since there is a potential for interactions.
Patients should be reminded of the importance of having their blood pressure and pulse monitored at regular intervals.

Drug Interactions
CNS Active Drugs: The use of MERIDIA® (sibutramine hydrochloride monohydrate) in combination with other CNS-active drugs, particularly serotonergic agents, has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of MERIDIA with other centrally-acting drugs is indicated (see **"CONTRAINDICATIONS"** and **"WARNINGS"**).
In patients receiving monoamine oxidase inhibitors (MAOIs) (e.g., phenelzine, selegiline) in combination with serotonergic agents (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine), there have been reports of serious, sometimes fatal, reactions ("serotonin syndrome;" see below). Because sibutramine inhibits serotonin reuptake, MERIDIA should not be used concomitantly with a MAOI (see **"CONTRAINDICATIONS"**). At least 2 weeks should elapse between discontinuation of a MAOI and initiation of treatment with MERIDIA. Similarly, at least 2 weeks should elapse between discontinuation of MERIDIA and initiation of treatment with a MAOI.
The rare, but serious, constellation of symptoms termed "serotonin syndrome" has also been reported with the concomitant use of selective serotonin reuptake inhibitors and agents for migraine therapy, such as Imitrex® (sumatriptan succinate) and dihydroergotamine, certain opioids, such as dextromethorphan, meperidine, pentazocine and fentanyl, lithium, or tryptophan. Serotonin syndrome has also been reported with the concomitant use of two serotonin reuptake inhibitors. The syndrome requires immediate medical attention and may include one or more of the following symptoms: excitement, hypomania, restlessness, loss of consciousness, confusion, disorientation, anxiety, agitation, motor weakness, myoclonus, tremor, hemiballismus, hyperreflexia, ataxia, dysarthria, incoordination, hyperthermia, shivering, pupillary dilation, diaphoresis, emesis, and tachycardia.
Because sibutramine inhibits serotonin reuptake, in general, it should not be administered with other serotonergic agents such as those listed above. However, if such a combination is clinically indicated, appropriate observation of the patient is warranted.
Drugs That May Raise Blood Pressure and/or Heart Rate: Concomitant use of MERIDIA and other agents that may raise blood pressure or heart rate have not been evaluated. These include certain decongestants, cough, cold, and allergy medications that contain agents such as ephedrine, or pseudoephedrine. Caution should be used when prescribing MERIDIA to patients who use these medications.
Drugs That Inhibit Cytochrome P450($3A_4$) Metabolism: *In vitro* studies indicated that the cytochrome P450($3A_4$)-mediated metabolism of sibutramine was inhibited by ketoconazole and to a lesser extent by erythromycin. Clinical interaction trials were conducted on these substrates. The potential for such interactions is described below.
Ketoconazole: Concomitant administration of 200 mg doses of ketoconazole twice daily and 20 mg sibutramine once daily for 7 days in 12 uncomplicated obese subjects resulted in moderate increases in AUC and C_{max} of 58% and 36% for M_1 and of 20% and 19% for M_2, respectively.
Erythromycin: The steady-state pharmacokinetics of sibutramine and metabolites M_1 and M_2 were evaluated in 12 uncomplicated obese subjects following concomitant administration of 500 mg of erythromycin three times daily and 20 mg of sibutramine once daily for 7 days. Concomitant erythromycin resulted in small increases in the AUC (less than 14%) for M_1 and M_2. A small reduction in C_{max} for M_1 (11%) and a slight increase in C_{max} for M_2 (10%) were observed.
Cimetidine: Concomitant administration of cimetidine 400 mg twice daily and sibutramine 15 mg once daily for 7 days in 12 volunteers resulted in small increases in combined (M_1 and M_2) plasma C_{max} (3.4%) and AUC (7.3%); these differences are unlikely to be of clinical significance.
Alcohol: In a double-blind, placebo-controlled, crossover study in 19 volunteers, administration of a single dose of ethanol (0.5 mL/kg) together with 20 mg of sibutramine resulted in no psychomotor interactions of clinical significance between alcohol and sibutramine. However, the concomitant use of MERIDIA and excess alcohol is not recommended.
Oral Contraceptives: The suppression of ovulation by oral contraceptives was not inhibited by sibutramine. In a crossover study, 12 healthy female volunteers on oral steroid contraceptives received placebo in one period and 15 mg sibutramine in another period over the course of 8 weeks. No clinically significant systemic interaction was observed; therefore, no requirement for alternative contraceptive precautions are needed when patients taking oral contraceptives are concurrently prescribed sibutramine.
Drugs Highly Bound to Plasma Proteins: Although sibutramine and its active metabolites M_1 and M_2 are extensively bound to plasma proteins (≥94%), the low therapeutic concentrations and basic characteristics of these compounds make them unlikely to result in clinically significant protein binding interactions with other highly protein bound drugs such as warfarin and phenytoin. *In vitro* protein binding interaction studies have not been conducted.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity
Sibutramine was administered in the diet to mice (1.25, 5 or 20 mg/kg/day) and rats (1, 3, or 9 mg/kg/day) for two years generating combined maximum plasma AUC's of the two major active metabolites equivalent to 0.4 and 16 times, respectively, those following a daily human dose of 15 mg. There was no evidence of carcinogenicity in mice or in female rats. In male rats there was a higher incidence of benign tumors of the testicular interstitial cells; such tumors are commonly seen in rats and are hormonally mediated. The relevance of these tumors to humans is not known.
Mutagenicity
Sibutramine was not mutagenic in the Ames test, *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes or micronucleus assay in mice. Its two major active metabolites were found to have equivocal bacterial mutagenic activity in the Ames test. However, both metabolites gave consistently negative results in the *in vitro* Chinese hamster V79 cell mutation assay, *in vitro* clastogenicity assay in human lymphocytes, *in vitro* DNA-repair assay in HeLa cells, micronucleus assay in mice and *in vivo* unscheduled DNA-synthesis assay in rat hepatocytes.
Impairment of Fertility
In rats, there were no effects on fertility at doses generating combined plasma AUC's of the two major active metabolites up to 32 times those following a human dose of 15 mg. At 13 times the human combined AUC, there was maternal toxicity, and the dams' nest-building behavior was impaired, leading to a higher incidence of perinatal mortality; there was no effect at approximately 4 times the human combined AUC.

Pregnancy
Teratogenic Effects-Pregnancy Category C
Radiolabeled studies in animals indicated that tissue distribution was unaffected by pregnancy, with relatively low transfer to the fetus. In rats, there was no evidence of teratogenicity at doses of 1, 3, or 10 mg/kg/day generating combined plasma AUC's of the two major active metabolites up to approximately 32 times those following the human dose of 15 mg. In rabbits dosed at 3, 15, or 75 mg/kg/day, plasma AUC's greater than approximately 5 times those following the human dose of 15 mg caused maternal toxicity. At markedly toxic doses, Dutch Belted rabbits had a slightly higher than control incidence of pups with a broad short snout, short rounded pinnae, short tail and, in some, shorter thickened long bones in the limbs; at comparably high doses in New Zealand White rabbits, one study showed a slightly higher than control incidence of pups with cardiovascular anomalies while a second study showed a lower incidence than in the control group.
No adequate and well controlled studies with sibutramine have been conducted in pregnant women. The use of MERIDIA during pregnancy is not recommended. Women of childbearing potential should employ adequate contraception while taking MERIDIA. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant while taking MERIDIA.

Nursing Mothers
It is not known whether sibutramine or its metabolites are excreted in human milk. MERIDIA is not recommended for use in nursing mothers. Patients should be advised to notify their physician if they are breast-feeding.

Pediatric Use
The efficacy of sibutramine in adolescents who are obese has not been adequately studied.
Sibutramine's mechanism of action inhibiting the reuptake of serotonin and norepinephrine is similar to the mechanism of action of some antidepressants. Pooled analyses of short-term placebo-controlled trials of antidepressants in children and adolescents with major depressive disorder (MDD), obsessive compulsive disorder (OCD), and other psychiatric disorders have revealed a greater risk of adverse events representing suicidal behavior or thinking during the first few months of treatment in those receiving antidepressants. The average risk of such events in patients receiving antidepressants was 4%, twice the placebo risk of 2%.
No placebo-controlled trials of sibutramine have been conducted in children or adolescents with MDD, OCD, or other psychiatric disorders. In a study of adolescents with obesity in which 368 patients were treated with sibutramine and 130 patients with placebo, one patient in the sibutramine group and one patient in the placebo group attempted suicide. Suicidal ideation was reported by 2 sibutramine-treated patients and none of the placebo patients. It is unknown if sibutramine increases the risk of suicidal behavior or thinking in pediatric patients. The data are inadequate to recommend the use of sibutramine for the treatment of obesity in pediatric patients.

Geriatric Use
Clinical studies of sibutramine did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Pharmacokinetics in elderly patients are discussed in **"CLINICAL PHARMACOLOGY."**

ADVERSE REACTIONS

In placebo-controlled studies, 9% of patients treated with sibutramine (n = 2068) and 7% of patients treated with placebo (n = 884) withdrew for adverse events.
In placebo-controlled studies, the most common events were dry mouth, anorexia, insomnia, constipation and

Continued on next page

Meridia—Cont.

headache. Adverse events in these studies occurring in ≥1% of sibutramine treated patients and more frequently than in the placebo group are shown in the following table.

	Obese Patients in Placebo-Controlled Studies	
	Sibutramine (n = 2068)	Placebo (n = 884)
BODY SYSTEM Adverse Event	% Incidence	% Incidence
BODY AS A WHOLE:		
Headache	30.3	18.6
Back pain	8.2	5.5
Flu syndrome	8.2	5.8
Injury accident	5.9	4.1
Asthenia	5.9	5.3
Abdominal pain	4.5	3.6
Chest pain	1.8	1.2
Neck pain	1.6	1.1
Allergic reaction	1.5	0.8
CARDIOVASCULAR SYSTEM		
Tachycardia	2.6	0.6
Vasodilation	2.4	0.9
Migraine	2.4	2.0
Hypertension/increased blood pressure	2.1	0.9
Palpitation	2.0	0.8
DIGESTIVE SYSTEM		
Anorexia	13.0	3.5
Constipation	11.5	6.0
Increased appetite	8.7	2.7
Nausea	5.9	2.8
Dyspepsia	5.0	2.6
Gastritis	1.7	1.2
Vomiting	1.5	1.4
Rectal disorder	1.2	0.5
METABOLIC & NUTRITIONAL		
Thirst	1.7	0.9
Generalized edema	1.2	0.8
MUSCULOSKELETAL SYSTEM		
Arthralgia	5.9	5.0
Myalgia	1.9	1.1
Tenosynovitis	1.2	0.5
Joint disorder	1.1	0.6
NERVOUS SYSTEM		
Dry mouth	17.2	4.2
Insomnia	10.7	4.5
Dizziness	7.0	3.4
Nervousness	5.2	2.9
Anxiety	4.5	3.4
Depression	4.3	2.5
Paresthesia	2.0	0.5
Somnolence	1.7	0.9
CNS stimulation	1.5	0.5
Emotional lability	1.3	0.6
RESPIRATORY SYSTEM		
Rhinitis	10.2	7.1
Pharyngitis	10.0	8.4
Sinusitis	5.0	2.6
Cough increase	3.8	3.3
Laryngitis	1.3	0.9
SKIN & APPENDAGES		
Rash	3.8	2.5
Sweating	2.5	0.9
Herpes simplex	1.3	1.0
Acne	1.0	0.8
SPECIAL SENSES		
Taste perversion	2.2	0.8
Ear disorder	1.7	0.9
Ear pain	1.1	0.7
UROGENITAL SYSTEM		
Dysmenorrhea	3.5	1.4
Urinary tract infection	2.3	2.0
Vaginal monilia	1.2	0.5
Metrorrhagia	1.0	0.8

The following additional adverse events were reported in ≥ 1% of all patients who received sibutramine in controlled and uncontrolled pre-marketing studies.

Body as a Whole: fever.

Digestive System: diarrhea, flatulence, gastroenteritis, tooth disorder.

Metabolic and Nutritional: peripheral edema.

Musculoskeletal System: arthritis.

Nervous System: agitation, leg cramps, hypertonia, thinking abnormal.

Respiratory System: bronchitis, dyspnea.

Skin and Appendages: pruritus.

Special Senses: amblyopia.

Urogenital System: menstrual disorders.

Other Adverse Events

Clinical Studies

Seizures: Convulsions were reported as an adverse event in three of 2068 (0.1%) sibutramine treated patients and in none of 884 placebo-treated patients in placebo-controlled premarketing obesity studies. Two of the three patients with seizures had potentially predisposing factors (one had a prior history of epilepsy; one had a subsequent diagnosis of brain tumor). The incidence in all subjects who received sibutramine (three of 4,588 subjects) was less than 0.1%.

Ecchymosis/Bleeding Disorders: Ecchymosis (bruising) was observed in 0.7% of sibutramine treated patients and in 0.2% of placebo-treated patients in pre-marketing placebo-controlled obesity studies. One patient had prolonged bleeding of a small amount which occurred during minor facial surgery. Sibutramine may have an effect on platelet function due to its effect on serotonin uptake.

Interstitial Nephritis: Acute interstitial nephritis (confirmed by biopsy) was reported in one obese patient receiving sibutramine during pre-marketing studies. After discontinuation of the medication, dialysis and oral corticosteroids were administered; renal function normalized. The patient made a full recovery.

Altered Laboratory Findings: Abnormal liver function tests, including increases in AST, ALT, GGT, LDH, alkaline phosphatase and bilirubin, were reported as adverse events in 1.6% of sibutramine-treated obese patients in placebo-controlled trials compared with 0.8% of placebo patients. In these studies, potentially clinically significant values (total bilirubin ≥2 mg/dL; ALT, AST, GGT, LDH, or alkaline phosphatase ≥3x upper limit of normal) occurred in 0% (alkaline phosphatase) to 0.6% (ALT) of the sibutramine treated patients and in none of the placebo-treated patients. Abnormal values tended to be sporadic, often diminished with continued treatment, and did not show a clear dose-response relationship.

Postmarketing Reports

Voluntary reports of adverse events temporally associated with the use of sibutramine are listed below. It is important to emphasize that although these events occurred during treatment with sibutramine, they may have no causal relationship with the drug. Obesity itself, concurrent disease states/risk factors, or weight reduction may be associated with an increased risk for some of these events.

Psychiatric: Cases of depression, suicidal ideation and suicide have been reported rarely in patients on sibutramine treatment. However, a relationship has not been established between the occurrence of depression and/or suicidal ideation and the use of sibutramine. If depression occurs during treatment with sibutramine, further evaluation may be necessary.

Hypersensitivity: Allergic hypersensitivity reactions ranging from mild skin eruptions and urticaria to angioedema and anaphylaxis have been reported (see **"CONTRAINDICATIONS"** and **"PRECAUTIONS-Information For Patients"**, and other reports of allergic reactions listed below).

Other Postmarketing Reported Events:

Body as a Whole: anaphylactic shock, anaphylactoid reaction, chest pressure, chest tightness, facial edema, limb pain, sudden unexplained death.

Cardiovascular System: angina pectoris, atrial fibrillation, congestive heart failure, heart arrest, heart rate decreased, myocardial infarction, supraventricular tachycardia, syncope, torsade de pointes, vascular headache, ventricular tachycardia, ventricular extrasystoles, ventricular fibrillation.

Digestive System: cholecystitis, cholelithiasis, duodenal ulcer, eructation, gastrointestinal hemorrhage, increased salivation, intestinal obstruction, mouth ulcer, stomach ulcer, tongue edema.

Endocrine System: goiter, hyperthyroidism, hypothyroidism.

Hemic and Lymphatic System: anemia, leukopenia, lymphadenopathy, petechiae, thrombocytopenia.

Metabolic and Nutritional: hyperglycemia, hypoglycemia.

Musculoskeletal System: arthrosis, bursitis.

Nervous System: abnormal dreams, abnormal gait, amnesia, anger, cerebrovascular accident, concentration impaired, confusion, depression aggravated, Gilles de la Tourette's syndrome, hypesthesia, libido decreased, libido increased, manic reaction, mood changes, nightmares, serotonin syndrome, short term memory loss, speech disorder, transient ischemic attack, tremor, twitch, vertigo.

Respiratory System: epistaxis, nasal congestion, respiratory disorder, yawn.

Skin and Appendages: alopecia, dermatitis, photosensitivity (skin), urticaria.

Special Senses: abnormal vision, blurred vision, dry eye, eye pain, increased intraocular pressure, otitis externa, otitis media, photosensitivity (eyes), tinnitus.

Urogenital System: abnormal ejaculation, hematuria, impotence, increased urinary frequency, micturition difficulty, urinary retention.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

MERIDIA is controlled in Schedule IV of the Controlled Substances Act (CSA).

Abuse and Physical and Psychological Dependence

Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., drug development of tolerance, incrementation of doses, drug seeking behavior).

OVERDOSAGE

Overdose Management

There is limited experience of overdose with sibutramine. The most frequently noted adverse events associated with overdose are tachycardia, hypertension, headache and dizziness. Treatment should consist of general measures employed in the management of overdosage: an airway should be established as needed; cardiac and vital sign monitoring is recommended; general symptomatic and supportive measures should be instituted. Cautious use of β-blockers may be indicated to control elevated blood pressure or tachycardia. The results from a study in patients with end-stage renal disease on dialysis showed that sibutramine metabolites were not eliminated to a significant degree with hemodialysis. (see **Pharmacokinetics-*Special Populations***-Renal Insufficiency).

DOSAGE AND ADMINISTRATION

The recommended starting dose of MERIDIA is 10 mg administered once daily with or without food. If there is inadequate weight loss, the dose may be titrated after four weeks to a total of 15 mg once daily. The 5 mg dose should be reserved for patients who do not tolerate the 10 mg dose. Blood pressure and heart rate changes should be taken into account when making decisions regarding dose titration (see **"WARNINGS"** and **"PRECAUTIONS"**).

Doses above 15 mg daily are not recommended. In most of the clinical trials, MERIDIA was given in the morning.

Analysis of numerous variables has indicated that approximately 60% of patients who lose at least 4 pounds in the first 4 weeks of treatment with a given dose of MERIDIA in combination with a reduced-calorie diet lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose of MERIDIA. Conversely, approximately 80% of patients who do not lose at least 4 pounds in the first 4 weeks of treatment with a given dose of MERIDIA do not lose at least 5% (placebo-subtracted) of their initial body weight by the end of 6 months to 1 year of treatment on that dose. If a patient has not lost at least 4 pounds in the first 4 weeks of treatment, the physician should consider reevaluation of therapy which may include increasing the dose or discontinuation of MERIDIA.

The safety and effectiveness of MERIDIA, as demonstrated in double-blind, placebo-controlled trials, have not been determined beyond 2 years at this time.

HOW SUPPLIED

MERIDIA® (sibutramine hydrochloride monohydrate) Capsules contain 5 mg, 10 mg, or 15 mg sibutramine hydrochloride monohydrate and are supplied as follows:

5 mg, NDC 0074-2456-12, blue/yellow capsules imprinted with "MERIDIA" on the cap and "-5-" on the body, in bottles of 30 capsules.

10 mg, NDC 0074-2457-12, blue/white capsules imprinted with "MERIDIA" on the cap and "-10-" on the body, in bottles of 30 capsules.

15 mg, NDC 0074-2458-12, yellow/white capsules imprinted with "MERIDIA" on the cap and "-15-" on the body, in bottles of 30 capsules.

5 mg, NDC 0074-2456-13, blue/yellow capsules imprinted with "MERIDIA" on the cap and "-5-" on the body, in bottles of 100 capsules.

10 mg, NDC 0074-2457-13, blue/white capsules imprinted with "MERIDIA" on the cap and "-10-" on the body, in bottles of 100 capsules.

15 mg, NDC 0074-2458-13, yellow/white capsules imprinted with "MERIDIA"on the cap and "-15-" on the body, in bottles of 100 capsules.

Storage: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP controlled room temperature]. Protect capsules from heat and moisture. Dispense in a tight, light-resistant container as defined in USP.

Manufactured for: Abbott Laboratories, North Chicago, IL 60064, U.S.A.

By: KNOLL BV, Barceloneta, PR 00617

IMITREX is a registered trademark of Glaxo Group Limited.

Sibutramine is covered by US Patent Nos. 4,746,680; 4,929,629; and 5,436,272.

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ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.

Patient Information

Read the Patient Information that comes with MERIDIA before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about MERIDIA?

Some people taking MERIDIA can have a large increase in blood pressure or heart rate (pulse). Do not take MERIDIA if your blood pressure is not well controlled. Contact your doctor if you experience an increase in blood pressure while taking MERIDIA.

Your doctor should check your blood pressure and heart rate before you start MERIDIA and continue checking it regularly while you are using MERIDIA. It is important to have regular check-ups while taking MERIDIA.

What is MERIDIA?

MERIDIA is a medicine that may help obese people, as determined by their doctor, lose weight and keep weight off. MERIDIA may help with weight loss because it affects areas of the brain that control hunger. You should use MERIDIA with a low calorie diet.

The use of MERIDIA for more than 2 years has not been studied.

MERIDIA has not been studied in children under 16 years of age.

Who should not take MERIDIA?
Do not take MERIDIA if you:
- have uncontrolled or poorly controlled high blood pressure.
- **are taking or have taken a medicine called a monoamine oxidase inhibitor (MAOI).** Ask your doctor or pharmacist if you are not sure if any of your medicines are MAOIs. Do not take MAOIs for at least 2 weeks before using MERIDIA. Do not take MAOIs for at least 2 weeks after stopping MERIDIA.
- **have an eating disorder called anorexia nervosa or bulimia nervosa.**
- **are taking weight loss medicines to control your appetite.**
- **are allergic to MERIDIA.** The active ingredient is sibutramine hydrochloride monohydrate. See the end of this leaflet for a complete list of ingredients in MERIDIA.

How should I take MERIDIA?
- Take MERIDIA exactly as prescribed. Your doctor may adjust your dose. Do not change your dose unless your doctor tells you to do so.
- You can take MERIDIA with or without food.
- If you miss a dose of MERIDIA, just skip it. Do not take an extra dose to make up for missed doses.
- If you take too much MERIDIA, call your doctor or Poison Control Center right away, or go to the emergency room.
- Tell your doctor if you do not lose at least 4 pounds in the first 4 weeks of taking MERIDIA and eating a low calorie diet. Your doctor may change your dose or stop MERIDIA. MERIDIA does not work for everyone.

What should I avoid while taking MERIDIA?
MERIDIA may not be the right medicine for you if you have certain medical conditions. Tell your doctor about all of your medical conditions, especially if you:
- **have high blood pressure.**
- **have or had heart problems** such as a heart attack, heart failure, chest pain or an irregular heartbeat.
- **had a stroke or stroke symptoms.**
- **have liver or kidney problems.**
- **have an eye problem called glaucoma.**
- **have a thyroid problem (hypothyroidism).**
- **have or had seizures (convulsions, fits).**
- **have bleeding problems.**
- **have or had gallstones.**
- **have depression.**
- **are over age 65.**
- **are under age 16.**
- **are pregnant or planning to become pregnant.** The effects of MERIDIA on your unborn baby are not known. If you can become pregnant, you should use birth control while taking MERIDIA. Tell your doctor right away if you get pregnant while taking MERIDIA.
- **are breastfeeding.** It is not known if MERIDIA passes into your milk. The effects of MERIDIA on your baby are not known. You should not breastfeed while taking MERIDIA.

Do not drive, operate heavy machinery or do other dangerous activities until you know how MERIDIA affects you.
Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Taking MERIDIA and certain other medicines may affect each other and may cause serious and in some cases life-threatening side effects. Make sure you tell your doctor if you take:
- medicines called MAOIs, see "Who should not take MERIDIA?"
- other weight loss medicines
- cough and cold medicines
- migraine medicines
- depression medicines
- narcotic pain-killers
- lithium
- tryptophan
- medicines that increase bleeding
- antibiotic medicines

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist each time you get new medicine. They can tell you if it is okay to take MERIDIA with other medicines.

What are the possible side effects of MERIDIA?
Common side effects of MERIDIA include: dry mouth, headache, loss of appetite, trouble sleeping, and constipation.
The following serious side effects have been reported with MERIDIA:
- **a large increase in blood pressure or heart rate in some people.** See "What is the most important information I should know about MERIDIA?"
- **seizures**
- **bleeding**
- **a rare, but life-threatening problem called "serotonin syndrome."** It may occur when people take drugs that affect a brain chemical called serotonin along with MERIDIA. Do not take other medicines with MERIDIA unless your doctor has told you it is okay to do so. Get medical help right away if you have any of the following symptoms especially when taking other medicines with MERIDIA:
  - feel weak, restless, confused, or anxious
  - lose consciousness
  - have a fever, vomiting, sweating, shivering or shaking
  - have a fast heartbeat

Certain weight loss medicines have been associated with a rare, but life-threatening condition that affects the blood pressure in lungs (pulmonary hypertension). Because the condition is so rare it is not known if MERIDIA may cause this disease. If you experience new or worsening shortness of breath notify your doctor immediately.
Tell your doctor if you get a rash or hives while taking MERIDIA. You may be having an allergic reaction.
Tell your doctor if you get effects that bother you or that do not go away.
These are not all the side effects of MERIDIA. For more information, ask your doctor or pharmacist.
MERIDIA is a controlled substance (CIV). This means that MERIDIA can be a target for people who abuse prescription medicines. Keep your MERIDIA in a safe place. Selling or giving away MERIDIA is against the law.

How should I store MERIDIA?
- Store MERIDIA at room temperature between 59° to 86° F (15° to 30° C). Never leave it in a hot or moist place.
- Safely throw away MERIDIA that is out of date or no longer needed.
- Keep MERIDIA and all medicines out of reach of children. If your child accidentally takes MERIDIA, call their doctor or Poison Control Center right away, or take your child to the emergency room.

General information about MERIDIA.
Medicines are sometimes prescribed for conditions other than those described in patient information leaflets. Do not use MERIDIA for a condition for which it was not prescribed. Do not give MERIDIA to other people, even if they have the same symptoms you have. It may harm them and it is against the law.
This leaflet summarizes the most important information about MERIDIA. If you would like more information, talk to your doctor. You can also ask your doctor or pharmacist for information that is written for health professionals.
For more information call Abbott Laboratories at 1-800-633-9110 or visit www.Meridia.net.

What are the ingredients in MERIDIA?
Active Ingredient: sibutramine hydrochloride monohydrate
Inactive Ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains titanium dioxide, USP; gelatin; FD&C Blue No. 2 (5- and 10-mg capsules only); D&C Yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].
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Manufactured for:
Abbott Laboratories, North Chicago, IL 60064, U.S.A.
By: KNOLL BV, Barceloneta, PR 00617
ABBOTT LABORATORIES
NORTH CHICAGO, IL 60064, U.S.A.
Shown in Product Identification Guide, page 303

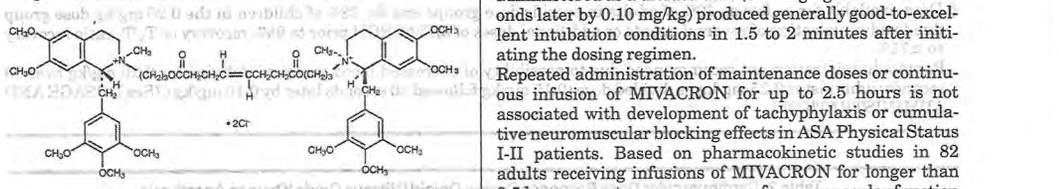
MIVACRON® INJECTION ℞

[mī-vsă-krŏn]
(mivacurium chloride)
℞ only

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION

MIVACRON (mivacurium chloride) is a short-acting, nondepolarizing skeletal muscle relaxant for intravenous (IV) administration. Mivacurium chloride is [*R*-[*R**,*R**-(E)]]-2,2'-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)] bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]isoquinolinium] dichloride. The molecular formula is $C_{58}H_{80}Cl_2N_2O_{14}$ and the molecular weight is 1100.18. The structural formula is:



The partition coefficient of the compound is 0.015 in a 1-octanol/distilled water system at 25°C.
Mivacurium chloride is a mixture of three stereoisomers: (1*R*, 1'*R*, 2*S*, 2'*S*), the *trans-trans* diester; (1*R*, 1'*R*, 2*R*, 2'*S*), the *cis-trans* diester; and (1*R*, 1'*R*, 2*R*, 2'*R*), the *cis-cis* diester. The *trans-trans* and *cis-trans* stereoisomers comprise 92% to 96% of mivacurium chloride and their neuromuscular blocking potencies are not significantly different from each other or from mivacurium chloride. The *cis-cis* diester has been estimated from studies in cats to have one-tenth the neuromuscular blocking potency of the other two stereoisomers.
MIVACRON Injection is a sterile, non-pyrogenic solution (pH 3.5 to 5.0) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. Multiple-dose vials contain 0.9% w/v benzyl alcohol.

CLINICAL PHARMACOLOGY

MIVACRON (a mixture of three stereoisomers) binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.
Pharmacodynamics: The time to maximum neuromuscular block is similar for recommended doses of MIVACRON and intermediate-acting agents (e.g., atracurium), but longer than for the ultra-short-acting agent, succinylcholine. The clinically effective duration of action of MIVACRON (a mixture of three stereoisomers) is one-third to one-half that of intermediate-acting agents and 2 to 2.5 times that of succinylcholine.
The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of MIVACRON is 0.07 mg/kg (range: 0.05 to 0.09) in adults receiving opioid/nitrous oxide/oxygen anesthesia. The pharmacodynamics of doses of MIVACRON $\geq ED_{95}$ administered over 5 to 15 seconds during opioid/nitrous oxide/oxygen anesthesia are summarized in Table 1. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 6 minutes (range: 3 to 9, n = 32) following an initial dose of 0.15 mg/kg MIVACRON and 7 to 8 minutes (range: 4 to 24, n = 85) following initial doses of 0.20 or 0.25 mg/kg MIVACRON.
Volatile anesthetics may decrease the dosing requirement for MIVACRON and prolong the duration of action; the magnitude of these effects may be increased as the concentration of the volatile agent is increased. Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC [Minimum Alveolar Concentration]) may decrease the effective dose of MIVACRON by as much as 25%, and may prolong the clinically effective duration of action and decrease the average infusion requirement by as much as 35% to 40%. At equivalent MAC values, halothane has little or no effect on the ED_{50} of MIVACRON, but may prolong the duration of action and decrease the average infusion requirement by as much as 20% (see CLINICAL PHARMACOLOGY: Individualization of Dosages subsection and PRECAUTIONS: Drug Interactions).
[See table 1 at bottom of next page]
Administration of MIVACRON over 30 to 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of MIVACRON may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity (see PRECAUTIONS: Reduced Plasma Cholinesterase Activity and CLINICAL PHARMACOLOGY: Individualization of Dosages subsection).
Interpatient variability in duration of action occurs with MIVACRON as with other neuromuscular blocking agents. However, analysis of data from 224 patients in clinical studies receiving various doses of MIVACRON during opioid/nitrous oxide/oxygen anesthesia with a variety of premedicants and varying lengths of surgery indicated that approximately 90% of the patients had clinically effective durations of block within 8 minutes of the median duration predicted from the dose-response data shown in Table 1. Variations in plasma cholinesterase activity, including values within the normal range and values as low as 20% below the lower limit of the normal range, were not associated with clinically significant effects on duration. The variability in duration, however, was greater in patients with plasma cholinesterase activity at or slightly below the lower limit of the normal range.
When administered during the induction of adequate anesthesia using thiopental or propofol, nitrous oxide/oxygen, and co-induction agents such as fentanyl and/or midazolam, doses of 0.15 mg/kg (2 X ED_{95}) MIVACRON administered over 5 to 15 seconds or 0.20 mg/kg MIVACRON administered over 30 seconds produced generally good-to-excellent tracheal intubation conditions in 2.5 to 3 and 2 to 2.5 minutes, respectively. A dose of 0.25 mg/kg MIVACRON administered as a divided dose (0.15 mg/kg followed 30 seconds later by 0.10 mg/kg) produced generally good-to-excellent intubation conditions in 1.5 to 2 minutes after initiating the dosing regimen.
Repeated administration of maintenance doses or continuous infusion of MIVACRON for up to 2.5 hours is not associated with development of tachyphylaxis or cumulative neuromuscular blocking effects in ASA Physical Status I-II patients. Based on pharmacokinetic studies in 82 adults receiving infusions of MIVACRON for longer than 2.5 hours, spontaneous recovery of neuromuscular function after infusion is independent of the duration of infusion and comparable to recovery reported for single doses (Table 1).
MIVACRON was administered as an infusion for as long as 4 to 6 hours in 20 adult patients and 19 geriatric patients. In most patients, after a brief period of adjustment, the rate of MIVACRON required to maintain 89% to 99% T_1 suppression remained relatively constant over time. There was a subset of patients in each group whose infusion rates did not stabilize quickly and decreased (by ≥30%) over the period of infusion. The rate of spontaneous recovery in these patients was comparable with that of patients having stable infusion rates and not dependent on the duration of infusion. These patients, however, tended to have higher infusion requirements (i.e., >8 mcg/kg/min) during the first 30 minutes of infusion than patients with stable infusion rates, although their final infusion rates were similar to those with stable infusion rates. There were no clinically important differences in infusion rate require-

Continued on next page

Mivacron—Cont.

ments between geriatric and young patients (see Pharmacokinetics: Special Populations: Geriatric Patients).

The neuromuscular block produced by MIVACRON is readily antagonized by anticholinesterase agents. As seen with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time and the greater the dose of anticholinesterase agent required for recovery of neuromuscular function.

In children (2 to 12 years), MIVACRON has a higher ED_{95} (0.10 mg/kg), faster onset, and shorter duration of action than in adults. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 5 minutes (n=4) following an initial dose of 0.20 mg/kg MIVACRON. Recovery following reversal is faster in children than in adults (Table 1).

Hemodynamics: Administration of MIVACRON in doses up to and including 0.15 mg/kg ($2 \times ED_{95}$) over 5 to 15 seconds to ASA Physical Status I-II patients during opioid/nitrous oxide/oxygen anesthesia is associated with minimal changes in mean arterial blood pressure (MAP) or heart rate (HR) (Table 2).

[See table 2 below]

Higher doses of ≥0.20 mg/kg ($\geq 3 \times ED_{95}$) may be associated with transient decreases in MAP and increases in HR in some patients. These decreases in MAP are usually maximal within 1 to 3 minutes following the dose, typically resolve without treatment in an additional 1 to 3 minutes, and are usually associated with increases in plasma histamine concentration. Decreases in MAP can be minimized by administering MIVACRON over 30 to 60 seconds (see CLINICAL PHARMACOLOGY: Individualization of Dosages subsection and PRECAUTIONS: General).

Analysis of 426 patients in clinical studies receiving initial doses of MIVACRON up to and including 0.30 mg/kg during opioid/nitrous oxide/oxygen anesthesia showed that high initial doses and a rapid rate of injection contributed to a greater probability of experiencing a decrease of ≥30% in MAP after administration of MIVACRON. Obese patients also had a greater probability of experiencing a decrease of ≥30% in MAP when dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight (see CLINICAL PHARMACOLOGY: Individualization of Dosages subsection and PRECAUTIONS: General).

Children experience minimal changes in MAP or HR after administration of doses of MIVACRON up to and including 0.20 mg/kg over 5 to 15 seconds, but higher doses (≥0.25 mg/kg) may be associated with transient decreases in MAP (Table 2).

Following a dose of 0.15 mg/kg MIVACRON administered over 60 seconds, adult patients with significant cardiovascular disease undergoing coronary artery bypass grafting or valve replacement procedures showed no clinically important changes in MAP or HR. Transient decreases in MAP were observed in some patients after doses of 0.20 to 0.25 mg/kg MIVACRON administered over 60 seconds. The number of patients in whom these decreases in MAP required treatment was small.

Pharmacokinetics: MIVACRON is a mixture of isomers which do not interconvert *in vivo*. The *cis-trans* and *trans-trans* isomers (92% to 96% of the mixture) are equipotent. The steady-state concentrations of the *cis-trans* and *trans-trans* isomers doubled after the infusion rate was increased from 5 to 10 mcg/kg/min, indicating that their pharmacokinetics is dose-proportional.

Table 3: Stereoisomer Pharmacokinetic Parameters* of Mivacurium in ASA Physical Status I–II Adult Patients† [n=18] During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	*trans-trans* isomer	*cis-trans* isomer
Elimination Half-life ($t_{1/2}$ min)	2.0 (1.0-3.6)	1.8 (0.8-4.8)
Volume of Distribution‡ (mL/kg)	147 (67-254)	276 (79-772)
Plasma Clearance (mL/min/kg)	53 (26-98)	99 (44-199)

* Values shown are mean (range).
† Ages 31 to 48 years.
‡ Volume of distribution during the terminal elimination phase.

The *cis-cis* isomer (6% of the mixture) has approximately one-tenth the neuromuscular blocking potency of the *trans-trans* and *cis-trans* isomers in cats. Neuromuscular blocking effects due to the *cis-cis* isomer cannot be ruled out in humans; however, modeling of clinical pharmacokinetic-pharmacodynamic data suggests that the *cis-cis* isomer produces minimal (<5%) neuromuscular block during a 2-hour infusion. In studies of ASA Physical Status I-II patients receiving infusions of MIVACRON lasting as long as 4 to 6 hours, the 5% to 25% and the 25% to 75% recovery indices were independent of the duration of infusion, suggesting that the *cis-cis* isomer does not affect the rate of post-infusion recovery.

Distribution: The volume of distribution of *cis-trans* and *trans-trans* isomers in healthy surgical patients is relatively small, reflecting limited tissue distribution (Table 3). The volume of distribution of *cis-cis* isomers is also small and averaged 335 mL/kg (range 192 to 523) in the 18 healthy surgical patients whose data are displayed in Table 3. The protein binding of mivacurium has not been determined due to its rapid hydrolysis by plasma cholinesterase.

Metabolism: Enzymatic hydrolysis by plasma cholinesterase is the primary mechanism for inactivation of mivacurium and yields a quaternary alcohol and a quaternary monoester metabolite. Tests in which these two metabolites were administered to cats and dogs suggest that each metabolite is unlikely to produce clinically significant neuromuscular, autonomic, or cardiovascular effects following administration of MIVACRON.

The mean ± S.D. *in vitro* $t_{1/2}$ values of the *trans-trans* and the *cis-trans* isomers were 1.3 ± 0.3 and 0.8 ± 0.2 minutes, respectively, in human plasma from healthy male (n = 5) and female (n = 5) volunteers. The mean *in vivo* $t_{1/2}$ values for the more potent *trans-trans* and *cis-trans* isomers in healthy surgical patients (Table 3) were similar to those found *in vitro*, suggesting that hydrolysis by plasma cholinesterase is the predominant elimination pathway for these isomers. The mean ± S.D. *in vitro* $t_{1/2}$ of the less potent *cis-cis* isomer was 276 ± 130 minutes, while the mean ± S.D. *in vivo* $t_{1/2}$ for the *cis-cis* isomer in healthy surgical patients was 53 ± 20 minutes. These data suggest that *in vivo*, pathways other than hydrolysis by plasma cholinesterase contribute to the elimination of the *cis-cis* isomer.

Elimination: The clearance (CL) values of the two more potent isomers, *cis-trans* and *trans-trans*, are very high and are dependent on plasma cholinesterase activity (Table 3). The combination of high CL and low distribution volume results in $t_{1/2}$ values of approximately 2 minutes for the two more potent isomers. The short $t_{1/2}$ and high CL of the more potent isomers are consistent with the short duration of action of MIVACRON.

The CL of the less potent *cis-cis* isomer is not dependent on plasma cholinesterase. The mean ± S.D. CL was 4.6 ± 1.1 mL/min/kg and $t_{1/2}$ was 53 ± 20 minutes in the 18 healthy surgical patients whose data are displayed in Table 3.

Renal and biliary excretion of unchanged mivacurium are minor elimination pathways; urine and bile are important elimination pathways for the two metabolites.

Special Populations: Geriatric Patients (≥60 years): Two pharmacokinetic/pharmacodynamic studies of MIVACRON have been conducted in geriatric patients. The first study compared the pharmacokinetics and pharmacodynamics of mivacurium in 19 geriatric patients with those in 20 adult patients receiving infusions for as long as 4 to 6 hours. The average infusion rate required to produce 89% to 99% T_1 suppression was slightly (~14%) lower in geriatric patients. This difference is not regarded as clinically important, but is most likely secondary to differences in pharmacokinetics (i.e., a lower CL of the *cis-trans* and *trans-trans* isomers in geriatric patients) (Table 4). The rate of post-infusion spontaneous recovery was not dependent on duration of infusion and appeared to be comparable in these geriatric patients and adult patients. Two pharmacodynamic studies in which patients received infusions for a shorter duration (2 to 3 hours) have shown that the infusion rate requirements were lower (by 38%) in geriatric patients (64 to 86 years of age) than in younger patients (18 to 41 years of age).

[See table 4 at top of next page]

The second pharmacokinetic/pharmacodynamic study showed no clinically important differences in the pharmacokinetics of the individual isomers nor the ED_{95} determined for 36 young adult patients (18 to 40 years) and 35 geriatric patients (≥65 years) during opioid/nitrous oxide/oxygen anesthesia. Following infusions for up to 3.5 hours in these patients, the rate of spontaneous recovery was slightly (~2 to 4 minutes, on average) slower in the geriatric patients than in young adult patients.

In a third study of the pharmacodynamics of 0.1 mg/kg MIVACRON administered to eight geriatric patients (68 to 77 years) and nine adult patients (18 to 49 years) during N_2O/O_2/isoflurane anesthesia, the time to onset was approximately 1.5 minutes slower in geriatric patients than in adult patients. In addition, the clinical duration was slightly (~3 minutes, on average) longer in geriatric patients than in adult patients; these differences are not considered clinically important.

Although these studies showed conflicting findings, in general, the clearances of the more potent isomers are most likely lower in geriatric patients. This difference does not lead to clinically important differences in the ED_{95} of MIVACRON or the infusion rate of MIVACRON required to produce 95% T_1 suppression in geriatric patients. However, the time to onset may be slower, the duration may be slightly longer, the rate of recovery may be slightly slower, therefore MIVACRON requirements may be lower in geriatric patients.

Patients with Renal Disease: An early clinical trial showed that the clinically effective duration of action of 0.15 mg/kg MIVACRON was about 1.5 times longer in kidney transplant patients than in healthy patients, presumably due to reduced clearance of one or more isomers. A second study was conducted in seven patients with mild to moderate renal impairment, eight patients with severe re-

Table 1: Pharmacodynamic Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial Dose of MIVACRON* (mg/kg)		Time to Maximum Block† (min)	Time to Spontaneous Recovery† 5% Recovery (min)	25% Recovery‡ (min)	95% Recovery§ (min)	T_4/T_1 Ratio ≥75%§ (min)
Adults						
0.07 to 0.10	[n=47]	4.9 (2.0-7.6)	11 (7-19)	13 (8-24)	21 (10-36)	21 (10-36)
0.15	[n=50]	3.3 (1.5-8.8)	13 (6-31)	16 (9-38)	26 (16-41)	26 (15-45)
0.20‖	[n=50]	2.5 (1.2-6.0)	16 (10-29)	20 (10-36)	31 (15-51)	34 (19-56)
0.25‖	[n=48]	2.3 (1.0-4.8)	19 (11-29)	23 (14-38)	34 (22-64)	43 (26-75)
Children 2 to 12 Years						
0.11 to 0.12	[n=17]	2.8 (1.2-4.6)	5 (3-9)	7 (4-10)	–	–
0.20	[n=18]	1.9 (1.3-3.3)	7 (3-12)	10 (6-15)	19 (14-26)	16 (12-23)
0.25	[n=9]	1.6 (1.0-2.2)	7 (4-9)	9 (5-12)	–	–

* Doses administered over 5 to 15 seconds.
† Values shown are medians of means from individual studies (range of individual patient values).
‡ Clinically effective duration of neuromuscular block.
§ Data available for as few as 40% of adults in specific dose groups and for 22% of children in the 0.20 mg/kg dose group due to administration of reversal agents or additional doses of MIVACRON prior to 95% recovery or T_4/T_1 ratio recovery to ≥75%.
‖ Rapid administration not recommended due to possibility of decreased blood pressure. Administer 0.20 mg/kg over 30 seconds; administer 0.25 mg/kg as divided dose (0.15 mg/kg followed 30 seconds later by 0.10 mg/kg). (See DOSAGE AND ADMINISTRATION.)

Table 2: Cardiovascular Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial Dose of MIVACRON*(mg/kg)		% of Patients With ≥30% Change: MAP Dec	MAP Inc	HR Dec	HR Inc
Adults					
0.07 to 0.10	[n=49]	0%	2%	0%	0%
0.15	[n=53]	4%	4%	4%	2%
0.20†	[n=53]	30%	0%	0%	8%
0.25†	[n=44]	39%	2%	0%	14%
Children 2 to 12 years					
0.11 to 0.12	[n=17]	0%	6%	0%	0%
0.20	[n=17]	0%	0%	0%	0%
0.25	[n=8]	13%	0%	0%	0%

* Doses administered over 5 to 15 seconds.
† Rapid administration not recommended due to possibility of decreased blood pressure. Administer 0.20 mg/kg over 30 seconds; administer 0.25 mg/kg as divided dose (0.15 mg/kg followed 30 seconds later by 0.10 mg/kg). (See DOSAGE AND ADMINISTRATION.)

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REVIEW

TOWARD A UNIFIED THEORY OF SEROTONIN DYSREGULATION IN EATING AND RELATED DISORDERS[1]

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SUMMARY

Patients with eating disorders (EDs) exhibit several clinical features and biologic findings indicative of serotonin (5-hydroxytryptamine, 5-HT) dysregulation. These include feeding disturbances, depression and suicide, impulsivity and violence, anxiety and harm avoidance, obsessive–compulsive features, seasonal variation of symptoms, as well as disturbances in neuroendocrine and vascular tissues, as well as other neurochemical systems linked to 5-HT, such as temperature. This review attempts to integrate available results from controlled studies in humans, with particular focus on cerebrospinal fluid (CSF), platelet and plasma studies, as well as pharmacologic challenge strategies using a variety of serotonergic agents. Taken together, these findings support the concept of altered post-synaptic, hypothalamic 5-HT receptor sensitivity in bulimia nervosa (BN), regardless of the presence of anorexia nervosa (AN) or major depression (MD), although these conditions may be associated with other disturbances in 5-HT function, perhaps pre-synaptic ones. The observation that different response measures of 5-HT function in the same subjects may be simultaneously increased, decreased and no different in patients compared to controls is consistent with a 5-HT dysregulation hypothesis. It may be that a variety of psychobiological stressors, such as dieting, binge-eating, purging, drug abuse, photoperiodic changes, as well as psychosocial–interpersonal stressors, perturb and interact with an already vulnerable 5-HT system.

Keywords—Serotonin; 5-hydroxytryptamine; m-chlorophenylpiperazine; L-tryptophan; Anorexia nervosa; Bulimia nervosa.

AN OVERVIEW OF THE EATING DISORDERS

Epidemiological studies suggest that the incidence and prevalence of the eating disorders (EDs), anorexia nervosa (AN) and bulimia nervosa (BN), have been on the rise over the last three to four decades (Casper, 1983). Historically, binge-eating was originally described as a symptom associated with AN and then with obesity (Stunkard, 1959). In recent times there has been disagreement as to whether BN occurring at normal weight is fundamentally the same or different from BN occurring at low weight or in the context of AN. This confusion is

[1]Owing to space limitations, the reference list in this paper has been significantly abbreviated. A complete reference list is available from the corresponding author.

evidenced by the multiple changes in diagnostic nomenclature and criteria that have taken place over the last several years and continues into the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV). Boskind-Lodahl and White (1978) used the term "bulimarexia" to refer to college-age females who binged and vomited, but who were not overtly anorexic. Other descriptive terms, such as the "dietary chaos syndrome" and the "abnormal normal weight control syndrome" were proposed to describe bulimic phenomenology not associated with overt AN. Russell (1979) was the first to coin the currently accepted term "bulimia nervosa" to describe both low and normal weight patients with bulimic behaviors. In his original description, he conceptualized BN as "an ominous variant of anorexia nervosa". In spite of this, DSM-III defined the syndrome "bulimia" as fundamentally distinct from AN. DSM-III-R uses Russell's term "bulimia nervosa" to describe the syndrome, but absent are the previous exclusion criteria for AN. Currently, DSM-IV does not allow both diagnoses in the same patient. Much has been learned about the psychobiology and psychoneuroendocrinology of EDs and related psychopathology over the last several years. These data may be applied to understanding and distinguishing the pathophysiology of each of these syndromes. One important biological system that appears to be involved in complex ways is serotonin (5-hydroxytryptamine, 5-HT).

THE BASIS FOR A THEORY OF SEROTONIN DYSREGULATION

There are many reasons to suspect that dysregulation of the neurotransmitter serotonin (5-HT) may be involved in the pathophysiology of the EDs. These are based on extensive animal and human data accumulated over the last several years in the basic and clinical neurosciences, some of which have been reviewed elsewhere (Brewerton, 1989; Brewerton et al., 1990; Brewerton et al., 1992b; Goldbloom & Garfinkel, 1990; Jimerson et al., 1990; Kaye & Weltzin, 1991). The role of 5-HT in EDs has been of particular interest given its well-established role as a central satiety agent.

Feeding and Satiety

Experimental and clinical evidence suggests that manipulations of the 5-HT system result in marked changes in feeding behaviors, particularly satiety responses, which are impaired in bulimic patients. These data may also be relevant to obese patients, a subset of whom exhibit clinically significant bingeing behavior (Stunkard, 1959). Obesity is also frequently found in the personal and family histories of patients with BN (Garfinkel et al., 1980; Strober, 1981). Pharmacologic enhancement of 5-HT neurotransmission in animals and man generally leads to increased satiety. An important exception to this is the induction of feeding in animals by 5-HT_{1A} receptor activation (Dourish et al., 1988), which may act by turning down 5-HT neurons through presynaptic stimulation. These findings also suggest that opposing components operate within the 5-HT system for the control of feeding, not unlike opposing adrenergic receptors regulating the cardiovascular system. Some 5-HT agonists also specifically decrease carbohydrate (CHO) consumption, while sparing protein intake (see Brewerton et al. (1994b) for a review). Conversely, attenuation of 5-HT neurotransmission by various methods leads to decreased satiety, increased food consumption and subsequent weight gain. Relevant clinical examples include the increased rate of weight gain reported in non-bulimic AN patients treated with the 5-HT antagonist cyproheptadine (Halmi et al., 1986) and the decrease in binge-eating in bulimic patients following fluoxetine (Fluoxetine Bulimia Nervosa Collaborative Group (FBNCG), 1992).

The effects of 5-HT on feeding are thought to be mediated centrally via the hypothalamus (Hoebel, 1985; Hoebel et al., 1989), although there is some evidence that peripheral mechanisms may play a part (Pollock & Rowland, 1981). A direct effect of 5-HT on metabolic rate which then alters feeding behavior (ischymetric theory) has also been postulated (Nicolaidis & Even, 1989).

Specific peripheral factors have been noted to be influential in regulating central 5-HT synthesis, as well as feeding behavior. CHO consumption itself leads to increased synthesis of central 5-HT in rats, largely via the effects of insulin on the ratio of L-tryptophan (L-TRP) to other large neutral amino acids (LNAAs), including valine, leucine, isoleucine, tyrosine, and phenylalanine, all of which compete for active transport across the blood–brain barrier (Fernstrom, 1985). Insulin preferentially enhances peripheral tissue utilization of these LNAAs to the relative exclusion of L-TRP, thereby increasing the amount of L-TRP available for transport across the blood–brain barrier and subsequent synthesis of central 5-HT. This mechanism of synthesizing central 5-HT from peripheral L-TRP of dietary origin is impaired by insulin resistance, which may be present in obesity, BN and AN, and can be experimentally induced in man by overeating. Insulin has also been reported to directly increase plasma L-TRP levels (Fernstrom & Wurtman, 1972). There is also evidence that enhanced peripheral 5-HT neurotransmission increases gastric motility which in turn increases satiety (Pollock & Rowland, 1981). Whether the decrease in gastric motility reported in both AN and BN patients is associated with impaired 5-HT neurotransmission is unknown.

Fasting

Acute dieting or weight loss can cause decreased plasma L-TRP levels (Goodwin et al., 1990) and upregulation of platelet 5-HT receptors in humans (Goodwin et al., 1987c) as well as increased neuroendocrine responsivity to intravenous L-TRP (Cowen & Charig, 1987; Goodwin et al., 1987a; Goodwin et al., 1987b). These data may be quite relevant to the EDs given the severe restriction of food intake common to both AN and BN. In one large series of patients, fasting led to bingeing behavior in over 85% of BN patients (Mitchell et al., 1986). Fasting and semi-starvation also clearly contribute to mood lability. Depressed mood has been induced in normal subjects (Young et al., 1985) and remitted depressed patients (Delgado et al., 1990) blindly receiving oral amino acid mixtures lacking L-TRP, presumably as a result of acutely lowering brain 5-HT. Changes in 5-HT receptor sensitivity, as well as related changes in dopamine function, could conceivably be involved in the inherently rewarding aspects of dieting experienced by ED patients (Jimerson et al., 1992). Although investigators disagree about the ultimate cause(s) of EDs, most agree that dieting is an important proximal cause which then goes on to perturb a variety of psychoneuroendocrinological systems. Recent animal evidence suggests that the compulsive exercising common to ED patients (Brewerton et al., 1995; Epling & Pierci, 1988) may partly be driven by semi-starvation-induced changes in serotonin metabolism (Altemus et al., 1993).

Mood

Further indirect evidence for abnormal serotonin activity in ED patients derives from several relationships to affective illness, particularly depression. The hypothesis that major depression (MD) involves a reduction in 5-HT function has evolved along several lines of evidence which have been reviewed elsewhere (Brewerton et al., 1992b; Jimerson et al.,

1990). One of the most consistent findings is that prolactin (PRL) responses to intravenous L-TRP (Brewerton et al., 1992b; Heninger et al., 1984) and oral fenfluramine (Coccaro et al., 1989; Siever et al., 1984) are blunted in patients with MD. The restoration of normal PRL responses to L-TRP in patients following antidepressant treatment is likely to reflect the therapeutic effect of these drugs on 5-HT neurotransmission. Both AN and BN patients also have high frequencies of depressed mood, lifetime histories of MD and therapeutic responsiveness to antidepressant medications (FBNCG, 1992). Both AN and BN patients also have higher frequencies of affective disorders in their first degree relatives compared to normal controls (Halmi et al., 1991; Kassett et al., 1989). Kaye and colleagues (Kaye et al., 1986) have shown that bingeing and vomiting alter mood and anxiety ratings, with most patients responding with acute but transient improvement of mood and anxiety. The strong relationship between MD and BN has led some investigators to postulate that they are essentially manifestations of the same illness (Pope & Hudson, 1988).

Anxiety

5-HT plays an important yet complex role in the modulation of anxiety, a symptom commonly reported by ED patients. High frequencies of obsessional symptoms and higher than expected rates of obsessive compulsive disorder (OCD) and other anxiety disorders have been described in patients with BN (Brewerton et al., 1993c) and AN (Halmi et al., 1991; Kaye et al., 1993). Animal and human studies indicate that anxiety is generally increased with enhanced 5-HT function (Charney et al., 1987, 1988), although an anxiolytic effect is produced by 5-HT_{1A} receptor activation (Engel et al., 1984). As previously noted, 5-HT_{1A} activation can also stimulate feeding in certain experimental paradigms, thereby linking eating with anxiety reduction. Of particular relevance to this discussion is that punishment-suppressed behaviors are suppressed by 5-HT enhancement and released by 5-HT attenuation. Theoretically, a functional 5-HT deficit in bulimic patients could conceivably contribute to the loss of control of typical "punishment-suppressed" bulimic behaviors, such as bingeing, vomiting, purging, stealing, drug abuse, sexual acting out, and various forms of auto-aggressive and socially unacceptable behaviors (Casper et al., 1980; Garfinkel et al., 1980), much like that seen in arson and other violence directed towards others in men (Linnoila et al., 1983). Conversely, restrictor AN patients are overall much less impulsive than their bulimic counterparts (Casper et al., 1980; Garfinkel et al., 1980; Strober, 1981) and have higher frequencies of Cluster C personality disorders, including obsessive–compulsive personality disorder and traits (Kaye et al., 1993). Both AN and BN patients score higher than controls on the harm avoidance subscale of the Tridimensional Personality Questionnaire (TPQ), a scale thought to reflect behavioral inhibition by 5-HT (Brewerton et al., 1993a). This psychobiological representation involving serotonin is remarkably parallel to the traditional psychoanalytic notion of OCD symptoms as defenses against aggressive impulses. Patients with OCD have been reported to have higher frequencies of EDs (Kasvikis et al., 1986; Pigott et al., 1991) and related psychometric features, all of which further suggests a psychobiologic relationship. Selective therapeutic responses following serotonin-specific reuptake inhibitor (SSRI) antidepressants and other data also attest to a serotonin link (see Table I).

Impulsivity, Aggression and Personality Disorders

As suggested above, some forms of aggression towards self and others can be conceptualized as impulsive, disinhibited behaviors and are thought to be modulated by

Table I. Comparison of 5-HT findings in the eating disorders, major depressive disorder (MD), obsessive–compulsive disorder (OCD) and personality disorder (PD)

	BN	BN ± AN	AN	MDD	OCD	PD
5-HT$_1$ mediated (5-HT$_2$ inhibitory)						
Baseline PRL	↓	↓	↓	0	↓[6]	0
PRL: following m-CPP	↓	↓	↓	0	↓[8],0[9]	↓[7]
following L-TRP	0	↓	0	↓	0[6]	0
following 5-HPT	↓	-	-	0	-	-
following d1-FEN	↓	↓	0[12]	↓	0[10]	↓,[11]
5-HT turnover						
CSF 5-HIAA	0,↓[1]	↓[2]	↓[3],0[4],↑[5]	0,↓	0,↑	0,↓
5-HT$_1$ mediated (5-HT$_2$ stimulatory)						
CORT: following m-CPP	0	0	0	0,↓	0[8,9]	↑
following L-TRP	0	0	0	0	0	-
following 5-HTP	0	-	-	↑	-	-
following d1-FEN	↓	↓	0	↓	0,[10]	-
5-HT$_{1c/2}$ mediated						
PLT 5-HT mediated aggregation	↑	↑	0	-	0	-
Peak ΔTEMP (m-CPP)	↑	↑	-	-	0	-
Headache responses (m-CPP)	↑	↑	-	0	0	-
5-HT uptake						
PLT 5-HT uptake	0,↑	-	0	0,↓	0,↓[13]	-
PLT IMI binding	↓	-	↓	0,↓	0,↓[14]	-
5-HT synthesis						
Plasma L-TRP/LNAA ratio	0	↓	↓	↓	0	-
Whole blood serotonin	0	0	↑	0	0,↓[15]	-
5-HT degradation						
PLT MAO	↓	-	0	0,↓	-	↓[16]

[1] Inversely correlated with weekly binge frequency. [2] (a) low-wt, (b) post-probenecid. [3] Low-wt. [4] Short-term weight recovered. [5] Long-term weight recovered. [6] See Charney et al. (1988). [7] See Hollander et al. (1990); Moss et al. (1990). [8] IV 0.1 mg/kg; (Charney et al., 1988) (females only); see Hollander et al. (1992). [9] Oral 0.5 mg/kg; see Zohar et al. (1987). [10] McBride et al. (1992). [11] Inversely correlated to aggression measures. [12] Trend toward decrease. [13] See Bastani et al. (1991); Marazziti et al. (1992); Weizman et al. (1986a). [14] See Bastani et al. (1991); Black et al. (1990); Kim et al. (1991). [15] See Hanna et al. (1991). [16] See Reist et al. (1990); Soloff et al. (1991); inversely correlated to measures of hostility/impulsivity.

5-HT neurotransmission (Brown et al., 1982; Coccaro et al., 1989; Linnoila et al., 1983). Early studies reported that a tryptophan (TRP) deficient diet or p-chlorophenylalanine (p-CPA) administration increased muricidal activity in rats, an effect reversed by TRP administration (Valzelli et al., 1981). In humans, lower levels of CSF 5-HIAA have been reported in several studies to be associated with suicide attempts and measures of aggression (Brown et al., 1982). Examination of various 5-HT parameters in post-mortem brain tissue has also linked 5-HT dysregulation to suicide. Patients with BN, with or without AN, exhibit clinical features, besides bingeing, that are indicative of impulsivity, such as a high frequency of suicide attempts, alcohol/drug abuse, stealing, and sexual promiscuity (Russell, 1979). Interestingly, several authors have noted the association between disturbed eating behaviors and self-mutilation (see Brewerton et al. (1992b) for references). These studies are relevant to a 5-HT hypothesis in the EDs given the similar features of BN in both normal weight and low weight patients. From a phenomenological point of view, BN patients have

similar degrees and types of psychopathology, regardless of weight (Garner et al., 1985), which tends to be qualitatively distinct from and more severe than that of non-bulimic anorexics (Casper, 1990; Casper et al., 1980; Garfinkel et al., 1980; Strober, 1981). Elucidation of the pathophysiology of the EDs may allow in the future for a clearer distinction between AN and BN. Investigators have hypothesized that 5-HT function is decreased in BN and increased in AN (Jimerson et al., 1992; Kaye & Weltzin, 1991), although the patient with both illnesses remains a conundrum in terms of a "too much vs too little hypothesis". A theory of 5-HT dysregulation which accounts for these paradoxes is therefore needed.

Alcoholism and Addiction

5-HT may be of pathophysiological significance in the development and maintenance of alcoholism and other addictions (Ballenger et al., 1979; Lee & Meltzer, 1991; Naranjo et al., 1986), which have phenomenological links to the EDs. Alcohol abuse is quite common in ED patients and their families (Bulik, 1987; Kassett et al., 1989). Low levels of CSF 5-HIAA have been reported in abstinent alcoholics (Ballenger et al., 1979; Borg et al., 1985) and in depressed patients with a family history of alcoholism (Rosenthal et al., 1980). During intoxication, CSF 5-HIAA levels significantly increase and correlate with blood ethanol concentrations (Borg et al., 1985). This phenomenon may be akin to the increase in central 5-HT following food ingestion in bulimia (Kaye et al., 1988a, 1989). Recent studies show that 5-HT reuptake inhibitors decrease alcohol intake (Naranjo et al., 1986), food intake and bulimic symptoms (FBNCG, 1992). In a prospective study of college freshman, Krahn and colleagues (1992) found that dieting behavior predicted subsequent alcohol abuse as well as binge-eating behavior. This line of reasoning hypothesizes that alcoholics, other types of addicts, and eating disordered patients may be seeking to modify brain 5-HT defects by superficially different, yet probably similar, psychobiologic mechanisms. Benkelfat et al. (1991) reported that m-CPP induced an alcohol-like "high" in abstinent alcoholics. A similar relationship may apply to compulsive exercising (Brewerton et al., 1995), as discussed above, and other addictive behaviors, such as cocaine abuse.

Seasonality

Seasonal variations in several parameters of 5-HT function have been identified in humans and include CSF 5-HIAA, platelet imipramine binding, platelet and hypothalamic 5-HT content, peak PRL responses following m-CPP and L-TRP (Brewerton, 1989; Brewerton et al., 1992b), as well as other 5-HT parameters (see Brewerton (1989) and Brewerton et al. (1993b)). Light has also been reported to alter central 5-HT receptor sensitivity and function (Brunel & de Montigny, 1987; Cox & Mason, 1987; Mason, 1988). Circannual 5-HT rhythms have been hypothesized to be important to the understanding of seasonal fluctuations reported in several 5-HT related neuropsychiatric conditions (Brewerton, 1989; Brewerton et al., 1988, 1993b), including suicide, affective illness, obesity, alcoholism, migraine, obsessive–compulsive disorder, as well as the EDs (Blouin et al., 1992; Brewerton et al., 1994a; Hardin et al., 1991; Nielsen, 1992). In a study of 111 ED patients at three locations, Brewerton and colleagues (1994) reported that BN patients, regardless of weight, had higher scores on the Seasonal Pattern Assessment Questionnaire (SPAQ) (Hardin et al., 1991) than normal controls and nearly as high as patients with seasonal affective disorder (SAD). Blouin et al. (1992) found a significant inverse correlation between binge frequency and the photoperiod, and Lam et al. (1994) demonstrated significant reductions in binge-

eating following phototherapy. Phototherapy may prove to be an important adjunctive treatment of the EDs, particularly BN. Re-establishing or re-entraining normal circadian rhythms with regular eating (three times per day) may also play a role in recovery.

Gender

It is well known that the majority of patients with eating and affective disorders are of the female sex. Although such asymmetry is often explained by social or perhaps hormonal factors, it may also be understood in light of differences in central 5-HT between the sexes, a subject reviewed by Carlsson and coworkers (1985). Female rats in comparison to male rats have higher brain 5-HT and 5-HIAA levels, a higher rate of brain 5-HT synthesis following pargyline with or without L-TRP, and a greater hypothermic response to the 5-HT agonist 8-OH-DPAT. Other workers have reported higher activity of TRP hydroxylase in female brains compared to male brains. The 5-HT system of female rats appears to be more perturbable and less adaptive to stress than that of male rats (Kennett et al., 1986). In humans, females have been reported to have higher CSF 5-HIAA levels and higher PRL responses to L-TRP than males (Heninger et al., 1984). Furthermore, the PRL responses to L-TRP (but not thyrotropin-releasing hormone) are markedly increased after 3 weeks of dieting in women, but not men (Goodwin et al., 1987a, 1987b). Some studies also suggest that females are "more seasonal" than males for other phenomena, e.g. affective illness, suicide and migraine (Brewerton & George, 1990).

Body Image and Perception

Psychedelic drugs such as lysergic acid diethylamide (LSD) structurally resemble 5-HT and act via 5-HT receptor mechanisms to produce profound mood-congruent alterations in the perception of self and body, including changes in body size (Grof, 1980; Masters & Houston, 1966). 5-HT receptor dysfunction could therefore conceivably be involved in the experiential changes in body image and self perception of both AN and BN patients. Of note is that the 5-HT antagonist cyproheptadine reportedly decreased "fear of becoming fat" in AN patients in comparison to placebo (Goldberg et al., 1980). Goldbloom and Olmsted (1993) have also reported improvement in measures of body image dissatisfaction and perfectionism in BN patients following double-blind, placebo-controlled administration of fluoxetine.

Could it be that cultural suggestions to "be thin" or environmental messages that one's body is "not good enough", "not thin enough", etc., produce clinically significant alterations in 5-HT function in susceptible individuals? This is comparable to the idea of alterations in 5-HT function accompanying and following psychotherapy. On several measures of hypnotizability BN patients scored significantly higher than controls, and interestingly, purging AN patients scored higher than pure restrictors (Pettinati et al., 1985). In another study, BN patients scored significantly higher on the Dissociative Experience Scale (DES) than controls (Demitrack et al., 1990), a phenomena related to hypnotizability and trauma. This susceptibility to suggestion might help to explain the etiological importance of socio-cultural factors in the development of the EDs (Garner et al., 1983), which must be taken into account in a comprehensive biopsychosocial model involving 5-HT.

Social Status and Victimization

Evidence from primate research indicates that social influences significantly affect 5-HT receptor function (McGuire & Raleigh, 1985; Raleigh et al., 1984, 1985). As social rank changes, measures of behavioral sensitivity to serotonergic agents change accordingly. These findings may be relevant to human social hierarchies, despite the significant species and gender differences. Nevertheless, it is interesting that the etiological conceptualization of "bulimarexia" (Boskind-Lodahl & White, 1978) was based on a feminist perspective in which the disorder is viewed as a pathological outcome of a male dominated society in which the self-esteem and social status of females is overly dependent on physical attractiveness to males. Furthermore, the role of sexual abuse in women (predominantly) by male perpetrators (predominantly) in the etiology of BN remains a controversial one (Pope & Hudson, 1992). However, using the National Women's Study as a data base ($n = 4{,}004$) (Resnick et al., 1993), our group recently found a significantly greater frequency of rape in a randomly selected, non-clinical sample of women ($n = 3{,}006$) meeting criteria for BN (26%) compared to those that did not (13%, $p \leqslant .001$, chi-square) (Dansky et al., 1993). Deakin and Graeff (1991) recently discussed how 5-HT brain systems are specifically involved in modulating adaptive responses to aversive events. It is clearly conceivable based on our current understanding that early traumatic events interact in complex neurodevelopmental ways to produce long-term changes in affected brain systems, including the HPA axis, neuropeptides, and the monoamines, including serotonin.

SEROTONIN AND OTHER NEUROCHEMICALS

Serotonin and Neuroendocrine Changes

5-HT is a major modulator of several hormones which have been reported to be dysfunctional in ED patients. 5-HT and 5-HT agonists have a stimulatory effect on the major stress hormone corticotropin-releasing hormone (CRH). In addition, increases in plasma concentrations of beta-lipotropin, beta-endorphin, and ACTH, all of which are cleavage products of the pro-opiomelanocortin molecule, are also modulated via serotonergic mechanisms. Serotonin dysregulation may therefore play a part in the dysregulation of the HPA axis as evidenced by hypercortisolism, increased levels of CSF immunoreactive CRH and opioid activity, decreased levels of CSF immunoreactive pro-opiomelanocortin-related peptides, and abnormal ACTH responses to CRH challenge in underweight AN patients (see Brewerton et al. (1992a) for references). In normal weight patients with BN, peak plasma PRL responses following m-CPP were inversely correlated with baseline measures of plasma cortisol (Brewerton et al., 1992b), thereby suggesting that chronic HPA activation dampens post-synaptic serotonin receptor sensitivity.

5-HT dysregulation may also contribute to the abnormalities in gonadotropin release and ovarian hormone production that have been noted in patients with AN and BN (Pirke et al., 1987a, 1987b), since 5-HT is known to have an inhibitory influence on both leuteinizing hormone (LH) and follicle-stimulating hormone (FSH).

Serotonin and Neuropeptides

Evidence suggests that several neuropeptides involved in the EDs either regulate or are regulated by 5-HT, e.g. opiate peptides have been reported to modulate 5-HT mechanisms involved in feeding (Gropetti et al., 1984). Endogenous opioids themselves, such as β-endorphin (β-END) and dynorphin-8 (DYN), are known to stimulate feeding behavior and to

regulate mood, perception and neuroendocrine function. Cholecystokinin-8 (CCK-8), a gut and brain octapeptide, is an important mediator of satiety and anxiety. Cerebrospinal fluid (CSF) concentrations of β-END and CCK-8 were significantly lower in 11 drug-free female patients with DSM-III-R defined BN compared to 17 normal controls (eight females, nine males), while DYN concentrations were no different (Brewerton et al., 1992a; Lydiard et al., 1993). Interestingly, CCK-8 function has been shown to depend on 5-HT integrity (Stallone et al., 1989). 5-HT also appears to modulate the secretion and activity of arginine vasopressin (AVP) (Spinedi & Negro-Vilar, 1983), which has been reported to be dysregulated in ED patients (Gold et al., 1983; Nishita et al., 1989) and OCD patients. Whether 5-HT dysfunction is related to other peptide disturbances in BN, such as alterations in CSF NPY and oxytocin, remains to be determined.

Serotonin and the Adrenergic System

An abundance of evidence in animals and humans attests to the interdependence of the serotonergic and the noradrenergic systems in that alterations in either one can produce changes in the other. Although an extensive discussion of this topic is beyond the scope of this paper, it is important to briefly note, given that alterations in norepinephrine (NE) regulation have been reported in both AN (Kaye et al., 1984a) and BN (Jimerson et al., 1987; Kaye et al., 1990; Pirke et al., 1985) patients. These alterations may be important to the understanding of many of the signs and symptoms of ED patients, e.g. depression, anxiety, bradycardia, changes in metabolic rate, etc. Nevertheless, alterations in adrenergic function can be secondary to serotonin dysfunction.

In animals, 5-HT receptors exist on some noradrenergic nerve terminals which when stimulated can inhibit or stimulate NE release, probably via stimulation of alpha-adrenoceptors in vascular tissue. 5-HT depletion by 5,7-DHT or pCPA results in upregulation of beta-adrenergic receptors, and downregulation of beta-adrenoceptors in rat cortex by desipramine is blocked by lesioning of the 5-HT system with 5,7-DHT. Chronic treatment with the 5-HT uptake inhibitor zimelidine in healthy human volunteers results in a significant reduction in standing plasma NE concentrations. Likewise, chronic fenfluramine treatment in humans lowers plasma NE concentrations. Taken together, these data suggest that the lower plasma NE levels in AN and BN patients are compatible with a serotonin dysregulation theory.

Conversely, the alpha-2 adrenergic agonist clonidine results in dose-dependent decreases in brain cortex concentrations of 5-HIAA. Beta-adrenoceptor antagonists block central 5-HT autoreceptors in rat frontal cortex, thereby resulting in increased 5-HT release. In humans, large doses of the beta-blocker propranolol in chronic schizophrenics result in a significant decrease in CSF 5-HIAA. An understanding of these two important monoamines as an integrated system may lead to a deeper understanding of 5-HT's true role in mediating psychopathology, not only of the eating disorders, but of other neuropsychiatric disorders as well (Sulser, 1987).

STUDIES OF 5-HT FUNCTION IN THE EATING DISORDERS

Given the relationships discussed above, a number of investigators have studied 5-HT function in patients with EDs using a variety of available techniques. In this section, the results from placebo-controlled studies in humans will be reviewed and summarized for AN and BN separately. Where applicable, comparisons between AN patients, BN patients, and

patients with both disorders will be made. Specifically, four major areas of research will be reviewed:

(1) studies of cerebrospinal fluid (CSF) concentrations of the major 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA);
(2) neuroendocrine, temperature, and other psychobiological response measures following acute challenges with various serotonergic agents, i.e. m-chlorophenylpiperazine (m-CPP), L-tryptophan (L-TRP), 5-hydroxytryptophan (5-HTP), dl-fenfluramine (dl-FEN), and chronic challenges with antidepressants, specifically the serotonin-specific reuptake inhibitors (SSRIs) such as fluoxetine (Prozac);
(3) platelet (PLT) studies of 5-HT function, including platelet 5-HT reuptake, ^{3}H-imipramine binding, ^{3}H-paroxetine binding, platelet MAO, platelet 5-HT content, as well as platelet 5-HT_2 receptor mediated aggregation; and
(4) plasma concentrations of L-TRP, the L-TRP/LNAA ratio, and whole blood serotonin (WBS). Finally, these data will be examined in light of a systems-oriented 5-HT dysregulation hypothesis in the EDs, much like described for norepinephrine (NE) in depression by Siever and Davis (1985).

In addition to a comprehensive literature review, the results presented in this paper will focus on studies by Brewerton and colleagues at the National Institute of Mental Health (NIMH) in which the neuroendocrine, temperature and other responses to two 5-HT agents, m-chlorophenylpiperazine (m-CPP) and L-tryptophan (L-TRP), were investigated in patients with BN ($n = 26$) and AN ($n = 12$) as well as controls ($n = 16$). The subjects and methods of these studies have been described in detail elsewhere (Brewerton et al., 1988b, 1990, 1992b, 1992c), but the psychopharmacologic aspects of these agents and their effects will be briefly reviewed.

m-Chlorophenylpiperazine (m-CPP)

m-CPP is a triazolopyridine metabolite of trazodone and a selective 5-HT receptor agonist, which has become an important probe of serotonin function in animals and man (Murphy et al., 1991). m-CPP produces significant elevations in PRL and temperature, which are blocked by the nonspecific 5-HT antagonist metergoline (Mueller et al., 1986). Animal studies indicate that m-CPP presumably exerts its effects via postsynaptic stimulation of 5-HT_1 receptors, and perhaps more specifically those of the 5-HT_{1C} subtype. Mediation of cortisol response appears to involve different neuroanatomical pathways and is stimulated by both 5-HT_1 and 5-HT_2 receptors (see Brewerton et al. (1992b)). The hyperthermic effect induced by m-CPP may also be mediated by 5-HT_2 receptor activation (Gudelsky et al., 1986). Migraine-like headaches induced by m-CPP may be mediated by 5-HT_2/5-HT_{1C} receptors (Brewerton et al., 1988b, 1992b). However, it is important to note that a considerable amount of functional overlap exists between 5-HT receptors and that their classification remains in transition. m-CPP also binds with high affinity to 5-HT_3 receptors, which also appear to be involved in feeding behavior.

L-Tryptophan (L-TRP)

L-TRP, an essential amino acid and dietary precursor of 5-HT, has been used extensively to evaluate 5-HT function in animals and man. L-TRP administration increases brain 5-HT in animals, CSF 5-hydroxyindoleacetic acid (5-HIAA) in man, and plasma PRL in man by a

Table II. Results of 5-HT studies in anorexia nervosa

No significant differences from controls
CSF 5-HIAA (STWR)(Kaye et al., 1984b, 1988b; Gerner et al., 1984)
CSF L-TRP (STWR)(Gerner et al., 1984)
PRL: L-TRP & d-FEN (low-wt, non-bulimic) (Goodwin et al., 1989; Halmi et al., 1993)
CORT following m-CPP and L-TRP (low-wt & STWR) (Brewerton et al., 1990)
PLT 5-HT mediated aggregation (low-wt & STWR) (McBride et al., 1991; Halmi et al., 1993)
PLT 5-HT uptake (low-wt) (Weizman et al., 1986a; Zemishlany et al., 1987)
PLT MAO content (non-depressed, low-wt) (Biederman et al., 1984)
Plasma L-TRP (low-wt, STWR) (Coppen et al., 1976; Hassanyeh & Marshall, 1991; Russell, 1967)
Plasma L-TRP/LNAA ratio (STWR) (Johnston et al., 1984; Kaye et al., 1988b)
Whole blood serotonin (McBride et al., 1991)
Significantly decreased in comparison to controls
CSF 5-HIAA (low-wt) (Gillberg, 1983; Kaye et al., 1984a, 1988b)
PRL: m-CPP & L-TRP (low-wt, STWR)(Brewerton et al., 1990)
PLT IMI binding (non-depressed, low-wt) (Weizman et al., 1986b)
Plasma L-TRP/LNAA ratio (low-wt) (Johnston et al., 1984; Kaye et al., 1984a)
Urinary 5-HIAA (low-wt) (Johnston et al., 1984)
Whole blood serotonin (Hassanyeh & Marshall, 1991)
Significantly increased in comparison to controls
CSF 5-HIAA (LTWR) (Kaye et al., 1991a)

STWR = short-term wt recovered, i.e. goal wt maintenance $\geqslant 3$ weeks. LTWR = long-term wt recovered, i.e. goal wt maintenance $\geqslant 6$ months.

pathway blunted or abolished by the 5-HT antagonists methysergide and metergoline (see Brewerton et al. (1992b) for references). As previously mentioned, PRL responses following intravenous L-TRP (Cowen & Charig, 1987; Heninger et al., 1984) have been reported to be blunted in patients with major depression. In contrast to m-CPP, response measures after L-TRP challenge reflect overall "flow-through" of 5-HT neurotransmission at both pre- and post-synaptic levels. PRL responses to L-TRP are enhanced by the 5-HT_2 antagonist ritanserin (Charig et al., 1986), so PRL release appears to be stimulated by 5-HT_1 receptor activation and inhibited by 5-HT_2 receptor activation.

Temperature Responses

In these studies, the effects of m-CPP and L-TRP on temperature were also examined (Brewerton et al., 1989). These data might help to clarify the mechanisms underlying the differential neuroendocrine responses in ED patients. Thermoregulation is controlled centrally by hypothalamic mechanisms involving 5-HT as well as other neurochemical systems. Temperature regulation by 5-HT appears to be dualistic in nature, as it too (like feeding, anxiety, neuroendocrine control, etc.) is subserved by 5-HT receptor subtypes with opposing or complementing actions (Gudelsky et al., 1986). Our results were similar to previous reports in humans (Mueller et al., 1986) in that m-CPP produced significant elevations in temperature in comparison to placebo in the total group of subjects ($p \leqslant .009$, RANOVA). Systemically administered L-TRP, like 5-HT itself, decreases temperature in animals (Francesconi & Mager, 1974), although it is unclear whether central or peripheral mechanisms are involved (Cox & Lee, 1981).

Table III. Results of 5-HT studies in bulimia nervosa

No significant differences from controls
CSF 5-HIAA$_1$ (overall turnover) (Jimerson et al., 1992; Kaye et al., 1990)
PRL: L-TRP (overall "flow through") (Brewerton et al., 1990, 1992b)
CORT: m-CPP and L-TRP (5-HT$_1$, 5-HT$_2$) (Brewerton et al., 1990, 1992b)
PLT 5-HT uptake (presynaptic pump) (Hallman et al., 1989)
Plasma L-TRP/LNAA ratio (precursor availability/transport) (Lydiard et al., 1988)
Whole blood serotonin (peripheral synthesis) (McBride et al., 1991)
Significantly decreased in comparison to controls
CSF 5-HIAA (post-probenecid, STWR AN + BN < AN) (Kaye et al., 1984b, 1988b)
PRL: m-CPP* (post-synaptic 5-HT$_1$) (Brewerton et al., 1990, 1992b)
PRL: L-TRP (MD only, presynaptic) (Brewerton et al., 1990, 1992b)
PRL: 5-HTP (5-HT$_1$) (Goldbloom & Garfinkel, 1990)
PRL: dl-FEN (5-HT$_1$) (Halmi et al., 1993; McBride et al., 1991)
PLT IMI binding (presynaptic pump) (Marazziti et al., 1988)
PLT MAO (degradation) (Hallman et al., 1989)
Baseline PRL (5-HT$_1$, 5-HT$_2$) (Brewerton et al., 1990, 1992b; Kaye et al., 1989)
Significantly increased in comparison to controls
PLT 5-HT mediated aggregation (5-HT$_2$) (Halmi et al., 1993; McBride et al., 1991)
PLT 5-HT uptake (presynaptic pump) (Goldbloom et al., 1988)
Peak ΔTEMP following m-CPP (5-HT$_{1C/2}$) (Brewerton et al., 1989)
Headache responses following m-CPP (5-HT$_{1C/2}$) (Brewerton et al., 1992c)

* Inversely correlated with weekly binge frequency.

Anorexia Nervosa

A summary of the results from studies of 5-HT function in AN is listed in Table II. Decreases in a variety of 5-HT parameters have been consistently reported in low weight patients and suggest reduced 5-HT synthesis, uptake, and turnover, as well as reduced post-synaptic 5-HT$_1$ receptor sensitivity. However, peripheral measures tend to normalize with refeeding, while hypothalamic post-synaptic (5-HT$_1$) receptor changes appear to linger in that blunted PRL responses following m-CPP and L-TRP persist following 3 weeks of goal weight maintenance. Taken together, many reported alterations in 5-HT function appear to be state-dependent, although they may play important roles in the maintenance of symptoms. Recent work by Kaye and colleagues (Kaye et al., 1991a) suggests enhanced 5-HT turnover in long-term ($\geqslant$6 months) weight-recovered restrictor AN patients. Given that CSF 5-HIAA was inversely correlated to previous lowest weight, this may suggest a rebound or withdrawal effect and would therefore also be a phase-dependent finding. Whether sustained abstinence and weight maintenance would ultimately lead to normalization of these serotonergic parameters remains to be determined in studies of very long-term, fully-recovered patients. Studies of 5-HT function in non-affected identical and fraternal twins, siblings, and other first degree relatives of ED patients, could begin to tease out trait-related disturbances. These results may be indicative of common psychobiological trait vulnerabilities involving 5-HT dysfunction. OCD patients have also been reported to have increased CSF concentrations of 5-HIAA, and restricting AN patients are more phenomenologically similar to OCD than BN (Kaye & Weltzin, 1991). A comparison of 5-HT studies between ED and OCD patients, as well as major depressive and personality disorders, can be seen in Table I. Some (Charney et al., 1988; Hollander et al., 1992) but not

all (Zohar et al., 1987) studies of OCD have reported blunted PRL responses following m-CPP. Brewerton and colleagues (1990) reported blunted PRL responses following m-CPP in AN patients, both at low weight and after attaining goal weight, whereas one study of PRL response following L-TRP in OCD patients showed no differences (Charney et al., 1988) from controls. PRL responses following L-TRP in AN patients have been reported to be both lower than (Brewerton et al., 1990) and no different than (Goodwin et al., 1989) healthy controls. However, Brewerton's sample was predominantly bulimic, while Goodwin's group was predominantly restrictor or non-bulimic (Goodwin, personal communication). This suggests further serotonergic differences (? presynaptic ones) between restrictor and non-restrictor AN patients.

Bulimia Nervosa

The results from studies of 5-HT function in BN are listed in Table III. In summary, patients with BN appear to be characterized by reduced PRL responses to a variety of serotonergic agents. The blunting following m-CPP indicates decreased post-synaptic hypothalamic 5-HT_1 receptor sensitivity that is independent of the presence of MD or AN (see Fig. 1) (Brewerton et al., 1990, 1992b). In contrast, only those BN patients with AN or MD exhibited blunting of PRL following L-TRP (see Fig. 2). Other investigators have also reported blunted PRL responses following other serotonergic agents, including 5-HTP (Goldbloom & Garfinkel, 1990) and dl-FEN (Halmi et al., 1993; McBride et al., 1991) in

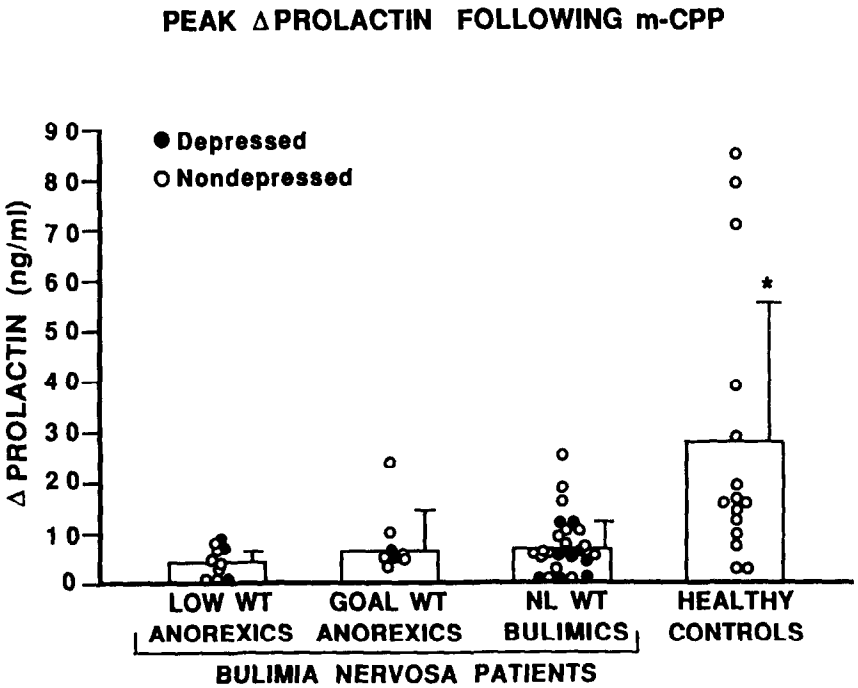

Fig. 1. Peak ΔPRL following m-CPP was blunted in patients with bulimia nervosa regardless of the presence of anorexia nervosa or major depression. Asterisk (*) indicates that healthy controls had significantly higher values than the combination of low weight (WT) and normal weight (NL WT) bulimics ($p \leqslant .0001$, Mann–Whitney test).

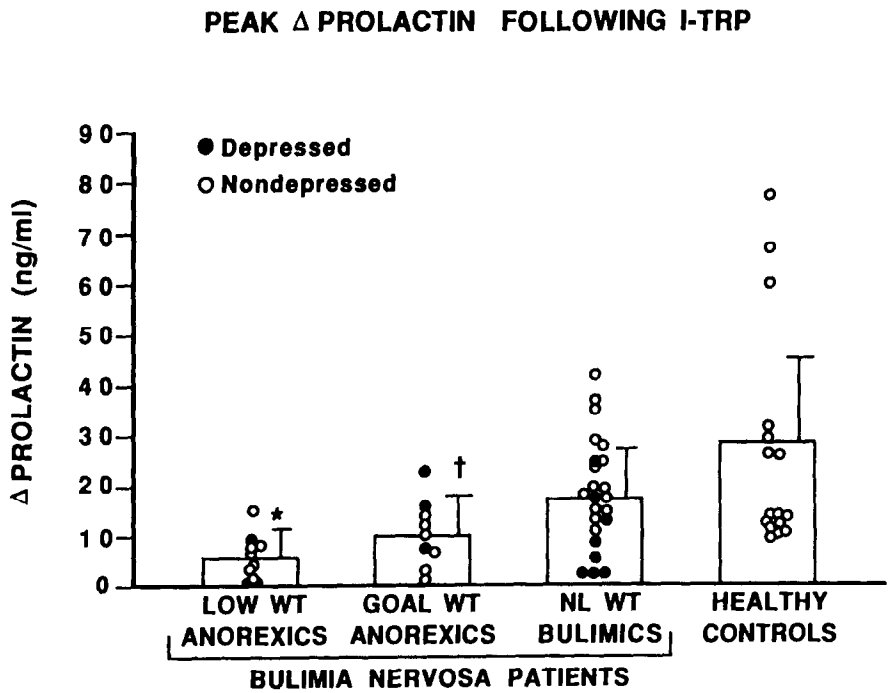

Fig. 2. Peak ΔPRL following L-TRP was higher in normal weight bulimics than bulimic anorexics at low weight (*, $p \leqslant .006$, unpaired t-test) and at goal weight (+, $p \leqslant .06$). Peak ΔPRL did not significantly increase in the paired group of bulimic anorexics after refeeding ($n = 9$, $p = .12$).

patients with BN. Following m-CPP, PRL responses were inversely correlated to baseline CORT in the patients (rho = -0.45, $p < .007$) and the total group (rho = -0.41, $p < .003$), but not in the controls alone (rho = 0.26) (see Fig. 3). There were also trends for PRL responses following m-CPP to be inversely correlated to binge frequency in the total group of patients with BN ($n = 36$, rho = -0.30, $p = .075$) and in patients with BN without AN ($n = 26$, rho = -0.37, $p \leqslant .06$) (Brewerton et al., 1992b) (see Fig. 4). The blunted responses could not be attributed to age, activity, medications, time of day or year, diet, or differences in peak m-CPP concentrations (see Fig. 5). Whether this presumed alteration in 5-HT functioning represents a causative factor in the pathogenesis of BN, is a sequelae of the disorder, or a combination of both cannot be stated with certainty. The trend for an inverse correlation between weekly binge frequency during the 4 weeks prior to admission and peak ΔPRL (Fig. 4) is compatible with either interpretation. Bingeing and vomiting, which may affect central 5-HT synthesis (Fernstrom, 1985; Kaye et al., 1988a, 1989), could conceivably result in downregulation of post-synaptic 5-HT receptors and blunted PRL responses. This effect, in fact, may involve activation of the HPA axis (Brewerton et al., 1992a).

CSF studies were contributory in that binge frequency was also found to be inversely correlated to CSF concentrations of 5-HIAA ($r = -0.43$, $p < .02$) (Jimerson et al., 1992), although this was not found in another study of bulimic patients (Kaye et al., 1990).

The results from these studies also suggest enhanced 5-HT_2 receptor sensitivity in patients with BN. Brewerton and colleagues (Brewerton et al., 1990, 1992c) reported that BN patients (regardless of the presence of AN or MD) had greater migraine-like HA responses

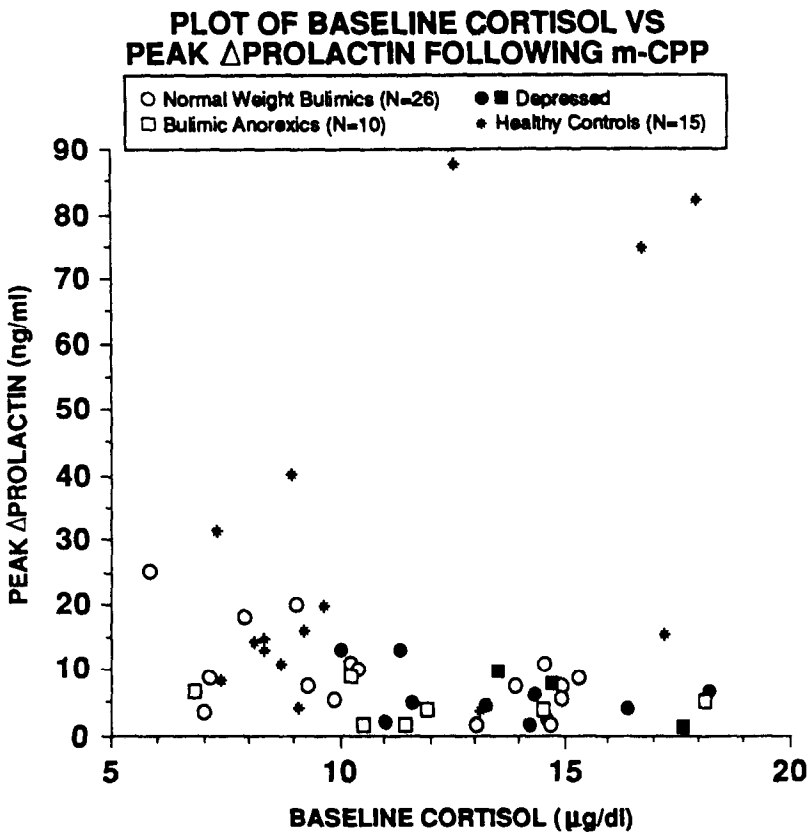

Fig. 3. Peak ΔPRL was negatively correlated to baseline CORT in the bulimia nervosa patients (rho = −0.45, $p \leqslant .007$) and the total group (rho = −0.41, $p \leqslant .003$), but not in the controls alone (rho = 0.26).

than controls following m-CPP. As discussed in detail elsewhere (Brewerton et al., 1992c), the enhanced migraine-like HA responses in the BN patients may indicate enhanced 5-HT_2 receptor or perhaps 5-HT_{1c} receptor sensitivity in CNS vascular tissues. Enhanced 5-HT-mediated platelet aggregation, a 5-HT_2 receptor-mediated phenomenon, lends further support to this hypothesis (McBride et al., 1991). The normal cortisol (CORT) responses following m-CPP (Fig. 6) and L-TRP (Fig. 7) are compatible with this view given the involvement of both 5-HT_1 and 5-HT_2 receptors in CORT secretion.

Other platelet studies suggest that BN patients have an impaired 5-HT reuptake mechanism (Goldbloom et al., 1988; Marazziti et al., 1988). Whether this reflects a central dysfunction remains unclear and awaits future studies. As discussed in detail previously, it is conceivable that alterations at other central yet anatomically distinct 5-HT pathways may contribute to a variety of psychopathology associated with BN.

Bulimia Nervosa Plus Anorexia Nervosa

Whether or not responses to 5-HT agents differ in low weight versus normal weight patients with BN may be relevant to the ultimate diagnostic classification of EDs. Therefore,

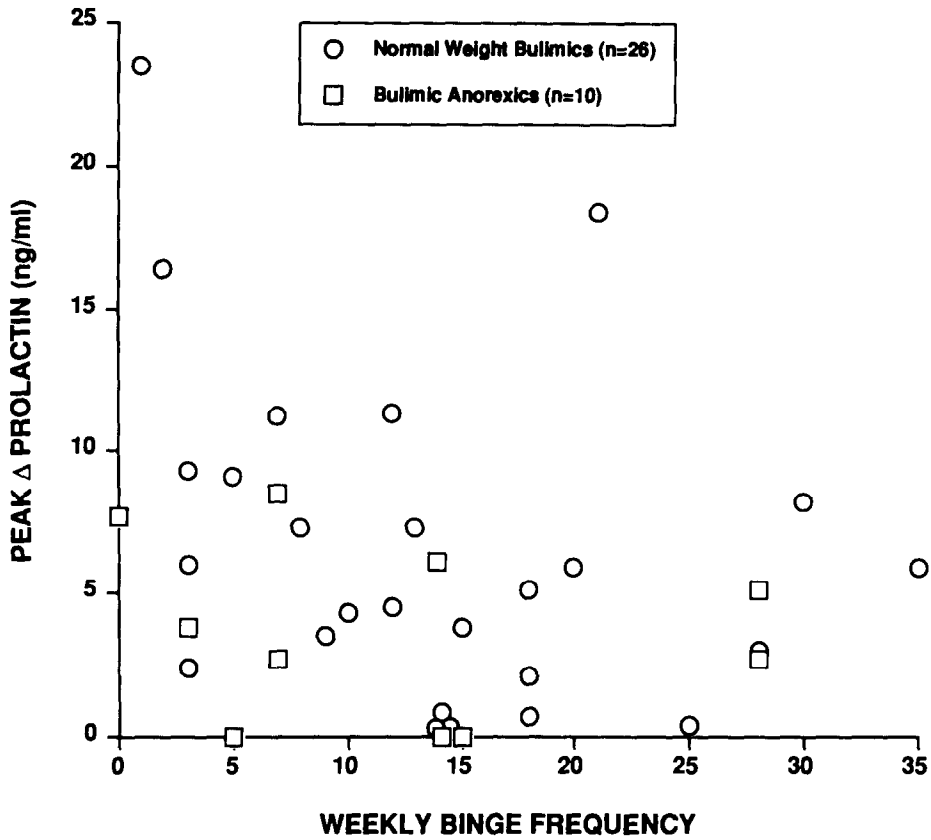

Fig. 4. PRL responses following m-CPP were inversely correlated to weekly binge frequency during the month prior to admission (rho = -0.30, $p = .075$) in the total group of BN patients. Patients with BN without AN had similar results ($n = 26$, rho = -0.37, $p \leqslant .06$).

all outcome measures obtained from these two groups of bulimic patients were compared. When no significant or near significant differences were found, these two groups were combined for comparison with normal controls using appropriate statistical techniques. The combination of low weight and normal weight BN patients into one group increases the power of finding a true difference in 5-HT receptor sensitivity between BN patients and controls, and simultaneously allows appraisal of the roles of weight, percent ABW, depression ratings, and other relevant variables by means of correlational analysis. Potential differences in outcome measures between patients with and without major depression were also investigated. As seen in Figs 1 and 2, respectively, both AN and BN patients had blunted PRL responses following m-CPP, but only the AN patients (who were predominantly bulimic) had blunted responses following L-TRP.

Results indicated that PRL responses to L-TRP differed between bulimic anorexics (whether at low or goal weight), who had blunted responses, and normal weight bulimics who had normal responses. The significant correlations between peak ΔPRL and weight ($\gamma = 0.45$, $p \leqslant .02$) and %ABW ($\gamma = 0.44$, $p \leqslant .02$) in the combined group suggest that weight loss per se may be a causative factor in these results. Although recent dieting or weight loss

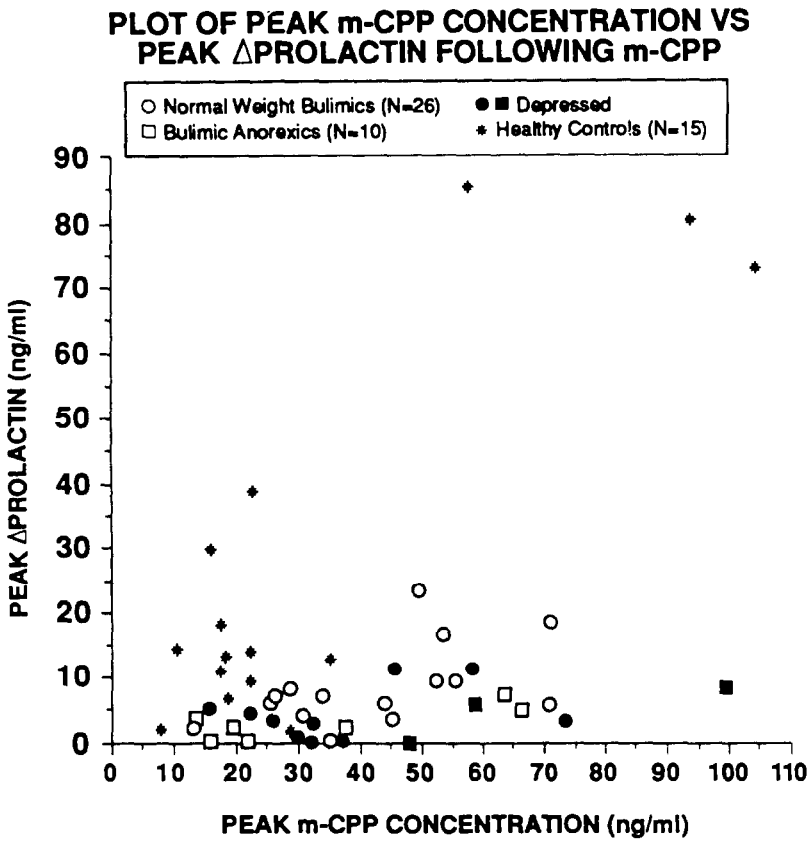

Fig. 5. Peak m-CPP concentrations were significantly correlated with peak ΔPRL in the patients (rho = 0.37, $p \leqslant .03$), but not in the controls (rho = 0.43, $p = .11$) or the total group (rho = 0.13). In an analysis of covariance using peak m-CPP concentration as the independent variable and peak ΔPRL as the dependent variable, peak ΔPRL remained significantly lower in patients than controls ($p \leqslant .0001$).

enhances PRL responsivity to L-TRP (Cowen & Charig, 1987; Goodwin et al., 1987b), prolonged starvation could lead to downregulation of 5-HT receptors and subsequently blunted PRL responses.

In the studies by Brewerton and colleagues (1989), temperature responses were also measured following each of the agents (m-CPP, L-TRP, and placebo). BN patients (regardless of the presence of AN or MD) had a lower baseline temperature (Fig. 8) and greater hyperthermic responses than controls (see Fig. 9). In comparison to normal weight bulimics (0.42 ± 0.20°C), the peak change in temperature was not significantly different in bulimic anorexics (0.51 ± 0.28°C). This combined group of low and normal weight bulimics had a significantly higher peak change in temperature (0.44 ± 0.22°C) than the controls (0.29 ± 0.25°C, $p \leqslant .05$, unpaired t-test) (Fig. 4). The peak change in temperature was significantly correlated to peak m-CPP concentrations in the patients (rho = 0.33, $p \leqslant .05$), but not in the controls or the total group. The peak change in temperature (ΔTEMP) remained significantly higher in patients than in controls ($p \leqslant .05$) after an analysis of covariance using peak m-CPP concentration as the dependent variable. There was a trend for patients with major depression to have lower peak ΔTEMP responses following m-CPP

(0.36 ± 0.19°C) than nondepressed patients (0.48 ± 0.23°C, $p \leqslant 0.1$). This could be due to decreased 5-HT_2 receptor sensitivity. The peak ΔTEMP was significantly correlated to peak ΔPRL in the patients (rho = 0.47, $p \leqslant .004$), but not in the controls or the total group. No other significant correlations were found. Since temperature elevations can be produced by 5-HT_2 receptor activation (Gudelsky et al., 1986) and m-CPP binds to 5-HT_2 receptors, one interpretation is that BN is associated with increased 5-HT_2 receptor sensitivity. This is also compatible with the blunted PRL responses following m-CPP, since activation of 5-HT_2 receptors appears to antagonize PRL release (Charig et al., 1986). On the other hand, since the peak ΔTEMP was correlated with the peak ΔPRL in the patients, this suggests some overlap in receptor stimulation.

Decreased baseline temperature and the enhanced temperature responsivity to m-CPP in the BN patients are compatible with a 5-HT dysregulation hypothesis, although disturbances in other systems involved in thermoregulation, such as noradrenergic or thyroid, may be involved. These alterations, whether primary or secondary, point out that 5-HT receptor sensitivity can be both increased and decreased in the same subjects depending on anatomical location of the receptor as well as its subtype.

Although the hypothermic effect of L-TRP could possibly be due to activation of 5-HT_{1A} receptors (Gudelsky et al., 1986), the lack of a difference between groups in maximum ΔTEMP following L-TRP may or may not be due to the role of peripheral factors (Cox & Lee, 1981). Challenge studies measuring PRL and temperature responses in bulimics and controls using specific 5-HT_{1A} agonists are lacking.

Adrenergic mechanisms could also explain the higher temperature elevations in BN patients. Beta-adrenergic agonists can result in both increased 5-HT_2 receptor sensitivity and

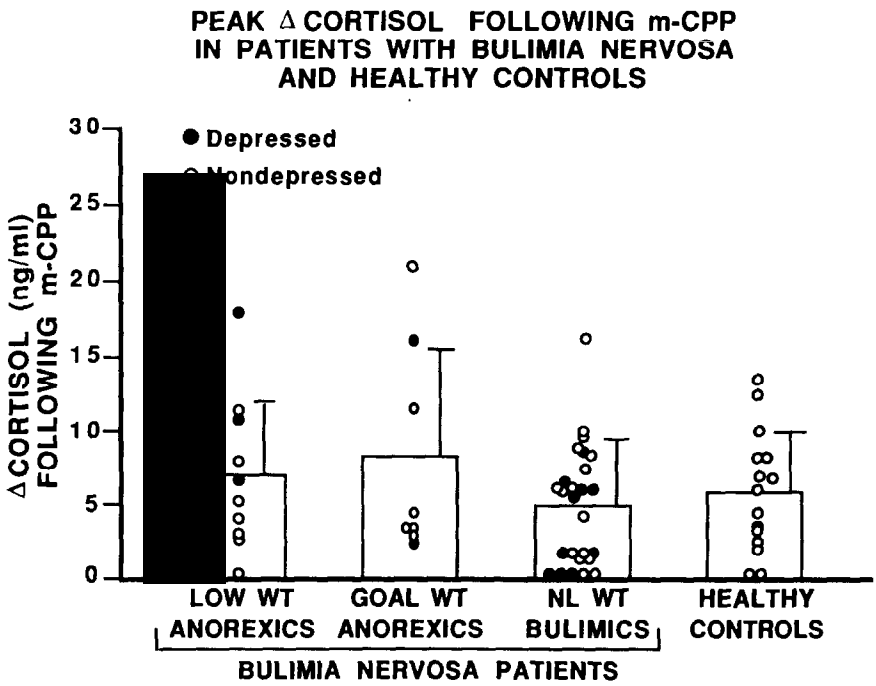

Fig. 6. Peak ΔCORT following m-CPP are similar across diagnoses.

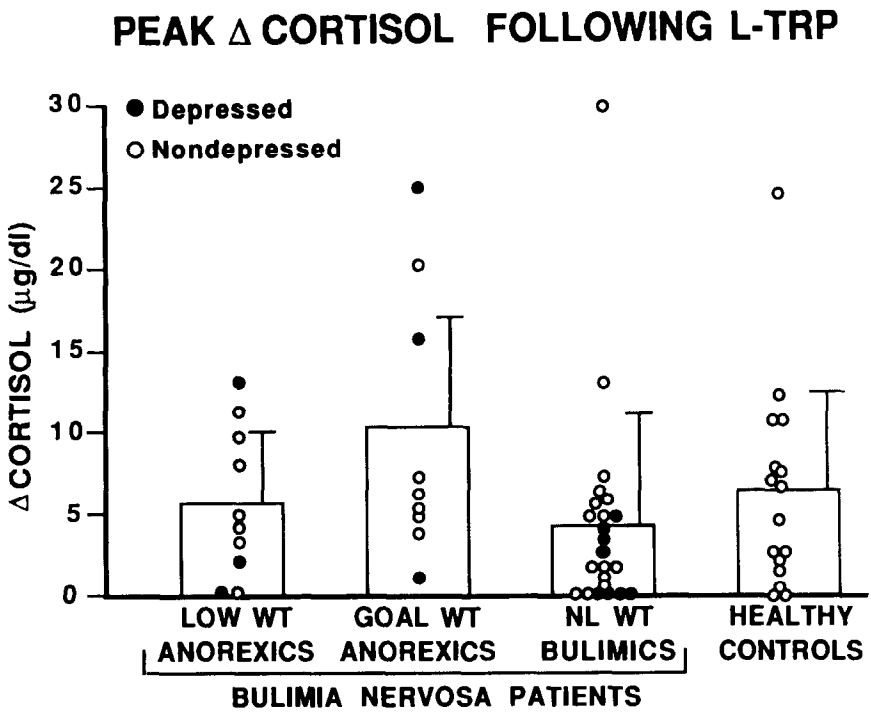

Fig. 7. Peak ΔCORT following L-TRP are similar across diagnoses.

density. 5-HT_2 receptor sensitivity can also be potentiated by either noradrenalin depletion or $alpha_2$-adrenoceptor antagonists, and decreased by $alpha_2$-adrenoceptor agonists. Bulimic patients have evidence of noradrenergic dysregulation (Jimerson et al., 1987), including increased sensitivity to the beta-adrenergic agonist isoproterenol and lower values of plasma noradrenalin in response to standing (Pirke et al., 1985). Lower CSF NE concentrations have also been reported in BN patients compared to healthy controls (Kaye et al., 1990).

DISCUSSION: A SEROTONIN DYSREGULATION HYPOTHESIS

Taken together, these data support a dysregulation hypothesis for 5-HT in the EDs. It is important to note that a dysregulated neurotransmitter system implies a relative failure of neurotransmitter regulation, rather than simple decreases or increases in activity. Siever and Davis (1985) defined it using six characteristics which have been applied to 5-HT in the EDs as follows.

Impairment in One or More Regulatory Mechanisms

As outlined in Tables I–III, there is now substantial evidence of impaired central 5-HT function in the EDs involving neuroendocrine, temperature, and vascular systems. Although PRL responses in the patients with concurrent major depression were predictably lower than those without, the difference was not significant; patients without major depression also had PRL responses following m-CPP significantly lower than controls. Minor depression, or dysthymia, which was present to a high degree in this and other samples, may be a possible

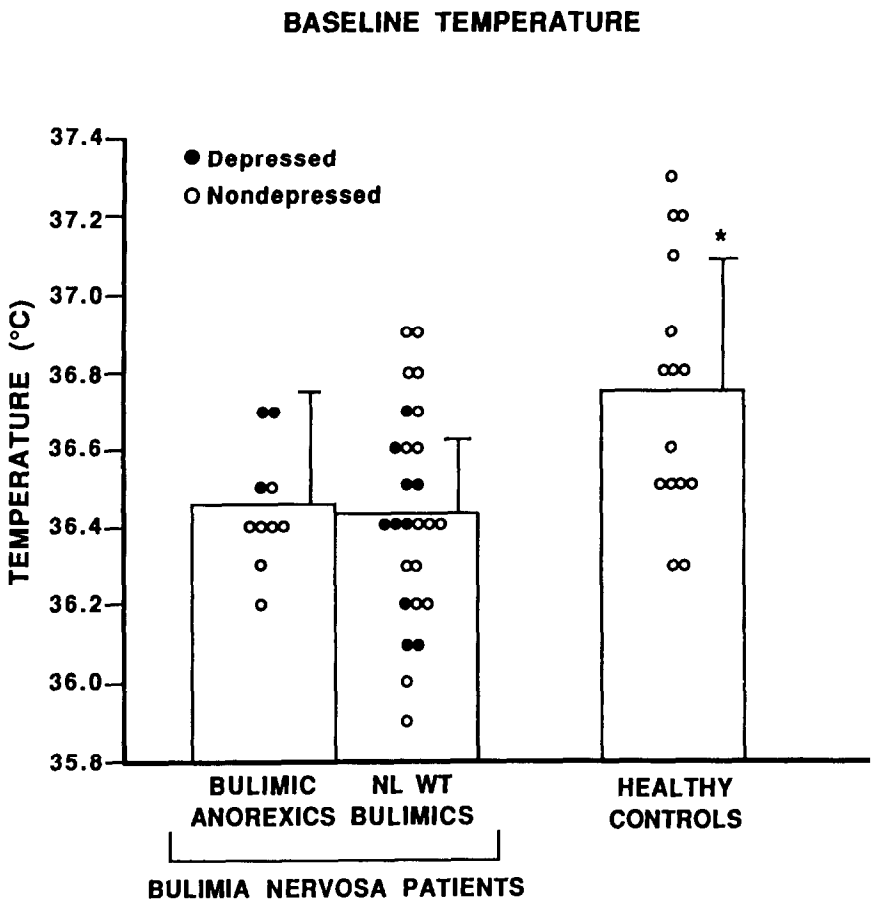

Fig. 8. Baseline temperature was not significantly different between normal weight bulimics and either low weight or goal weight bulimic anorexics. The combined group of bulimia nervosa patients had a significantly lower baseline temperature (36.43 ± 0.24°C) than the controls (36.75 ± 0.33, $p < .0003$).

contributing factor to these findings. However, peak ΔPRL did not correlate with either HAM-D or Beck Depression Inventory scores. In a study of patients with major depression (MD), Kahn et al. (1990) found equivalent PRL and CORT responses following oral m-CPP (0.25 mg/kg). Further m-CPP challenges in non-bulimic, weight-stable patients are certainly warranted, but these findings are distinctly different from reports of normal neuroendocrine responses following m-CPP in other diagnostic groups, such as major depression (Kahn et al., 1990), panic disorder (Kahn et al., 1991), OCD (Hollander et al., 1992; Zohar et al., 1987), and Alzhemier's disease (Lawlor et al., 1989). However, our results are similar to those reported in patients with antisocial personality disorders and substance abuse (Moss et al., 1990), and in one group of female OCD patients (Charney et al., 1988). All of these groups had blunted PRL responses following m-CPP in comparison to controls (see Table I).

More Erratic Basal Output

Decreased baseline PRL levels (Brewerton et al., 1992b; Kaye et al., 1989) and the erratic availability of L-TRP due to binge-eating, purging (Kaye et al., 1988a, 1989), and fasting or

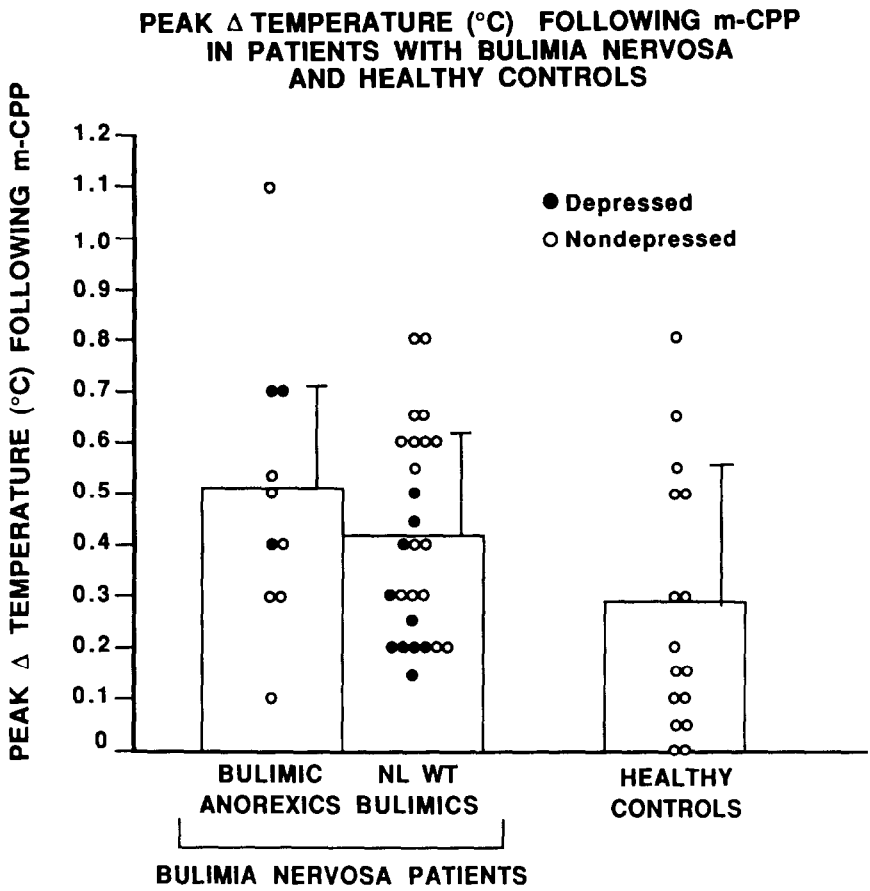

Fig. 9. Peak ΔTEMP following m-CPP was not significantly different between low weight bulimic anorexics and normal weight (NL WT) bulimics. The combined group of bulimia nervosa patients had significantly higher peak ΔTEMP than healthy controls (*, $p \leqslant .05$, unpaired t-test).

dieting (Delgado et al., 1990; Goodwin et al., 1987a, 1987b, 1987c, 1990) support this provision. The strong negative correlation between peak ΔPRL and baseline CORT (see Fig. 3) in the BN patients suggests that stress or chronic activation of the hypothalamic–pituitary–adrenal (HPA) axis may further compromise post-synaptic 5-HT receptor sensitivity. Brewerton and colleagues (1992a) reported that CSF concentrations of beta-endorphin (β-END) were significantly lower in BN patients than controls, a finding that may also be indicative of chronic HPA activation. Dieting has been observed to markedly perturb the 5-HT system in women, resulting in increased PRL responsivity to L-TRP (Goodwin et al., 1987a, 1987b) and platelet 5-HT receptor upregulation (Goodwin et al., 1987c). Enhanced PRL sensitivity to m-CPP following 6 days of a low-TRP diet has been shown in animals (Franklin et al., 1993). These effects are opposite to the observed blunting of responses seen in AN and MD patients for L-TRP, and in AN and BN for m-CPP. As discussed previously, semistarvation and hyperactivity in animals also increase 5-HT turnover in the mediobasal hypothalamus, so the compulsive exercising that is common to

EDs could lead to downregulation of post-synaptic 5-HT receptors (see Brewerton et al., (1995) for references).

Disrupted Normal Periodicities

As previously noted, circadian and circannual variations in the onset and/or severity of symptoms, e.g. fasting, binge-eating, and purging, have been reported (Blouin et al., 1992; Brewerton et al., 1994a; Hardin et al., 1991; Mitchell et al., 1985; Nielsen, 1992). BN patients, regardless of weight, have higher scores on the Seasonal Pattern Assessment Questionnaire (SPAQ) (Brewerton et al., 1994a; Hardin et al., 1991) than normal controls and nearly as high as patients with seasonal affective disorder (SAD). Blouin and colleagues (1992) reported a highly significant inverse correlation between binge frequency and the photoperiod. Absent or irregular menses associated with hypoestrogenemia are common in BN (Brewerton et al., 1992b) and necessary for the diagnosis of AN. Ferrari and colleagues (1990) reported alterations in the circadian patterns of PRL and CORT in patients with EDs and have presented other evidence indicative of what they term "internal desynchronization". Brambilla and colleagues (1988) have reported dysregulated melatonin (MT) rhythms in patients with AN and obesity, which is pertinent given that the feeding schedules of mammals are well-known entrainers of circadian rhythms.

Less Selectively Responsive to Stimuli

A lack of satiety to foods in BN and too much satiety and a lack of hunger in AN has been demonstrated (Halmi et al., 1993). Kaye and colleagues (1989) also reported blunted neuroendocrine responses to testmeals in a group of BN patients in comparison with controls.

Slow Recovery to Basal Activity Following Perturbation(s)

BN and AN tend to be chronic disorders characterized by recurrence and limited degrees of complete recovery. Furthermore, neuroendocrine abnormalities persist despite 3–4 weeks of abstinence in the BN patients and refeeding to goal weight in the AN patients (see Figs 1 and 2) (Brewerton et al., 1990, 1992b). As previously mentioned, Kaye's finding of enhanced CSF 5-HIAA in long-term weight recovered ($\geqslant 6$ months) AN patients may also be a phase-dependent rebound part of the recovery process given its reciprocal relationship to previous low-weight.

Clinically Efficacious Drugs Restore Efficient Regulation

A large multicenter, placebo-controlled, double-blind trial of fluoxetine in BN has demonstrated significant reductions in binge-purge frequency and depression (FBNCG, 1992), as well as improvement in several subscale scores on the Eating Disorders Inventory (Goldbloom & Olmsted, 1993), e.g. body dissatisfaction, perfectionism. These data indicate significant changes in core ED symptoms as a result of chronic enhancement of 5-HT function. Furthermore, the higher doses of fluoxetine required for BN compared with MD is compatible with their neuroendocrine–serotonergic profiles, i.e. the higher doses needed for BN may be necessary to overcome or compensate for the blunted post-synaptic 5-HT_1 receptor and/or enhanced 5-HT_2 receptor sensitivity. In a preliminary study of bulimic patients ($n = 20$) on long-term fluoxetine treatment ($\leqslant 6$ months), our group has found a significant correlation between reduction in binge frequency since beginning treatment and total fluoxetine–norfluoxetine blood levels (Head et al., 1992). While AN appears to be more

refractory to psychopharmacologic treatments alone, controlled (Halmi et al., 1986) and open studies of serotonergic agents in combination with other forms of treatment are encouraging (Gwirtsman et al., 1990; Head et al., 1992; Kaye et al., 1991b) and should be further pursued in placebo-controlled, double-blind conditions. In particular, such studies in which serotonin-specific reuptake inhibitors (SSRIs) and other serotonergic agents are used as prophylaxis of recurrent weight-loss after inpatient refeeding to normal weight are needed. It is important to state before closing that ultimately these changes in the serotonergic system in ED patients no doubt occur at a molecular level, the details of which remain to be fully determined.

SUMMARY AND CONCLUSIONS

Historically, initial interest in 5-HT centered on its vasoactive properties and possible role in vascular disorders, such as migraine. In psychiatry, 5-HT was first linked to depression and suicide, then aggression and impulsivity. Reports of 5-HT's role in obsessive–compulsive, panic, and personality disorders (PD), as well as alcoholism, have further extended the purview of 5-HT dysfunction across major diagnostic categories. All of these are clinical features and disorders associated with EDs. More recent evidence has linked 5-HT to other clinical features of the EDs, such as seasonal variation in symptomatology and propensity towards migraine.

5-HT function (or dysfunction) appears to depend not only upon which receptor subtypes are involved, but where they are located—both on the neuron and within the neuronal systems. In pharmacologic challenge studies, the nature of the drug, its dose, rate and route of administration, duration of action and baseline state of the organism are all modifying variables and must be taken into consideration when interpreting data. These findings are indicative of the complexity of the 5-HT system which is known to modulate a variety of neurochemical and neuroendocrine systems reported to be disturbed in the eating disorders.

In this paper the theoretical and experimental evidence has been presented in support of a 5-HT dysregulation hypothesis in the EDs, AN and BN. This, of course, is not a new idea in itself, but the concept has been updated and integrated into a more specific dysregulation hypothesis that can account for the diversity, complexity, and comorbidity of the EDs. Taken together, the findings described above suggest that post-synaptic 5-HT receptor sensitivity is altered in hypothalamic–pituitary serotonergic pathways and vascular tissues of BN patients and that additional disturbances in 5-HT function, probably involving presynaptic mechanisms, are associated with AN and MD. Similar alterations in other 5-HT pathways at or above the level of the hypothalamus may contribute to binge eating and other behavioral symptoms. The question of whether 5-HT receptor sensitivity is decreased or increased is an oversimplification of an extremely complex system within a system and depends on exact anatomical location and differential involvement of the 5-HT receptor subtypes involved. Further studies exploring the functional integrity of 5-HT receptors and their subtypes are warranted in BN patients, as well as in patients with non-bulimic AN, minor and major depression without an eating disorder, migraine, and personality disorders with and without substance abuse. As our knowledge about the 5-HT system and its receptor types and subtypes in humans is increased, our understanding of the role of 5-HT in these disorders will be enhanced and further clarified, but unique serotonergic mechanisms are likely to be responsible for specific phenomenology across diagnoses.

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A Placebo-Controlled Trial of d-Fenfluramine in Bulimia Nervosa

THOMAS A. FAHY, IVAN EISLER and GERALD F. M. RUSSELL

d-Fenfluramine is a 5-HT agonist which decreases food intake and excessive carbohydrate intake in humans. A placebo-controlled trial of d-fenfluramine (45 mg/day) was conducted in 43 patients with bulimia nervosa. The patients entered an eight-week trial of medication during which they also received cognitive–behavioural therapy. Treatment response was assessed using food diaries to record eating behaviour, and self-rating questionnaires to measure psychopathology. The drug trial, and a follow-up assessment after a further eight weeks, were completed by 39 patients. Abnormal eating behaviour and psychopathology improved significantly in both the d-fenfluramine and placebo groups during the treatment trial. The study failed to show that the addition of d-fenfluramine affords an advantage over brief psychotherapy alone. Although d-fenfluramine is effective in suppressing the overeating, excessive snacking, and excessive carbohydrate consumption which are frequently found in overweight or obese patients, this study suggests that the drug is not an effective treatment for bulimia nervosa.

In a review of studies employing strict diagnostic criteria for bulimia nervosa, Fairburn & Beglin (1990) estimate the prevalence of the disorder among adolescent girls and young women in Western societies to be approximately 1%. Given this high prevalence, and the expense of intensive psychotherapeutic approaches to treatment, a safe and effective drug treatment which could be combined with less intensive and time-consuming psychological interventions would be an important clinical advance.

In a review of 12 controlled studies, Hudson & Pope (1990) found that 10 reported a significant benefit of tricyclics and monoamine oxidase inhibitors over placebo. Despite good initial results, enthusiasm for the standard antidepressants has been dampened by the finding of high relapse rates on follow-up (Pope *et al*, 1985). Interest has begun to focus on the therapeutic efficacy of drugs with serotonin (5-HT) agonist activity. A body of experimental and clinical research suggests that 5-HT has an inhibitory effect on feeding behaviour (Leibowitz & Shor-Posner, 1986), and that abnormal 5-HT function may play a role in the onset or maintenance of abnormal eating patterns in bulimia nervosa (Kaye *et al*, 1987; Marazziti *et al*, 1988; Goldbloom & Garfinkel, 1990; Goldbloom *et al*, 1990). Controlled trials of the serotonergic antidepressant fluoxetine have reported a beneficial effect on binge frequency in an eight-week out-patient trial (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992), in a six-week out-patient trial (Freeman *et al*, 1990), and in a small open trial over four weeks (Freeman & Hampson, 1987), but no significant benefits were detected in a five-week trial on in-patients also receiving an intensive course of behaviour therapy (Fichter *et al*, 1991). In common with many out-patient drug trials in bulimia nervosa, the interpretation of the report by Freeman and colleagues is complicated by a high drop-out rate among study entrants.

d-Fenfluramine is a powerful inhibitor of 5-HT uptake (Borroni *et al*, 1983) and has an additional weak effect by releasing 5-HT (Mennini *et al*, 1981). d-Norfenfluramine, a metabolite of d-fenfluramine formed in the liver, has a combined effect as a potent uptake inhibitor and releaser of 5-HT (Garattini *et al*, 1989). In normal-weight humans, d-fenfluramine at doses of 30 mg a day decreases motivation to eat (Silverstone *et al*, 1987), reduces the size of large meals, and inhibits between-meal snacking by increasing satiation (Hill & Blundell, 1986). It is also claimed that d-fenfluramine causes selective reduction of intake of carbohydrate-rich food (Wurtman & Wurtman, 1984; Wurtman *et al*, 1985). d-Fenfluramine is rapidly absorbed following oral administration and has a plasma half-life of 20 hours in humans (Pinder *et al*, 1975). Steady-state levels are arrived at within four to eight days when the drug is administered two or three times daily.

Robinson *et al* (1985) were the first to investigate the acute effects of fenfluramine in bulimia nervosa. In two separate experiments, 15 women were administered 60 mg fenfluramine or placebo under test conditions, after which they were invited to eat from a supply of food of their choice. Fenfluramine-treated patients consumed fewer calories and were less likely to classify their eating as binges.

The role of fenfluramine in the clinical management of bulimia nervosa remains unclear. In a placebo-controlled trial of d-fenfluramine (30 mg/day),

Russell *et al* (1988) found no difference in outcome between study completers. However, when the large number of non-completers (17/42) were included in the analysis, or when this group was examined in isolation, the d-fenfluramine group had a significantly greater reduction in binge eating and self-induced vomiting. The problem of interpreting treatment studies with high drop-out rates poses a difficulty. We would argue that high drop-out and relapse rates mean that drug treatment alone is unlikely to prove effective for most patients with bulimia nervosa. However, medications such as d-fenfluramine may have an important clinical benefit by promoting rapid symptom reduction and reducing the need for intensive psychotherapy.

The objective of this study was to assess the efficacy and safety of d-fenfluramine in the treatment of out-patients with bulimia nervosa who were also receiving a psychological intervention. The study design took into account the need to ensure good compliance, minimise drop-outs, and provide a clinically relevant model of treatment.

Method

This study consisted of a double-blind controlled trial in 43 patients allocated at random to d-fenfluramine or placebo. Randomisation occurred following a two-week assessment. All patients entered an eight-week treatment phase which included pharmacotherapy and psychotherapy. A daily dose of 45 mg of d-fenfluramine was chosen in view of the equivocal result in a previous trial (Russell *et al*, 1988).

Patients were randomised to the d-fenfluramine or placebo groups. The drug was started with one 15 mg capsule at 3 p.m. and increased weekly to 15 mg twice daily, then 15 mg three times daily. The d-fenfluramine and placebo capsules were supplied by Les Laboratoires Servier (Gidy-France).

All patients received an eight-week course of cognitive–behavioural psychotherapy which was an abbreviation of the method developed by Fairburn and colleagues (Fairburn, 1985). In an attempt to bring the binge–vomit cycle under control, the patient was first asked to monitor food intake, self-induced vomiting, and laxative abuse using numbered blank food diaries which were supplied at weekly intervals, beginning one week before drug treatment. All subsequent sessions began with a detailed review of the food diary. The rationale for self-monitoring was discussed, and the food diary was used to illustrate that binge episodes often followed periods of intense dieting, and that overeating was followed in turn by even stricter dieting. The physical consequences of binge eating, self-induced vomiting, and laxative abuse were discussed. Information was also given on the relative lack of efficacy of self-induced vomiting and laxative abuse as aids to weight loss. In addition to these educational interventions, the patient was asked to weigh herself only at the out-patient department, eat three meals each day, avoid prolonged episodes without food, not to engage in other activities when eating, and practise leaving food on the plate.

The second half of treatment concentrated on the interactions between thoughts, mood, and eating pattern. The function of binge eating as relief from dysphoria or tension, or a distraction from unpleasant thoughts was discussed, using the food diary as a focal point. Food diaries were used to record events and thoughts which preceded binge episodes. This record was used as a focus to explore dysfunctional attitudes and attributional errors, often concerning food and body weight, which were challenged using the method described by Beck *et al* (1979).

Weekly therapy sessions continued until the end of drug treatment (session 9), and all patients were reviewed four and eight weeks later (sessions 10 & 11). Patients who were experiencing special problems, such as failure to respond or depression, were offered extra appointments between sessions 9 and 11. These extra sessions were offered at the discretion of the therapist and the number of extra appointments was recorded as one of the measures of outcome.

The referral letters of all patients received at the Maudsley Hospital Eating Disorder Unit were scrutinised. All patients referred with a history of binge eating were assessed. Subjects meeting the inclusion criteria for the trial were female out-patients aged 18–45 years, satisfying DSM-III-R (American Psychiatric Association, 1987) and Russell's (1979) criteria for bulimia nervosa, with a duration of illness of at least one year and body weight no more than 20% below the average body weight expressed in the tables of the Society of Actuaries (Diem & Lentner, 1970) or body mass index of at least 18 kg/m^2. Patients were excluded from the trial if they suffered any concurrent physical or psychiatric illness, were pregnant or planning to become pregnant, or were taking any other psychotropic drugs. Subjects were withdrawn from the study if they failed to comply with the protocol, if they failed to take the test substance for a period of 15 days, or if they reported side-effects of sufficient severity to require termination of the drug.

The patients' progress was assessed using data gathered from clinical examination, structured interviews, and self-rating scales. The following variables were the most important measures of progress:

(a) weight – measured weekly, and calculated as body mass index (kg/m^2)
(b) frequency of binge eating, self-induced vomiting and laxative abuse – this information was derived from weekly food diaries; binges were defined as periods of intense overeating (approximately 1500 kcal or more) associated with a subjective experience of loss of control
(c) Eating Attitudes Test (EAT; Garner & Garfinkel, 1979)
(d) The Bulimic Investigatory Test (BITE; Henderson & Freeman, 1987) – this self-rating instrument measures bulimic symptoms and behaviour; the questionnaire generates two scales, symptoms (maximum score 30, criterion score 20) and severity

(maximum 39, 5 or more is rated as clinically significant and 10 or more indicates a high degree of severity)

(e) Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979).

The measures derived from food diaries were rated weekly, beginning two weeks before the start of drug treatment (T−2) and continuing until the cessation of medication (T8). The EAT and BITE questionnaires were administered on alternate weeks during drug treatment and the MADRS was administered at four-weekly intervals. After eight weekly sessions the patients were asked to continue self-monitoring and were offered out-patient appointments at four and eight weeks after the end of active treatment (T12 & T16). At T16 all patients were interviewed and completed the EAT, BITE and MADRS.

To ensure compliance with medication, patients were given a new box of medication at each out-patient appointment. They were asked to return all unused tablets at their next appointment. The number of tablets taken during the week was then calculated. The food diary sheets also included a section which prompted the patient to take the medication.

Patients

Patients were recruited over an 18-month period commencing 1 March 1988. A total of 70 patients was assessed by interview, of whom 43 fulfilled the study entry criteria. The majority of unsuitable cases failed to meet the severity criteria for bulimia nervosa. Twenty-three were allocated to the placebo group and 20 to the d-fenfluramine group.

The majority of patients were single women in their mid-twenties. The sample was well educated (39 with O level or higher, 22 with A level or higher). There was no significant difference between treatment groups in body mass index (within the normal range in both groups), weight history, duration of bulimia, or severity of eating disturbance. A history of anorexia nervosa was elicited in 44% of patients (d-fenfluramine 7/20, placebo 12/23). The only significant difference between groups, was that patients treated with placebo were more likely to be married or divorced (5/23 v. 0/20, $P=0.03$). Clinical features are outlined in Table 1.

Table 1
The clinical features of d-fenfluramine and placebo groups

Variable	Group				Two-tailed *t*-test
	Active ($n=20$) mean	(s.e.m.)	Placebo ($n=23$) mean	(s.e.m.)	*P*
Age	23.0	(0.6)	25.0	(1.4)	0.21
Body mass index	22.0	(0.7)	22.9	(0.7)	0.93
Maximum weight: kg	69.7	(2.2)	67.6	(2.2)	0.50
Minimum weight: kg	48.3	(2.1)	49.1	(1.7)	0.76
Desired weight: kg	53.5	(1.0)	51.2	(1.1)	0.14
Duration of bulimia: years	4.5	(0.7)	4.7	(1.0)	0.85
Binge frequency[1]	6.6	(1.3)	5.1	(0.8)	0.33
Vomit frequency	6.2	(1.6)	7.8	(1.6)	0.49
Purge frequency	1.4	(0.6)	2.0	(0.5)	0.50
BITE symptoms	26.3	(0.4)	26.0	(0.4)	0.63
BITE severity	13.9	(0.9)	14.8	(0.8)	0.44
EAT	51.7	(3.7)	57.6	(3.4)	0.29
MÅDRS	13.1	(1.7)	13.0	(1.3)	0.94

1. Weekly binge, vomit and purge frequency from food diaries.

Records from food diaries covering the assessment phase revealed severely abnormal eating behaviours. There was no difference between treatment groups in frequency of binge eating, self-induced vomiting, and laxative abuse. The eating disorder was well established in both groups, with a mean duration of between four and five years.

The average BITE symptom scores were well in excess of the criterion scores for bulimia, and the BITE severity scores were above the range indicating a high degree of severity (Henderson & Freeman, 1987).

Analysis of pre-treatment binge and vomit frequency using the kernel density estimate method described by Wegman (1972) showed that their distribution was not markedly skewed and that parametric tests were appropriate methods of analysis for these variables.

Four patients dropped out of the study before completing treatment. All dropouts occurred before the fourth week of drug treatment and after completion of the study it was found that all had been treated with placebo. Their reasons for withdrawal from the study were as follows. *Patient 1:* was withdrawn at week 3 following suicide attempts which led to compulsory admission to hospital. *Patient 2:* withdrew after three weeks when she stopped attending appointments. At one-year follow-up she said that she had been frustrated by her slow rate of improvement, and had difficulties attending out-patient appointments because of commitments to work and, as a single mother, to her child. *Patient 3:* stopped attending at week 3 and declined to offer any explanation. She lived 40 miles from the study centre and had difficulty attending the clinic. *Patient 4:* refused contact following her second appointment. She had been trying to conceal her eating disorder and treatment from her husband.

The analysis of treatment response retained dropouts by using their last value on various measures carried forward.

Results

Table 2 shows the average frequency of binge episodes and self-induced vomiting during the pre-treatment week and at weeks 8 and 16. Figure 1 illustrates the reduction in the frequency of binge eating in both treatment groups. There was a rapid reduction in symptoms over the first four weeks of treatment. Over the eight weeks on medication there was a significant reduction in binge frequency in both treatment groups (pre-treatment v. post-treatment binge frequency, paired *t*-test, placebo $P=0.002$, d-fenfluramine $P=0.0008$).

The data were analysed using multivariate analysis of variance with repeated measures (Norusis/SPSS Inc, 1988) to compare changes between groups. A separate analysis

Table 2
Frequency of binge eating and purging in patients treated with d-fenfluramine (dF) or placebo (Pl)

Variable	*n*	Mean (s.e.m.)			MANOVA Between-group difference TO → T8 (TO → 16)
		TO	T8	T16	
Binges/week					
dF	20	6.6 (1.3)	3.1 (1.2)	3.4 (0.97)	$P=0.35$ ($P=0.34$)
Pl	23	5.1 (0.8)	2.7 (0.82)	2.4 (0.96)	
Self-induced vomiting/week					
dF	20	6.2 (1.6)	2.9 (1.3)	3.2 (1.0)	$P=0.73$ ($P=0.81$)
Pl	23	7.8 (1.6)	4.6 (1.4)	3.8 (1.0)	
BITE severity					
dF	20	13.9 (0.9)	6.8 (1.0)	6.8 (1.2)	$P=0.69$ ($P=0.74$)
Pl	23	14.8 (0.8)	8.4 (1.1)	8.1 (1.1)	
BITE symptom					
dF	20	26.3 (0.4)	16.7 (1.7)	18.2 (1.9)	$P=0.005$ ($P=0.04$)
Pl	23	26.0 (0.4)	21.1 (1.4)	19.3 (1.5)	
EAT					
dF	20	51.7 (3.7)	28.1 (3.7)	31.3 (4.5)	$P=0.26$ ($P=0.31$)
Pl	23	57.6 (3.4)	41.6 (3.7)	37.1 (4.3)	
MADRS					
dF	20	13.1 (1.7)	8.2 (1.9)	8.7 (1.7)	$P=0.11$ ($P=0.32$)
Pl	23	13.0 (1.3)	11.6 (1.1)	9.3 (1.5)	
Weight: kg					
dF	20	59.2 (1.7)	58.7 (1.8)	60.2 (1.9)	$P=0.36$ ($P=0.45$)
Pl	23	58.2 (1.9)	53.7 (1.9)	58.3 (2.0)	

was performed for changes during drug treatment (8 weeks) and over the entire treatment period (16 weeks). There were no significant differences in course or outcome between the two treatment groups (Table 2). The course of self-induced vomiting in both groups was similar to binge frequency, with a significant reduction in both treatment groups (pre-treatment v. post-treatment vomit frequency, paired *t*-test, placebo $P=0.008$, d-fenfluramine $P=0.002$), but no difference between groups.

The BITE severity score, which reflects the patient's estimated frequency of combined abnormal types of eating behaviour decreased rapidly in both groups over the first four weeks of treatment and remained at this reduced level for the full 16 weeks (Table 2, Fig. 2). By 16 weeks the score had declined to a level just above the cut-off point for clinical significance. Both groups showed significant reduction in BITE severity scores (placebo $P<0.001$, d-fenfluramine $P<0.001$), but there was no significant difference between groups.

Other measures of psychopathology, including the BITE symptom and EAT scores showed a rapid early improvement (Table 2). The change within treatment groups was significant for both measures (BITE symptom, paired *t*-test, placebo $P=0.002$, d-fenfluramine $P<0.001$; EAT, placebo $P<0.001$, d-fenfluramine $P<0.001$). There was no difference between groups on EAT score, but the d-fenfluramine group had a significantly better course as measured on the BITE symptom score (Table 2).

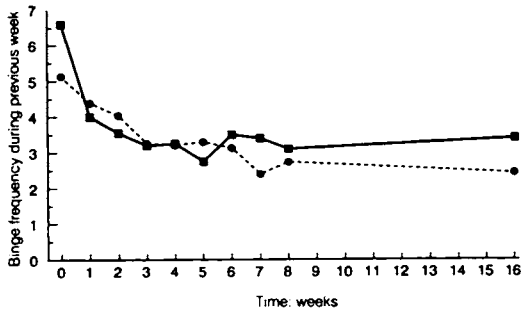

Fig. 1 Binge frequency in patients with bulimia nervosa treated with d-fenfluramine ($n=20$, —■—) or placebo ($n=23$, -●-).

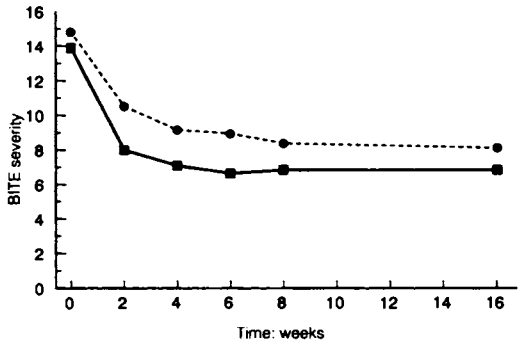

Fig. 2 BITE severity score in patients with bulimia nervosa treated with d-fenfluramine ($n=20$, —■—) or placebo ($n=23$, -●-).

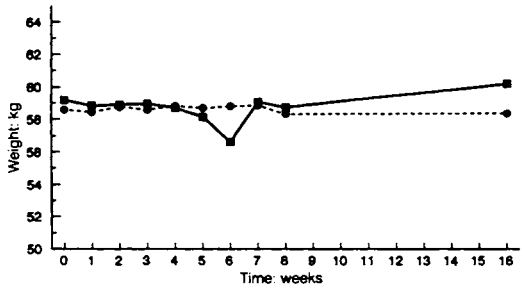

Fig. 3 Weight in patients with bulimia nervosa treated with d-fenfluramine ($n=20$, —■—) or placebo ($n=23$, -●-).

All patients were asked to complete BITE and EAT questionnaires one year after the start of treatment. These questionnaires were completed by 37 patients. There was no difference between treatment groups in BITE symptom score ($P=0.77$), BITE severity score ($P=0.78$) or EAT score ($P=0.84$).

During the first six to seven weeks of drug treatment the placebo group showed a tendency to gain a small amount of weight, and the d-fenfluramine group lost weight (Fig. 3). These changes were not significant between groups (Table 2).

Before the study, it was hypothesised that one of the therapeutic effects of d-fenfluramine would be to reduce the number of therapeutic sessions needed by patients. Between T8 and T16, patients who were treated with placebo were seen for an average of 1.8 (s.e.m. = 0.3) additional appointments and those on d-fenfluramine were seen for an average of 2.1 (s.e.m. = 0.4) sessions. The difference between groups was not significant (Mann–Whitney, $P=0.83$).

A separate analysis was performed on patients with 'poor prognostic' indicators, that is, high depression scores and with personality disorders recorded on the Personality Assessment Schedule (Tyrer, 1988). In the 25 patients with a MADRS score of 10 or greater at the start of treatment, there was no evidence that d-fenfluramine was associated with a better response to treatment than placebo (multivariate analysis with repeated measures, change in binge frequency between groups $P=0.54$, self-induced vomiting $P=0.77$). A similar result was obtained on comparing the response in patients with MADRS scores of 15 or above. Similarly, in the 21 patients with personality disorders and personality difficulties, there was no difference in response between those treated with d-fenfluramine or placebo (binge frequency $P=0.35$, self-induced vomiting $P=0.08$).

It is possible that d-fenfluramine, or similar drugs, may be most useful as a second line treatment in patients who fail to respond to simple educational and psychotherapeutic measures – treatment-resistant cases. To test this proposal, the effect of medication on poor responders was assessed by excluding those patients who were asymptomatic at the end of treatment (binge frequency + self-induced vomit frequency at T7 and T8 = 0, $n=8$). In the remaining 31 patients there was no evidence of a difference between treatment groups in change in binge frequency (multivariate analysis with repeated measures, $P=0.45$) or self-induced vomiting ($P=0.55$). Similarly, there was no evidence that d-fenfluramine modified symptoms in those who continued to binge most frequently at the end of active treatment (i.e. more than four binge episodes during the last two weeks of active treatment, $n=13$; difference in binge frequency $P=0.81$, self-induced vomiting $P=0.55$).

Blood samples were taken at the beginning of treatment, after four weeks on medication, and at the end of eight weeks on medication. Plasma levels of d-fenfluramine and d-norfenfluramine were measured by Servier laboratories. None of the placebo-treated patients recorded quantifiable levels of the drug before or during treatment, thus indicating that none of the patients were taking the drug illicitly. Only one of the d-fenfluramine group did not have measurable levels of the drug on at least one subsequent test. There was no significant correlation between binge frequency at T8 and plasma levels of d-fenfluramine (correlation −0.15) or d-norfenfluramine (−0.5).

Discussion

Previous treatment trials have shown that cognitive–behavioural therapy is an effective treatment for many patients with bulimia nervosa. However, this treatment is labour intensive and it remains unclear what proportion of cases will benefit from less time-consuming treatments. Drug trials have also demonstrated symptomatic improvement in a large proportion of cases, but many patients relapse after treatment. This study was designed to assess the benefits of an appetite suppressant drug as an adjunct to a psychotherapeutic intervention which could be used in an ordinary clinical environment. Consideration was also given to the need to reduce dropouts and maximise patient compliance with treatment.

The patients selected for the study suffered from severe bulimia nervosa. Randomisation between treatment groups was carried out successfully. The treatment package achieved the goal of a low drop-out rate. Only 9% of study entrants dropped out before the end of active treatment, compared with 40% in a previous study of d-fenfluramine or placebo alone (Russell *et al*, 1988). This result is consistent with other studies which report relatively low drop-out rates in trials of psychotherapy. In the study by Fichter *et al* (1991), a drop-out rate of 0% was achieved by admitting all patients to hospital during the course of a fluoxetine trial. Freeman *et al*'s (1990) fluoxetine-treated out-patients received no psychological treatment, but 35% dropped out.

The analysis of treatment response revealed that both d-fenfluramine and placebo groups showed a clinical and statistically significant improvement in

abnormal eating behaviour, including binge eating and self-induced vomiting, and in abnormal attitudes to eating and body image as measured by the EAT and BITE questionnaires. The response to treatment was rapid, with the greatest reduction in symptoms occurring during the first three weeks. After eight weeks of active treatment, 12 patients (31%) were binge-free for at least two weeks, and 10 (26%) were free of self-induced vomiting for at least two weeks. Only eight patients (20%) were asymptomatic during the last two weeks of drug treatment, but 21 (54%) no longer fulfilled criteria for bulimia nervosa (i.e. less than two binge episodes per week). At 16 weeks, 14 patients (37%) were no longer binge eating and 18 (47%) were not vomiting; 28 patients (74%) no longer fulfilled the criteria for bulimia nervosa.

This study failed to detect any clinically significant difference in treatment response between the d-fenfluramine and placebo groups. The improvement in frequency of binge eating and self-induced vomiting was similar in both groups during the eight weeks of drug treatment and there was no evidence of a rebound effect in the d-fenfluramine group following discontinuation of the medication. Similarly, there was no difference in the improvement of psychiatric symptoms as measured by questionnaires or interviews, and there was no difference in outcome measured at the end of drug treatment, after a further eight weeks, or after one year.

It is possible that the beneficial effects of d-fenfluramine treatment in bulimia nervosa, reported in an acute study by Robinson *et al* (1985), are submerged in the more powerful therapeutic effects of the cognitive–behavioural therapy. Fichter *et al* (1991) favoured such an explanation for their failure to elicit a therapeutic advantage of fluoxetine over placebo in patients who had undergone an intensive in-patient behavioural psychotherapy programme. Their conclusion is supported by the findings of Freeman *et al* (1990) who reported a beneficial effect of fluoxetine in out-patients who received no specific psychological treatment. Further evidence of such a ceiling effect comes from Mitchell *et al* (1988) who found that intensive behaviour therapy was superior to imipramine in bulimia nervosa; the drug was superior to placebo, but the combination of psychotherapy and pharmacotherapy was not more effective than psychotherapy and placebo. In the current study it is not clear that patients had reached such a ceiling effect. Clinical improvement was significant, but fell short of the levels recorded by Fairburn *et al* (1991) and Freeman *et al* (1988) following 16 weeks of cognitive–behavioural therapy.

Bulimic patients are a heterogeneous group and it is likely that not all patients require the same intensity of treatment. Patients with minor illnesses may benefit from brief interventions which provide education, dietary advice, and an introduction to self-monitoring techniques. Non-responders and those patients with features suggestive of a poorer prognosis including depression and personality disorder, are likely to require more intensive treatment, including structured psychotherapy. Medication may still have a role in the control of symptoms in patients who have failed to respond to a full psychological intervention. Although d-fenfluramine is effective in suppressing the overeating, excessive snacking, and carbohydrate consumption which are often present in overweight or obese patients (Wurtman *et al*, 1985), the most parsimonious interpretation of our results is that the drug is not an effective treatment for the severe abnormal eating disturbance of bulimia nervosa. In addition, given the drug's lack of antidepressant effects, d-fenfluramine does not lead to a mood-dependent improvement in abnormal eating behaviours.

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Fourth Edition

DSM-IV™

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Eating Disorders

The Eating Disorders are characterized by severe disturbances in eating behavior. This section includes two specific diagnoses, Anorexia Nervosa and Bulimia Nervosa. **Anorexia Nervosa** is characterized by a refusal to maintain a minimally normal body weight. **Bulimia Nervosa** is characterized by repeated episodes of binge eating followed by inappropriate compensatory behaviors such as self-induced vomiting; misuse of laxatives, diuretics, or other medications; fasting; or excessive exercise. A disturbance in perception of body shape and weight is an essential feature of both Anorexia Nervosa and Bulimia Nervosa. An Eating Disorder Not Otherwise Specified category is also provided for coding disorders that do not meet criteria for a specific Eating Disorder.

Simple obesity is included in the *International Classification of Diseases* (ICD) as a general medical condition, but does not appear in DSM-IV because it has not been established that it is consistently associated with a psychological or behavioral syndrome. However, when there is evidence that psychological factors are of importance in the etiology or course of a particular case of obesity, this can be indicated by noting the presence of Psychological Factors Affecting Medical Condition (p. 675).

Disorders of Feeding and Eating that are usually first diagnosed in infancy or early childhood (i.e., Pica, Rumination Disorder, and Feeding Disorder of Infancy or Early Childhood) are included in the section "Feeding and Eating Disorders of Infancy or Early Childhood" (p. 94).

307.1 Anorexia Nervosa

Diagnostic Features

The essential features of Anorexia Nervosa are that the individual refuses to maintain a minimally normal body weight, is intensely afraid of gaining weight, and exhibits a significant disturbance in the perception of the shape or size of his or her body. In addition, postmenarcheal females with this disorder are amenorrheic. (The term *anorexia* is a misnomer because loss of appetite is rare.)

The individual maintains a body weight that is below a minimally normal level for age and height (Criterion A). When Anorexia Nervosa develops in an individual during childhood or early adolescence, there may be failure to make expected weight gains (i.e., while growing in height) instead of weight loss.

Criterion A provides a guideline for determining when the individual meets the threshold for being underweight. It suggests that the individual weigh less than 85% of that weight that is considered normal for that person's age and height (usually computed using one of several published versions of the Metropolitan Life Insurance tables or pediatric growth charts). An alternative and somewhat stricter guideline (used in the ICD-10 Diagnostic Criteria for Research) requires that the individual have a body mass index (BMI) (calculated as weight in kilograms height in meters^2) equal to or below 17.5 kg m^{-2}. These cutoffs are provided only as suggested guidelines for the clinician, since it is unreasonable to specify a single standard for minimally normal weight that applies to all individuals of a given age and height. In determining a minimally normal weight, the clinician should consider not only such guidelines but also the individual's body build and weight history.

Usually weight loss is accomplished primarily through reduction in total food intake. Although individuals may begin by excluding from their diet what they perceive to be highly caloric foods, most eventually end up with a very restricted diet that is sometimes limited to only a few foods. Additional methods of weight loss include purging (i.e., self-induced vomiting or the misuse of laxatives or diuretics) and increased or excessive exercise.

Individuals with this disorder intensely fear gaining weight or becoming fat (Criterion B). This intense fear of becoming fat is usually not alleviated by the weight loss. In fact, concern about weight gain often increases even as actual weight continues to decrease.

The experience and significance of body weight and shape are distorted in these individuals (Criterion C). Some individuals feel globally overweight. Others realize that they are thin, but are still concerned that certain parts of their bodies, particularly the abdomen, buttocks, and thighs, are "too fat." They may employ a wide variety of techniques to estimate their body size or weight, including excessive weighing, obsessive measuring of body parts, and persistently using a mirror to check for perceived areas of "fat." The self-esteem of individuals with Anorexia Nervosa is highly dependent on their body shape and weight. Weight loss is viewed as an impressive achievement and a sign of extraordinary self-discipline, whereas weight gain is perceived as an unacceptable failure of self-control. Though some individuals with this disorder may acknowledge being thin, they typically deny the serious medical implications of their malnourished state.

In postmenarcheal females, amenorrhea (due to abnormally low levels of estrogen secretion that are due in turn to diminished pituitary secretion of follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) is an indicator of physiological dysfunction in Anorexia Nervosa (Criterion D). Amenorrhea is usually a consequence of the weight loss but, in a minority of individuals, may actually precede it. In prepubertal females, menarche may be delayed by the illness.

The individual is often brought to professional attention by family members after marked weight loss (or failure to make expected weight gains) has occurred. If individuals seek help on their own, it is usually because of their subjective distress over the somatic and psychological sequelae of starvation. It is rare for an individual with Anorexia Nervosa to complain of weight loss per se. Individuals with Anorexia Nervosa frequently lack insight into, or have considerable denial of, the problem and may be unreliable historians. It is therefore often necessary to obtain information from parents or other outside sources to evaluate the degree of weight loss and other features of the illness.

Criterion A provides a guideline for determining when the individual meets the threshold for being underweight. It suggests that the individual weigh less than 85% of that weight that is considered normal for that person's age and height (usually computed using one of several published versions of the Metropolitan Life Insurance tables or pediatric growth charts). An alternative and somewhat stricter guideline (used in the ICD-10 Diagnostic Criteria for Research) requires that the individual have a body mass index (BMI) (calculated as weight in kilograms/height in meters^2) equal to or below 17.5 kg/m^2. These cutoffs are provided only as suggested guidelines for the clinician, since it is unreasonable to specify a single standard for minimally normal weight that applies to all individuals of a given age and height. In determining a minimally normal weight, the clinician should consider not only such guidelines but also the individual's body build and weight history.

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Subtypes

The following subtypes can be used to specify the presence or absence of regular binge eating or purging during the current episode of Anorexia Nervosa:

Restricting Type. This subtype describes presentations in which weight loss is accomplished primarily through dieting, fasting, or excessive exercise. During the current episode, these individuals have not regularly engaged in binge eating or purging.

Binge-Eating/Purging Type. This subtype is used when the individual has regularly engaged in binge eating or purging (or both) during the current episode. Most individuals with Anorexia Nervosa who binge eat also purge through self-induced vomiting or the misuse of laxatives, diuretics, or enemas; some individuals included in this subtype do not binge eat, but do regularly purge after the consumption of small amounts of food. It appears that most individuals with Binge-Eating/Purging Type engage in these behaviors at least weekly, but sufficient information is not available to justify the specification of a minimum frequency.

Associated Features and Disorders

Associated descriptive features and mental disorders. When seriously underweight, many individuals with Anorexia Nervosa manifest depressive symptoms such as depressed mood, social withdrawal, irritability, insomnia, and diminished interest in sex. Such individuals may have symptomatic presentations that meet criteria for Major Depressive Disorder. Because these features are also observed in individuals without Anorexia Nervosa who are undergoing starvation, many of the depressive features may be secondary to the physiological sequelae of semistarvation. Symptoms of mood disturbance must therefore be reassessed after partial or complete weight restoration.

Obsessive-compulsive features, both related and unrelated to food, are often prominent. Most individuals with Anorexia Nervosa are preoccupied with thoughts of food. Some collect recipes or hoard food. Observations of behaviors associated with other forms of starvation suggest that obsessions and compulsions related to food may be caused or exacerbated by undernutrition. When individuals with Anorexia Nervosa exhibit obsessions and compulsions that are not related to food, body shape, or weight, an additional diagnosis of Obsessive-Compulsive Disorder may be warranted.

Other features sometimes associated with Anorexia Nervosa include concerns about eating in public, feelings of ineffectiveness, a strong need to control one's environment, inflexible thinking, limited social spontaneity, and overly restrained initiative and emotional expression.

Compared with individuals with Anorexia Nervosa, Restricting Type, those with the Binge-Eating/Purging Type are more likely to have other impulse-control problems, to abuse alcohol or other drugs, to exhibit more mood lability, and to be sexually active.

Associated laboratory findings. Although some individuals with Anorexia Nervosa exhibit no laboratory abnormalities, the semistarvation characteristic of this disorder can affect most major organ systems and produce a variety of disturbances. The induced vomiting and abuse of laxatives, diuretics, and enemas can also cause a number of disturbances leading to abnormal laboratory findings.

Hematology: Leukopenia and mild anemia are common; thrombocytopenia occurs rarely.

Chemistry: Dehydration may be reflected by an elevated blood urea nitrogen (BUN). Hypercholesterolemia is common. Liver function tests may be elevated. Hypomagnesemia, hypozincemia, hypophosphatemia, and hyperamylasemia are occasionally found. Induced vomiting may lead to metabolic alkalosis (elevated serum bicarbonate), hypochloremia, and hypokalemia, and laxative abuse may cause a metabolic acidosis. Serum thyroxine (T_4) levels are usually in the low-normal range; triiodothyronine (T_3) levels are decreased. Hyperadrenocorticism and abnormal responsiveness to a variety of neuroendocrine challenges are common.

In females, low serum estrogen levels are present, whereas males have low levels of serum testosterone. There is a regression of the hypothalamic-pituitary-gonadal axis in both sexes in that the 24-hour pattern of secretion of luteinizing hormone (LH) resembles that normally seen in prepubertal or pubertal individuals.

Electrocardiography: Sinus bradycardia and, rarely, arrhythmias are observed.

Electroencephalography: Diffuse abnormalities, reflecting a metabolic encephalopathy, may result from significant fluid and electrolyte disturbances.

Brain imaging: An increase in the ventricular-brain ratio secondary to starvation is often seen.

Resting energy expenditure: This is often significantly reduced.

Associated physical examination findings and general medical conditions. Many of the physical signs and symptoms of Anorexia Nervosa are attributable to starvation. In addition to amenorrhea, there may be complaints of constipation, abdominal pain, cold intolerance, lethargy, and excess energy. The most obvious finding on physical examination is emaciation. There may also be significant hypotension, hypothermia, and dryness of skin. Some individuals develop lanugo, a fine downy body hair, on their trunks. Most individuals with Anorexia Nervosa exhibit bradycardia. Some develop peripheral edema, especially during weight restoration or on cessation of laxative and diuretic abuse. Rarely, petechiae, usually on the extremities, may indicate a bleeding diathesis. Some individuals evidence a yellowing of the skin associated with hypercarotenemia. Hypertrophy of the salivary glands, particularly the parotid glands, may be present. Individuals who induce vomiting may have dental enamel erosion and some may have scars or calluses on the dorsum of the hand from contact with the teeth when using the hand to induce vomiting.

The semistarvation of Anorexia Nervosa, and the purging behaviors sometimes associated with it, can result in significant associated general medical conditions. These include the development of normochromic normocytic anemia, impaired renal function (associated with chronic dehydration and hypokalemia), cardiovascular problems (severe hypotension, arrhythmias), dental problems, and osteoporosis (resulting from low calcium intake and absorption, reduced estrogen secretion, and increased cortisol secretion).

Specific Culture, Age, and Gender Features

Anorexia Nervosa appears to be far more prevalent in industrialized societies, in which there is an abundance of food and in which, especially for females, being considered attractive is linked to being thin. The disorder is probably most common in the United States, Canada, Europe, Australia, Japan, New Zealand, and South Africa, but little

systematic work has examined prevalence in other cultures. Immigrants from cultures in which the disorder is rare who emigrate to cultures in which the disorder is more prevalent may develop Anorexia Nervosa as thin-body ideals are assimilated. Cultural factors may also influence the manifestations of the disorder. For example, in some cultures, disturbed perception of the body may not be prominent and the expressed motivation for food restriction may have a different content, such as epigastric discomfort or distaste for food.

Anorexia Nervosa rarely begins before puberty, but there are suggestions that the severity of associated mental disturbances may be greater among prepubertal individuals who develop the illness. However, data also suggest that when the illness begins during early adolescence (between ages 13 and 18 years), it may be associated with a better prognosis. More than 90% of cases of Anorexia Nervosa occur in females.

Prevalence

Prevalence studies among females in late adolescence and early adulthood have found rates of 0.5%–1.0% for presentations that meet full criteria for Anorexia Nervosa. Individuals who are subthreshold for the disorder (i.e., with Eating Disorder Not Otherwise Specified) are more commonly encountered. There are limited data concerning the prevalence of this disorder in males. The incidence of Anorexia Nervosa appears to have increased in recent decades.

Course

The mean age at onset for Anorexia Nervosa is 17 years, with some data suggesting bimodal peaks at ages 14 and 18 years. The onset of this disorder rarely occurs in females over age 40 years. The onset of illness is often associated with a stressful life event, such as leaving home for college. The course and outcome of Anorexia Nervosa are highly variable. Some individuals with Anorexia Nervosa recover fully after a single episode, some exhibit a fluctuating pattern of weight gain followed by relapse, and others experience a chronically deteriorating course of the illness over many years. Hospitalization may be required to restore weight and to address fluid and electrolyte imbalances. Of individuals admitted to university hospitals, the long-term mortality from Anorexia Nervosa is over 10%. Death most commonly results from starvation, suicide, or electrolyte imbalance.

Familial Pattern

There is an increased risk of Anorexia Nervosa among first-degree biological relatives of individuals with the disorder. An increased risk of Mood Disorders has also been found among first-degree biological relatives of individuals with Anorexia Nervosa, particularly relatives of individuals with the Binge-Eating Purging Type. Studies of Anorexia Nervosa in twins have found concordance rates for monozygotic twins to be significantly higher than those for dizygotic twins.

Differential Diagnosis

Other possible causes of significant weight loss should be considered in the differential diagnosis of Anorexia Nervosa, especially when the presenting features are atypical

(such as an onset of illness after age 40 years). In **general medical conditions** (e.g., gastrointestinal disease, brain tumors, occult malignancies, and acquired immunodeficiency syndrome [AIDS]), serious weight loss may occur, but individuals with such disorders usually do not have a distorted body image and a desire for further weight loss. The **superior mesenteric artery syndrome** (characterized by postprandial vomiting secondary to intermittent gastric outlet obstruction) should be distinguished from Anorexia Nervosa, although this syndrome may sometimes develop in individuals with Anorexia Nervosa because of their emaciation. In **Major Depressive Disorder**, severe weight loss may occur, but most individuals with Major Depressive Disorder do not have a desire for excessive weight loss or excessive fear of gaining weight. In **Schizophrenia,** individuals may exhibit odd eating behavior and occasionally experience significant weight loss, but they rarely show the fear of gaining weight and the body image disturbance required for a diagnosis of Anorexia Nervosa.

Some of the features of Anorexia Nervosa are part of the criteria sets for **Social Phobia, Obsessive-Compulsive Disorder,** and **Body Dysmorphic Disorder.** Specifically, individuals may be humiliated or embarrassed to be seen eating in public, as in Social Phobia; may exhibit obsessions and compulsions related to food, as in Obsessive-Compulsive Disorder; or may be preoccupied with an imagined defect in bodily appearance, as in Body Dysmorphic Disorder. If the individual with Anorexia Nervosa has social fears that are limited to eating behavior alone, the diagnosis of Social Phobia should not be made, but social fears unrelated to eating behavior (e.g., excessive fear of speaking in public) may warrant an additional diagnosis of Social Phobia. Similarly, an additional diagnosis of Obsessive-Compulsive Disorder should be considered only if the individual exhibits obsessions and compulsions unrelated to food (e.g., an excessive fear of contamination), and an additional diagnosis of Body Dysmorphic Disorder should be considered only if the distortion is unrelated to body shape and size (e.g., preoccupation that one's nose is too big).

In **Bulimia Nervosa,** individuals exhibit recurrent episodes of binge eating, engage in inappropriate behavior to avoid weight gain (e.g., self-induced vomiting), and are overly concerned with body shape and weight. However, unlike individuals with Anorexia Nervosa, Binge-Eating/Purging Type, individuals with Bulimia Nervosa are able to maintain body weight at or above a minimally normal level.

Diagnostic criteria for 307.1 Anorexia Nervosa

A. Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected).

B. Intense fear of gaining weight or becoming fat, even though underweight.

(continued)

☐ **Diagnostic criteria for 307.1 Anorexia Nervosa** *(continued)*

C. Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.

D. In postmenarcheal females, amenorrhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration.)

Specify type:

Restricting Type: during the current episode of Anorexia Nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)

Binge-Eating/Purging Type: during the current episode of Anorexia Nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)

307.51 Bulimia Nervosa

Diagnostic Features

The essential features of Bulimia Nervosa are binge eating and inappropriate compensatory methods to prevent weight gain. In addition, the self-evaluation of individuals with Bulimia Nervosa is excessively influenced by body shape and weight. To qualify for the diagnosis, the binge eating and the inappropriate compensatory behaviors must occur, on average, at least twice a week for 3 months (Criterion C).

A *binge* is defined as eating in a discrete period of time an amount of food that is definitely larger than most individuals would eat under similar circumstances (Criterion A1). The clinician should consider the context in which the eating occurred—what would be regarded as excessive consumption at a typical meal might be considered normal during a celebration or holiday meal. A "discrete period of time" refers to a limited period, usually less than 2 hours. A single episode of binge eating need not be restricted to one setting. For example, an individual may begin a binge in a restaurant and then continue it on returning home. Continual snacking on small amounts of food throughout the day would not be considered a binge.

Although the type of food consumed during binges varies, it typically includes sweet, high-calorie foods such as ice cream or cake. However, binge eating appears to be characterized more by an abnormality in the amount of food consumed than by a craving for a specific nutrient, such as carbohydrate. Although individuals with Bulimia Nervosa consume more calories during an episode of binge eating than persons without Bulimia Nervosa consume during a meal, the fractions of calories derived from protein, fat, and carbohydrate are similar.

Comorbidity of Bulimia Nervosa and Alcohol Use Disorders: Results from the National Women's Study

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Abstract: **Objective:** *The nature of the relationship between bulimia nervosa (BN) and alcohol abuse/alcohol dependence (AA/AD) and the extent to which women with BN+AA differ from women with BN–AA were examined in a national sample of women (N = 3,006).* **Method:** *The sample of was generated by multistage geographic sampling and interviews were conducted by telephone.* **Results:** *AA was higher in women with BN compared to women without BN or binge eating disorder, only when the influence of major depressive disorder (MDD) and posttraumatic stress disorder (PTSD) was controlled. Prevalence rates of AA and AD were similar in women with BN, MDD, and PTSD. Analyses indicated that the relationship between BN and AA/AD may be indirect and influenced by associations with MDD and PTSD. Women with BN+AA did not differ from those with BN–AA on most variables concerning victimization, family of origin, and disordered eating.* **Discussion:** *Evaluation of MDD and PTSD in women presenting for treatment of BN and/or alcohol use disorders (AUDs) is recommended. © 2000 by John Wiley & Sons, Inc.* Int J Eat Disord 27: 180–190, 2000.

Key words: *alcohol abuse; bulimia nervosa; major depressive disorder*

INTRODUCTION

The rate at which bulimia nervosa (BN) and alcohol use disorders (AUDs) co-occur in clinical and community samples has been well documented (Brewerton et al., 1995; Bulik, Sullivan, McKee, Weltzin, & Kaye, 1994; Garfinkel et al., 1995; Goldbloom, 1993; Herzog, Keller, Sacks, Yeh, & Lavori, 1992; Higuchi, Suzuki, Yamada, Parrish, & Kono, 1993; Holderness, Brooks-Gunn, & Warren, 1994; Hudson, Pope, Yurgelun-Todd, Jonas, & Frankenburg, 1987; Kaye et al., 1996; Kessler et al., 1994; Lilenfeld et al., 1997; Mitchell, Specker, & Edmonson, 1997; Schukit et al., 1996). Researchers have studied treatment-

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seeking samples of women with BN and found prevalence rates for AUDs as high as 30–50% (Beary, Lacey, & Merry, 1986; Braun, Sunday, & Halmi, 1994; Bulik, 1987; Bulik, Sullivan, Carter, & Joyce, 1997; Casper, Eckert, Halmi, Goldberg, & Davis, 1980; Garfinkel, Moldofsky, & Garner, 1980; Kaye et al., 1996). Specifically, Beary et al. (1986) found that by age 35, 50% of individuals with BN had met criteria for alcohol abuse/alcohol dependence (AA/AD) at some point during their lives. Also, AUDs were reported to be as high as 42% among inpatient women with BN (Braun et al., 1994). In a study of outpatient women with BN, Bulik et al. (1997) found that 47% of their sample met criteria for lifetime AD.

In addition to documenting the high prevalence of AUDs in women with BN, researchers have compared women with BN to groups of female controls. In general, significantly higher rates of alcohol misuse have been observed in women with BN compared with depressed women or healthy controls (Garfinkel et al., 1995; Hudson et al., 1987; Kaye et al., 1996). Garfinkel et al. (1995) observed in a community sample that 41.8% of individuals classified as meeting criteria for full BN and 27.3% of those meeting criteria for partial BN had drinking problems, whereas the rate of drinking problems among controls was 20.9%.

Researchers also have begun to examine characteristics which may differentiate women with BN and substance use disorders (SUDs), women with BN−SUDs, and controls. It is believed that by identifying characteristics specific to women with comorbid BN and AUDs, therapeutic interventions can be tailored to meet their needs and more accurate predictions regarding therapy prognosis can be made. In general, researchers have documented higher rates of psychiatric comorbidity, impulsivity, and Axis II pathology among the women with comorbid BN+SUD than in women with BN−SUD, although few differences have been found pertaining to symptoms of disordered eating (Bulik et al., 1994; Grilo, Becker, Levy, Walker, Edell, & McGlashan, 1995; Levy & Walker, 1995; Lilenfeld et al., 1997; Strasser, Pike, & Walsh, 1992). Researchers have also found that treatment-seeking women with BN with a past history of an SUD had significantly higher baseline scores on measures of anxiety and depression, more psychiatric inpatient hospitalizations, more suicide attempts, more disruption in work, more frequent stealing, and higher levels of diuretic use than treatment-seeking women with BN and no past history of an SUD (Hatsukami, Mitchell, Eckert, & Pyle, 1986; Strasser et al., 1992). Taken together, these studies indicate that women with BN+SUD have significantly higher levels of psychopathology and other problems with social, occupational, and interpersonal functioning than women with BN−SUD.

Although these studies provide important information concerning the relationship between BN and SUDs, there are several methodologic limitations that make it difficult to draw firm conclusions. First, an overwhelming majority of the researchers utilized treatment-seeking samples of women with eating disorders. Second, several authors (Hatsukami et al., 1986; Lilenfeld et al., 1997; Strasser et al., 1992) studied AUDs and SUDs together as a single group without providing justifications for assuming that women with AUDs and those who misuse other drugs constitute a single homogeneous group. Similarly, women with a history of substance abuse were grouped together with women with a history of substance dependence. Moreover, several authors have acknowledged the high degree of comorbidity of BN and other Axis I disorders such as major depressive disorder (MDD) and posttraumatic stress disorder (PTSD; Dansky, Brewerton, Kilpatrick, & O'Neil, 1997). However, whether highly prevalent disorders such as MDD and PTSD directly influence the relationship between BN and AUDs has never been studied.

The central goals of this study were to address the limitations highlighted above by (a)

examining the prevalence of BN and AUDs in a national sample of women, (b) exploring the nature of the relationship between BN and AUDs, taking into account possible mediating effects of comorbid MDD and PTSD, and (c) determining whether women with BN+AA differ in important ways from those with BN−AA.

METHOD

Participants

A national household probability sample of 3,006 women participated in the third wave of the National Women's Study (NWS), which occurred in 1992. Respondents completed structured telephone interviews of approximately 40 min duration during which they were screened for demographic characteristics, trauma history, PTSD, BN, MDD, and AUDs. The mean age for the sample was 46.1 years (SD = 17.3). The sample was predominantly Caucasian (86%) with a mostly African-American minority group (11%).

Sampling Procedures

The original sample of 4,009 female adults (Wave 1 sample) was generated by multistage geographic sampling procedures (for further details see Dansky et al., 1997; Resnick, Kilpatrick, Dansky, Best, & Saunders, 1993; Kilpatrick, Acierno, Resnick, Saunders, & Best, 1997). Since the original sample was identified in 1989, the data were weighted according to estimates of the 1989 U.S. Census figures for age and race to ensure that the sample data were representative of women in the U.S. population. This weighting program altered the size of the sample such that the new Wave 3 sample size was 3,031.

Survey Instrument

BN

Participants who endorsed a screening question pertaining to binge eating were asked additional questions, including those necessary to diagnose BN according to criteria defined in the 3rd. Rev. ed. of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III-R; American Psychiatric Association, 1987) and binge eating disorder (BED) according to criteria in the 4th ed. (DSM-IV; APA, 1994; see Dansky, et al., 1997, for details).

PTSD

PTSD was assessed using the NWS PTSD Module (Kilpatrick, Resnick, Saunders, & Best, 1989). This instrument is described in detail in Dansky et al. (1997) and Resnick et al. (1993). Intrusive symptoms, symptoms of avoidance, and symptoms of increased arousal were evaluated. Concurrent validity and reliability have been documented for this instrument (Dansky, Saladin, Brady, Kilpatrick, & Resnick, 1995; Resnick et al., 1993; Kilpatrick et al., 1997).

MDD

The screening instrument for major depression was based on DSM-III-R criteria. Respondents were first asked about decreased interest in meaningful activities and depressed mood. Then, symptoms such as changes in weight, changes in sleep patterns,

restlessness, lethargy, feelings of worthless or guilt, problems with concentration, and thoughts about hurting themselves were evaluated. Participants were classified as having MDD if they experienced symptoms that met criteria for a major depressive episode at some point during their lifetime.

AUDs

To diagnose lifetime AA and AD, participants were asked frequency, age at onset, and recency of use of alcohol. In addition, they were assessed for alcohol-related difficulties at home, work, or in the community. Although the NWS survey instrument was designed prior to the publication of the DSM-IV, the questions probed for symptoms of both abuse and dependence and close approximations of these diagnoses were made. Positive endorsement of one or more of the following alcohol-related problems warranted an AA diagnosis: trouble with a boss, trouble with friends, trouble with the police, criticism by family members, driving while intoxicated, being charged with driving while intoxicated, a car accident, an accident at home, neglecting important obligations, and physical altercations. AD was diagnosed if a participant endorsed symptoms from at least three of following five categories: tolerance to alcohol, alcohol withdrawal, need for increased amounts of alcohol, and alcohol-related problems (as described above for AA).

Other Background Measures

All participants were asked about the following background variables: age; race; socioeconomic status; marital status; suicidality; whether members of their family of origin had drinking problems, drug problems, emotional problems, or had been arrested; whether they had grown up with their family of origin; whether they had felt while growing up that they could count on members of their family; whether they had witnessed domestic violence in their family of origin; and cigarette use.

Data Analysis

Weighted data were used in all statistical tests with the exception of the hierarchical log linear analysis. Groups were compared using chi-square tests, Fisher's exact tests, or *t*-tests. Hierarchical log linear analyses were utilized to examine interactions among AA/AD, BN, PTSD, and MDD. All analyses pertaining to diagnostic groups involved lifetime, as opposed to current, diagnoses.

RESULTS

The sample prevalence rates of BN, PTSD, MDD, AA, and AD were 2.4%, 12.5%, 15.1%, 22%, and 6.3%, respectively. Prevalence rates for lifetime AA and AD by eating disorder status are depicted in Figure 1. Chi-square statistics were calculated to examine the prevalence rate of AA and AD in women with BN, those with BED, and those without BN or BED (NonBN/NonBED). Although the rate of AA was not significantly higher in women with BN (31%) than women in the NonBN/NonBED group (21.7%), there was a significant difference between these two groups for the prevalence of AD [13.2% vs. 6.0%; $\chi^2(1) = 6.27$, $p < .05$]. No significant differences in the rates of AA and AD were observed when comparing women with BN and those with BED or when comparing women with BED and women in the NonBN/NonBED group.

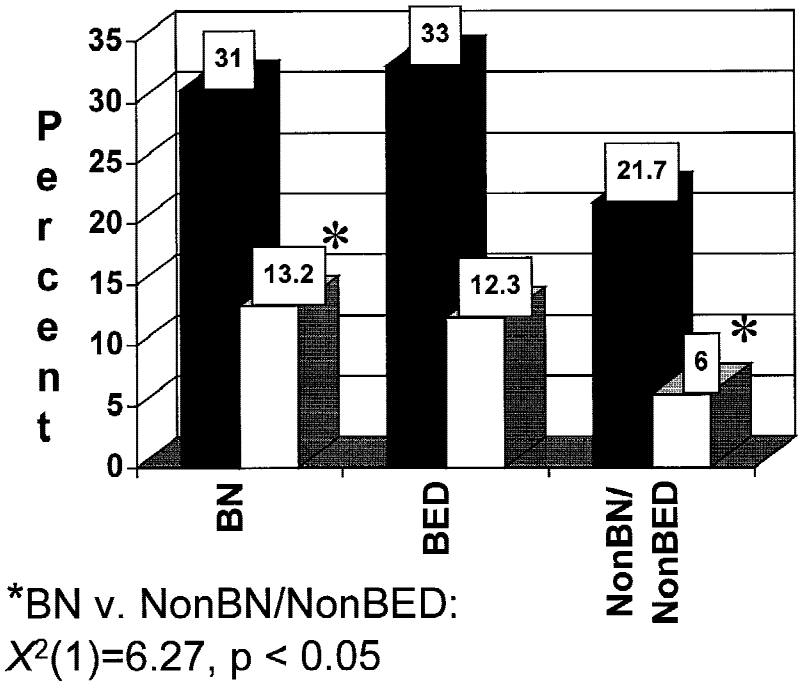

Figure 1. Prevalence rates of alcohol abuse and alcohol dependence by eating disorder status. ■ = AA; □ AD.

Prevalence Rates of AA and AD in Women with BN, MDD, PTSD

Given that the NonBN/NonBED group included women who met criteria for other psychiatric disorders such as PTSD or MDD which are highly comorbid with AUDs, the prevalence rate of AA was examined in five separate groups of women: BN, PTSD only, MDD only, PTSD+MDD only, and women who did not meet criteria for any of these psychiatric disorders (Control; Figure 2). Any participant with BN was classified in the BN group, regardless of PTSD and MDD status. The prevalence of AA in women with BN was 31%, compared with 18.8% of those in the Control group, 36.9% of those with PTSD only, 28.3% of those with MDD only, and 36.7% of those with PTSD+MDD [$\chi^2(4) = 67.44$, $p < .001$]. Post-hoc two-by-two chi-square analyses indicated significant differences between women in the Control group compared to women in each of the other four groups. There were no significant differences between women with BN and women classified in each of the other three psychiatric groups. Similar results were obtained when examining the prevalence of AD in these groups. The prevalence rates of AD in women in the Control, BN, PTSD only, MDD only, and PTSD+MDD groups were 4.3%, 13.2%, 15%, 9.4%, and 15%, respectively. Once again, there were significant differences between women in the Control group and women in each of the four psychiatric groups regarding the prevalence rates of AD but no significant differences observed between the four psychiatric groups. These results demonstrate that although the prevalence of AA was not significantly higher in women with BN than women in the NonBN/NonBED group, the prevalence of AA was significantly higher when women with MDD and PTSD were removed from the non-eating disordered group.

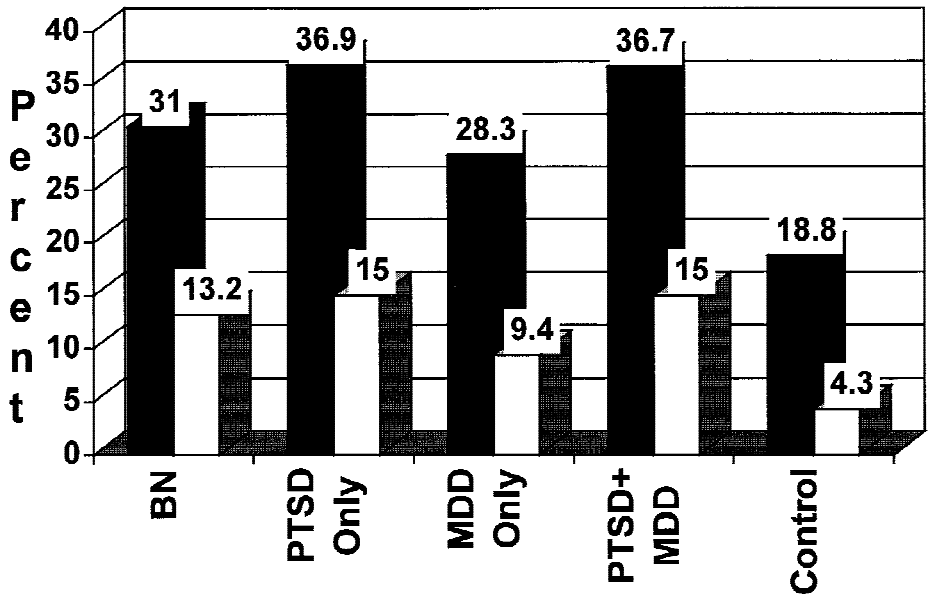

Figure 2. Prevalence of alcohol abuse (AA) and alchohol dependence (AD) by psychiatric group status. ■ = AA; □ = AD.

MDD and PTSD as Moderators in the Relationship Between BN and AA/AD

In order to further assess the ways in which BN, PTSD, MDD, and AA/AD may interact with each other, hierarchical log linear analyses were conducted. For the first hierarchical log linear analysis, respondents were classified as being positive (1) or negative (2) for BN, PTSD, MDD, and AA. A backward elimination method was selected to assess first, second, third, and fourth order effects. The final model contained the following interactions:

$$\text{PTSD} \times \text{MDD} \times \text{AA (Partial } \chi^2(1) = 5.01,\ p < 0.05)$$
$$\text{PTSD} \times \text{BN (Partial } \chi^2(1) = 13.14,\ p < 0.001)$$
$$\text{MDD} \times \text{BN (Partial } \chi^2(1) = 5.13,\ p < 0.05)$$

Small significance levels ($p < .05$) associated with high partial chi-square values are desirable. Nonsignificant p levels associated with small likelihood ratio chi-square values, as was found here [best model likelihood ratio $\chi^2(5) = 4.70$, $p = .453$], are associated with good models.

Analogous results were obtained when a second hierarchical log linear analysis was conducted to examine interactions between BN, PTSD, MDD, and AD. One third order and two second order interactions were generated [best model likelihood ratio $\chi^2(5) = 4.25$, $p = .513$]:

$$\text{PTSD} \times \text{MDD} \times \text{AD (Partial } \chi^2(1) = 4.70,\ p < 0.05)$$
$$\text{PTSD} \times \text{BN (Partial } \chi^2(1) = 12.76,\ p < 0.001)$$
$$\text{MDD} \times \text{BN (Partial } \chi^2(1) = 4.98,\ p < 0.05)$$

In both models, the results indicate that BN interacted directly with PTSD and MDD but did not interact directly with AA or AD. However, the three-way interactions indicate that AA and AD interacted directly with both PTSD and MDD.

Comparisons Between BN+AA and BN−AA Groups

Chi-square statistics were used to compare women with BN+AA ($n = 22$) and women with BN−AA ($n = 50$) to determine, in a non-treatment-seeking sample, whether women with the BN+AA comorbidity had higher levels of psychopathology, experienced more stressful life events, or had higher rates of family members with alcohol, drug, or emotional problems. There were no significant differences between women in the BN+AA and the BN−AA groups for PTSD (34.5% vs. 37.9%); MDD (38.1% vs. 35.3%); feeling "so low you wanted to die" (30.1% vs. 31.8%); feeling so "low" that suicide was contemplated (37.1% vs. 38.4%); history of completed rape (35.1% vs. 22.8%); history of childhood rape (21.6% vs. 16.0%); age at first rape (13.8 years old vs. 14.2 years old); history of aggravated assault (23.7% vs. 28.2%); witnessing domestic violence in the family of origin (21.2% vs. 22.4%); feeling that there was no one to "count on" during childhood (13.1% vs. 9.9%); reporting a family member with a drinking problem (28.3% vs. 28.2%); reporting a family member with a drug problem (13.5% vs. 9.9%); reporting a family member with an emotional problem (24.6% vs. 21.5%); reporting a family member had been arrested (13.5% vs. 7.7%); symptoms of binge eating such as eating too fast (71.5% vs. 68.5%), eating when already full (97.8% vs. 94.7%), eating large quantities of food (79.8% vs. 59.8%), and feeling badly about the amount of food consumed (90.6% vs. 89.1%); and certain symptoms of purging such as excessive exercise (55.0% vs. 66.2%) and use of diuretics (44.7% vs. 32.5%).

Given the exploratory nature of the analyses, corrections were not made to control for the possibility of obtaining significant results due to the relatively large number of analyses conducted. However, it is important to note that only two of the comparisons reported below were at the $p < .05$ level of significance. There were marginal differences between women in the BN+AA and BN−AA groups for a history of sexual molestation [34.8% vs. 16.2%; $\chi^2(1) = 3.12$, $p < .1$] and a history of direct assault [any sexual or physical assault: 69.5% vs. 47.6%; $\chi^2(1) = 2.96$, $p < .1$]. Furthermore, women in the BN+AA group were significantly less likely to attempt to eat large quantities while alone than women in the BN−AA group [46.1% vs. 71.%; $\chi^2(1) = 4.35$, $p < .05$]. However, women with comorbid BN+AA were more likely to report a history of vomiting [60.2% vs. 34.4%; $\chi^2(1)= 4.21$, $p < .05$] and a history of abusing laxatives [43.9% vs. 17.9%; $\chi^2(1) = 5.37$, $p < .05$] than women with BN without a history of AA. In addition, there was a trend for women in the BN+AA group to be younger at the time of their first binge than women in the BN−AA group [21.6 years old vs. 26.67 years old; $t(67) = 1.69$, $p < .1$]. There was also a trend for a higher prevalence of lifetime use of tobacco cigarettes for women with BN+AA than women in the BN−AA group [87.2% vs. 57.9%; $\chi^2(1) = 3.01$, $p < .1$].

DISCUSSION

Approximately one third (31%) of women who have a history of BN also have a history of AA and more than one in eight (13%) have a history of AD. These rates, observed in a non-treatment-seeking sample, are comparable to prevalence rates obtained by other researchers in samples of inpatients and outpatients (Beary et al., 1986; Braun et al., 1994;

Bulik et al., 1997; Hudson et al., 1987; Kaye et al., 1996). Similarly, the result in the present investigation, wherein the prevalence rate of AD in women with BN was significantly higher than that observed in women who do not meet criteria for BN or BED, also is consistent with findings documented by Garfinkel et al. (1995) and Lilenfeld et al. (1997).

Although the prevalence of AD was significantly higher in women with BN than in women in the NonBN/NonBED group, the prevalence rate of AA was significantly higher in women with BN only after women with MDD and/or PTSD were removed from the comparison group. Furthermore, the prevalence of these AUDs were equally high in women who met lifetime criteria for PTSD or MDD as women with BN. This finding that the prevalence of AUDs was similar among women with BN and women with MDD contradicts results described by Hudson et al. (1987), who observed higher rates of AA or AD in depressed women than in bulimic women. It is possible that these divergent findings reflect the fact that Hudson et al.'s sample comprised treatment-seeking women and women who responded to advertisements, whereas the current investigation consisted of a national probability sample conducted via the telephone using random sampling techniques. The results reported here suggest that the risk of AA or AD in women with BN may be quite similar to the risk present in women with other types of psychiatric disorders.

One aspect of the nature of the relationship between BN and AUDs was addressed by hierarchical log linear analyses. The results indicated that other psychiatric disorders such as PTSD and MDD, which are commonly observed in women with BN and in women with AUDs, appear to impact how BN and AUDs are related. Specifically, AA and AD were not directly associated with BN. Instead, AA and AD were significantly related to PTSD and MDD, which, in turn, were associated with BN. A plausible conclusion is that the associations between BN and AA or AD are due, at least in part, to the strong relationship between AA/AD and diagnoses such as PTSD and MDD, which tend to be prevalent among women with BN. High prevalence rates of MDD and anxiety disorders among women with BN have been documented by several researchers (Brewerton et al., 1995; Bulik, 1987; Dansky et al., 1997; Garfinkel et al., 1995; Hatsukami et al., 1986; Hudson et al., 1987; Steer, Butler, & Cooper, 1990; Williamson, Kelly, Davis, Ruggiero, & Blouin, 1985). One implication of this finding is that evaluation of MDD and PTSD seems crucial in any person presenting for treatment of BN or AA/AD.

The indirect relationship observed between BN and AUDs in the present investigation is congruous with recently published data concerning lines of inheritance for these two disorders (Lilenfeld et al., 1997b; Kaye et al., 1996; Strober, Freeman, Bower, & Regali, 1996). Lilenfeld et al. (1997a, 1997b) studied samples of women with BN and non-BN controls and found that relatives of women with BN+SUDs had a significantly higher prevalence rate of drug dependence than relatives of women in the BN−SUD group. However, the women's BN status per se was unrelated to relatives' substance abuse status. Strober et al. (1996) came to a similar conclusion studying binge eating among women with anorexia nervosa utilizing a large epidemiologic sample: "There was no indication of a high level of familial crossover between eating disorders and alcohol dependence." Thus, regardless of BN status, women with an SUD are more likely to have relatives with a SUD than women without a SUD.

Women with BN+AA did not differ from women with BN−AA regarding the prevalence of comorbid PTSD, suicidality, depression, family of origin variables, history of rape or aggravated assault, and most symptoms of binging. However, women in the BN+AA group were significantly more likely to report the use of vomiting and laxatives as methods of purging than women in the BN−AA group. Additionally, there was a trend for a

higher prevalence of sexual molestation and direct assault in the BN+AA group, as well as a trend for a higher rate of cigarette smoking. Higher rates of laxative abuse and cigarette smoking have been documented previously by Bulik and her colleagues (1997) with an outpatient sample.

The trend for a higher rate of direct assault in the BN+AA group is consistent with the extremely high rates of victimization (between 75% and 95%) documented in treatment-seeking samples of women with SUDs (Brown & Wolfe, 1994; Dansky et al., 1995; Grice, Brady, Dustan, Malcolm, & Kilpatrick, 1995). The finding in the current investigation that the prevalence of PTSD was similar in the BN+AA and BN−AA groups contrasts with Lilenfeld and colleagues' (1997) observation that "posttraumatic stress disorder was more associated with the non-substance-dependent type of BN." Sampling differences may account for this discrepancy, although the low prevalence rate of PTSD in their control group (7%) suggests that measurement differences (particularly when evaluating trauma history, which is the "entry" into diagnosing PTSD) may account for the discrepancy. Weaver (1998) evaluated traumatic events using the SCID and NWS screen (the instrument utilized in the current study) and found that 7% of a sample of battered women reported childhood sexual abuse in response to the SCID trauma screening questions, compared with 53% using the behaviorally specific NWS protocol. Regardless of the cause of the discrepant findings, the role of PTSD in the relationship between BN and AA/AD remains a topic for future investigation.

The lack of differences between women in the BN+AA and BN−AA groups for most variables associated with psychopathology is consistent with results from studies that demonstrate that a lifetime history of AA or AD is not predictive of outcome after treatment for BN (Mitchell, Pyle, Eckert, & Hatsukami, 1990; Strasser et al., 1992). However, these treatment outcome results must be interpreted with some caution, since all women with a current SUD at time of study intake were excluded. In addition, outcomes on measures of substance use severity were not reported. Similarly, comparisons in the present investigation pertained to lifetime diagnoses (in order to have adequate statistical power), and therefore, it is difficult to generate recommendations pertaining to treatment interventions for patients presenting with current BN and current AA/AD.

One potential limitation in this study was the use of nonstandardized measures to diagnose psychiatric disorders, although the prevalence rates of BN, MDD, AA, and AD are consistent with prevalence rates documented in other large samples (Garfinkel et al., 1995; Gotestam, & Agras, 1995; Hoek, 1993; Kendler et al., 1991; Kessler et al., 1994; Schukit et al., 1996), and the reliability of the instrument to diagnose PTSD has been documented (Dansky et al., 1995; Resnick et al., 1993). Furthermore, the present results were subject to limitations that accompany the use of retrospective measures, for example, negative response set and selective memory. This is a limitation encountered in any research that is not a prospective design or direct observation. The questionnaire also did not include questions designed to determine the age of onset for BN diagnosis. Therefore, the extent to which AA or AD contributed to or was a product of the development of BN could not be examined. Finally, it is conceivable that a confounding variable that was not measured in this study may more directly influence the relationship between AA/AD and BN than did PTSD and MDD.

Despite the limitations noted above, the results demonstrate that AUDs are highly prevalent among women with BN and that the presence of comorbid PTSD and MDD may increase the risk that an AUD will occur. Future studies pertaining to BN and AUDs are necessary to examine, prospectively, whether the presence of one disorder increases

the likelihood that the second disorder will develop, and to more fully understand the extent to which the presence of one disorder influences the expression of the other.

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The National Women's Study: Relationship of Victimization and Posttraumatic Stress Disorder to Bulimia Nervosa

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Objective: *In recent years there has been increased interest regarding the role of crime victimization in the development and/or maintenance of eating disorders, particularly bulimia nervosa.* **Method:** *To examine the relationship among assault, bulimia nervosa, and binge eating disorder, a national, representative sample of 3,006 women completed structured telephone interviews.* **Results:** *Lifetime prevalence of completed, forcible rape for respondents with bulimia nervosa was 26.6%, as compared with 11.5% for respondents with binge eating disorder and 13.3% for respondents without bulimia nervosa or binge eating disorder. Compared to respondents without bulimia nervosa or binge eating disorder, aggravated assault history was significantly more prevalent in women with bulimia nervosa (26.8%), as was a lifetime history of posttraumatic stress disorder (36.9%). Characteristics of sexual assault experiences were not associated with dysfunctional eating patterns. Specific types of disordered eating such as compensatory behaviors in bulimia nervosa were associated with higher rates of victimization.* **Conclusions:** *In sum, the significantly higher rates of both sexual and aggravated assault among women with bulimia nervosa compared with women without such a diagnosis support the hypothesis that victimization may contribute to the development and/or maintenance of bulimia nervosa.* *© 1997 by John Wiley & Sons, Inc.*
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A number of researchers have investigated the relationship between sexual assault and the development and/or maintenance of bulimia nervosa (BN). In recent review articles, Pope and Hudson (1992) concluded that there is little evidence that childhood sexual trauma is a risk factor for BN and Conners and Morse (1993) stated that the overall rate

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of sexual abuse among individuals with an eating disorder is comparable to the rate of sexual abuse in the general population. In addition, in three recent studies, authors concluded that childhood sexual assault was not a significant risk factor in the development of BN (Kinzl, Traweger, Guenther, & Biebl, 1994; Pope, Mangweith, Negrao, Hudson, & Cordas, 1994; Rorty, Yager, & Rossotto, 1994). However, these studies include methodological limitations such as no comparison group (Pope et al., 1994; Kinzl et al., 1994), small sample size (Pope et al., 1994; Rorty et al., 1994), limited age range of participants (Kinzl et al., 1994; Pope et al., 1994; Rorty et al., 1994), nonrandom sampling (Kinzl et al., 1994; Pope et al., 1994; Rorty et al., 1994), and/or failure to assess physical assaults which occurred in the absence of sexual assault experiences (Rorty et al., 1994).

When all the research findings concerning the co-occurrence of sexual trauma and eating disorder are considered together, an overwhelming majority of researchers interpreted their results as demonstrating that while sexual trauma may not be a sole *causal factor* for eating disorders, it appears to be a *risk factor* (Beckman & Burns, 1990; Bulik, Sullivan & Rorty, 1989; Calam & Slade, 1989; Goldfarb, 1987; Garfinkel et al., 1995; Hall, Tice, Beresford, Wooley, & Klassen, 1989; Hastings & Kern, 1994; McClelland, Mynors-Wallis, Fahy, & Treasure, 1991; Miller, McCluskey-Fawcett, & Irving, 1993; Oppenheimer, Howells, Palmer, & Chaloner, 1985; Palmer, Oppenheimer, Dignon, Chaloner, & Howells, 1990; Palmer & Oppenheimer, 1992; Root & Fallon, 1988; Sloan & Leichner, 1986; Steiger & Zanko, 1990; Waller, 1991; Wonderlich, Wilsnack, & Wilsnack, 1995). Furthermore, the topic of sexual trauma among eating-disordered individuals remains a central focus of many research investigations. This controversy is likely due to methodological differences between investigations, including operational definitions of sexual assault and sampling techniques. As noted by Conners and Morse (1993), one difficulty in interpreting existing evidence concerning sexual assault and eating disorders is that a majority of the populations sampled were either treatment seeking or college students. For instance, Root and Fallon (1988) studied women seeking treatment for BN; Hall and colleagues (1989) assessed inpatients diagnosed with eating disorders; and Steiger and Zanko (1990) compared eating-disordered outpatients with other psychiatric outpatients and nontreatment-seeking controls.The prevalence of disordered eating and sexual abuse in college students was examined by a number of researchers (Beckman & Burns, 1990; Calam & Slade, 1989; Bailey & Gibbons, 1989; Smolak, Levine, & Sullin, 1990). To date, no one has studied the relationship between sexual assault and BN in a national, representative sample of women.

How sexual assault and BN were operationally defined varies greatly among studies. Some researchers only examined childhood sexual trauma (e.g., Palmer et al., 1990), whereas others included noncoercive sexual acts as abuse (e.g. Beckman & Burns, 1990). Additionally, as Conners and Morse (1993) pointed out the diagnostic criteria utilized to identify eating-disordered groups vary greatly from study to study. Thus, it is impossible to make accurate generalizations based on studies with such discrepant methodologies.

In addition to these difficulties, the relationship between other types of victimization besides sexual assault, such as, aggravated assault and BN has been largely neglected by researchers. This may be due to the fact that many researchers were interested in examining childhood sexual abuse as an etiological factor in the development of BN, and researchers may conceptualize aggravated assaults as occurring more frequently during adulthood. Although identifying possible etiological factors for BN is important, it is also critical to examine the extent to which different types of victimization and BN occur together. Scant data also exist regarding the relationship between posttraumatic stress disorder (PTSD) and eating disorders. A number of researchers have examined the pres-

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ence of anxiety symptoms among eating-disordered patients (Steere, Butler, & Cooper, 1990; Williamson et al., 1987), but no one has specifically evaluated the comorbidity of PTSD and eating disorders. Additionally, it is important to determine whether PTSD functions as a mediator between victimization and BN. The possibility exists that victimization is only associated with BN due to the relationships between victimization and PTSD and between PTSD and BN.

Research also suggests that the presence of assault characteristics such as the perception of life threat and physical injury can greatly affect prevalence rates of certain psychiatric disorders such as PTSD (Resnick, Kilpatrick, Dansky, Saunders, & Best, 1993). Therefore, is it conceivable that the same is true for BN in that individuals with BN may have experienced rapes that were perceived to be more life threatening or that resulted in higher levels of physical injury. Several researchers have explored assault characteristics such as repetitive or series sexual assaults, but not in any systematic fashion. It is possible that certain rape characteristics are more closely associated with BN than others and that careful assessment of such characteristics by researchers and clinicians may be warranted (Bulik et al., 1989).

Furthermore, it is possible that particular characteristics of eating disorders are more closely associated with a history of sexual abuse than others. Waller (1991) found that women classified with restricting anorexia nervosa had lower rates of sexual abuse in their history than women with nonrestricting BN. Based on this finding, the author speculated that a history of sexual abuse may determine the *nature* of the eating disorder that develops, as opposed to being the risk factor responsible for the development of an eating disorder in the first place. Therefore, the relationship between victimization and certain types of disordered eating behaviors was explored in the present investigation.

Finally, since binge eating disorder (BED) was a proposed diagnostic category for the 4th ed. of the *Diagnostic and statistical manual of mental disorders* (DSM-IV; American Psychiatric Association [APA], 1994) and is still under investigation as a potential diagnosis, it is important to examine whether individuals with BED differ from those diagnosed with BN or those without an eating disorder with respect to victimization history (Williamson et al., 1987). Thus, the central goals of the present study were to (1) determine the prevalence of victimization among women diagnosed with BN or BED, as compared with nonbulimic/nonbinge eating-disordered women; (2) evaluate the nature of any relationships among victimization, eating disorders, and PTSD; and (3) illuminate any characteristics of disordered eating which may be more highly associated with a victimization history.

METHODS

Participants

A national household probability sample of 3,006 women were participants in the third wave of the National Women's Study. Respondents completed structured telephone interviews of approximately 40 min duration during which they were screened (in the following order) for sexual harassment, major depression, trauma history, dieting behavior, BN, BED, alcohol and drug use, PTSD, and demographics. Only data regarding eating disorders, victimization, and PTSD were analyzed in the present study. The mean age for the weighted sample was 46.1 years ($SD = 17.3$), and the weighted sample was predomi-

nantly Caucasian (86%) with a mostly African American minority group (11%), which reflects the racial composition of American women.

Sampling Procedures

The original sample of 4,009 female adults (Wave 1 sample) was generated by multistage geographic sampling procedures, wherein stratified samples of counties in four regions of the country were generated as primary sampling units during the first of a two-stage sampling procedure. The second stage of the sampling procedure involved systematic selection of residential telephone exchanges within the primary sampling units. Random digit dialing was used to target households within each strata. To ensure random selection within a household, the female adult with the most recent birthday was interviewed (for further details see Resnick et al., 1993).

Wave 3 interviews occurred between January and May 1992, and interviews were conducted by Schulman, Ronca, and Bucuvalas (SRBI), a New York-based survey research firm. Only well-trained, experienced female SRBI interviewers were used. Interviewers were blind to the purpose of the investigation. The consent and completion rate for designated respondents in Wave 1 was 85.2%, and 75% of the Wave 1 participants completed the Wave 3 interview. A majority of the respondents who were lost to attrition was due to a failure to locate those respondents, rather than their refusal to participate. Since the original sample was identified in 1989, the data were weighted according to estimates of the 1989 United States Census figures for age and race. The weighting program was used to ensure that sample data were representative of women in the U.S. population.

Survey Instrument

BN and BED Screening

The following question was used to screen for BN and BED: ''Sometimes people will overeat on holidays or special occasions and feel guilty about it afterwards. Not counting those types of situations, have you ever had an episode where you felt out of control about your eating and ate much more food in one sitting than most people?'' Participants who responded affirmatively were then asked their age when they first had an episode of this type of eating, how often they had such episodes during their ''worst period,'' how long their worst period lasted, when they most recently had an episode, whether they considered the episodes to be binges, and whether they used compensatory methods (vomiting, laxatives, diuretics, or excessive exercise).

Respondents who indicated that they binged for 3 or more months were asked about the characteristics of their binges (eating more rapidly than usual, eating until they were uncomfortably full, eating large amounts of food throughout the day with no planned meals, eating alone due to embarrassment by how much they were eating, eating due to feeling disgusted, depressed, or guilty with themselves). These characteristics were based on the proposed DSM-IV indicators of a loss of control as outlined in the criteria for BED. Finally, respondents provided their current weight, height, frequency with which they weighed themselves, subjective ratings of the amount they need to lose to be ''just right,'' and their level of satisfaction with their weight.

A diagnosis of BN was assigned to respondents who met the following criteria:

1. Episodes of eating large amounts of food in a brief time period.

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2. During their worst period, the episodes occurred at least several times each week.
3. Worst period lasted at least 3 months.
4. Engaged in at least two types of binge eating behaviors which are indicators of a loss of control as outlined in the proposed DSM-IV criteria for BED.
5. Compensation for a binge by excessive exercise, vomiting, and laxative or diuretic use.

A diagnosis of BED was given to respondents who met all of the criteria for BN but indicated that they did not engage in compensatory behaviors and their worst period of binging lasted for at least 6 months.

Victimization Screening

Participants responded to the following screening questions:

> Another type of stressful event that many women have experienced is unwanted sexual advances. Women do not always report such experiences to the police or discuss them with family or friends. The person making the advances isn't always a stranger, but can be a friend, boyfriend, or even a family member. Such experiences can occur anytime in a woman's life—even as a child. Regardless of how long ago it happened or who made the advances. . . .
>
> 1. Has a man or boy ever made you have sex by *using force* or threatening to harm you or someone close to you? Just so there is no mistake, by sex we mean putting a penis in your vagina.
> 2. Has anyone ever made you have oral sex *by force or threat of harm.* Just so there is no mistake, by oral sex we mean that a man or boy put his penis in your mouth or someone penetrated your vagina or anus with their mouth or tongue.
> 3. Has anyone ever made you have anal sex *by force or threat of harm?*
> 4. Has anyone ever put fingers or objects in your vagina or anus against your will *by using force or threats?*

Participants who endorsed any of the above items were asked about their first completed rape, their most recent completed rape, and their worst completed rape experience (if the worst one was different from the first and most recent rapes). They answered questions pertaining to their age at the time of the rape, whether the rape was a single event or a series of events, their relationship with the perpetrator, whether they feared that they might have been killed or seriously injured during the incident, and degree of physical injury sustained.

In the ''contact sexual molestation'' section of the interview participants responded to the following opening question:

> In addition to these types of incidents, sometimes women can experience unwanted sexual advances that do not involve sexual penetration, but do involve some type of sexual touching or fondling. These types of incidents can occur anytime in a woman's life, including when she is a child or a teenager. The incidents may not have been reported to the police or other authorities and a woman may not have even told anyone about them. The person making the unwanted sexual advances may not be a stranger, but can be a friend, neighbor, relative, boyfriend, or even a close family member.

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> (Not counting the incidents you have already told me about) Has anyone ever touched your breasts or pubic area or made you touch his penis *by using force or threat of force?*

Participants classified as ''contact sexual assault victims'' were those whose sexual assault did not involve any vaginal penetration but did involve contact with their or the perpetrator's breast or genital areas.

The introductory question in the ''nonsexual contact/attempted sexual assault'' section was as follows:

> Other than the incidents that we've already discussed, have there been any other situations that did not involve actual sexual contact between you and another person, but did involve an attempt by someone to *force you* to have any kind of unwanted sexual contact?

Respondents in this category were those who had experienced an attempted sexual assault but no actual physical contact was made with their or the perpetrator's breast or genital areas.

''Aggravated assault'' was measured by asking respondents the following screening questions:

> Another type of stressful event women sometimes experience is being *physically* attacked by another person. *Not counting any incidents already described to me,* has anyone—including family members or friends—ever attacked you with a gun, knife, or some other weapon, regardless of when it happened or whether you ever reported it or not?
>
> Has anyone—including family members or friends—ever attacked you without a weapon, but with the intent to kill or seriously injure you?

''Direct assault'' included any incident of rape, molestation, attempted sexual assault, or aggravated assault.

PTSD Screening

PTSD was assessed using the National Women's Study (NWS) PTSD module (Resnick et al., 1993; Robins, Helzer, Croughan, & Ratcliff, 1981). The NWS PTSD module was modified from the Diagnostic Interview Schedule (DIS) used in the National Vietnam Veterans Readjustment Study (NVVRS; Robins et al. 1981; Kulka, Schlenger, Fairbank, et al., 1990). Participants were screened for symptoms of PTSD (using criteria outlined in the 3rd rev. ed. of the *Diagnostic and statistical manual of mental disorders* [DSM-III-R; APA, 1987]), regardless of whether they had experienced an event which met PTSD-Criterion A (an event outside of range of usual human experience that would produce marked distress in almost anyone). Subjects were classified as meeting Criterion A, the necessary stressor criterion for PTSD, if they reported the occurrence of at least one traumatic event (i.e., indirect victimization due to homicide of a significant other, major accidents, natural disasters, direct sexual or physical assault, etc.) at some time during their lives. The remaining symptom criteria were obtained via a structured interview schedule to assess intrusive symptoms, symptoms of avoidance, and symptoms of increased arousal.

The PTSD measure was prefaced with the following: ''People experience a variety of

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moods and feelings from time to time. In your case, has there ever been a period of a month or more during which . . . .'' Statements following this probe were specifically phrased to assess symptom presence such as ''you had repeated bad dreams or nightmares.'' Lifetime PTSD was assigned if a respondent ever met the DSM-II-R criteria by having the necessary number of Criterion B (one re-experiencing), C (three avoidance), and D (two increased arousal) symptoms. Current PTSD was assigned if a respondent met criteria for PTSD within six months of the telephone interview. Concurrent validity obtained from a slightly modified version of the NWS PTSD module with the SCID-PTSD module administered by trained clinicians was good with a kappa of .77 for Lifetime PTSD. Reliability of the PTSD diagnostic interview also was acceptable (Dansky, Brady, Saladin, Kilpatrick, & Resnick, 1995; Resnick et al., 1993).

Statistical Analyses

The variables measured in this study can be categorized in three groups: (1) victimization history, (2) eating disorders, and (3) symptoms of PTSD. Data analyses were conducted to accomplish the following two goals: (1) descriptive analysis and (2) hypothesis testing. Prevalence rates were generated in order to provide information about the frequency of occurrence of all three groups of variables. Comparisons between respondents with and without eating disorders were performed using the chi-square statistic, and Fisher's exact tests were used for *post hoc* analyses when any cell size was below 5. As described below, a hierarchical logistic regression was calculated to test the extent to which victimization and PTSD were independently and interactively related to BN. All statistical procedures were performed using the SPSS 5.0 software (Norusis, 1992).

RESULTS

Lifetime Prevalence Data

Overall, 13.6% of the respondents reported a rape had occurred at some point during their lives. The lifetime prevalence rates for sexual molestation, nonsexual contact/attempted sexual assault, and aggravated assault were as follows: 12.3%, 9.5%, and 8.9%, respectively. Additionally, when all categories of direct assault were collapsed into one, 31.7% of the respondents reported some type of direct victimization.

The lifetime prevalence rates for BN and BED were 2.4% and 1.0%, respectively, and are reported in more detail elsewhere (Brewerton & Dansky, 1995). Respondents were classified in one of three categories: BN, BED, or not meeting criteria for BN or BED (NonBN/NonBED). The prevalence rates of direct assaults among BN, BED, and NonBN/NonBED respondents are presented in Table 1.

Group Comparisons for Direct Assault

Chi-square analyses were conducted to compare the proportion of respondents with victimization histories in the BN, BED, and NonBN/NonBED groups. Overall, there was a significant difference among the three groups regarding the proportion of rape to nonrape victims [$\chi^2(2) = 10.6$, $p < .01$]. Further chi-square analyses calculated to identify significant differences between each group revealed that the proportion of rape victims was significantly higher among the BN respondents as compared with NonBN/NonBED respondents [post hoc $\chi^2(1) = 9.05$, $p < .01$; 26.6% vs. 13.3%; Table 1]. There were no

Table 1. Prevalence of direct assault among bulimia nervosa (BN), binge eating disorder (BED), and NonBN/NonBED respondents

	BN (n = 72)	BED (n = 30)	NonBED/NonBN (n = 2,929)
Completed rape	26.6%[1]	11.5%	13.3%
Contact sexual molestation	22.0%[2]	12.9%	12.1%
Nonsexual contact/attempted sexual assault	10.7%	17.3%	9.3%
Aggravated assault	26.8%[3,4]	9.3%	8.5%
Direct crime victimization	54.4%[5]	43.3%	31.0%

Note: Post hoc chi-square analyses: [1]BS vs. NonBN/NonBED $X^2(1) = 9.05$ $p < .01$; [2]BN vs. NonBN/NonBED $X^2(1) = 5.83$, $p < .05$; [3]BN vs. NonBN/NonBED $X^2(1) = 25.68$, $p < .001$; [4]BN vs. BED Fisher's exact = 0.053 (marginal); [5]BN vs. NonBN/NonBED $X^2(1) = 16.41$, $p < .001$.

significant differences in rape prevalence between BN and BED respondents or between BED and NonBN/NonBED respondents.

Differences among the three groups were also found for contact sexual molestation and aggravated assault [overall $\chi^2(2) = 6.37$, $p < .05$ and $\chi^2(2) = 29.12$, $p < .001$, respectively]. As can be seen in Table 1, the BN respondents were significantly more likely to have reported a sexual molestation than NonBN/NonBED respondents [post hoc $\chi^2(1) = 5.83$, $p < .05$; 22.0% vs. 12.0%], but no other group differences were found for this variable. A greater proportion of the BN respondents reported an aggravated assault than NonBN/NonBED [post hoc $\chi^2(1) = 25.68$, $p < .001$; 26.8% vs. 8.5%] or BED respondents [post hoc Fisher's exact = .053; 26.8% vs. 9.3%], although BED and NonBN/NonBED respondents did not differ with respect to the prevalence of aggravated assault.

When respondents were categorized in terms of whether they had experienced any type of direct victimization or not, significant differences were found among the three comparison groups [overall $\chi^2(2) = 19.61$, $p < .001$]. BN respondents were significantly more likely to have reported some type of direct assault experience than NonBN/NonBED respondents [post hoc $\chi^2(1) = 16.41$, $p < .001$; 54.4% vs. 31.0%], while no other group differences were detected.

Rape Characteristics

Since respondents were asked to provide detailed information about their completed rape experiences, characteristics of respondents' first, most recent, and worst rape experiences were combined and analyzed. Of the 413 participants in the entire weighted sample who had experienced a rape, 15.9% reported having experienced two rapes and 31.9% reported three or more rapes during their lifetime. Among rape victims, 37.4% reported that they had experienced at least one rape prior to their 12th birthday (childhood rape; n = 150), 30.9% had been assaulted at or between age 12 and 17 (adolescent rape; n = 124), and 31.7% had been assaulted at age 18 or older with no childhood rape experience (adult rape; n = 127). Regarding series assaults, wherein the same perpetrator raped the respondent more than once, 42% of the rape victims indicated that at least one of their rapes was a ''series'' rape. Moreover, 48.3% of the rape victims indicated that at least one rape had involved the perception of life threat and 37.9% reported at least one rape had resulted in physical injury. The breakdown of rape victims by type of rape penetration was as follows: 77.5% penile-vaginal rape, 29.0% oral rape, 8.5% anal rape,

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and 45.5% digital rape. (Note: as mentioned above, 47.8% of the rape victims reported rape characteristics for more than one rape.)

Analyses were calculated between respondents in the eating groups to address whether specific characteristics of sexual abuse are associated with disordered eating. Since the number of rape victims with BED was less than 5, the chi-square analyses were limited to comparing rape victims with BN and those without BN or BED (Table 2). Completed rape victims with BN and those in the NonBN/NonBED group were compared for the following rape characteristics with no significant differences observed: penile-vaginal, oral, anal, digital, series, life threat, physical injury, and familial rape (Table 2).

When rape victims with BN and those without BN or BED were compared for the proportion of rapes occurring during childhood, no significant differences were detected. However, a significantly greater proportion of all women in the BN group (12%) as compared with all women in the NonBN/NonBED group (5%) had at least one childhood rape [i.e., rape occurred before age 12; $\chi^2(1) = 4.48$, $p < .05$]. There was no significant difference between these two groups regarding the proportion of women who experienced their first (or only) rape during adolescence (ages 12–17) or adulthood (age 18 or older). Furthermore, the average age at which participants were first raped was 14.7 ($SD = 8.1$), whereas the average age at which participants first binged was 27.6 ($SD = 14.3$).

Since the age variables likely were affected by the weighting program (which was designed to further enhance the representativeness of the sample), the ages of onset for binging and first rape experience were recalculated with unweighted data (which included the representative sample and the oversample of women aged 18–34). The average age of onset of binging in this unweighted sample was 23.58 ($SD = 11.29$) for all respondents who reported binging and 21.39 ($SD = 10.73$) for respondents with BN. The average age of first rape for all respondents was 14.58 ($SD = 7.61$) and 14.7 ($SD = 8.05$) for respondents with BN. Of the 23 respondents with BN (unweighted data) who reported a rape experience, 65% ($n = 15$) reported that their first binge occurred after their first rape experience, and 8.7% reported the same age for their first rape and first binge. More than three fourths (77.8%) of the women with BN who experienced a childhood rape (rape below age 12) were raped prior to their first binge episode. Unfortunately, data were not available concerning age of first sexual molestation experience and first aggravated assault. Therefore, it is impossible to determine the time sequencing of any type of victimization and onset of binging. However, it appears that in a majority of cases wherein respondents with BN reported a rape, the rape predated the onset of binging.

Table 2. Rape characteristics in rape victims with bulimia nervosa (BN) and those without BN or binge eating disorder (BED)

	BN ($n = 19$)	NonBED/NonBN ($n = 391$)
At least one childhood rape	44.6%	37.1%
At least one adolescent rape	21.9%	31.4%
Penile-vaginal rape	90.7%	76.9%
Oral rape	36.9%	28.8%
Anal rape	7.5%	8.6%
Digital rape	62.7%	44.9%
Series rape	54.6%	41.6%
Rape with perception of life threat	66.5%	47.2%
Rape with physical injury	49.7%	37.4%
Rape by a family member	55.4%	35.9%

Characteristics of Disordered Eating

To test the relationship between certain disordered eating behaviors and victimization, respondents who endorsed the binge eating screening were classified as High Bingers if (during their worst period) they reported binging at least several times a week or Low Bingers if they binged once a week or less. When the prevalence rates for rape, sexual molestation, attempted sexual assault, aggravated assault, and all direct assault for High and Low Bingers were compared with chi-square analyses, no group differences were detected.

Respondents who indicated that they had used at least one method of compensating for a binge were grouped into high and low groups; ''High Compensators'' were those who used two or more methods of compensating for a binge, whereas ''Low Compensators'' used one method to purge. It was impossible to classify respondents according to the frequency with which they compensated, because this information, unfortunately, was not collected. In contrast to the findings obtained with High versus Low Bingers (no group differences), there were significant differences found between High and Low Compensators. Specifically, the proportion of rape victims among High Compensators was almost twice as high as among Low Compensators [$\chi^2(1) = 10.99$, $p < .001$; 31.0% vs. 15.5%]. Likewise, a significantly higher rate of aggravated assault was observed among the High Compensators as compared with the Low Compensators [$\chi^2(1) = 6.27$, $p < .05$; 18.3% vs. 8.9%]. No group differences were found for sexual molestation, attempted sexual assault, or direct victimization in general.

A third set of analyses in which disordered eating behaviors were examined entailed classifying respondents as ''High Loss of Control'' (three or more indices of a loss of control) or ''Low Loss of Control'' (one or two indices of a loss of control). Similar to the results with High and Low Compensators, the proportion of rape victims was almost twice as high among respondents in the High Control Behavior than the Low Control Behavior group [$\chi^2(1) = 5.83$, $p < .05$; 22.1% vs. 11.1%]. In addition, the prevalence of nonsexual contact/attempted sexual assault was significantly higher in the High Control Behavior group as compared with Low Control Behavior group [$\chi^2(1) = 4.95$, $p < .05$; 14.3% vs. 6.0%]. When the prevalence of direct assault in general was examined for respondents in the High and Low Control Behavior groups, it was found that 50.8% of the respondents in the High Control Behavior group reported a direct assault, whereas 32.4% of respondents in the Low Control Behavior group reported such an experience [$\chi^2(1) = 9.63$, $p < .01$]. Comparisons for sexual molestation and aggravated assault yielded nonsignificant results.

Finally, although specific characteristics of victims' rape experience did not appear to be associated with BN or BED, it was hypothesized that certain elements of a rape may be associated with particular types of disordered eating behaviors. Chi-square analyses were calculated to test whether vomiting was associated with oral rape and whether laxative use was related to anal rape. The results of these analyses were nonsignificant.

PTSD

The proportion of respondents with and without a history of Lifetime and Current PTSD were compared by chi-square analyses among respondents in the BN, BED, and NonBN/NonBED groups (Figure 1). There were significant differences among respondents in the BN, BED, and NonBN/NonBED groups for Lifetime PTSD [overall $\chi^2(2) = 42.07$, $p < .001$; 36.9%, 21.0%, and 11.8%, respectively] in that the prevalences of Lifetime PTSD were higher among respondents in the BN group as compared with respondents in

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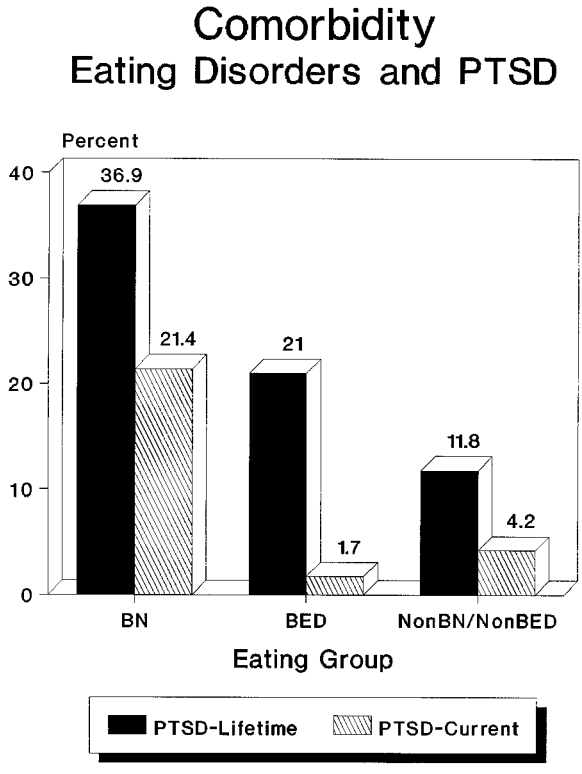

Figure 1. Comorbidity of eating disorders and posttraumatic stress disorder.

the NonBN/NonBED group [post hoc $\chi^2(1) = 40.31$, $p < .001$]. Slightly different results were obtained for the prevalence of Current PTSD among the three groups [overall $\chi^2(2) = 48.62$, $p < .001$; 21.4%, 1.7%, and 4.2%, respectively]; respondents with BN were significantly more likely to have PTSD than respondents with BED [post hoc $\chi^2(1) = 6.2$, $p < .05$] or those in the NonBN/NonBED group [post hoc $\chi^2(1) = 47.77$, $p < .001$]. The rate of Current PTSD in women with BN is remarkable in that respondents with BN were 13 times more likely than respondents with BED and 5 times more likely than respondents without BN or BED to have PTSD within the 6 months prior to their interview.

To further examine relationships among victimization, PTSD, and BN, analyses were conducted with respondents classified in one of three groups: direct victims with a lifetime history of PTSD (Victim + PTSD; $n = 256$), direct victims negative for PTSD (Victim − PTSD; $n = 691$), and nonvictims (Nonvictim; $n = 2{,}054$). The prevalence of BN among respondents with a history of victimization + PTSD (7.9%) was significantly higher than the prevalence rates of BN among respondents in the Victim − PTSD and Nonvictim groups [2.7% and 1.6%; $\chi^2(2) = 38.68$ $p < .001$]. The comorbidity rates for BN and PTSD and for BN and direct victimization are noteworthy (Figure 2).

Multivariate Analyses

The results of the univariate chi-square analyses described above revealed numerous significant results, including significant associations between (1) direct victimization and BN, (2) PTSD and BN, and (3) direct victimization and PTSD. In order to test the extent to which victimization and PTSD were independently and interactively related to BN, a

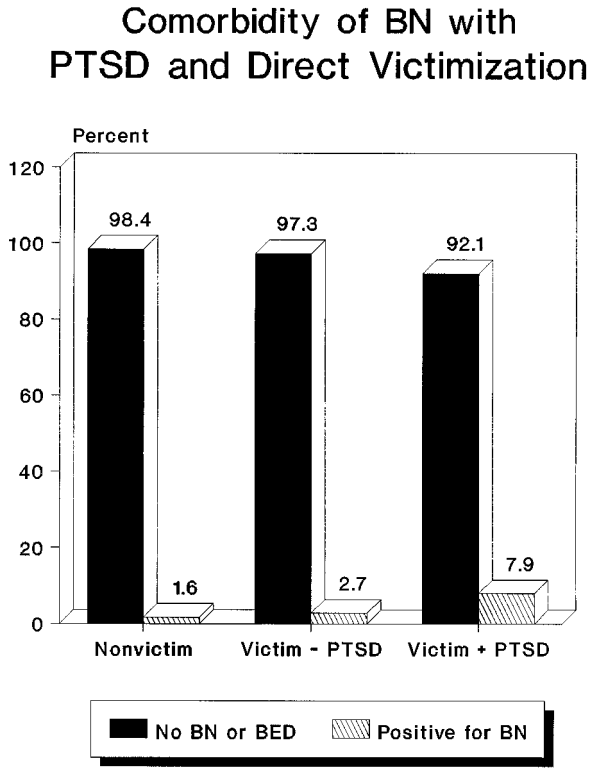

Figure 2. Comorbidity of bulimia nervosa with posttraumatic stress disorder and Direct Victimization.

hierarchical logistic regression model was created. Lifetime PTSD was entered into the regression equation on the first step to assess whether the addition of direct victimization in the second step would significantly improve the model's goodness of fit. In order to maximize cell sizes, the direct crime victim category was utilized, rather than entering each type of victimization (rape, sexual molestation, attempted sexual assault, and aggravated assault). The final step of the regression was the interaction term (Lifetime PTSD × Direct Victimization). The results did not reveal a significant interaction between PTSD and Direct Victimization; and therefore, the final model included the two main effects (Table 3).

Table 3. Logistic regression testing the relationship between posttraumatic stress disorder (PTSD), direct crime, and bulimia nervosa (BN)

Interval	Odds Ratio	Confidence Interval (95%)
Step 1		
PTSD	3.36	1.97–5.73
Step 2*		
Direct crime	1.86	1.12–3.11
Step 3		
PTSD × direct crime	NS	

*Model chi-square improvement $X^2(1) = 5.64$, $p = .02$.

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Direct Victimization added significantly to the model, which already included Lifetime PTSD [chi-square improvement = 5.64 (1), $p < .05$]. Interpretation of the odds ratio for Lifetime PTSD indicates that the odds of having BN was 3.36 times greater among women with PTSD than among women negative for PTSD. Further, the odds of having BN was 1.86 times higher among victims of direct assault (physical and/or sexual assault) than women in the Nonvictim group, controlling for PTSD status. Thus, women with assault histories have a significant risk for suffering from BN even after the influence of comorbid PTSD is controlled.

DISCUSSION

This is the first study to systematically assess the relationship between crime victimization, PTSD, and the eating disorders in a large, nationally representative sample of women. Overall, the analyses demonstrate that when compared to NonBN/NonBED respondents, those respondents with BN had a significantly higher prevalence of rape, sexual molestation, aggravated assault, direct victimization, as well as current and lifetime diagnosis of PTSD. Even when the effect of PTSD was controlled, a higher prevalence of sexual molestation was found among respondents with BN as compared with those without BN or BED. In contrast, the respondents with BED did not differ from NonBN/NonBED respondents for these types of assault. These findings suggest that women diagnosed with BN and women diagnosed with BED differ on important variables such as history of sexual assault or aggravated assault and lend support for further investigation of BED as a diagnostic category.

The results obtained in the current investigation are consistent with Steiger and Zanko's (1990) results in that there was a higher prevalence of sexual assault among women with BN as compared to other types of eating disorders and normal controls. Based on their comparisons of women with BN with those with AN, the authors hypothesized that the etiology of binging may be linked with the experience of trauma, whereas restricting may not. Waller (1991) pointed out that rather than the diagnosis of an eating disorder itself, certain aspects of disordered eating may be associated with sexual abuse. Although results obtained in the current investigation did not support that aspects such as rate of binging and laxative use were associated with sexual abuse, they did in a more broad sense provide support for the hypothesis that specific aspects of disordered eating were more closely associated with sexual assault than others.

Specifically, it appears that purging, rather than binging, may be a central component connected with a history of sexual assault. Since purging is the central difference between BN and BED, and only BN was significantly associated with a history of sexual assault, it can be hypothesized that the purging or compensatory behavior exhibited by women with BN (or the combination of binging with purging) may be the critical aspect associated with past victimization. This hypothesis was further supported by the finding that the prevalence of sexual assault was almost twice as high among respondents who used two or more methods to compensate for a binge as compared with respondents who used one method. However, it was also found that a higher degree of loss of control over eating was associated with a higher prevalence of sexual assault. Therefore, it is unclear whether a history of sexual assault is associated with a particular type of eating behavior or with the severity or chronicity of disordered eating behaviors. This is a question that requires future exploration.

While the data support further examination of particular components of eating disor-

ders that may be associated with sexual assault, particular components or characteristics of rape were not found to be associated with BN or BED. The data did not support the notion that rapes which involved oral-genital contact or were perpetrated by a family member would be more prevalent among eating-disordered women than women not suffering from BN or BED. On the other hand, threefourths of the women with BN who were raped during childhood were raped prior to their first binge. This latter finding contrasts sharply with Pope and his colleagues (1994) finding that childhood sexual abuse predated the onset of BN in 15% of the American cases. The methodological differences between the two studies may account for this discrepancy. Specifically, the Pope et al. (1994) sample included only 33 female college students in Boston with a median age of 20, whereas the present sample included a national sample of 3,006 women with an average age of 46.1. The Pope et al. study entailed in-person interviews, whereas in the present investigation the questions were administered by telephone. Finally, the definition of sexual assault differed in the two investigations. The findings in the present investigation support childhood sexual assault, particularly when accompanied by PTSD, as one possible contributing factor in the development of BN.

When all the findings are considered together, it is difficult to continue to specifically pinpoint childhood sexual abuse as the major etiological factor for disordered eating patterns. However, victimization and PTSD clearly are risk factors to be included in multifactorial models regarding the etiology of BN. It is conceivable that an individual who is already vulnerable by experiencing subclinical disordered eating patterns will endure an exacerbation of the disordered eating in the form of compensatory behaviors when she is faced with coping with victimization. In other words, the addition of victimization to the stresses encountered by the vulnerable individual may result in BN, rather than the subclinical disordered eating patterns which are thought to be prevalent in the general population (Kilpatrick, Saunders, Best, & Von, 1987; Fairburn & Beglin, 1990), among college students (Leon, Carroll, Chernyk, & Finn, 1985; Nevo, 1985), and among grade school children (Childress, Brewerton, Hodges, & Jarrell, 1993).

Additionally, the current findings that respondents with BN had higher rates of Lifetime PTSD than respondents without BN or BED support further research into the nature of the relationship between eating disorders and anxiety disorders. Whether respondents developed both PTSD and an eating disorder after experiencing a traumatic event or the disordered eating was a response to heightened anxiety associated with PTSD is a question which merits further investigation. Regardless of the direction of the association between eating disorders and PTSD, the findings that (a) 1 in 3 respondents with BN had PTSD during their lifetime, (b) 1 in 5 respondents with BN had Current PTSD, and (c) 1 in 5 respondents with BED had a lifetime history of PTSD suggest that treatment protocols for eating-disordered patients include assessment and interventions, if necessary, for PTSD.

Future research in this area should target a broader sample, including men, women, adolescents, and children in the general population. Furthermore, it would be important to assess all types of eating disorders (including anorexia nervosa) and to focus on the sequencing of the development of eating disorders and when victimization experience(s) occurred. Moreover, rape characteristics and details concerning disordered eating patterns should be carefully measured, since how these features are related remains unclear.

Several methodological limitations may have influenced the present results. First, the generalizabiltiy of the results is restricted to women, since men were not included in the sample. However, previous research has demonstrated that the majority of both sexual assault victims and eating-disordered individuals are female. In addition, it is highly

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likely that the women in the present sample are representative of women in the United States due to the rigorous sampling methods employed in selecting the study participants. The present results also are subject to limitations that accompany the use of retrospective measures, for example, negative response set and selective memory. These are limitations encountered in any research that is not a prospective design or direct observation. Furthermore, the questionnaire did not include questions designed to determine the age of onset of all types of victimization or BN, and therefore, no statements can be made regarding the extent to which victimization contributed to the development of BN. Finally, it is conceivable that a confounding variable that was not measured in this study may account for any relationship between victimization/PTSD and BN. Despite these limitations, the results from the current investigation clearly indicate that future research concerning all types of victimization and eating disorders is important and necessary.

Clinical exploration of issues associated with victimization among eating-disordered patients seems warranted. Oppenheimer and colleagues (1985) suggest that sexual victimization may lead a girl or woman to feel revulsion about her body in ways that may intermix with concerns about body weight, shape, and size (Hall et al., 1989). Moreover, a number of authors have pointed out that women with a history of sexual abuse and those with eating disorders may have difficulties with intimacy, trust, anger, and negative perceptions of their bodies (Oppenheimer et al., 1985; Palmer & Oppenheimer, 1992; Leon et al., 1985). Therefore, addressing issues such as anger and powerlessness and providing behavioral methods of reducing anxiety may target difficulties associated with both the eating disorder and the aftermath of victimization.

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SPECIAL REPORT

Pharmacotherapy for Patients With Eating Disorders

by Timothy D. Brewerton, M.D.

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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 $5\text{-}HT_2$-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.

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Psychiatry Research 62 (1996) 31–42

PSYCHIATRY RESEARCH

Studies of serotonin function in anorexia nervosa[1]

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Abstract

Neuroendocrine, temperature, test-meal, and psychometric responses are reviewed following challenges with the post-synaptic 5-HT receptor agonist *m*-chlorophenylpiperazine (*m*-CPP), the 5-HT precursor L-tryptophan (L-TRP), and placebo in 12 patients with anorexia nervosa (AN) and 16 healthy controls. A subset of the AN patients ($n = 8$) were rechallenged 3–4 weeks after attaining a predetermined goal weight. AN patients had blunted prolactin (PRL) responses to both *m*-CPP and L-TRP at low-weight and at goal-weight in comparison to controls, although there was a tendency toward normalization with weight gain. There were trends for blunted growth hormone (GH) responses following both L-TRP and *m*-CPP in the low-weight but not the goal-weight AN patients. Cortisol (CORT) responses following *m*-CPP and L-TRP were not significantly different among any of the groups. Temperature and test-meal measures were largely unaffected by serotonergic agents in the patients, although *m*-CPP decreased meal size in the controls. Psychometric responses were variable and are briefly described. Taken together, these findings indicate that responsiveness in post-synaptic hypothalamic-pituitary serotonergic pathways is altered in AN patients. Although there were some trends toward normalization of responsiveness following goal-weight attainment, many differences tended to persist in the patients despite an average increase of 13 kilograms. These may represent changes in serotonergic function at levels in the CNS "above" the hypothalamus.

Keywords: Meta-chlorophenylpiperazine; Tryptophan; Prolactin; Growth hormone

1. Basic mechanisms: focus on serotonin

A theory of serotonin (5-hydroxytryptamine, 5-HT) dysregulation has been proposed for the eating disorders, including anorexia nervosa (AN) (Brewerton et al., 1987, 1990; Brewerton, 1993, 1995). This is based on data linking 5-HT to alterations in eating behavior, mood, anxiety, body image, and neuroendocrine control, all of which have been discussed in more detail elsewhere (Blundell 1984, 1986; Brewerton et al., 1990, 1992a; Jimerson et al., 1990a, 1990b, 1992; Brewerton, 1993; 1995). AN and depressive illness have been noted to have overlapping signs and symptoms, family histories and neuroendocrine abnormalities which may be associated with 5-HT dysfunction (Brewerton et al., 1990; Brewerton, 1993, 1995; Kaye et al., 1984a; Halmi,

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Eckert and La Du, 1986; Jimerson et al., 1990b). In addition, there appears to be an association between AN, anxiety and its disorders (Brewerton, Hand and Bishop, 1993; Brewerton, 1995), such as obsessive-compulsive disorder (OCD) (Kaye et al., 1991b; Pigott et al., 1991; Halmi et al., 1991), which is also reported to be linked to 5-HT dysfunction (Insel et al., 1985; Zohar and Insel, 1987). Furthermore, 5-HT is known to modulate several hormones which have been reported to be dysfunctional in AN patients, including corticotropin releasing hormone (CRH) and related hormones (Gerner et al., 1984; Gold et al., 1986), gonadotropins (Russell, 1967), arginine vasopressin (AVP) (Gold et al., 1983) as well as prolactin (PRL) (Brewerton et al., 1990, 1992a).

2. Methods

Given the data implicating serotonergic involvement in the clinical and neuroendocrine features of AN, Brewerton and colleagues (1990) at the National Institute of Mental Health (NIMH) measured a variety of responses to the 5-HT agonist *m*-chlorophenylpiperazine (*m*-CPP) and the 5-HT precursor L-tryptophan (L-TRP) in comparison to placebo as a means of evaluating central 5-HT function in patients with eating disorders, including 12 with AN (mean age = 26.8 ± 5.3 years; mean weight = 35.7 ± 4.6 kg), as well as 16 healthy age-matched women (mean age = 25.6 ± 5.9 years, NS, unpaired *t*-test; mean weight = 57.5 ± 6.3 kg, $P \leqslant 0.0001$). At the time of admission all patients met DSM-III and DSM-III-R criteria (retrospectively) for AN (American Psychiatric Association, 1987). Ten of the 12 low-weight anorexic patients met DSM-III-R criteria for bulimia nervosa (BN), and of the 8 restudied, 7 had BN. Normal controls were free of any present or past major psychiatric illness as determined by the SADS-L (Schedule for Affective Disorders and Schizophrenia — Lifetime Version; Spitzer and Endicott, 1975). Controls also had no history of obesity or major psychiatric disorder in a first degree relative. Each subject gave written informed consent and was studied at the NIMH Clinical Center Eating Disorders Unit after overnight bedrest and caloric fast. All subjects were inpatients, were metabolically stable, and had been abstinent from fasting, binge eating, purging, and exercise for at least 3–4 weeks. Subjects had also been off all medications for at least 4 weeks by the time of initial drug challenge. The caloric intake for all AN patients was initially prescribed as approximately 30 kcal/kg per day in an attempt to maintain weight ± 1 kg of admission weight until after the initial research phase. Patients were then prescribed food so as to increase weight by at least 1.4 kg per week until a predetermined goal weight was reached (based on the 10th percentile from the Frisch tables plus 5 pounds). Double-blind administration of *m*-CPP (0.5 mg/kg, p.o.), L-TRP (100 mg/kg, i.v.), or placebo was performed on separate days in random order at least 2 days apart. Blood was drawn for neuroendocrine analysis, and temperature and vital signs were obtained throughout the course of each study day. The detailed methods of these studies have been described previously (Brewerton et al., 1988, 1992a, 1992b).

A variety of psychometric instruments were also employed during each study day in order to assess the effects of serotonergic agents versus placebo on mental states. In this article we present data obtained from 100 mm visual analog scales (VAS), which were designed to rate the degree (from "not at all" to "extremely") of a variety of feeling states (anxious, distressed, hungry, urge to eat, fat, full, helpless, tense, sad and confused). These scores were obtained at baseline and then every 30 min up to 210 min after drug administration and immediately following a standardized test-meal consisting of 3500 kcal (Brewerton et al., 1994).

For the purposes of this article, all data were analyzed for a time effect (R) using repeated measures analysis of variance (RANOVA) with diagnosis (Dx) and treatment (Tx) as grouping variables. Separate analyses were done for *m*-CPP versus placebo, and L-TRP versus placebo. All variances are reported as standard deviations (SD).

3. Results

3.1. Neuroendocrine responses

3.1.1. Prolactin and cortisol

We have previously reported that prolactin (PRL) responses following *m*-CPP and L-TRP are blunted in AN patients (Brewerton et al., 1990). Although there was a trend toward normalization with weight gain, goal-weight patients also had significantly blunted responses. Cortisol (CORT) responses were not significantly different from controls at either weight phase following either agent.

3.1.2. Growth hormone

The growth hormone (GH) responses following *m*-CPP and L-TRP in a subset of AN patients and controls are shown in Figs. 1 and 2, respectively. No statistically significant differences were found over time for either diagnosis, treatment, or their interaction following *m*-CPP. A clearer stimulatory effect for L-TRP was seen at both weight phases (low-weight AN: $P \leqslant 0.0009$, RANOVA; goal-weight AN: $P \leqslant 0.002$), although no significant time × diagnosis effect was observed. However, trends for significant differences in response pattern by diagnosis were seen between the low-weight AN patients and controls following both *m*-CPP ($P \leqslant 0.07$) and L-TRP ($P \leqslant 0.07$) (see Figs. 1 and 2).

3.2. Temperature responses

Oral temperature readings were analyzed over time by diagnosis and treatment using RANOVA. No significant diagnostic differences were noted following either *m*-CPP or L-TRP. As previously reported (Mueller, Murphy and Sunderland, 1986), *m*-CPP induced significant temperature increases in the total subject population ($P \leqslant 0.001$), while L-TRP showed no consistent effect.

3.3. Test-meal responses

On each study day all subjects were offered a standardized meal immediately following the procedure. This consisted of approximately 3500 calories with 50% carbohydrate (CHO), 20%

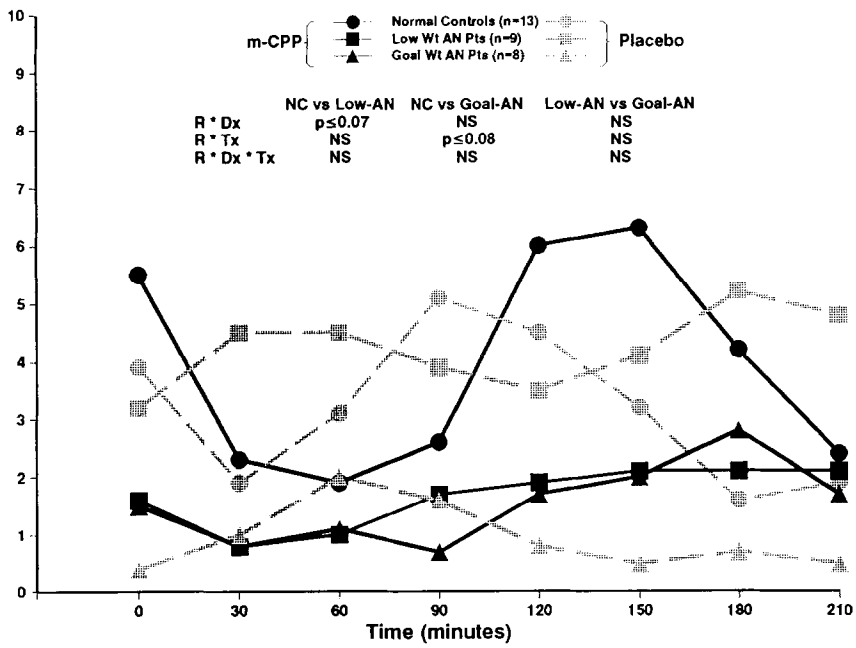

Fig. 1. Growth hormone responses following *m*-CPP in anorexia nervosa patients and controls.

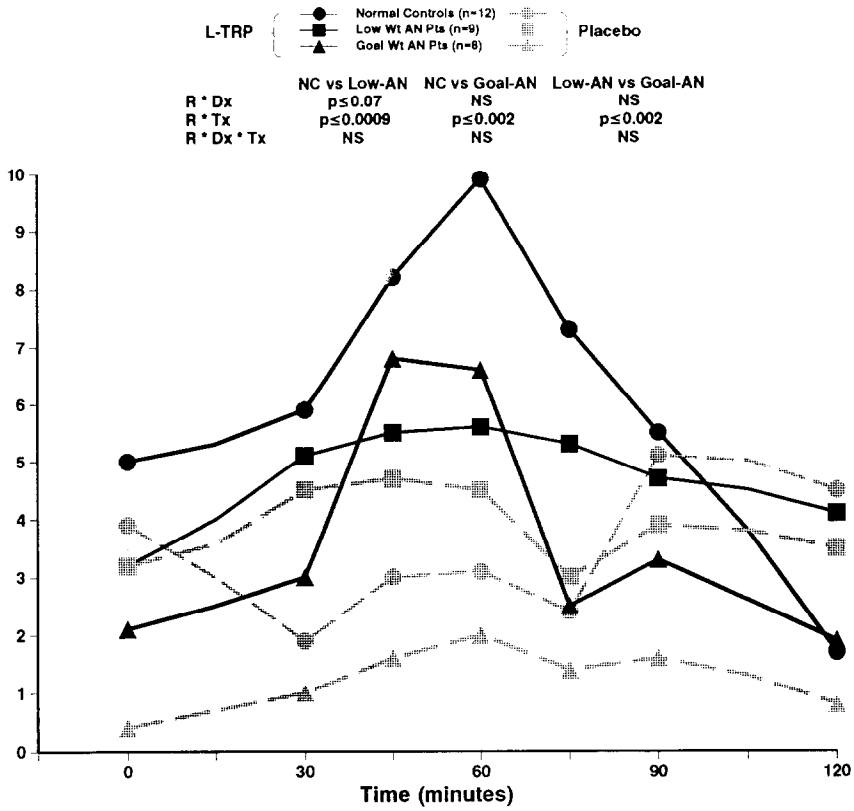

Fig. 2. Growth hormone responses following L-TRP in anorexia nervosa patients and controls.

protein (PRO), and 30% fat (Brewerton et al., 1994). Subjects were instructed "to eat as much or as little" as they desired, but were not allowed to purge after the meal. Results of two-way ANOVAs using diagnosis (Dx) (low-weight AN versus control; goal-weight AN versus control) and treatment (Tx) (*m*-CPP versus placebo; L-TRP versus placebo) as grouping variables are shown in Table 1. On each line statistics are given for Dx, Tx, and Dx × Tx interaction, respectively. As shown in Fig. 3, normal controls, but not AN patients, ate significantly less on the *m*-CPP study day compared with the placebo daily.

3.4. Psychometric responses

Baseline VAS measures are shown in Fig. 4. A summary of the RANOVA analyses for the visual analog scales (VAS) is shown in Table 2. Similarly, statistics are given for time × diagnosis (R × Dx), time × treatment (R × Tx), and time × diagnosis × treatment (R × Dx × Tx), respectively, for each comparison.

Significant differences over time by diagnosis were found between controls and AN patients following *m*-CPP versus placebo (see top of Table 2) for all VAS ratings except sadness ($P < 0.07$; see Fig. 5), helpless (NS), and confused (NS). Differences in sadness ($P \leqslant 0.0001$) (see Fig. 6) and helplessness ($P \leqslant 0.0001$) responses by diagnosis became highly significant after goal weight attainment. Significant time × treatment effects were found for distressed (Fig. 6), hungry (Fig. 7), and full (Fig. 8), while fat ratings did not change (Fig. 9).

Significant differences over time by diagnosis

Table 1
Two-way ANOVA results for test-meal responses

	Low-weight AN versus controls					
	m-CPP			L-TRP		
	Dx	Tx	Dx × Tx	Dx	Tx	Dx × Tx
Size (kcal)	$P \leqslant 0.003$	NS	NS	$P \leqslant 0.00009$	NS	NS
Duration (min)	$P \leqslant 0.0003$	NS	NS	$P \leqslant 0.0006$	NS	NS
Content						
CHO (%)	NS	NS	NS	NS	NS	NS
PRO (%)	$P \leqslant 0.1$	NS	NS	NS	NS	NS
Fat (%)	NS	NS	NS	NS	NS	NS
	Goal-weight AN versus controls					
	m-CPP			L-TRP		
	Dx	Tx	Dx × Tx	Dx	Tx	Dx × Tx
Size (kcal)	$P < 0.0001$	NS	NS	$P \leqslant 0.0001$	NS	NS
Duration (min)	$P \leqslant 0.09$	NS	NS	NS	NS	NS
Content						
CHO (%)	NS	NS	NS	NS	NS	NS
PRO (%)	NS	NS	NS	NS	NS	NS
Fat (%)	NS	NS	NS	$P \leqslant 0.09$	$P \leqslant 0.09$	$P \leqslant 0.09$

were found between controls and AN patients following L-TRP versus placebo (see bottom of Table 2) for all VAS ratings except urge to eat (NS) and confused (NS). Differences in urge to eat responses by diagnosis following L-TRP became significant ($P \leqslant 0.002$) after weight gain. Time × treatment effects were only significant for hungry (Fig. 10) and urge to eat.

3.5. Comment

The significantly altered PRL responses observed in this study do not appear to be due to differences in age, level of activity, medications, time of day, or drug levels. Although the weights of the patients at both phases were significantly lower than those of controls, the neuroendocrine responses were not found to be correlated to weight. Although we did see some degree of normalization of function, differences persisted at goal weight. We may not have studied these patients long enough after attaining goal weight and their goal weights may have been too low, given that they were still significantly lower than those of the controls.

Our PRL results following L-TRP are in contrast to the findings by Goodwin and colleagues (1989), who reported no significant difference in PRL responses between a group of AN patients and controls. However, Dr. Goodwin has indicated that all of these patients were of the non-bulimic (or restrictor) subtype (personal communication). These patients were also similar in weight to our patients.

Whether our finding of an alteration in 5-HT functioning represents a causative factor in the pathogenesis of AN, is a sequela of the disorder, or a combination of both cannot be stated with certainty. However, the tendency for PRL responses following *m*-CPP to normalize in the 8 paired AN patients after refeeding suggests that these changes are at least partly secondary to starvation. Dieting for 2–3 weeks has been reported to cause 5-HT receptor upregulation and to enhance PRL responses to L-TRP (Goodwin, Fairburn and Cowen, 1987a; Goodwin et al., 1987b). Although all of our patients were studied after a 3–4 week period of careful weight maintenance and abstinence from fasting, exercising,

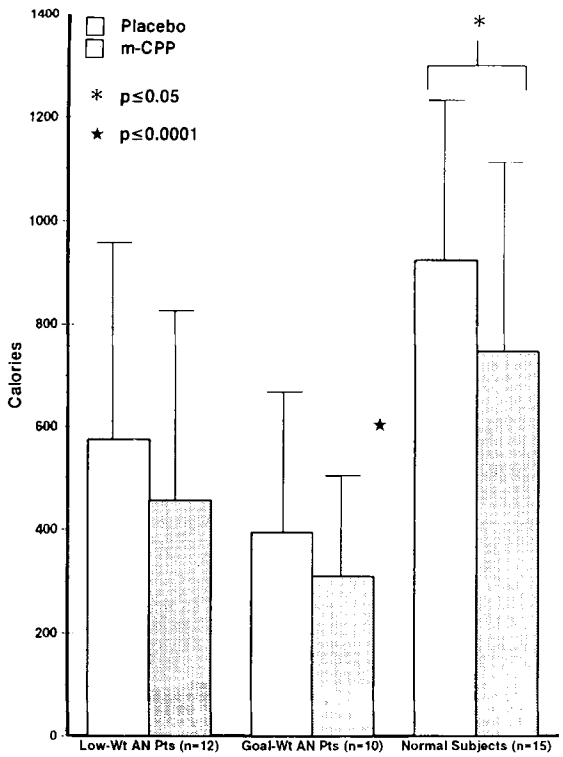

Fig. 3. Test-meal size following *m*-CPP in anorexia nervosa patients and controls.

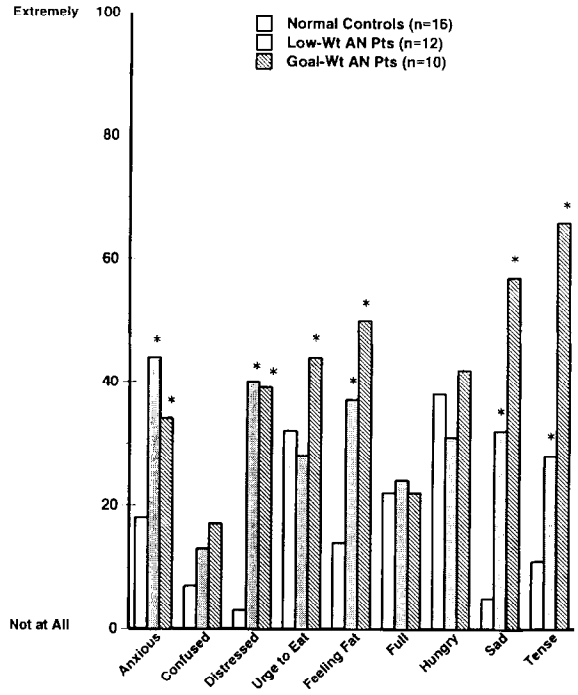

Fig. 4. Visual analog baseline ratings. Asterisk (*) indicates significant difference ($P \leqslant 0.05$) compared with controls.

binge eating and purging, it is quite possible that our findings represent persistent effects of chronic dieting or starvation. However, it remains to be determined whether these abnormal responses will completely normalize with full recovery. Long-term weight recovered AN patients are needed for study. Since most of the AN patients in this study also had a history of BN, it may be that these findings are more closely associated with binge eating and vomiting (Brewerton et al., 1992a). These behaviors could conceivably result in downregulation of post-synaptic 5-HT receptors. Other evidence supports a difference in 5-HT function between bulimic versus non-bulimic AN patients. For example, lower post-probenecid CSF 5-hydroxyindoleacetic acid (5-HIAA) concentrations have been reported in weight-recovered bulimic anorexic patients compared with non-bulimic anorexic patients (Kaye et al., 1984b), and Halmi and colleagues (1986) found a differential response to serotonergic agents. Whether the blunted neuroendocrine responses in our study reflect a premorbid state which predisposes patients toward AN and/or BN requires further study using a variety of serotonergic probes.

In contrast to the blunted PRL responses following *m*-CPP, CORT and GH responses for the AN patients at either weight phase did not significantly differ from those of the controls. The differences between PRL, CORT and GH responsivity seen in this study and others is probably reflect the fact that different anatomical pathways and 5-HT receptor subtypes are involved in their stimulation. This has been extensively reviewed elsewhere for PRL and CORT (Brewerton et al., 1992a). The specific 5-HT receptor subtype that mediates GH responses is not known.

The reasons for the lack of significant differen-

Table 2
Two-way RANOVA results for visual analog responses

	Low-weight AN versus controls					
	m-CPP			L-TRP		
	Dx	Tx	Dx × Tx	Dx	Tx	Dx × Tx
Anxious	$P \leqslant 0.0009$	NS	NS	$P \leqslant 0.005$	NS	NS
Distressed	$P \leqslant 0.05$	$P \leqslant 0.02$	$P \leqslant 0.002$	$P \leqslant 0.007$	NS	NS
Hungry	$P \leqslant 0.004$	$P \leqslant 0.007$	NS	$P \leqslant 0.02$	$P \leqslant 0.00001$	NS
Urge to eat	$P \leqslant 0.02$	NS	NS	NS	$P \leqslant 0.006$	NS
Feeling fat	$P \leqslant 0.002$	NS	NS	$P \leqslant 0.00001$	NS	NS
Helpless	NS	NS	NS	NS	NS	NS
Tense	$P \leqslant 0.05$	NS	NS	$P \leqslant 0.02$	NS	NS
Sad	$P \leqslant 0.07$	NS	$P = 0.1$	$P \leqslant 0.02$	NS	$P \leqslant 0.07$
Confused	NS	NS	NS	NS	NS	NS
Full	$P \leqslant 0.03$	$P \leqslant 0.04$	NS	$P \leqslant 0.003$	NS	NS
	Goal-weight AN versus controls					
	m-CPP			L-TRP		
	Dx	Tx	Dx × Tx	Dx	Tx	Dx × Tx
Anxious	$P \leqslant 0.008$	NS	NS	$P \leqslant 0.08$	NS	NS
Distressed	$P \leqslant 0.001$	NS	NS	$P \leqslant 0.02$	NS	NS
Hungry	$P \leqslant 0.01$	$P \leqslant 0.00001$	NS	$P \leqslant 0.0009$	$P \leqslant 0.0003$	NS
Urge to eat	$P \leqslant 0.09$	NS	NS	$P \leqslant 0.002$	$P \leqslant 0.009$	NS
Feeling fat	NS	$P \leqslant 0.09$	NS	NS	NS	NS
Helpless	$P \leqslant 0.00001$	NS	$P \leqslant 0.07$	$P \leqslant 0.002$	NS	NS
Tense	$P \leqslant 0.04$	NS	NS	NS	NS	NS
Sad	$P \leqslant 0.00001$	NS	NS	$P \leqslant 0.00001$	$P \leqslant 0.07$	$P \leqslant 0.02$
Confused	NS	NS	NS	NS	NS	NS
Full	NS	NS	NS	$P \leqslant 0.01$	$P \leqslant 0.01$	NS

ces in temperature responses between AN patients and controls following either serotonergic agent are not clear, but the finding suggests no difference in 5-HT receptor sensitivity in these hypothalamic pathways. However, oral temperature may not accurately reflect core body temperature, and the degree of variance may have been too large to detect a difference. Temperature is also highly regulated by a multiplicity of neurochemical systems.

Test-meal responses were significantly different between controls and AN patients at both weight phases in that patients ate significantly less than controls regardless of treatment effect. This could indicate increased 5-HT tone in hypothalamic pathways mediating satiety responses.

In terms of the psychometric responses reported in this article, diagnostic differences were found for the following measures after *m*-CPP and/or L-TRP in the same AN patients regardless of weight phase: anxiety, tension, depression, hunger, urge to eat, feeling fat, and feeling full. *M*-CPP caused significant increases in distress and decreases in hunger and urge to eat, which are compatible with its anxiogenic and appetite suppressant properties (Mueller, Murphy and Sunderland, 1986; Brewerton et al., 1992a; Brewerton, Murphy and Jimerson, 1994). These effects were generally more pronounced in the patients than the controls.

These findings are compatible with altered receptor sensitivity in other 5-HT pathways at or

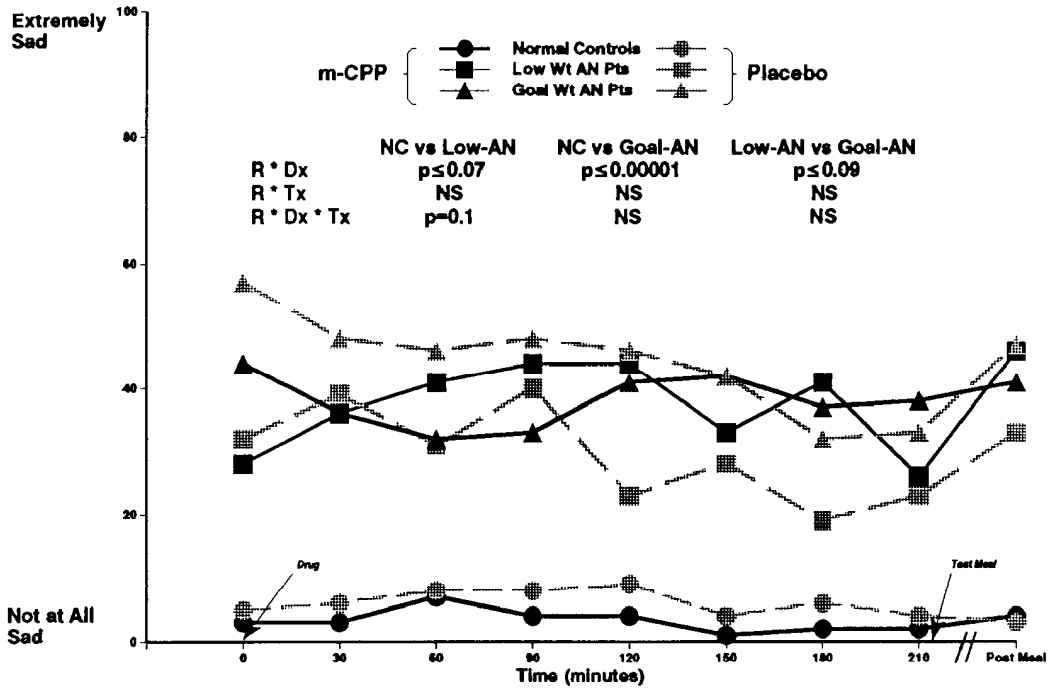

Fig. 5. Sadness ratings: *m*-CPP versus placebo.

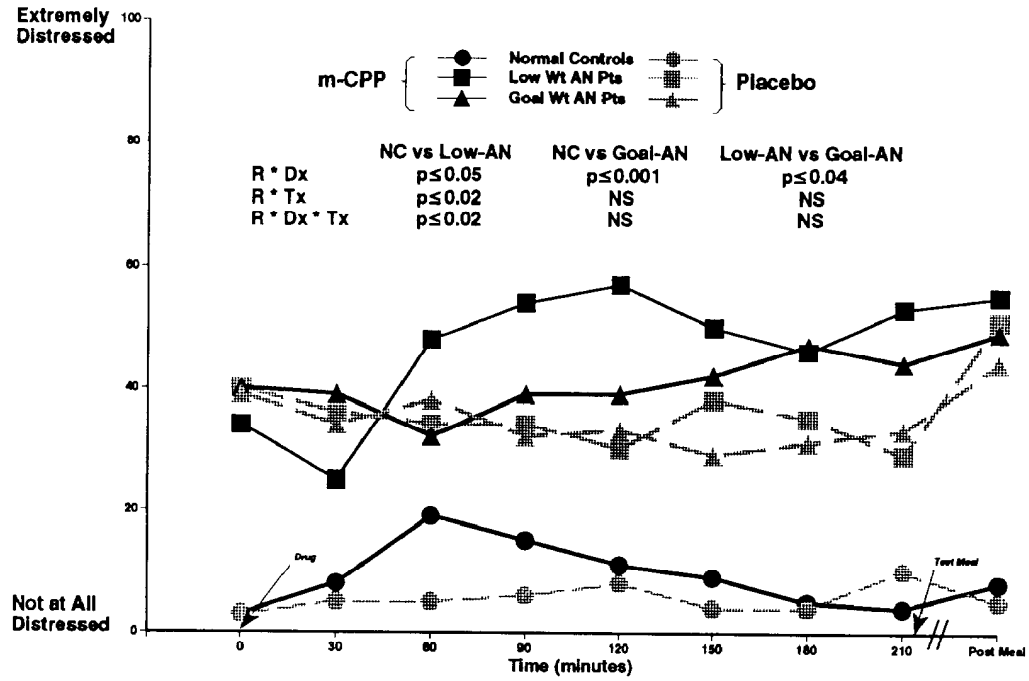

Fig. 6. Distressed ratings: *m*-CPP versus placebo.

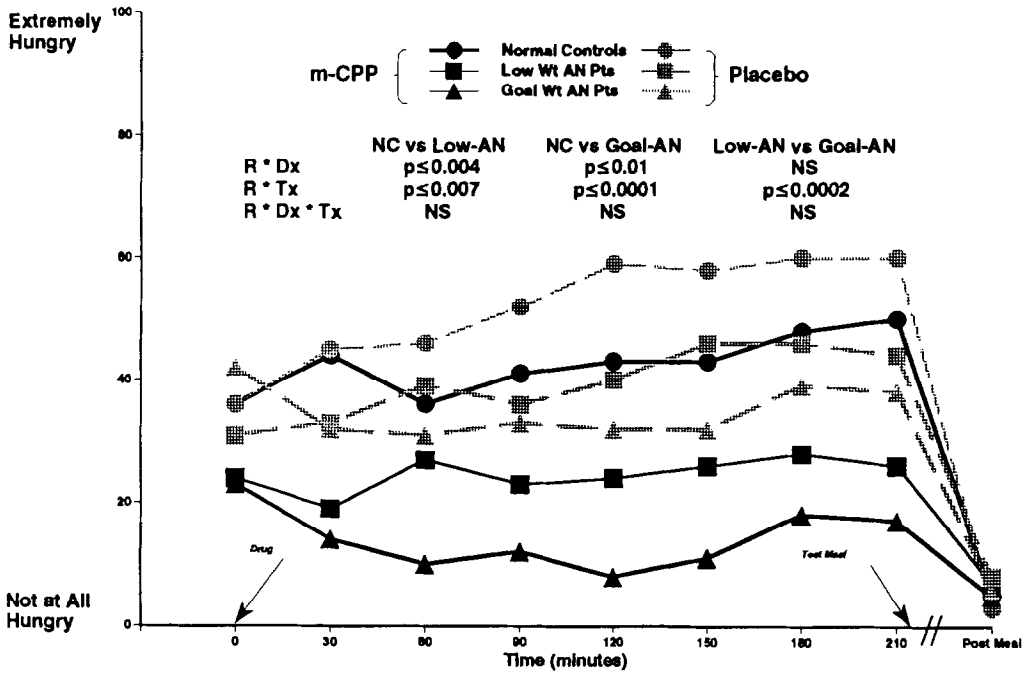

Fig. 7. Hunger ratings: *m*-CPP versus placebo.

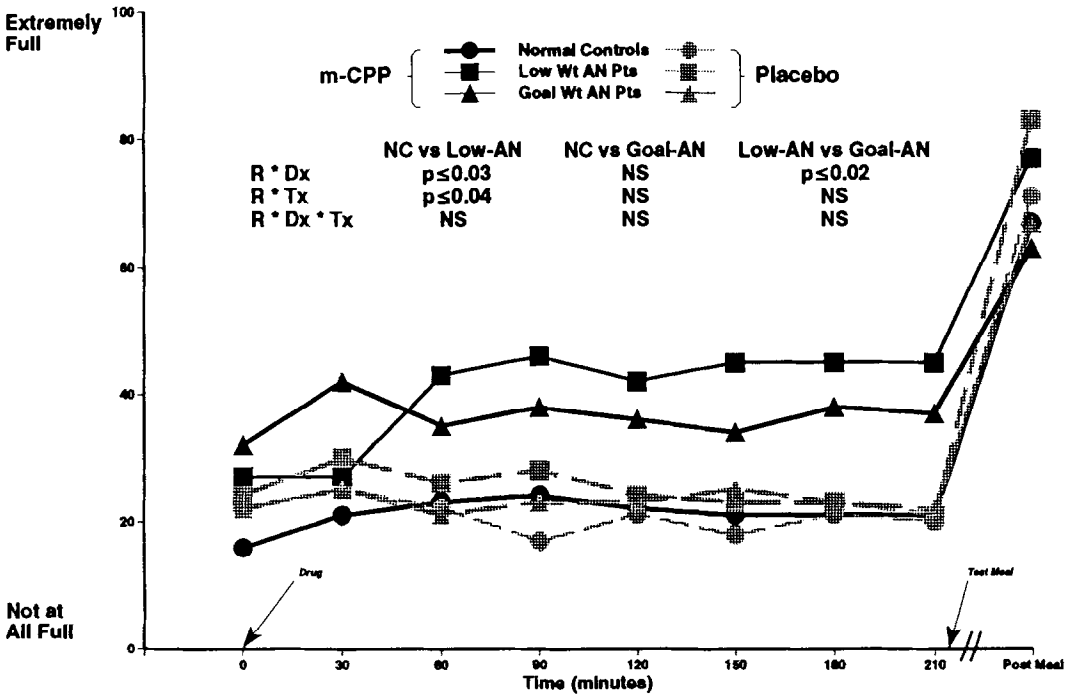

Fig. 8. Fullness ratings: *m*-CPP versus placebo.

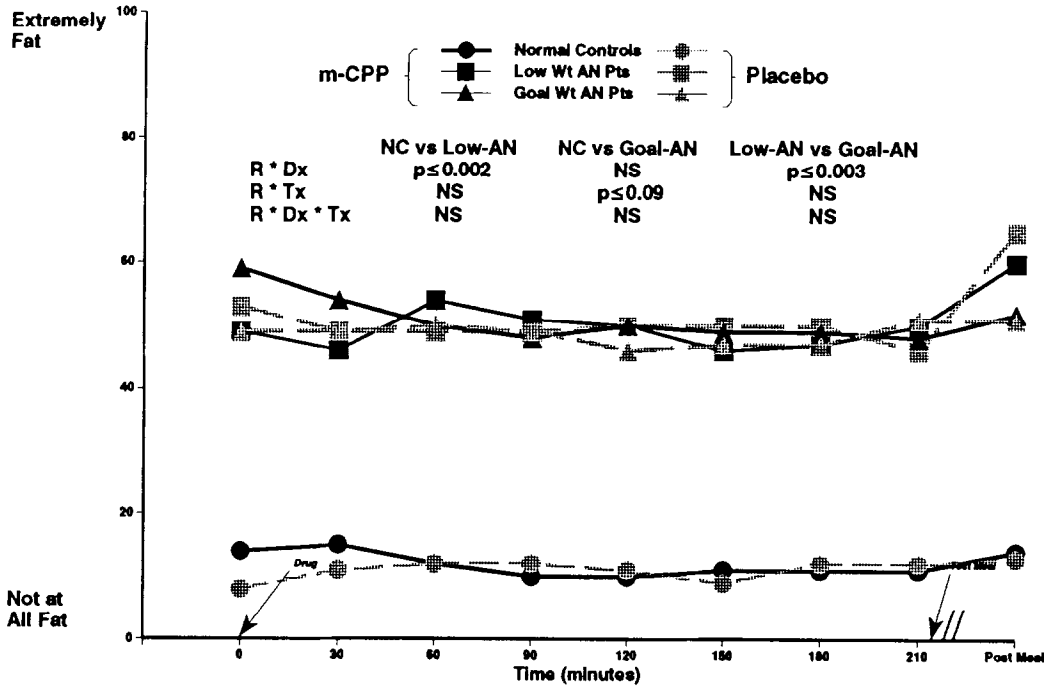

Fig. 9. Fat ratings: *m*-CPP versus placebo.

above the level of the hypothalamus, such as the limbic system, and may contribute to an array of psychiatric symptoms observed in AN patients. Further studies exploring the role of altered 5-HT receptor function in patients with AN, particularly after long-term recovery, are warranted. In addition, challenge studies of first degree relatives of AN patients, such as unaffected siblings, and perhaps other high risk individuals prior to the development of AN may be elucidating.

4. Clinical aspects and treatment implications

These data are likely to have certain implications for the clinical approaches used in the treatment of AN. Refeeding is clearly essential, as the tendency toward normalization of responses with weight gain indicates. Food of course also provides essential nutrients necessary for normal brain development and function, including L-TRP for synthesis of 5-HT. Other measures of 5-HT function, including decreases in plasma L-TRP, urinary 5-HIAA, platelet [^{3}H]imipramine binding, and basal CSF 5-HIAA have been reported in AN (see Brewerton et al., 1990; Brewerton, 1993, 1995), but all of these measures appear to normalize upon weight restoration (Kaye et al., 1988b). These findings may thus help patients and their families realize that AN is not only associated with measurable abnormalities of the 5-HT system, but that increased weight is associated with a tendency toward normalization of function.

Unlike many other reports of serotonergic abnormalities in AN, our data indicate that many abnormalities persist after initial weight gain. Therefore, other forms of treatment, including psychotherapy and pharmacotherapy with serotonergic agents (Gwirtsman et al., 1990; Kaye et al., 1991b), are also probably necessary, as clinical practice has dictated. It remains to be seen whether abnormal neuroendocrine responses following serotonergic agents have a role in predicting treatment outcome. Just how long it

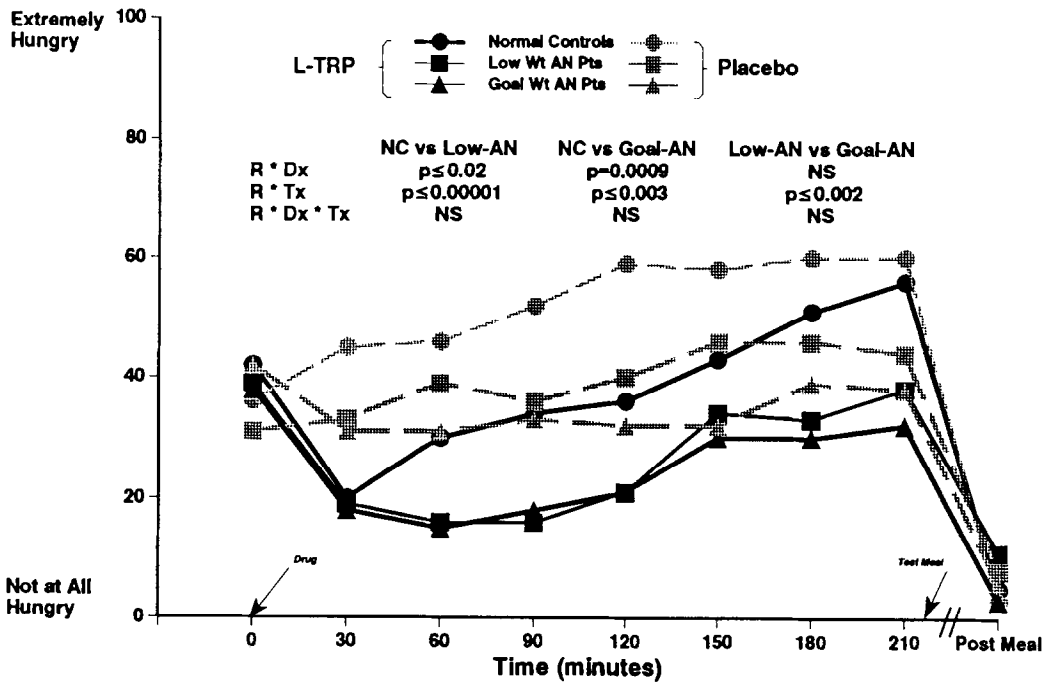

Fig. 10. Hunger ratings: L-TRP versus placebo.

takes to normalize the effects of starvation and to manifest predominately trait rather than state findings is not known, but is likely to be several months. Kaye and associates (1991a) reported that long-term weight recovered AN patients (who maintained a normal goal weight for at least 6 months) were found to have significantly higher levels of CSF 5-hydroxyindoleacetic acid (5-HIAA) than controls. It therefore must be emphasized to patients, their families and therapists that not only is refeeding required, but that recovery is a slow process.

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Testmeal Responses Following m-Chlorophenylpiperazine and L-Tryptophan in Bulimics and Controls

Timothy D. Brewerton, M.D., Dennis L. Murphy, M.D., and David C. Jimerson, M.D.

A wealth of data support a role for serotonin (5-HT) function in the mediation of satiety responses, that are impaired in patients with bulimia nervosa. Testmeal results are presented in which 26 bulimic patients and 17 normal controls were given in randomized, double-blind–fashion, placebo, and the 5-HT agents m-chlorophenylpiperazine (m-CPP, 0.5 mg/kg p.o.) and L-tryptophan (L-TRP, 100 mg/kg I.V.). Three and one–half hours after drug administration, subjects were allowed to eat and lib from a standardized testmeal of 3,500 calories, after which postprandial vomiting was not allowed. M-CPP, but not L-TRP, significantly decreased meal size in the combined group, the controls, and to a lesser extent, the bulimics ($p \leq .06$). Maximum m-CPP concentrations were inversely correlated to the number of calories consumed in the total group. Following m-CPP, there were significant decreases in carbohydrate, protein, and fat intake in the total group of subjects. There were also trends for decreased carbohydrate and protein intake in the bulimics following m-CPP. There were trends for both m-CPP and L-TRP to reduce fat intake in the controls. Differences in the effects between m-CPP and L-TRP are likely due to differential involvement of 5-HT receptor subtypes at presynaptic and postsynaptic sites. These studies in humans confirm reports in animals that m-CPP decreases food intake, including carbohydrates, protein, and fat in a mixed testmeal.
[Neuropsychopharmacology 11:63–71, 1994]

Serotonergic manipulations are known to result in marked changes in feeding behaviors, particularly satiety responses (Blundell 1977, 1984, 1986; Blundell and Latham, 1978, 1980, 1982; Latham and Blundell 1979; Samanin et al. 1982; Silverstone and Goodall 1986; Garattini et al., 1988, 1989), which are dysfunctional in bulimic patients (Owen et al. 1985; Chiodo and Latimer 1986; Kissileff et al. 1986). Pharmacologic enhancement of 5-HT neurotransmission in animals and man generally leads to increased satiety (Blundell 1984, 1986), with the exception of 5-HT_{1A} receptor activation that induces feeding in animals in specific paradigms (Dourish et al. 1985, 1986, 1988). Conversely, attenuation of 5-HT neurotransmission by various methods leads to decreased satiety and increased food consumption and weight gain (Blundell and Latham 1978, 1980, 1982; Blundell 1984, 1986). The effects of 5-HT on feeding are thought to be mediated centrally via the medial hypothalamus (Leibowitz and Shor-Posner 1986; Leibowitz et al. 1988; Leibowitz 1990), although there is some evidence that peripheral mechanisms may play a part (Pollock and Rowland 1981; Davies et al. 1983; Fletcher and Burton 1984).

Patients with bulimia nervosa have several disturbances which suggest dysregulation of 5-HT function, including affective dysregulation, anxiety, impulsivity, and addiction (Brewerton et al. 1986, 1989, 1990a, 1990b, 1992c in press; Jimerson et al. 1990).

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Given these relationships, we studied the feeding responses in normal weight patients with bulimia nervosa and with healthy controls following challenge with the 5-HT precursor L-tryptophan (L-TRP) and the 5-HT agonist m-chlorophenylpiperazine (m-CPP) as well as placebo (both IV solution and capsules). A more detailed discussion of the neuroendocrine and neuropharmacological aspects, including side-effect profile, of these drugs as challenge agents has been studied (Brewerton et al., 1988, 1990a, 1990b, 1992c; Murphy et al., 1991).

SUBJECTS AND METHODS

The demographic features of the normal weight bulimic patients and the age and weight-matched female normal controls have been described (Brewerton et al. 1992b), but will be briefly reviewed and are in Table 1. There was not complete overlap between the m-CPP and L-TRP patient and control groups. All subjects were studied after at least four weeks off all medications, including birth control pills. At the time of admission, all patients met DSM-III criteria (American Psychiatric Association, 1980) for bulimia; retrospectively, all patients were also found to meet DSM-III-R criteria (American Psychiatric Association 1987) for bulimia nervosa. None of the patients with bulimia met present or past DSM-III criteria for anorexia nervosa. Normal controls were selected on the basis of an absence of present or past major psychiatric illness as determined by the SADS-L (Spitzer and Endicott 1975). There was no significant difference in the weights of patients as compared to controls (Table 1). All subjects were in good general health, not pregnant, and free of significant medical illness on the basis of a thorough medical evaluation including a physical examination, EKG, and appropriate laboratory tests. In addition, controls were eliminated on the basis of a lifetime family history of any psychiatric disorder or obesity in a first degree relative. Each subject received an oral and written explanation of the purposes, procedures, and potential hazards of the project, and then gave informed consent.

All subjects were studied at the National Institute of Mental Health Clinical Center Eating Disorders Unit after overnight bedrest and a 14 hour fast (except for water). In addition, 20 of the 26 bulimic subjects were inpatients at the time of the study, and had been abstinent from binging and vomiting for at least four weeks. Inpatients were treated on a highly structured, locked, inpatient unit with supervised meals and bathroom use. The daily caloric intake for all inpatients was prescribed and consisted of approximately 30 kcal/kg. All meals were prepared and checked by experienced dieticians for an appropriate balance of macronutrients, minerals, and vitamins. Patients were not allowed to exercise and were checked periodically by nursing staff to prevent excessive activity. All subjects also observed limited activity levels and a low monoamine, alcohol free, low caffeine diet for at least 72 hours prior to the study. Subjects who smoked were not allowed to do so on the days of the study. A 20 gauge intravenous catheter attached to a heparinized double stopcock was inserted by 9:00 A.M. on each of the procedure days. Double-blind administration of m-CPP (0.5 mg/kg p.o.), L-TRP (100 mg/kg IV), or placebo was performed on separate days in random order of at least 48 hours apart. Each subject had an infusion of saline, or L-TRP, and the same number of capsules (placebo or m-CPP), except for six patients with indwelling venous lines who received only capsules on each day of two days (placebo or m-CPP). Plasma levels of m-CPP and L-TRP were measured by high pressure liquid chromatography (Miller and Devane 1986; Larsson et al. 1988).

The Hamilton Depression Scale (HAMD) (Hamilton 1960) was administered by one of the authors (TDB), and subjects completed the Beck Depression Inventory (BDI) (Beck 1961) on the morning of each study day. Subjects completed a side-effects check list throughout the procedure.

All subjects were given a standardized testmeal consisting of 3,500 calories, including 50% carbohydrates, 30% fat, and 20% protein, presented between three and a half hours and four hours post drug administration. Subjects were instructed "to eat as much or as little as desired" in "as long or as short a period of time as desired." No vomiting was allowed. Outcome measures included meal size, duration, and macronu-

Table 1. Demographic Characteristics of Bulimics and Controls

	Bulimics		Controls	
	m-CPP (n = 26)	L-TRP (n = 23)	m-CPP (n = 15)	L-TRP (n = 16)
Age (yr)	24.7 ± 4.8	24.1 ± 4.8	26.4 ± 5.3	26.8 ± 5.3
Weight (kg)	54.7 ± 4.9	55.3 ± 5.2	57.5 ± 6.3	57.5 ± 6.2
ABW (%)	92.7 ± 7.9	92.4 ± 7.7	95.6 ± 7.7	95.5 ± 7.8

* m-CPP indicates m-chlorophenylpiperazine; L-TRP, L-tryptophan; and ABW, average body weight. Data are given as mean ± SD.

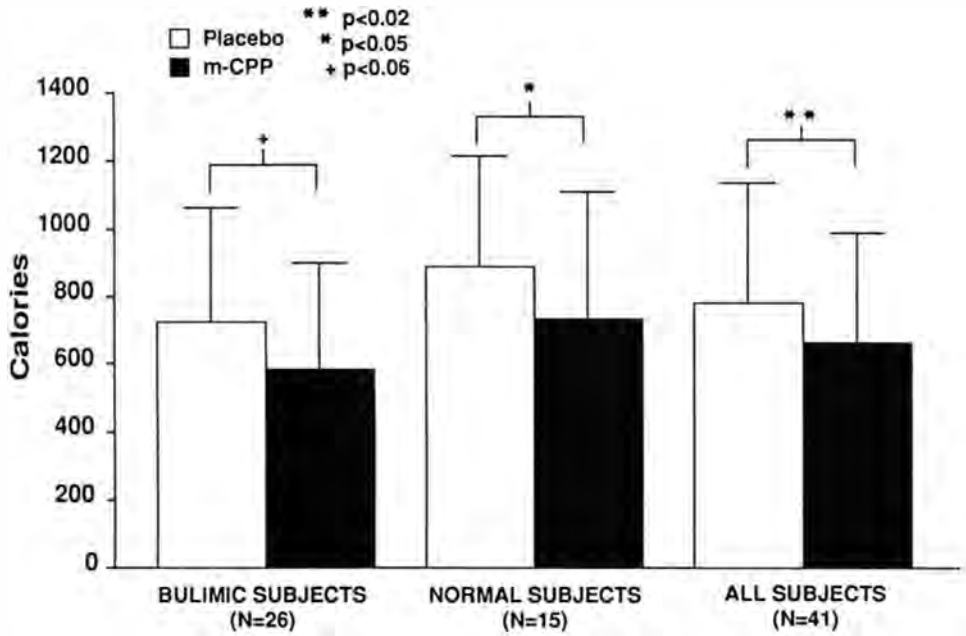

Figure 1. Testmeal size following m-CPP. Bulimic subjects ($p \leq .06$), controls ($p \leq .05$) and the total group of subjects ($p \leq .02$) ate significantly less following m-CPP than following placebo.

trient content (i.e., protein, carbohydrate, and fat). Macronutrients were calculated as both absolute amount in grams as well as percentage of total intake.

Data Analysis

Before analysis, all data were tested for normal distribution and homogeneity of variance using the Statistical Analysis System (SAS) Proc Unvariate. All data were parametric and were analyzed across groups using the unpaired *t*-test, and were analyzed within groups using the paired *t*-test. All variances are reported as SD. Peak drug concentrations and depression ratings (HAMD and BDI) were correlated with all testmeal variables using Pearson γ. A priori, it was decided to test each drug separately versus placebo, and the data were ana-

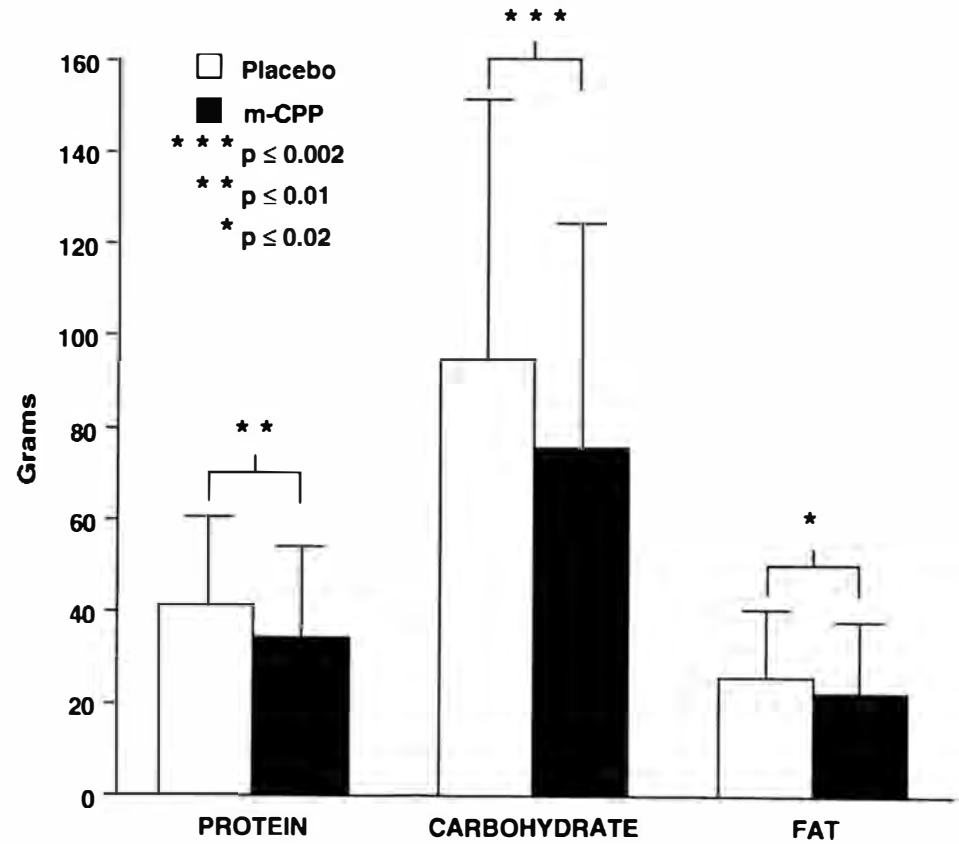

Figure 2. Macronutrient content following m-CPP in all subjects (n = 41). In the total group of subjects m-CPP in comparison to placebo significantly reduced carbohydrate ($p \leq .002$, paired *t*-test), protein ($p \leq .01$), and fat intake ($p \leq .02$).

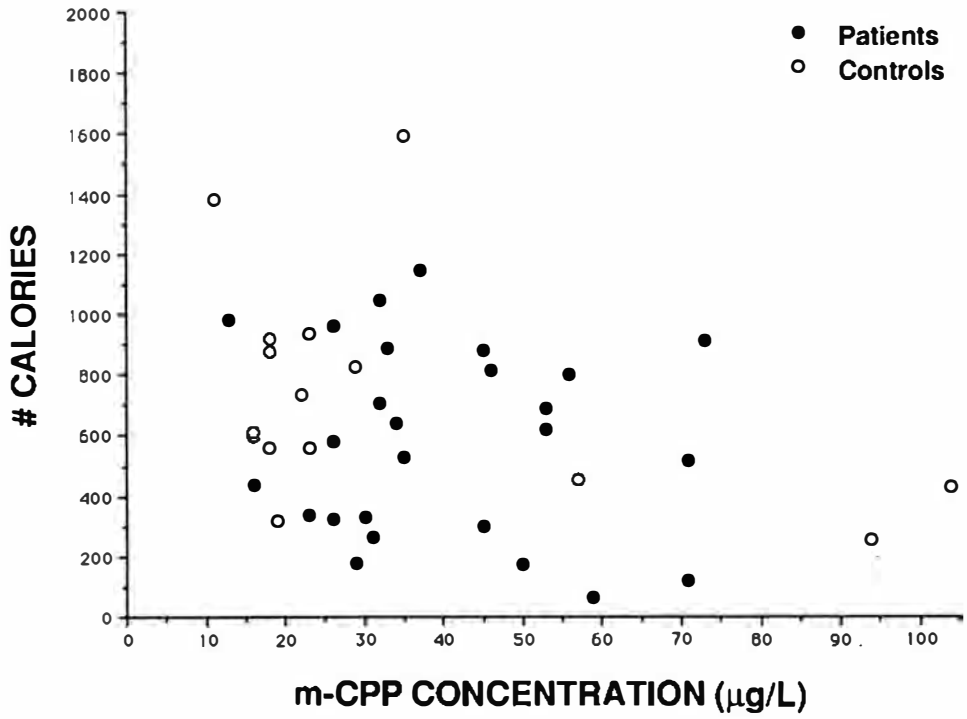

Figure 3. Maximum m-CPP concentrations were correlated with the total number of calories consumed in the total group ($n = 41$, $r = -0.33$, $p < .03$). There was a trend for this in the controls ($n = 16$, $r = -0.45$, $p < .07$), but not the bulimics.

lyzed as such. Different sample sizes and incomplete overlap among subjects from drug to drug also indicated separate analyses. This strategy has been used in reporting neuroendocrine results (Brewerton et al. 1992c). In addition, the outpatient bulimics were combined with the inpatient bulimics because there were no significant differences in any of the testmeal parameters between these two groups, and these patients served to increase the power of the statistics for treatment and diagnosis effects.

RESULTS

M-CPP versus Placebo

Testmeal duration was not significantly different between m-CPP and placebo in the bulimics (m-CPP: 24.5 ± 11.7 min), the controls (m-CPP: 18.1 ± 6.3 min), or the total group. In the total group of subjects, meal size (kcal) was significantly reduced following m-CPP compared to placebo ($n = 41$, $p < .02$). In addition, meal

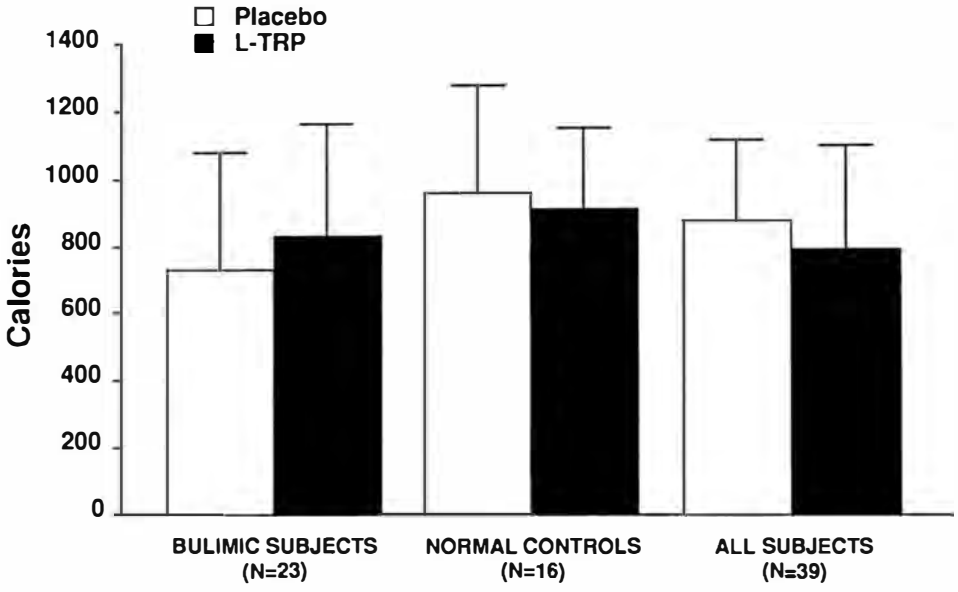

Figure 4. Testmeal size following L-TRP. There were no significant differences in testmeal size for the bulimics, the controls, or the total group of subjects following L-TRP as compared to placebo.

size was significantly reduced following m-CPP in the controls alone (736 ± 373 versus 887 ± 330 cal, $p \leqslant .05$, paired t-test), and there was a similar trend in the bulimics alone (584 ± 314 versus 725 ± 337 cal, $p \leqslant .06$) (Figure 1).

In the total group, m-CPP reduced the carbohydrate ($p \leqslant .002$, paired t-test), protein ($p \leqslant .01$), and fat intake ($p \leqslant .02$) in comparison to placebo (Figure 2). Maximum m-CPP concentrations were significantly correlated with the total number of calories consumed ($r = -0.33$, $p < .03$) (Figure 3) and fat intake ($r = -0.33$, $p = .033$). A trend was noted for a significant correlation with carbohydrate intake as well ($r = -0.27$, $p = .08$).

There was a trend for bulimics to eat less carbohydrate (gms) after m-CPP than placebo ($p < .1$). There was also a trend for bulimics to eat less protein (in both absolute gms and % total intake) after m-CPP than placebo ($p \leqslant .1$), and there was a trend for controls to eat less fat (gms) after m-CPP ($p < .1$).

There were no significant correlations between maximum m-CPP concentrations and any of the testmeal measures in the patients alone. However, in the controls, there was a trend for maximum m-CPP concentrations to be inversely correlated with the total number of calories eaten ($n = 16$, $r = -0.45$, $p < .07$) (Figure 3), as well as the number of grams of protein ($r = -0.44$, $p < .09$) and fat consumed ($r = -0.45$, $p < .08$).

L-TRP versus Placebo

There were no significant differences in testmeal duration or size in the bulimics, the controls (Figure 4) or the total group. There were no significant differences in macronutrient selection in the total group of subjects. However, there was a trend for bulimics to eat less protein (% total cal) ($p \leqslant .09$) and for controls to eat less fat (gms) after L-TRP ($p \leqslant .1$) (Figure 5). In comparison to placebo, there was a significant difference in change in fat intake (gms) after L-TRP between bulimics and controls ($p \leqslant .05$), (i.e., overall, bulimics ate more fat [4.5 ± 16.8 gms] and controls at less [−3.9 ± 8.4 gms]). There were no significant correlations between maximum L-TRP concentrations and any of the testmeal measures in the patients, the controls, or the combined groups. There was a trend for maximum L-TRP concentrations to be correlated with fat intake in the patients alone ($n = 23$, $r = 0.36$, $p = .088$).

Placebo

Testmeal duration was significantly longer in the bulimics ($n = 26$, 24.3 ± 9.2 minutes) as compared to the controls ($n = 17$, 17.3 ± 6.1 min, $p \leqslant .05$, unpaired t-test) on the placebo day. There was also no statistically significant difference in meal size between bulimics (725 ± 337 cal) and controls (887 ± 330 cal) on the

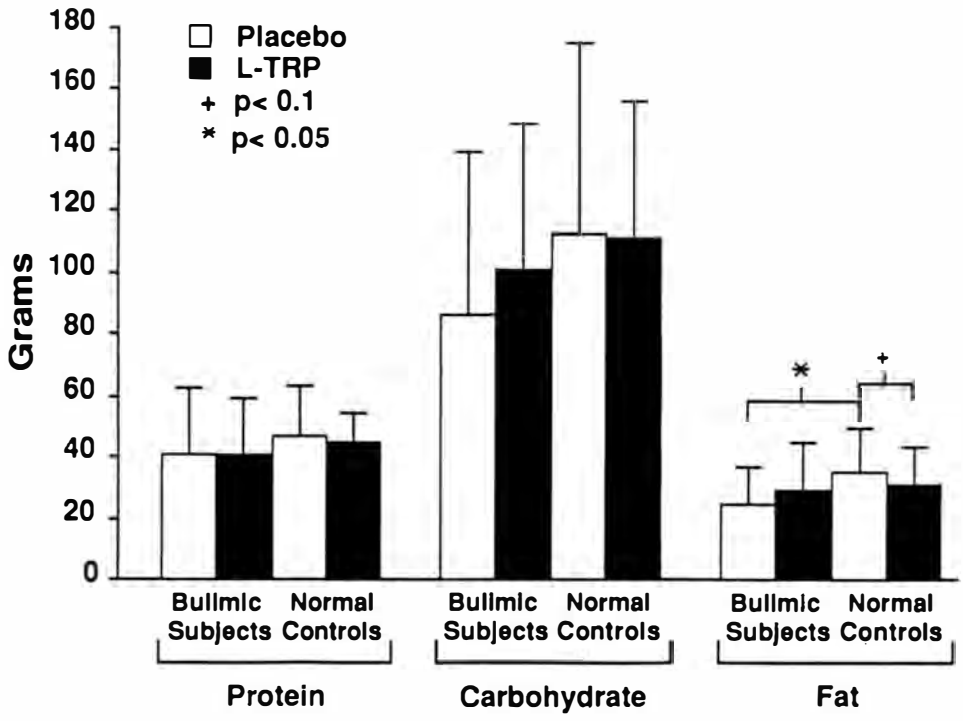

Figure 5. Testmeal content following L-TRP. Bulimics ate less fat than controls following placebo ($p \leqslant .05$), and there was a trend for controls to eat less fat after L-TRP ($p \leqslant .1$).

placebo day (Figures 1, 4). There was a trend for bulimics to eat significantly less fat (23.7 ± 12.9 gms) than controls (31.0 ± 13.3 gms, $p \leqslant .1$) (Figure 4). There were no other significant differences in macronutrient content between bulimics and controls on the placebo study day.

Depression Ratings

No significant or near significant correlations were found between any of the testmeal measures and HAMD and BDI scores.

Side Effects

As previously reported (Brewerton et al. 1992c), mild nausea was the most common side effect for both agents. Maximum nausea ratings were significantly higher following both agents in comparison to placebo, but there were no significant differences between m-CPP and L-TRP. In addition, maximum ratings were not correlated to any of the testmeal measures.

DISCUSSION

M-CPP significantly decreased testmeal size in the total group of volunteers ($p \leqslant .002$) and the healthy controls alone ($p < .05$), and there was a trend for this effect in the bulimics alone ($p < .06$). This is compatible with reports in animals that m-CPP and other serotonergic agents decrease food intake (Samanin et al. 1982; Kennett et al. 1987, 1990; Kennett and Curzon 1988a, 1988b; Aulakl et al. 1989). Recent evidence indicates that m-CPP's effects on feeding are specifically mediated via 5-HT_{1C} receptors (Kennett and Curzon 1988a, 1988b; Kennett et al. 1990, 1991). The finding of a significant inverse correlation between m-CPP levels and total calories consumed is compatible with this hypothesis. In the total group of subjects, m-CPP induced decreases in food intake were nonspecific in that all macronutrients were suppressed to significant degrees; however, the strongest case could be made for its effect on carbohydrates, because this was the most robust finding.

Following the L-TRP challenge, bulimic patients ate slightly more, and controls ate slightly less after L-TRP, although these were not statistically significant differences. Nor were there differences in the total group. The lack of significant effect by intravenous L-TRP is similar to studies of oral L-TRP in humans in which few effects (Wurtman and Wurtman 1981a, 1981b; Silverstone and Goodall 1986) or no effects were observed (Hrboticky et al. 1985; Krahn and Mitchell 1985; Russ et al. 1991). These data add to considerable doubt about the extent to which L-TRP induced increases in 5-HT turnover actually cause enhanced 5-HT neurotransmission (Trulson 1985). Yet, L-TRP significantly enhanced prolactin and cortisol secretion in these same patients, probably as a result of enhanced 5-HT function (Brewerton et al. 1992c).

Following placebo, bulimics ate fewer calories compared to controls, although this was a nonsignificant difference and was probably a result of restrained eating in the bulimic subjects, given the vomiting restriction.

The effects of the 5-HT agents on the macronutrient content of the testmeal differed somewhat by diagnosis. There was at least a trend for both m-CPP and L-TRP to reduce the percentage of protein ingested in the bulimics, but not the controls. M-CPP also reduced the grams of protein ingested in the bulimics, but not the grams of protein ingested in the controls. The case for a role of 5-HT in the direct regulation of protein intake is controversial and weak, and most of his work has been done in animals (Anderson 1979; Curtis-Prior 1983; Shor-Posner et al. 1986; Fernstrom 1987; Peters and Harper 1987), so these data are provocative.

There is a much stronger case for a role for 5-HT in the regulation of carbohydrate intake (Fernstrom 1987). Our finding of a lack of effect of L-TRP on carbohydrate intake in normal controls is contrary to studies in some (Latham and Blundell 1979; Gibbons et al. 1981), but not all animal studies (Peters et al. 1984). However, following m-CPP, carbohydrate intake was decreased in the total group of subjects and the bulimic patients. Furthermore, there was a trend for a significant inverse correlation between maximum m-CPP concentrations and carbohydrate intake in the total group of subjects. Other serotonergic agents, such as fenfluramine (Wurtman and Wurtman 1977; Burton et al. 1981; Li and Anderson 1984; Kim and Wurtman 1988a), fluoxetine (Wurtman and Wurtman 1977; Kim and Wurtman 1988b), the 5-HT reuptake inhibitor. CGS10686B (Kim and Wurtman 1988b), as well as the postsynaptic agonist MK-212 (Wurtman and Wurtman 1979), have all been shown to suppress carbohydrate ingestion in animals. There are no other studies in humans of m-CPP on food intake, but oral administration of L-TRP (Wurtman and Wurtman 1981a, 1981b; Silverstone and Goodall 1986) and fenfluramine (Wurtman and Wurtman 1977, 1981a, 1981b; Rogers et al. 1979; Hill and Blundell, 1990) have been reported to decrease carbohydrate intake in man.

M-CPP also reduced the amount of fat intake in the total group and both agents reduced the grams of fat intake in the controls, but not the bulimics alone. In addition, fat intake was significantly and inversely correlated with maximum m-CPP concentrations in the total group of subjects. There was also a significant difference in change in fat intake (gms) after L-TRP between bulimics and controls (bulimics ate more fat and controls ate less). Bulimic subjects ate fewer grams of fat than controls in this setting, which is compatible with clinical observations that bulimics and other restrained

eaters avoid fat consumption. These results suggest that 5-HT may also play a role in modulating fat intake, perhaps via its effects on the opiate system (Marks-Kaugman 1982; Shor-Posner et al. 1985; Leibowitz and Shor-Posner 1986; Brewerton et al. 1992b).

Neither m-CPP, nor L-TRP produced significant differences in testmeal duration in the bulimics, the controls, or the total group. This has been demonstrated in animal studies to increase following enhancement of 5-HT function (Leibowitz et al. 1988). Meal duration may be a less sensitive measure of 5-HT's effects on human feeding, which is more complex and multi-determined. Not surprisingly, bulimics took significantly more time to eat than the controls, regardless of the drug. Patients knew that they were subject to possible observation during eating and that they would not be able to purge following the testmeal; this situation may have increased food-related anxiety and avoidance behavior (Katzman and Wolchik 1984; Johnson et al. 1986; Davis et al. 1988). The effects of the artificial nature of this eating paradigm on our results must be acknowledged.

Administration of the two agents may be important in interpreting our results. Although all agents were administered at the same time (10 A.M.), the plasma levels of the intravenously administered L-TRP peaked earlier than the orally administered m-CPP. L-TRP may therefore have had a more rapid onset of action and a longer interval until the testmeal was presented than m-CPP may have had. However, L-TRP still has to be metabolized to 5-HT, enter the vesicles and be released, whereas m-CPP has a direct action on receptor sites. On the other hand, peak neuroendocrine responses to IV L-TRP occurred approximately one and a half hours earlier than the peak neuroendocrine responses to oral m-CPP (Brewerton et al. 1992c). Other differences between m-CPP and L-TRP that could possibly explain diversity in feeding responses include presynaptic versus postsynaptic mechanisms, the subtype(s) of 5-HT receptor, the anatomic loci of action, comparative drug dose, and amount of prestudy fasting. It is impossible to determine the degree to which nausea contributed to the suppression of food intake. The effects of enhanced 5-HT function on other neurotransmitters (e.g., norepinephrine, acetylcholine, and peptides), such as the opiates (Brewerton et al. 1992b) and CCK-8 (Brewerton et al. 1992a; Lydiard RB et al. 1993), may also be important in understanding these results. Nevertheless, the observation that bulimics and controls demonstrated some diversity in their responses to both serotonergic agents is consistent with a serotonin dysregulation hypothesis of bulimia nervosa (Brewerton et al. 1986, 1989, 1991a, 1991b, 1992; Brewerton, in press; Jansen et al. 1989; Goldbloom and Garfinkel, 1990; Jimerson et al. 1990; Liebowitz, 1990).

In summary, this study determined that the serotonin receptor agonist m-CPP produced a significant decrease in calorie intake in volunteers consuming a standardized test meal. Meal size was inversely correlated with peak m-CPP drug levels, and the drug effects were not significantly different for bulimic patients and for controls. Decreased food intake following m-CPP was relatively nonselective across macronutrients; the decrease in percentage was not significantly different for protein or fat, although the most robust decrease was for carbohydrates.

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SPD489 in Adults Aged 18-55 Years With Moderate to Severe Binge Eating Disorder

This study is ongoing, but not recruiting participants.

Sponsor:
Shire Development LLC

Information provided by (Responsible Party):
Shire Development LLC

ClinicalTrials.gov Identifier:
NCT01718509

First received: October 29, 2012
Last updated: July 9, 2013
Last verified: July 2013
History of Changes

Purpose

The primary objective of the study is to demonstrate the efficacy of SPD489 compared with placebo in adults (18 55 years of age inclusive) with moderate to severe **Binge Eating Disorder** at Visit 8 (Weeks 11 and 12) as measured by the number of **binge** days (defined as days during which at least 1 **binge** episode occurs) per week as assessed by clinical interview based on subject diary

Condition	Intervention	Phase
Binge Eating Disorder	Drug: SPD489 (**Lisdexamfetamine** dimesylate) Drug: Placebo	Phase 3

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Investigator)
Primary Purpose: Treatment

Official Title: The SPD489-344, Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Placebo-controlled, Dose-optimization Study to Evaluate the Efficacy, Safety, and Tolerability of SPD489 in Adults Aged 18-55 Years With Moderate to Severe **Binge Eating Disorder**

Resource links provided by NLM:

MedlinePlus related topics: Eating Disorders

Drug Information available for: Lisdexamfetamine Lisdexamfetamine dimesylate

U.S. FDA Resources

Further study details as provided by Shire Development LLC:

Primary Outcome Measures:

- **Binge** Days Per Week [Time Frame: up to 12 weeks] [Designated as safety issue: No]

Secondary Outcome Measures:

- Clinical Global Impression-Improvement (CGI-I) [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- 4-Week Cessation From **Binge Eating** Behavior [Time Frame: last 28 days prior to final visit] [Designated as safety issue: No]
- Body weight [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- Triglyceride levels [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- Cholesterol levels [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- Glycosolated Hemoglobin (HbA1c) Levels [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- **Binge** Episodes Per Week [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- 1-Week Cessation From **Binge Eating** Behavior [Time Frame: last 7 days prior to visit] [Designated as safety issue: No]
- Yale-Brown Obsessive Compulsive Scale Modified for **Binge Eating** (YBOCS-BE) Score [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- **Eating** Inventory Score (also known as the Three-Factor **Eating** Questionnaire) [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- **Binge Eating** Scale (BES) Score [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- Frontal Systems Behavior Score (FrSBe) [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- EuroQoL Group 5 Dimension 5-Level Self-Report Questionnaire (EQ-5D-5L) [Time Frame: up to 12 weeks] [Designated as safety issue: No]
- Amphetamine Cessation Symptom Assessment (ACSA) Total Score [Time Frame: up to 12 weeks] [Designated as safety issue: Yes]

Enrollment:	390
Study Start Date:	November 2012
Estimated Study Completion Date:	September 2013
Primary Completion Date:	June 2013 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: SPD489 (**Lisdexamfetamine** dimesylate)	Drug: SPD489 (**Lisdexamfetamine** dimesylate) 50 or 70 mg administered orally, once-daily for up to 12 weeks Other Name: **Vyvanse**, Venvanse, LDX
Placebo Comparator: Placebo	Drug: Placebo Administered once-daily, orally, for up to 12 weeks

Detailed Description:

Not Required

Eligibility

Ages Eligible for Study:	18 Years to 55 Years
Genders Eligible for Study:	Both
Accepts Healthy Volunteers:	No

Criteria

Inclusion Criteria:

The subject cannot be enrolled in the study before all of the following inclusion criteria (including test results) are met:

1. Subject is between 18-55 years of age.
2. Subject meets the following Diagnostic and Statistical Manual of Mental Disorders Fourth Edition - Text Revision (DSM-IV-TR) criteria for a diagnosis of BED:
3. Subject has a BED diagnosis.
4. Subject's BED is of at least moderate severity with subjects reporting at least 3 binge eating days per week.
5. Female subjects must have a negative serum B-HCG pregnancy test and a negative urine pregnancy test and agree to comply with any applicable contraceptive requirements.

Exclusion Criteria:

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Subject has concurrent symptoms of bulimia nervosa or anorexia nervosa.
2. Subject is receiving psychotherapy (eg, supportive psychotherapy, cognitive behavior therapy, interpersonal therapy) or weight loss support (eg, Weight Watchers) for BED.
3. Subject has used psychostimulants to facilitate fasting or dieting as a part of their BED.
4. Subject has a lifetime history of psychosis, mania, hypomania, dementia, or ADHD.
5. Subject is considered a suicide risk, has previously made a suicide attempt, or is currently demonstrating active suicidal ideation.
6. Subject has known history of symptomatic cardiovascular disease, advanced arteriosclerosis, structural cardiac abnormality, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems.
7. Subject has a history of moderate or severe hypertension.
8. Subject is female and pregnant or nursing.
9. Subject has had bariatric surgery, lap bands, duodenal stents, or other procedures for weight loss.

Contacts and Locations

Please refer to this study by its ClinicalTrials.gov identifier: NCT01718509

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Sponsors and Collaborators

Shire Development LLC

Investigators

Principal Investigator: Susan McElroy, MD University of Cincinnati

More Information

No publications provided

Responsible Party:	Shire Development LLC
ClinicalTrials.gov Identifier:	NCT01718509 History of Changes
Other Study ID Numbers:	SPD489-344
Study First Received:	October 29, 2012
Last Updated:	July 9, 2013
Health Authority:	United States: Food and Drug Administration

Additional relevant MeSH terms:

Bulimia
Binge-Eating Disorder
Eating Disorders
Mental **Disorders**
Hyperphagia
Signs and Symptoms, Digestive
Signs and Symptoms
Dextroamphetamine
Dopamine Uptake Inhibitors
Dopamine Agents
Neurotransmitter Agents
Molecular Mechanisms of Pharmacological Action
Pharmacologic Actions
Neurotransmitter Uptake Inhibitors
Physiological Effects of Drugs
Central Nervous System Stimulants
Central Nervous System Agents
Therapeutic Uses

ClinicalTrials.gov processed this record on July 14, 2013

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