Clinical Handbook of Eating Disorders

An Integrated Approach

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Neurotransmitter Dysregulation in Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder

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The current system of psychiatric diagnosis, DSM-IV (1), addresses two official eating disorder (ED) syndromes—anorexia nervosa (AN) and bulimia nervosa (BN)—and a third (still provisional) diagnostic entity—binge eating disorder (BED). However, BED has all but officially been recognized as a distinct eating syndrome. AN, BN, and BED are all polysymptomatic syndromes, defined by maladaptive attitudes and behaviors around eating, weight, and body image, but typically including "nonspecific" disturbances of self-image, mood, impulse regulation, and interpersonal functioning. All three syndromes are known to be associated with significant mortality and morbidity, both medical and psychiatric (2,3). Despite popular beliefs, there is no convincing evidence that cultural factors alone cause eating disorders. Indeed, during the past few years (and especially the last decade) investigations into the role of neurotransmitters and other neuromodulators in the eating disorders have been highly productive, and have implicated primary

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neurotransmitter disturbances in the etiology of both AN and BN. Furthermore, recent data clearly identify strong genetic factors in AN and BN, which appear to share common genetic vulnerabilities (4,5) linked to obsessionality, perfectionism, anxiety, and/or behavioral inhibition (6,7). One powerful piece of evidence to support monoamine involvement in the eating disorders is the observation that antidepressant medications can be beneficial in controlled studies, not only in BN patients but in recovered AN patients as well (8).

However, it is also clear that some disturbances are consequences of the abnormal eating practices and nutritional disturbances that characterize these disorders (9), which in turn exacerbate or perpetuate signs and symptoms (10). This perspective, taken together with the disorders' consequences, challenges, and costs, compels us toward a better understanding of the biological mechanisms underlying all stages and types of eating disorders. The identification of the psychobiological underpinnings of these conditions may be useful in many ways, including the development of improved medical and psychopharmacological interventions, improved education and psychotherapy for patients and their families, and improved prevention efforts at a primary level.

It must be emphasized that most measurements of neurotransmitter function provide only a glimpse into the state of the organism at that moment. Sorting out what is trait and what is state related has been a challenging focus of neurotransmitter research in the eating disorders.

MONOAMINES

The classical monoaminergic neurotransmitter systems, including serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE), and dopamine (DA), have been fairly extensively studied in the eating disorders using available techniques in biological psychiatry. Most of these studies have been conducted during the active state of illness, during which severe nutritional compromise may represent an important confound. Dieting and/or semistarvation clearly depletes central monoamines and leads to altered neurotransmitter levels and receptor sensitivity in animals and humans (11–15). To avoid this problem, a more recent strategy has been to study "recovered" patients, i.e., AN and BN patients who have attained normalization of eating and weight, resumption of menses and/or normalization of gonadal hormone levels, and abatement of typical cognitive features to subclinical levels. This strategy attempts to minimize starvation state–related effects and to reveal potential trait-related disturbances or vulnerabilities. However, the long-term effects of chronic malnutrition and disordered eating behaviors on the brain (similar to substance use disorders) should not be minimized. Studies of

transmitter function in at-risk premorbid individuals as well as nonaffected identical and fraternal twins, siblings, and other first-degree relatives of ED patients could begin to confirm trait-related disturbances.

Neurotransmitter function in patients with EDs have been investigated using a variety of existing techniques and methodologies, each of which has its own advantages and disadvantages. Studies of cerebrospinal fluid (CSF) concentrations of the major metabolites have been a popular strategy and include measures of 5-hydroxyindoleacetic acid (5-HIAA) for 5-HT, 3-methoxy-4-hydroxyphenylglycol (MHPG) for NE, and homovanillic acid (HVA) for DA. Some studies have also examined actual concentrations of 5-HT and NE, but not DA. Such studies measure transmitter metabolism of the whole brain and spinal cord and lack any anatomical specificity.

Neuroendocrine and other psychobiological response measures have been studied following acute challenges with various agents, including amino acid precursors, e.g., L-tryptophan (L-TRP) and 5-hydroxytryptophan (5-HTP) for 5-HT, presynaptic receptor agonists, e.g., *dl*-fenfluramine (*dl*-FEN) or *d*-fenfluramine (*d*-FEN) for 5-HT, postsynaptic receptor agonists, e.g., *m*-chlorophenylpiperazine (*m*-CPP) for 5-HT, and isoproterenol (ISOP) for NE. Longer term challenges with receptor antagonists, e.g., antipsychotics for DA and 5-HT, and antidepressants, especially the serotonin-specific reuptake inhibitors (SSRIs), also illuminate the role of neurotransmitters in the eating disorders. Acute amino acid precursor depletion, most notably of L-TRP (16–19), has been another important source of information about the role of central 5-HT function in eating and related disorders.

Platelet (PLT) and leukocyte studies are possibly reflective of central neurotransmitter function but are always at least one step removed from the nervous system, e.g., platelet 5-HT reuptake, ^{3}H-imipramine binding, ^{3}H-paroxetine binding, platelet monoamine oxidase (MAO), platelet 5-HT content, as well as platelet receptor–mediated aggregation (5-HT_2 and α-adrenergic).

Plasma concentrations of neurotransmitter precursors, e.g., L-TRP, L-tyrosine (L-TYR), and their competing large neutral amino acids (LNAAs), neurotransmitters themselves, e.g., NE, DA, and whole-blood serotonin (WBS), as well as the usual metabolites, MHPG, HVA, and 5-HIAA.

Brain imaging receptor-binding studies are a promising avenue but remain relatively unexplored in the eating disorders.

For each neurotransmitter, the results from controlled studies in humans will be reviewed and summarized for both AN and BN. Where applicable, comparisons between restricting AN patients, bingeing–purging AN patients, and normal-weight BN patients will be made. Very little work of this nature has been done in BED patients but when available will be mentioned.

NOREPINEPHRINE

There are a number of reasons to suspect NE involvement in the eating disorders. Most notably, NE pathways at the level of the hypothalamus are known to be involved in the initiation of feeding (20). Disturbances in these pathways may therefore be involved in the pathophysiology of the profoundly altered feeding behaviors classically associated with the eating disorders. In addition, NE's role in the modulation of mood, anxiety, neuroendocrine control, metabolic rate, sympathetic tone, and temperature make it a likely candidate for study (21–26). It has been recognized for some time that low-weight anorexic patients, and to some degree bulimic patients, have reduced body temperature, blood pressure, pulse, and metabolic rate (25,27,28). Investigations in this area have shown that low-weight AN patients have reduced measures of plasma, urinary, and CSF MHPG (27,29–31). In contrast, reports of plasma NE levels in the eating disorders has been more variable (32,33), and this appears to be linked not only to weight but to the stresses associated with the illness (25). AN patients tend to have higher plasma NE levels at admission, which then decrease as treatment and weight gain progresses (25,34).

When ill, BN patients demonstrate lower values of plasma NE at baseline (21,28) and in response to abstinence (35), standing (36), test meal challenge (37), and mental challenge (37). They also have other evidence of blunted sympathetic activation in response to mental stress (38). However, despite low baseline plasma NE levels, BN patients show normal responses to exercise (39) but reduced responses to orthostasis (40).

In AN patients, depression has been found to be significantly worse in those patients with the lowest Δ change in plasma NE concentrations to orthostasis (41). Reduced urinary MHPG levels have also been related to the presence of comorbid major depression (29,42). It is therefore important in such studies to control for psychiatric comorbidity.

Like the plasma NE studies, CSF NE levels have been reported to be no different in AN patients than controls at low weight and after short-term weight gain, but then significantly lower after weight recovery of at least 6 months (26,31,32). In BN patients, reduced CSF NE levels have been reported during the active state of the illness (23,43). However, upon long-term recovery, concentrations of CSF MHPG have been reported to normalize in both AN and BN (7) despite earlier reports of lower levels (32). Given that CSF NE concentrations have not yet been reported in long-term (> 1 year) recovered AN or BN patients, the extent to which adrenergic alterations seen in the eating disorders are trait related remains unclear. Nevertheless, available evidence suggests exquisite sensitivity of this system to malnutrition or stress.

Challenge studies using the β-adrenergic agonist isoproterenol in underweight anorexic patients revealed erratic secretion of plasma NE in response to increasing doses (24). Bulimic patients demonstrated significantly increased chronotropic responses to isoproterenol (44). Challenge studies with adrenergic agents in recovered patients have not been reported.

The number of platelet α_2 receptors has been reported to be reduced in both AN and BN compared to controls (33,45), suggesting increased postsynaptic receptor sensitivity that is probably secondary to dieting or semistarvation. In summary, peripheral and central sympathetic nervous activity is reduced in both AN and BN, although it tends to normalize with recovery. Taken together, the preponderance of the evidence so far leads to the conclusion that these changes are a result of chronic starvation or intermittent dieting (26). However, a trait-related disturbance of the adrenergic system cannot be ruled out at this time (35).

Studies of adrenergic receptors on human leukocytes have been another strategy to investigate adrenergic function in the eating disorders. Buckholtz et al. (46) reported altered β-adrenergic receptor affinity on circulating lymphocytes of BN patients compared to those of controls. However, in a similar study of a mixed group of eating disorder patients, Lonati-Galligani and Pirke (40) reported lower receptor number (B_{max}) but normal affinity (K_d) in low-weight AN patients, whereas both measures were no different from controls in the BN patients and the weight-recovered AN patients. Gill and colleagues (47) reported differential changes in α- and β-adrenoceptor linked ($^{45}Ca^{2+}$) uptake in platelets from patients with AN, further documenting an adrenergic disturbance in eating disorder patients. However, the issue of cause versus effect remains unanswered in platelet and leukocyte studies.

DOPAMINE

DA is also suspect in the neuropathophysiology of the eating disorders given its reported involvement in the regulation of feeding, mood, activity, perception, sexual/social behavior, hormone and peptide release, and to some extent aggression (48–51). Notably, DA is involved in the hedonic reward responses to eating and its maintenance as well as to other pleasurable activities (52–54).

The majority of studies of DA metabolism in the eating disorders have consistently shown that low-weight AN patients have reduced measures of peripheral and central DA activity, including decreased plasma (27) and CSF HVA (31). In BN patients, reduced CSF HVA levels also have been reported in BN patients with frequent binge–purge episodes (23,50) but not in those less severely ill. Furthermore, binge frequency was inversely correlated with CSF HVA levels in one study (50). Upon long-term recovery, concentrations

of CSF HVA have been reported to normalize in BN (8), whereas a trend for decreased CSF HVA levels persisted in six restricting AN patients compared to controls and to bingeing and/or purging AN patients (7). This suggests a possible trait-related disturbance specific to restricting AN, although this finding needs replication given the small sample size. These results could also still be due to nutritional factors given that patients in this study weighed significantly less than those in the BN group and may still have been at the low end of the normal weight range.

Anecdotal reports of the successful use of dopaminergic antagonists (typical antipsychotic agents) in the treatment of AN patients (55) have been generally followed by equivocal results in controlled studies (56,57). Atypical antipsychotic agents may show more promise in the adjunctive treatment of AN given their combined antidopaminergic and antiserotonergic effects (58–60), but the results of placebo-controlled studies remain to be seen.

Genetic investigations into the role of DA have been limited to the Bal I DRD3 receptor polymorphisms in which no differences were found between AN patients and controls (61). However, the polymorphisms of other genes coding for DA receptors could be tested. Interestingly, Corcos and colleagues (62) reported significantly lower IgG and IgM autoantibodies to DA in BN patients compared to controls. There was also a trend for lower levels of IgM autoantibodies to DA in the eating-disordered group. The relevance of these findings to the pathophysiology of the eating disorders remains uncertain but invokes possible autoimmune mechanisms.

SEROTONIN

Several lines of reasoning point to disturbances of 5-HT function in the pathophysiology and neuropsychopharmacology of the EDs (8,9,63), including serotonin's role in feeding (64,65), satiety (66,67), dieting/fasting (11,12), mood regulation (16), anxiety (68), obsessive-compulsiveness/perfectionism/behavioral inhibition (69), harm avoidance (70,71), impulsivity/aggression (72,73), motor activity (74,75), gender (76,77), seasonality (66,78,79), body image/perception (80), and social behavior (81–83) (see Table 1).

Reductions in a variety of 5-HT parameters have been consistently reported in low-weight AN patients. Although no significant differences have been found in absolute plasma L-TRP levels (84–86), the plasma L-TRP/LNAA ratio is reduced in the low weight state (30,87,88) but normalizes upon short-term weight recovery (22,30). In BN, Gendal and Joyce (89) reported that the L-TRP/LNAA ratio inversely correlated with the desire to binge-eat. In addition, symptomatic bulimic relapse or worsening of symptoms has been reported following acute L-TRP depletion in BN (17–19).

TABLE 1 Monoamines and the Phenomenology of the Eating Disorders

Factor	Norepinephrine	Dopamine	Serotonin
Activity/exercise	X	X	X
Fasting effects	X	X	X
Mood regulation	X	X	X
Hormone regulation	X	X	X
Neuropeptide regulation	X	X	X
Trauma effects	X	X	X
Temperature	X		X
Anxiety	X		X
Blood pressure/pulse	X		X
Metabolic rate	X		
Feeding initiation/hunger	X		
Body image/perception		X	X
Impulsivity/aggression		X	X
Sexual behavior		X	X
Feeding maintenance/hedonic reward		X	
Novelty/sensation seeking		X	
Harm avoidance			X
Behavioral inhibition			X
Feeding termination/satiety			X
Obsessive-compulsiveness/perfectionism			X
Social hierarchy/rank			X
Gender differences			X
Seasonality/light effects			X
Circadian rhythmicity			X
Age/developmental effects			X

Other significant findings include decreased CSF L-TRP levels (90) and decreased CSF 5-HIAA levels (22,88,91) during low-weight status with normalization of these levels with short-term weight recovery (STWR, goal weight maintenance ≥3 weeks). Strikingly, Kaye and colleagues (69,92) have reported abnormally elevated CSF 5-HIAA levels following long-term weight recovery (LTWR, goal weight maintenance ≥6–12 months), and interpret these findings as indicating that AN may correspond to a primary state of excessive 5-HT tone, which is then masked by malnutrition-induced *reductions* in 5-HT activity during active illness. In other words, they propose that the pathophysiology of AN actually involves a hyperserotonergic trait and, furthermore, postulate that this trait may correspond to behavioral traits of obsessionality and inhibition. Corroborating the notion of hyperserotonergic status in AN, Kaye and colleagues have noted long-term weight-restored anorexics to display *elevated* 5-HT_{1a} receptor binding, measured by positron emission tomography (PET) (93).

In BN, reduced levels of CSF 5-HIAA are consistently reported only in the subgroup of patients displaying more frequent binge–purge episodes (23,50). Suggesting a possible link to severity of bulimic symptomatology, binge frequency has been found to correlate inversely with CSF 5-HIAA concentrations (50). In a small pilot study, Brewerton and colleagues (94) have reported no difference in CSF 5-HT levels between BN patients and controls. However, upon recovery for at least a year, BN patients have been reported to have elevated CSF 5-HIAA levels compared to healthy controls (95), much like those described earlier as being characteristic of long-term recovered anorexics. As in AN, this finding has been linked to obsessive-compulsive personality traits, perfectionism, and behavioral inhibition, associated with a hypothetical tendency toward hyperserotonergic status. However, we note, that the Kaye et al. study of recovered BN may be confounded by small weight discrepancies between their (heavier) recovered bulimics and lighter comparison controls. Such weight differentials could underlie discrepant levels of 5-HT metabolism.

Decreased prolactin (PRL) responses following *m*-CPP (96–98), L-TRP (96,97), and fenfluramine (FEN) (99–101) have been reported in AN and indicate an anatomically specific alteration in 5-HT receptor sensitivity at the level of the hypothalamus, which could conceivably also occur in other brain pathways (9). Blunting of PRL following *m*-CPP persists into short-term weight recovery, although trends toward normalization of PRL responses, after refeeding and weight gain, have been reported (97). With at least a year of recovery, neurohormonal responses to *m*-CPP normalize in restricting AN patients (92). Apparently, full normalization of PRL responsivity to serotonergic agents occurs after full weight restoration, normalization of hypothalamic-pituitary-gonadal function, and abatement of overt eating disorder symptoms (7). However, the appetite-suppressing effect of FEN is significantly diminished in recovered AN patients despite normalization of hormonal release (102).

Platelet (PLT) studies contribute to the demonstration of serotonergic dysfunction in AN. Significant increases/reductions in PLT imipramine (IMI) binding (103), but not PLT 5-HT uptake (103,104) or PLT MAO content (42), have been reported in low-weight AN patients. However, a more recent study reported decreased PLT MAO in AN (105), which was inversely correlated with impulsivity and positively correlated with persistence (which is similar to rigidity). In a related vein, Finocchiaro and colleagues (106) conducted a novel study of indole metabolism and reported altered phytohemagglutinin stimulated, light-induced [^{3}H]thymidine incorporation into the DNA of peripheral blood mononuclear leukocytes in AN patients compared to controls. The authors concluded that the white cells of AN patients show a failure in the regulation of 5-HT and melatonin metabolism in response to light.

As in AN, neurobiological indices in active BN are often consistent with reduced 5-HT tone. For example, findings in BN show a consistent pattern of PRL blunting following *m*-CPP (107–110), fenfluramine (99,101,111–113), and 5-hydroxytryptophan (5-HPT) (114), but not L-TRP (9,107). PRL responses following L-TRP are low only in the BN patients with concurrent major depression, again emphasizing the need to control for comorbidity. PRL responses following *m*-CPP are inversely correlated to baseline cortisol (CORT) (9). Self-reported binge frequency also has been shown to be inversely correlated to PRL responses following *m*-CPP (9) and fenfluramine (101,111,113) in BN patients. Given that this presumed alteration in hypothalamic postsynaptic 5-HT functioning normalizes with recovery from BN (8,95,115), these serotonergic abnormalities could be understood to be a *result* of bingeing, purging, and/or dieting rather than a *cause* of these behaviors, although other vulnerabilities of the 5-HT system may also exist and interact with these psychosomatic behaviors. There is only one serotonergic challenge study reported in BED (101), which found that PRL responses following *d*-FEN were no different in patients with BED than in controls. This lends support to the idea that purging, dieting, and weight loss (rather than bingeing per se) have greater roles in creating the serotonergic abnormalities noted above. Dieting, bingeing, and vomiting all may affect central 5-HT synthesis (13,14,22,116,117) and could conceivably result in down-regulation of postsynaptic 5-HT receptors and blunted PRL responses. In addition, these behaviors may involve activation of the HPA axis, which in turn appears to dampen 5-HT receptor sensitivity (9,107). Despite findings linking recovery from BN to normalization of blunted endocrine responses after 5-HT agonists (95,115), other findings (based on PET techniques) suggest persistent reductions in postsynaptic 5-HT_{2a} receptor activity even in fully recovered bulimics (118). Such findings associate BN with a stable reduction in 5-HT neurotransmission at some central sites—and present the possibility that such tendencies exist independently of disorder sequelae in BN patients.

In BN, platelet studies indicate reduced PLT IMI binding (119) and PLT MAO (120). PLT 5-HT uptake has been reported to be increased in one study (121) but not another (120). Steiger et al. (110,122) reported reduced PLT paroxetine binding in groups of BN patients compared to healthy controls.

Possible Trait-Linked Effects

Independently of dietary factors, personality trait variations might explain some of the variations in 5-HT status seen in eating disorder sufferers. In non-eating-disordered populations, correspondence between 5-HT function and personality trait variations has been well established. For example, impul-

sivity has been consistently linked to decreased 5-HT activity; suicide, fire setting, violence, and borderline personality disorder (BPD, for which impulsivity is pathognomonic) have all been linked to decreased 5-HT metabolism (as indicated by reduced CSF 5-HIAA) (123,124). Likewise, impulsive suicidality and aggression have been linked to low platelet 5-HT content and reduced PRL response to 5-HT agonists (123,124). On the opposite side of the same coin, findings in non eating-disordered samples have (at least inconsistently) associated anxiety or compulsivity with *increased* 5-HT tone. For example, patients with obsessive-compulsive disorder have been reported to display elevated CSF 5-HIAA (125) and increased PRL response after the 5-HT agonist fenfluramine (126). Furthermore, the partial 5-HT agonist *m*-CPP has been observed to increase obsessionality in obsessive-compulsive patients, and anxiety in patients with generalized anxiety disorder (127–129). Likewise, heightened anxiety has been associated with elevated 5-HT activity in both generalized anxiety disorder (130) and AN (131). Such findings have encouraged some theorists to propose that "impulsive" and "compulsive" traits occupy opposite poles of a continuum of 5-HT under- to overactivation (132,133). While this notion remains controversial, it is tempting to contemplate the possibility that 5-HT findings in restrictive versus bulimic ED variants may reflect variations associated with differential loadings of compulsive or impulsive traits in these ED subgroups.

In keeping with the notion outlined above, various studies report that personality trait variations account for variations of 5-HT indices in ED patients, at least when actively eating disordered. Waller and colleagues (134) observed that hostile bulimics, compared to less hostile ones (by self report), showed smaller neuroendocrine responses following buspirone (which they presumed to be a 5-HT_{1a} agonist). Likewise, Carrasco and colleagues (135) observed systematically lower platelet MAO concentrations (taken as a proxy for reduced 5-HT activity) in bulimics with impulsive or "borderline" traits. Results of several studies by Steiger and his colleagues are comparable. In one study, PRL responses after *m*-CPP were measured in bulimic women who reported, or who denied, a history of self-mutilative or suicidal impulsivity (136). (Incidentally, these two groups of women, were quite comparable on indices of binge and purge frequency and body mass). Compared to normal eaters, the self-harming bulimics were clearly blunted, as far as 5-HT function was concerned; the non-self-harming bulimics were not. In other words, an association was observed between blunting of the *m*-CPP-stimulated PRL response and self-destructiveness, comparable to that obtained in non-eating-disordered populations (137). This observation suggests that hypoactivity of the 5-HT system in BN may be more strongly linked to self-aggressive impulsivity than it is to binge–purge symptoms per se. However, in the study by Brewerton et al. (107), no such differences were found between bulimic patients with and without a history of suicidality. Another study by Steiger's

group examined platelet ^{3}H-paroxetine binding in normal women and in bulimic women, and assessed effects of "nonplanning impulsivity" (i.e., the tendency to act without considering consequences) (110). Both bulimic groups displayed reductions in density (B_{max}) of paroxetine binding sites. However, in bulimics, the extent of reduction in binding site density was inversely correlated with "nonplanning." In other words, reduced peripheral 5-HT reuptake corresponded to increased impulsivity. This effect parallels inverse relationships noted between platelet 5-HT binding and aggressive impulsivity (138) or self-mutilation (138) in personality-disordered subjects, raising the notion that in BN we could be observing a constitutional (trait-linked) susceptibility to underactivity of the 5-HT system. Furthermore, if exacerbated by effects of dieting, such susceptibilities could cause certain people to become especially impulsive and/or prone to binge eating.

Taken together, research findings from plasma, CSF, and pharmacological challenge studies suggest reduced 5-HT synthesis, uptake, and turnover, as well as altered postsynaptic 5-HT receptor sensitivity during the active phases of both AN and BN. Consequently, many reported alterations in 5-HT function appear to be state dependent, although they may have important biological roles in the perpetuation of symptoms, particularly mood dysregulation, increased anxiety, obsessionality, impulsivity, self-aggression, and perhaps the resistance to and difficulty in learning healthier coping strategies (139).

However, to avoid presenting an oversimplified, unidirectional hypothesis of 5-HT alterations in the eating disorders, it is necessary to note some findings suggesting heightened 5-HT receptor sensitivity at certain central sites in eating disorder patients with active symptoms. For example, Brewerton (9) reported enhanced temperature and migraine headache responses to *m*-CPP but not L-TRP in BN patients (regardless of the comorbid presence of AN or MD) (9,140,141). As discussed in detail elsewhere (141), the enhanced migraine-like HA responses in the BN patients may indicate enhanced 5-HT_2 receptor sensitivity in CNS vascular tissues. Enhanced 5-HT-mediated platelet aggregation, a 5-HT_2 receptor–mediated phenomenon, has also been reported in BN (142) and AN (99,112,142) and lends further support to this hypothesis. The normal cortisol responses following *m*-CPP and L-TRP in AN and BN are compatible with this view given the involvement of both 5-HT_1 (facilitative) and 5-HT_2 receptors (inhibitive) in cortisol secretion. These presumed alterations in 5-HT receptor sensitivity, whether primary or secondary, demonstrate that 5-HT receptor sensitivity can be both decreased and increased in the same subjects depending on the anatomical location of the receptor as well as the receptor subtype. We (9,143) have argued in favor of a dysregulation hypothesis of serotonin dysfunction in the eating and related disorders, proposing that there is a failure in transmitter regulation in the face of a variety of psychobiological perturbations potentially affecting

monoamine function, including dieting, fasting, purging, substance abuse, excessive exercising, medical illnesses, family stresses or losses, sociocultural pressures, traumatic events, puberty, other developmental tasks/challenges, and changes in the seasons. Certainly, evidence suggests that a model of neurotransmitter alterations in the eating disorders stated in terms of a unidirectional (high versus low activity) concept will not be adequate.

Interest in 5-HT activity in the EDs has led to quite a catalogue of studies on 5-HT system genes—controlling activity of 5-HT receptors, tryptophan hydroxylase (TPH, the rate-limiting enzyme for 5-HT synthesis), and 5-HT transporter (reuptake) mechanisms (144). Collier et al. (145) reported a statistically significant 5-HT2A-1438G/A receptor gene polymorphism in a group of restricting AN patients compared to healthy controls. This finding has been replicated in at least two other studies in AN (146,147) as well as in OCD (147), but not in BN (147). Nacmias et al. (146) reported that other serotonergic polymorphisms of the 5-HT_{2a} as well as those of the 5-HT_{2c} receptors showed no differences in AN patients compared to controls. Likewise, no differences between AN patients and controls have been reported for serotonin transporter gene–linked polymorphisms (5-HTTLPR) (148,149), tryptophan hydroxylase polymorphisms (150), and 5-HT1Dbeta and 5-HT7 gene polymorphisms (151).

For BN, there have been various association studies: Studies on 5-HT_{2c} polymorphisms in BN detect no syndrome-linked associations (144). Similarly, three of four available studies on the 5-HT_{2a} receptor gene indicate absence of association with BN (146,147,152). However, a fourth (in a heterogeneous anorexic–bulimic sample) associates the 5-HT_{2a} "G" allele with proneness to bulimic symptoms, borderline personality, and generalized impulsivity (153). Such findings imply that common genetic factors might mediate concurrence of bulimic eating patterns and traits of a borderline/impulsive type. Yet another recent study, first to examine the 5-HT transporter gene (promoter region, 5HTTLPR) in BN, indicates a short-allele variation to confer sevenfold risk of BN (154). The short (s) allele of 5HTTLPR has been linked to reduced transcription of 5-HT transporter protein, decreased 5-HT reuptake in lymphoblasts (155), and traits like suicidality (156), neuroticism, and impulsivity (157). Preliminary findings from our lab provide a second indication of relevance of the 5-HT transporter (5-HTT) gene to binge eating and impulsivity (158). Results in 48 women with binge eating syndromes showed individuals carrying the short (s) allele of 5HTTLPR (either s/s or s/l genotypes) to show more impulsivity and lower density of paroxetine-binding sites than did long (l) allele homozygotes. These results, if they hold up, would cross-validate (at a genetic level) a link between impulse control problems and hyposerotonergic status, indicating convergence among impulsive traits, low 5-HT transporter activity, and the s allele.

Evidence from Pharmacological Effects

It is well known that serotonin-specific antidepressant medications can be beneficial in controlled studies of BN patients (159) but not in low-weight AN patients (160,161). More recent data indicate a prophylactic effect of fluoxetine following weight gain in recovered AN patients (8). SSRIs don't work during the low-weight state, presumably because of central depletion of 5-HT and other monoamines with starvation. There is significantly less 5-HT centrally to be inhibited by SSRIs.

Finally, recent evidence indicates significant antibulimic responses to 5-HT_3 antagonists, such as ondansetron (162,163). Although the authors attribute this therapeutic response to the drug's ability to reduce vagal tone, the role of the 5-HT_3 receptor remains intriguing given its antianxiety effects (164). These findings open important new arenas for future research involving possible serotonergic-cholinergic mechanisms, which has been a relatively unexplored area in the eating disorders.

MAO/ISATIN

Isatin, or tribulin, is an endogenous indole associated with stress, which inhibits MAO (165). Brewerton et al. (94) reported significantly higher CSF concentrations of isatin in BN patients compared to healthy controls. There was also a trend for CSF isatin concentrations to be inversely correlated with CSF concentrations of the serotonin metabolite 5-HIAA ($n = 14$, $\rho = -0.51$, $p = 0.06$), although CSF isatin levels were not significantly correlated with CSF MHPG or HVA. The increase in isatin levels has been hypothesized to be in response to the resultant monoamine depletion secondary to the effects of the illness on monoaminergic function. As noted previously, platelet MAO has been reported to be decreased in BN (120) and in AN (105). This decrease may represent a compensatory change in response to monoamine depletion during the active state of the disorders.

RELATIONSHIP TO OTHER SYSTEMS

Neurotransmitter systems do not exist in a vacuum but are exquisitely interdependent with other brain and body systems and the environment as well. It is important to think about systems (e.g., 5-HT) and their subsystems (presynaptic, postsynaptic, receptor subtypes) in the context of larger systems (brain, environment) and interacting systems/subsystems (e.g., NE, DA, neurohormones, neuropeptides) with complex feedback and counterfeedback mechanisms at multiple anatomical levels. An extensive discussion of this

rather far-reaching topic is beyond the scope of this chapter but is discussed in more detail elsewhere (9).

CONCLUSIONS

Taken together, available findings implicate abnormalities of all monoamine neurotransmitter systems during the active phases of both AN and BN. Upon normalization of weight and neurohormonal function, most transmitter anomalies resolve or atleast improve. Some data show persistent particularities of the 5-HT system, and suggest that observed tendencies may reflect psychological traits found in both AN and BN, including obsessionality, perfectionism, high harm avoidance, and behavioral inhibition, on the one hand, and recklessness, failure to consider consequences of actions, self-destructiveness, and behavioral disinhibition, on the other. Furthermore, some evidence may be consistent with association between greater behavioral inhibition and excessive 5-HT activity (at some loci in the system), and behavioral disinhibition and reduced 5-HT neurotransmission (also at some loci in the system). The findings in question create a case for the idea that any given individuals' 5-HT functioning probably varies in function of constitutionally determined (latent or manifest) personality trait tendencies. In this light, it is intriguing to contemplate the ways in which constitutional traits associated with hypoactivity of the 5-HT system (e.g., impulsivity) may predispose to binge eating—and traits associated with elevated 5-HT tone (like compulsivity or harm avoidance) may predispose to dietary restriction.

Some evidence suggests prolonged alterations in NE metabolism, but this is most likely due to persistent low-grade dietary restraint following recovery. Preliminary data indicate a DA deficit in restricting AN patients, but this result remains to be replicated in larger samples. Recent findings also emphasize the importance of neurotransmitter precursor substrate availability to normal brain function and especially to the process of recovery from an eating disorder. Future research directions will include further exploration of neurotransmitter-related gene candidates, in vivo receptor imaging studies, and improved psychopharmacological interventions based on biological alterations characteristic of the different stages and features of these dangerous disorders.

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Psychopharmacology of Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder

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As the fundamental causes of eating disorders remain unknown, it is no surprise that development of successful treatments has not come easily. Nonetheless, much progress has been made. The current mainstays of treatment of eating disorders are psychological interventions, including cognitive therapy, behavioral therapy, family therapy, and nutritional counseling (1). Clinicians have generally looked to medication to augment the effects of psychological intervention, or as a primary intervention when such treatment is unavailable or ineffective.

The role of psychopharmacology in eating disorders has been greatly clarified in the last decade. But, as in the case of other psychiatric disorders, the limited understanding of the basic pathophysiology handicaps the ability to design psychopharmacological treatments. In the absence of a specific biological model, a range of differing perspectives has prompted attempts to identify medication treatments for anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED). In general, studies of medications in AN have been disappointing. In contrast, in BN, antidepressants are clearly effective at reducing binge eating and purging behaviors. Studies of BED are

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at an earlier stage but have already yielded promising findings. A consistent observation across the eating disorders is the need for double-blind, placebo-controlled studies to assess efficacy, as a medication often looks promising in case studies or open trial but fails to show superiority to placebo in a rigorously controlled trial.

This chapter will review the current data on the use of medications in the management of AN, BN, and BED with the intention of providing the clinician with information needed to make decisions about pharmacological treatment. The data will be reviewed according to what has been shown to be useful on the basis of controlled trials. Each illness—and stage of illness in the case of AN—will be considered separately and different outcome measures will be discussed when available.

ANOREXIA NERVOSA

Anorexia nervosa is characterized by a relentless pursuit of thinness and fear of becoming fat: patients starve themselves to extremes of low weight, resulting in amenorrhea and risk of death. Treatment must target multiple aspects of the disorder as patients need to gain weight, extinguish eating-disordered behaviors, and alter cognitions that foster these behaviors. Current recommendations focus on a multidisciplinary approach to treatment, including psychotherapies with cognitive–behavioral components. Inpatient treatment for patients at very low weight focuses on behavioral interventions and nutritional counseling to encourage eating and weight gain in conjunction with beginning to challenge cognitive disturbances. Nonetheless, AN has been difficult to treat and has a high relapse rate. Thus medications are under investigation both to facilitate initial treatment and to prevent relapse.

Study of the management of AN lends itself to multiple possible outcome measures. The major initial concern is weight restoration, which can be readily assessed by the amount and the rate of weight gain. In the long term, rate of relapse is an important outcome, defined as significant weight loss or reemergence of restrictive or binge–purge behaviors. Interwoven through both phases of treatment (weight gain and relapse prevention) is the complex problem of body image dissatisfaction.

Many psychopharmacological interventions have been tried, beginning with the work of Dally and Sargant on antipsychotics in the 1960s. Due to the limited understanding of the biological basis of AN, medication trials have been driven by unproven theoretical models and/or by an interest in taking advantage of medication side effects. While anecdotal reports of successful treatments have been published, only a small number of randomized controlled

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trials have been conducted, and definitive psychopharmacological treatment has not been identified.

Antidepressants

Antidepressant treatment for AN is a reasonable notion given the common concomitant symptoms of anxiety and depression. Many patients with AN describe low mood, low energy, poor concentration, loss of interest, and social isolation. The ritualized behaviors around eating and the obsessive preoccupation with shape and weight can be conceptualized as on the spectrum of obsessive-compulsive disorder (OCD), a syndrome that is also responsive to antidepressant medication.

Controlled trials of several different medications to promote weight gain have been generally discouraging. Initial studies involved tricyclic antidepressants (TCAs), with the hope that the side effect of weight gain would add to the benefits of treating mood disturbance. There have been three randomized controlled trials of TCAs. In one, clomipramine was associated with a slower rate of weight gain than placebo despite increased appetite, and there were no long-term effects at 1 and 4 years (2). In a study of amitriptyline versus placebo, there was no significant difference in weight gain (3). A second study of amitriptyline, which also had a third arm in which subjects received the serotonin (5-HT) antagonist cyproheptadine, showed no major benefit of amitriptyline (4). TCAs are known to prolong the QTc interval, which is also affected by AN. These observations, coupled with concerns that TCAs in children and adolescents may be linked to sudden death (5), suggest that TCAs should be rarely used for patients with AN at low weight.

In light of their benign side effect profile and efficacy in many other disorders, selective serotonin reuptake inhibitors (SSRIs) would appear promising in the management of in AN. Initial anecdotal evidence that fluoxetine might be beneficial for weight gain and mood symptoms (6) was supported in an open trial (7). However, the single randomized placebo-controlled trial of fluoxetine did not support these results. Attia et al. (8) conducted this trial of 33 patients with AN at low weight. All patients received inpatient care in addition to either fluoxetime (60 mg/day) or placebo for 7 weeks or until they reached 90% of ideal body weight and maintained it for a week. Fluoxetine conferred no benefit on weight gain, irrespective of subtype (restricting versus binge–purge). This finding is consistent with an open trial of Strober et al. (9) who administered fluoxetine to 33 inpatients.

While the studies of medication treatment in the acute phase focused on weight gain, some studies also included measures of other dimensions of AN. Mood symptoms have been found to improve with weight gain, with no added

benefit from medication (8,34). The open trial of Strober et al. described above (9) examined severity of weight phobia and abnormal eating behaviors and found no evidence that fluoxetine treatment was of benefit. Attia and colleagues (8) assessed the effect of medication on body image dissatisfaction, a core component of AN, and noted significant improvement with weight gain in scores on Body Satisfaction Questionnaire (BSQ) in both placebo and fluoxetine groups, although not to within the normal range in either group.

Somewhat more promising results have been found in the relapse prevention phase, but there is just one randomized controlled trial. Thirty-five women with AN, restricting subtype, entered a double-blind, randomized, controlled trial after inpatient weight restoration and received either fluoxetine (10–60 mg/day) or placebo for 11 months (10). Subjects receiving medication were significantly more likely than those who received placebo to maintain near-normal weight for one year. Interpretation of data from the randomized trial is limited in that dosage of fluoxetine was not controlled for, nor was additional treatment (i.e., psychotherapy) restricted. Subjects were limited to those with restricting subtype, and there is no information on the effect of medication on parameters other than weight. In addition, a naturalistic study of Strober et al. (11) comparing relapse among patients receiving open fluoxetine treatment to relapse among a group of matched, historical controls failed to detect evidence of a benefit from fluoxetine. Nonetheless, the study of Kaye et al. (10) is virtually the only placebo-controlled examination of medication in AN that found a statistically and clinically significant impact of medication compared to placebo. Further study is needed to determine replicate and extend this finding.

In summary, there is little reason to think that antidepressants add substantially to the standard inpatient management of AN. Given the widespread benefits of antidepressant medication in other, seemingly related psychiatric disorders, the lack of impact of antidepressants is surprising. Kaye et al. (12) have shown that patients at low weight have low levels of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin, which improve with weight gain. Low levels of 5-HIAA suggest that patients have low levels of brain serotonin, which is consistent with the finding that dieting in non-eating-disordered women reduces tryptophan levels (the amino acid that is the substrate for serotonin) and reduces serotonin production (13). Thus, it may be that antidepressants are ineffective at low weight because they have insufficient substrate (14). This is supported by the finding that tryptophan depletion has been shown to reverse the effects of SSRIs in depressed patients (13).

Notably, virtually all studies of patients at low weight have been conducted in an inpatient setting, where nonpharmacological interventions are effective in producing weight gain. At least theoretically, there is potential

for benefit from medication in an outpatient setting, where weight gain tends to be slower.

Antipsychotics

Pharmacological treatment in AN began with antipsychotics. The theoretical rationale for the use of this class of medication derives from the near-delusional quality of beliefs about shape and weight held by some patients with AN. Dally and Sargant (15) studied chlorpromazine (1600 mg/day) and found that while the rate of weight gain was enhanced compared to historical controls, there were significant negative effects including seizures and the emergence of binge–purge behavior. Furthermore, benefits were not sustained over long-term follow-up. Pimozide was studied subsequently in a randomized, controlled trial of hospitalized patients (16). The authors found a trend toward slightly higher daily weights while on pimozide, but effects on psychological symptoms were inconsistent. In a study of sulpiride among hospitalized patients receiving either medication or placebo for 3 weeks, there was no significant effect of medication on weight gain (17). Due to the known long-term side effects of the older antipsychotics and the side effects noted in some of the early studies, these medications are not generally recommended for management of AN.

With the advent of the new generation of antipsychotics, which have a lower incidence of tardive dyskinisia, extrapyramidal symptoms, and decreased likelihood of seizures, the possible usefulness of this class of medications has again been raised. Olanzapine would appear particularly promising as the prominent side effect of weight gain might be advantageous in AN. There have been several case reports of the use of olanzapine (5–10 mg/day) comprising about 10 hospitalized patients who had been refractory to other treatments (18–20). The patients described in these reports held near-delusional beliefs about their bodies, with no other psychotic symptoms. Mehler et al. (20) reported that while there was no dramatic improvement in the rate of weight gain after initiation of medication, there was a marked improvement in patient's cognitive style. One patient with a history of restricting developed binge–purge behavior while taking olanzapine (19). Olanzapine is a potentially promising intervention for AN, but its efficacy has not yet been established. In light of the research on antidepressants, where promising case reports and open studies were not born out in randomized controlled trials, further study of olanzapine and other second-generation antipsychotics is needed before definitive conclusions can be drawn. In addition, an important clinical consideration is whether patients will agree to a medication so clearly associated with weight gain.

Other Agents

A number of other medication classes have been tried, targeting primarily the weight gain phase of AN. Cyproheptadine, an antihistaminic agent that acts centrally to decrease serotonin activity, has been studied in several controlled trials after it was noted to cause weight gain in other conditions. Results have been mixed. In the first placebo-controlled trial (21), cyproheptadine did not improve weight gain. A second study found that cyproheptadine was associated with improved weight gain in a subgroup of severely ill patients (22). In a trial comparing amitriptyline, cyproheptadine, and placebo (mentioned above) (4), the authors noted no significant weight gain in the cyproheptadine group. However, they did note a difference between subtypes such that individuals with the restricting subtype showed an increased rate of weight gain with cyproheptadine whereas individuals with the binge–purge subtype showed an increased rate of weight gain with amitriptyline.

Consistent with patients' complaints about feelings of fullness and early satiety, patients with AN have been found to have slowed gastric emptying (23). Open trials of motility agents have been conducted using metoclopramide, bethanacol, cisapride, and domperidone (14). Few agents have been subjected to randomized controlled trials. Metaclopramide was found to decrease gastric emptying time (24), but a randomized controlled trial could not be completed because of the emergence of depression likely related to the CNS effects of the drug (25). Cisapride is a motility agent with mixed agonist/antagonist properties. It is an antagonist at the serotonin 5-HT_3 receptor and an agonist at the 5-HT_4 receptor. Cisapride was shown to improve gastric emptying time in a small, randomized, placebo-controlled study ($N = 12$) (26), but improvements in weight gain were not noted . In a larger study, Szmukler et al. (27) described improvement in gastrointestinal symptoms but no difference between medication and placebo groups with respect to gastric emptying or weight gain. Thus, the clinical benefits of cisapride in AN are uncertain. Furthermore, it was recently withdrawn from the market in the United States due to cardiac conduction effects, including prolonged QT interval and reports of sudden death.

Patients often describe their eating disorder symptoms as overwhelmingly strong urges to eat or to diet in a manner that bears some similarity to descriptions of drug cravings. Several studies have been conducted to examine the potential utility of opiate antagonists. Open trials of intravenous naloxone and oral naltrexone in underweight patients suggested improved weight gain (28). One placebo-controlled trial of naltrexone (200 mg daily) using a crossover design was conducted in patients with AN and BN (29). While the authors did not report results on weight gain in AN, they found that binge eating and purging rates diminished.

Zinc deficiency has notable similarities to AN. It is associated with weight loss, dysphoria, appetite and taste changes, and amenorrhea. Zinc deficiencies have been noted in low-weight AN populations (30), an unsurprising finding given the level of overall malnutrition. In contrast to most studies of AN, a number of the studies of zinc supplementation were conducted in children and adolescents. Three randomized controlled trials (30–32) and one open trial (33) of zinc supplementation (50–100 mg elemental zinc/day) have been reported. In a randomized controlled trial in children (31), there was no significant weight effect in the zinc-treated group. In adolescents, Katz et al. (30) found improvement in depression and anxiety in the adolescents who received zinc, but no effect on weight gain. In contrast, Birmingham et al. (32) found that zinc supplementation was associated with an increased rate of weight gain, even without evidence of zinc deficiency. In light of these mixed results, the utility of zinc supplementation is uncertain.

Other novel approaches to improving weight gain have included lithium, for its weight gain and mood stabilizing properties, and tetrahydrocannabinol (THC) for its appetite-enhancing effect. Lithium was associated with a small weight increase in one small, short-duration placebo-controlled trial (34). THC was compared to diazepam in a small randomized, double-blind trial using a crossover design (35). There was no benefit from THC with respect to food intake or weight gain, and THC was associated with significant side effects, including paranoia, sleep disturbance, and interpersonal sensitivity.

A major medical complication of AN is osteoporosis/osteopenia. Estrogen replacement therapy has been used to treat osteoporosis in postmenopausal women and therefore has been explored as an adjunctive treatment in AN. However, a randomized controlled trial assessing the bone densities of subjects receiving estrogen and progestin versus no medication found no significant changes in the hormone-treated group (36). Those patients who resumed menses showed improvement in bone density. These data suggest that, at present, the best documented intervention to arrest bone loss in AN is weight gain sufficient to restore regular menstruation.

BULIMIA NERVOSA

Bulimia nervosa is characterized by recurrent binge eating followed by inappropriate compensatory behaviors, such as vomiting. Because in DSM-IV, AN has diagnostic precedence over BN, patients with AN who meet criteria for BN are considered as having the binge–purge subtype of AN. Thus, most patients with BN are of normal weight. Like patients with AN,

those with BN have a disturbance of body image and unduly value their shape and weight when evaluating their self-esteem. Bulimia nervosa is more common than AN, with a prevalence of 1–5% in adolescent and young adult women (37). BN tends to be managed in the outpatient setting, making clinical trials less complicated and costly than with AN and, presumably for these reasons, more numerous. In addition, studies of medications in the management of BN have yielded more promising results, most notably with antidepressants.

Antidepressants

The study of antidepressant medications resulted from the observation that patients with BN, like those with AN, often describe depressive symptoms. Over the past 20 years, many antidepressants have been found to be more effective than placebo in reducing binge–purge episodes in normal-weight women with BN (38,39). While TCAs (40–45), monoamine oxidase inhibitors (46–48) and SSRIs (49–51) have all been shown to be effective, there are no direct comparisons to suggest superiority of one drug over another. SSRIs have come into favor due to their overall acceptable side-effect profile. Open trials of sertraline (52) and fluvoxamine (53,54) have reported good results, but only fluoxetine, at a dose of 60 mg daily, has been shown to be effective in randomized, controlled trials (49,50). Antidepressants consistently decrease eating-disordered behaviors and improve mood in patients with BN, regardless of the presence of major depressive episode (49). In addition, two randomized controlled trials have suggested efficacy of SSRIs in prevention of relapse (55,56).

While studies of antidepressants have generally been favorable, the study of bupropion must be mentioned for its significant side effects. In this trial of 55 women with BN (57), bupropion (up to 450 mg/day) was effective at reducing binge–purge behavior. The study was terminated prematurely, however, because four women experienced grand mal seizures. Because of this association, bupropion is specifically not recommended in management of BN, and the package insert indicates that bupropion is contraindicated in the treatment of patients with a current or past diagnosis of BN or AN.

The clinical significance of the difference between antidepressant medication and placebo is complicated by the broad range of effect between studies. The improvement in binge frequency reported in controlled trials ranges from 31% to 91% decrease (58,59). Remission rate (cessation of binge–purge behavior) was often not reported and when reported, ranged from 4% to 34% (58). The improvement in BN with antidepressant medication is clear, but the low remission rate suggests that there are limitations to this treatment.

Medication trials have generally focused on binge–purge behaviors as the primary outcome, but a few studies have also assessed body image dissatisfaction. Most use the BSQ or the Eating Disorders Inventory Body Dissatisfaction Scale (EDI-BD), which are self-report measures that address how patients feel about body parts or their whole body. While these measures do not address all of the dimensions of body dissatisfaction, they may serve as a crude measure of this important variable. Interestingly, some, (45,49) but not all, (60–62) studies suggest that it is possible to see change in body dissatisfaction with medication treatment alone. Thus, the impact of antidepressants on body dissatisfaction remains unclear.

Overall, the use of antidepressant medications in the management of BN is well supported but there remain some gaps in the knowledge base. The current data are mostly derived from short-term studies that range from 6 to 8 weeks duration. Most trials have been conducted with normal weight women who use self-induced vomiting to purge. Thus, it is unknown if these results can be generalized to apply to other patients, such as men, adolescents, and those who compensate for binge eating through other behaviors, e.g., excessive exercise. Areas for further study include the optimal duration of treatment and the long-term efficacy of antidepressants.

Anticonvulsants

An early clinical model conceptualized BN as a seizure disorder, with binge–purge episodes thought to represent paroxysmal events. Small trials with the anticonvulsants phenytoin (63) and carbamazepine (64) did not suggest a robust response to medication. A recent case report (65) of a woman with epilepsy and BN who was treated with topiramate and showed improvement in binge–purge behaviors and in attitude about shape and weight raised the possibility that topiramate may have benefit in the management of BN. Results from a randomized, double-blind, placebo-controlled trial of topiramate (25–400 mg/day) have been presented, showing reduction in binge and purge duration and frequency (66). Although preliminary, these results are encouraging.

Other Agents

Some agents have been studied based on biological models, as opposed to clinical models, of BN. These models have focused mainly on the potential role of serotonin, which has been shown to impact various aspects of feeding. As increased serotonergic function tends to decrease food intake, it was hypothesized that medications that increase serotonin would decrease binge eating behavior (67). L-Tryptophan, the amino acid precursor of serotonin, was examined in a randomized, placebo-controlled trial ($N = 13$), but no

drug–placebo difference was detected (68). Fenfluramine, a serotonergic agent that both blocks reuptake and increases release, was studied with mixed results. In a randomized, placebo-controlled trial using a crossover design, fenfluramine was shown to decrease binge–purge frequency (69). However, in two subsequent placebo-controlled trials, the medication showed no benefit (70,71). Fenfluramine was withdrawn from the market in 1997 due to an association with cardiac valve abnormalities.

Another model for treatment of BN focuses on the feeding behaviors of patients, specifically their difficulty in identifying satiety. This model postulates that binge eating and purging might lead to desensitization of the vagal nerve afferents, which have a key role in signaling satiety. Subjects with BN were found to have an increased somatosensory pain threshold, which may indirectly reflect altered vagal nerve activity (72). Based on these observations, Faris and colleagues (73) conducted a 4-week randomized, placebo-controlled trial in BN and found that ondansetron (24 mg/day), a medication that blocks 5-HT_3 receptors involved in visceral stimulation of the vagal nerve, was associated with a significant decrease in binge–purge behaviors.

One clinical model of BN focused on the similarities between binge–purge behaviors and addictive behaviors, drawing on the evidence that endogenous opiates may be involved in appetite changes. In a small, open trial of naltrexone, an opiate antagonist, 7 of 10 patients with BN improved with complete or partial remission (74). One randomized, controlled trial including AN and BN patients found a decrease in binge–purge behaviors with naltrexone (100–200 mg/day) (29), whereas a randomized, controlled trial using a lower dose (50 mg/day) showed no benefit (75).

Lithium has also been studied. Hsu et al. (60) conducted a randomized, placebo-controlled, 8-week trial of lithium (mean lithium level = 0.62) in patients with BN. Both placebo and medication groups improved, and there was no significant difference between the groups.

Combination Treatment

While the above data clearly support the efficacy of antidepressants in BN, controlled trials have also shown the efficacy of psychotherapy alone (see Chapters 17, 19, and 20). Seven randomized controlled trials have, in different ways, compared treatments in an attempt to assess the benefits of psychotherapy versus pharmacotherapy versus a combination of the two. Overall, the studies suggest that cognitive–behavioral therapy (CBT) alone is probably more effective in reducing binge eating and purging behaviors, but that the addition of medication provides some additional benefit.

The first study, conducted by Mitchell and colleagues (62), randomized subjects to one of four treatment arms for 10 weeks: imipramine alone,

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placebo alone, intensive group therapy alone, or imipramine with intensive group therapy. The psychotherapy intervention provided was an unusually intensive group therapy, which included joint meals with the therapist on five occasions during the first week of treatment. Outcome measures assessed eating behaviors, affective symptoms, and attitudinal measures. The reduction in eating-disordered behaviors in response to intensive group therapy was impressive, and no added benefit from imipramine could be detected. On the other hand, combination treatment significantly improved affective symptoms more than either treatment alone. In a follow-up study, Keel et al. (76) found that 10 years posttreatment, all three active treatment groups showed significant improvement in social functioning as compared with placebo. There were no significant differences on measures of depression, body image, or eating disorder behavior.

A study of the combination of individual CBT with desipramine reached broadly similar conclusions. Agras and colleagues (77) randomly assigned patients to one of five treatment arms: desipramine for 16 weeks, desipramine for 24 weeks, CBT only for 16 weeks, CBT and desipramine for 16 weeks, and CBT for 16 weeks and desipramine for 24 weeks. Response to CBT was clearly superior to that for desipramine alone. There were some indications that patients receiving CBT combined with 24 weeks of desipramine had the best outcome, but these results were not statistically robust.

The finding of Mitchell et al. (62) that medication may add to the benefits of psychological treatment was also noted in a study by our own group (78). Patients were randomly assigned to one of five treatment arms for 16 weeks: medication alone, CBT and medication, CBT and placebo, supportive psychotherapy (SPT) and medication, SPT and placebo. The design allowed for a change in medication from the TCA desipramine to the SSRI fluoxetine under double-blind conditions. Patients assigned to receive active medication were given desipramine, but if response was not satisfactory or if significant side effects developed, patients were switched to fluoxetine. It was clear that CBT was more effective than SPT in reducing disturbed eating behaviors. In addition, active medication augmented the improvement in both behavioral and attitudinal measures associated with psychological treatment.

Goldbloom et al. (79) conducted a study of combination treatment with three treatment arms: fluoxetine alone, CBT alone, and fluoxetine and CBT combined. This study was limited by a significant dropout rate (43%), which contributed to an inability to detect statistically significant differences between treatments on most measures. There was a significant difference in subjective reports of binge episodes, which were most improved with combination treatment.

In another study of fluoxetine, medication or placebo was combined with 8 weeks of nutritional counseling (80). The nutritional intervention had

components similar to CBT, but with a psychoeducational focus replacing cognitive restructuring. While the authors report on this as an assessment of combined treatment, the psychotherapy intervention is sufficiently different from CBT that it is difficult to compare findings. Nonetheless, there was a rapid and significant improvement in both groups in binge eating and purging. There were few differences between fluoxetine and placebo groups, but some indications that fluoxetine augmented improvement in some psychological spheres, such as concerns with shape and weight. Bacaltchuk et al. (81) performed a meta-analysis of the studies of psychotherapy plus pharmacotherapy in BN. While their conclusions are subject to the usual limitations of meta-analyses, in the short term remission was more likely with combination of medication and psychotherapy than with either treatment alone.

Conclusions drawn from the above studies must be considered with caution. One major problem is that the largest studies were conducted before the widespread use of SSRIs, making it difficult to extrapolate from these data to current clinical practice. The limited information available suggests that CBT is likely to be more effective and more acceptable to patients than is a course of antidepressant medication. However, the data are reasonably consistent in indicating that the addition of an antidepressant to psychotherapy modestly augments improvement in psychological symptoms and, perhaps, in disturbance of eating behavior. The effectiveness of medication in reducing relapse is uncertain.

BINGE EATING DISORDER

The more recently recognized syndrome of binge eating disorder is characterized by episodes of binge eating without compensatory behaviors. Although not required for the diagnosis, BED is usually associated with obesity. As is the case with AN and BN, several clinical features of BED can be appropriately viewed as outcome measures. The ideal intervention would reduce the binge eating behavior, improve psychological disturbances such as depression and overconcern with body image, and promote weight loss. To date, most treatment studies have focused on the behavioral and psychological components, leaving weight loss as a secondary goal. As this disorder is relatively newly codified in the DSM-IV, only a small number of controlled medication studies have been published.

Antidepressants

Based on the efficacy of antidepressants in the management of BN and the similarities between these two disorders, most research has focused on antidepressants. An early placebo-controlled trial of "nonpurging BN" found

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that desipramine was effective in the short-term reduction of binge eating (82). However, symptoms reemerged 4 weeks after medication discontinuation. A randomized, controlled trial has also shown imipramine to be effective (83). More recently, two studies have found benefits from SSRIs. In one randomized controlled trial of fluvoxamine (50–300 mg/day) (84) and one randomized controlled trial of sertraline (50–200 mg/day) (85), the authors reported a significant reduction in binge eating behavior as well as a decrease in BMI in the medication groups as compared with placebo. As with most of the medication trials in eating disorders, these short-term results do not provide information as to sustained benefit of medications.

Other Agents

As with AN and BN, a number of other classes of medication have received some attention as being of possible use in the management of BED. Topiramate is the latest to show promise. In one open label-study of 13 patients with BED, topiramate was associated with weight loss (86). Appolinario et al. (87) reported a case study of a patient who responded to topiramate after other treatments had been unsuccessful. McElroy et al. (88) conducted a placebo-controlled, double-blind trial of topiramate in 61 patients with BED. Topiramate-treated subjects showed significantly greater reductions in binge frequency, binge day frequency, and other measures of symptom severity, as well as significant reduction in BMI.

Trials of dexfenfluramine yielded some promising results. Dexfenfluramine was associated with a decrease in binge eating, and when used in combination with phentermine, with weight loss, as well (89,90). However, dexfenfluramine has since been withdrawn from the market due to its association with cardiac valve abnormalities. An open trial of sibutramine, an appetite suppressant approved for the management of obesity, suggested that use of this agent was associated with improvement in both binge eating and weight loss (91). A controlled trial has been conducted, but results are not yet available. The opiate antagonist naltrexone was studied in a randomized placebo-controlled trial which also included an imipramine arm (89). While both medication groups showed improvement, there was no difference from placebo.

Combination Treatment

Antidepressant medications appear to provide short-term benefit in the management of BED, but the benefits do not appear to be sustained beyond the discontinuation of the medication. Several studies have examined the benefits of combined treatment, but, at present, the data are insufficient to support clear conclusions (83,92–95).

CONCLUSIONS AND TREATMENT RECOMMENDATIONS

Anorexia Nervosa

Psychopharmacological interventions have not been shown to provide significant benefit to underweight patients with AN. The mainstays of treatment are nonpharmacological, and focus on nutritional rehabilitation and relapse prevention. There is preliminary evidence that fluoxetine may be of benefit for relapse prevention after patients have regained to a normal or near-normal weight.

Bulimia Nervosa

The data on the use of antidepressants in the treatment of BN are convincing in indicating that that fluoxetine is safe and beneficial. While it is likely that other SSRIs would be effective, only fluoxetine has been examined in placebo-controlled trials, and should be used in a dose of 60 mg/day. Most patients can be rapidly titrated to this dose over the course of a week. There are no available data to guide treatment for relapse prevention or to suggest recommended length of treatment. Bupropion is not recommended in the management of BN because of the risk of seizure. There are consistent indications that medications modestly enhance the benefits of psychological treatment.

Binge Eating Disorder

While emerging data suggest that SSRIs and, perhaps, antiobesity agents may provide some benefits, at present there is insufficient information to make firm treatment recommendations regarding the use of medication for BED.

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