116

PSYCHOPHARMACOLOGY OF EATING DISORDERS

WALTER H. KAYE B. TIMOTHY WALSH

Anorexia nervosa (AN) and bulimia nervosa (BN) are disorders characterized by aberrant patterns of feeding behavior and weight regulation, and disturbances in attitudes toward weight and shape and the perception of body shape. In AN, there is an inexplicable fear of weight gain and unrelenting obsession with fatness even in the face of increasing cachexia. BN usually emerges after a period of dieting, which may or may not have been associated with weight loss. Either self-induced vomiting, or some other means of inappropriate compensation for the excess of food ingested follows binge eating. The majority of people with BN have irregular feeding patterns and satiety may be impaired. Although current AN is an exclusion for the diagnosis of BN, some 25% to 30% of individuals with BN presenting to treatment centers have a prior history of AN; however, all BN subjects have pathologic concern with weight and shape. Common to individuals with AN or BN are low selfesteem, depression, and anxiety.

In certain respects, both diagnostic labels are misleading. Individuals affected with AN rarely have complete suppression of appetite, but rather exhibit a volitional and often an ego syntonic resistance to feeding drives, eventually becoming preoccupied with food and eating rituals to the point of obsession. Similarly, BN may not be associated with a primary pathologic drive to overeat; rather, individuals with BN, like those with AN, have a seemingly relentless drive to restrain their food intake, an extreme fear of weight gain, and often a distorted view of their actual body shape. Loss of control with overeating usually occurs intermittently and typically only some time after the onset of dieting behavior. Episodes of binge eating ultimately develop in a significant proportion of people with AN (1), whereas 5% of those with BN eventually develop AN (2). Considering that restrained eating behavior and dysfunctional cognitions relating weight and shape to self-concept are shared by patients with both of these syndromes, and that transitions between these syndromes occur in many, it has been argued (3) that AN and BN share at least some risk and liability factors in common.

The etiology of AN and BN is presumed to be complex and multiply influenced by developmental, social, and biological processes (4,5); however, the exact nature of these interactive processes remains incompletely understood. Certainly, cultural attitudes toward standards of physical attractiveness have relevance to the psychopathology of eating disorders (EDs), but it is unlikely that cultural influences in pathogenesis are prominent. Dieting behavior and the drive toward thinness are quite commonplace in industrialized countries throughout the world, yet AN and BN affect only an estimated .3% to .7%, and 1.7% to 2.5%, respectively, of women in the general population. Moreover, the fact that numerous clear descriptions of AN date from the middle of the nineteenth century suggests that factors other than our current culture play an etiologic role. Also, both syndromes (particularly AN) have a relatively stereotypic clinical presentation, sex distribution, and age of onset. This supports the possibility that there are significant biologic vulnerabilities to developing an ED.

PHENOMENOLOGY

Variations in feeding behavior have been used to subdivide individuals with AN into two meaningful diagnostic subgroups that differ in other psychopathologic characteristics (6,7). In the restricting subtype of AN, subnormal body weight and an ongoing malnourished state are maintained by unremitting food avoidance; in the binge eating/purging subtype of AN, there is comparable weight loss and malnutrition, yet the course of illness is marked by episodes of binge eating, and/or by some type of compensatory action such as self-induced vomiting or laxative abuse. Individuals with the binge eating/purging subtype of AN are also more

Walter H. Kaye: Western Psychiatric Institute & Clinics, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania.

B. Timothy Walsh: Columbia University College of Physicians & Surgeons, New York, New York.

likely to exhibit histories of behavioral dyscontrol, substance abuse, and overt family conflict in comparison to those with the restricting subtype of AN. Personality traits of marked perfectionism, conformity, obsessionality, constriction of affect and emotional expressiveness, and reduced social spontaneity are particularly common in individuals with AN. These traits typically appear in advance of the onset of illness and persist even after long-term weight recovery, indicating they are not simply epiphenomena of acute malnutrition and disordered eating behavior (8–11).

Individuals with BN remain at normal body weight, although many aspire to ideal weights far below the range of normalcy for their age and height. The core features of BN include repeated episodes of binge eating followed by compensatory self-induced vomiting, laxative abuse, or pathologically extreme exercise, as well as abnormal concern with weight and shape. The DSM-IV has specified a distinction within this group between those individuals with BN who engage in self-induced vomiting or abuse of laxatives, diuretics, or enemas (purging type), and those who exhibit other forms of compensatory action such as fasting or exercise (nonpurging type). Beyond these differences, it has been speculated (12) that there are two clinically divergent subgroups of individuals with BN differing significantly in psychopathologic characteristics: a so-called multi-impulsive type, in whom BN occurs in conjunction with more pervasive difficulties in behavioral self-regulation and affective instability; and a second type whose distinguishing features include self-effacing behaviors, dependence on external rewards, and extreme compliance. Individuals with BN of the multi-impulsive type are far more likely to have histories of substance abuse and display other impulse control problems such as shoplifting and self-injurious behaviors.

Most cases of AN emerge during the period of adolescence, although the condition can be observed in children. Whether or not prepubertal onset of the illness confers a more or less ominous prognosis is not known. Recovery from the illness tends to be protracted, but studies of long-term outcome reveal the illness course to be highly variable: Roughly 50% of individuals eventually have reasonably complete resolution of the illness, whereas 30% have lingering residual features that wax and wane in severity long into adulthood. Ten percent of people with AN pursue a chronic, unremitting course; the remaining 10% of those affected eventually die from the disease.

BN is usually precipitated by dieting and weight loss, yet it can occur in the absence of apparent dietary restraint. The frequency of binge episodes, their duration, and the amount of food consumed during any one episode all vary considerably among patients. Age of onset is somewhat more variable in BN than AN, with most cases developing during the period from mid- to late adolescence through the mid-twenties. Follow-up studies of clinical samples 5 to 10 years after presentation show 50% of patients recovered, whereas nearly 20% to 30% continued to meet full criteria

for BN (13). Following onset disturbed eating behavior waxes and wanes over the course of several years in a high percentage of clinic cases. Approximately 30% of remitted women relapse into BN symptoms.

PERSISTENT PSYCHOLOGICAL DISTURBANCES AFTER RECOVERY

People who have an ED often have a variety of symptoms aside from pathologic eating behaviors. Physiologic symptoms include an abundance of neuroendocrine, autonomic, and metabolic disturbances (see the following). Psychological symptoms include depression, anxiety, substance abuse, and personality disorders. Determining whether such symptoms are a consequence or a potential cause of pathologic feeding behavior or malnutrition is a major methodologic issue in the study of EDs. It is impractical to study EDs prospectively because of their low incidence, early age of onset, and difficulty of premorbidly identifying those who will develop an ED. However, subjects can be studied after long-term recovery from an ED. The assumed absence of confounding nutritional influences in recovered ED women raises a possibility that persistent psychobiological abnormalities might be trait-related and potentially contribute to the pathogenesis of this disorder. A limited number of studies have investigated people who have recovered from AN and BN. Although the definition of recovery from an ED has not been formalized, investigators tend to include people formerly ill with AN after they are at a stable and healthy body weight for months or years and have not been malnourished or engaged in pathologic eating behavior during that period of recovery. For BN, investigators tend to include subjects who have been abstinent from binge eating and purging for months or years. Some investigators include criteria of normal menstrual cycles and a minimal duration of recovery, such as 1 year of time.

Investigators (8-11) have found that women who were long-term recovered from AN had a persistence of obsessional behaviors as well as inflexible thinking, restraint in emotional expression, and a high degree of self- and impulse-control. In addition, they have social introversion, overly compliant behavior, and limited social spontaneity as well as greater risk avoidance and harm avoidance. Moreover, individuals who are long-term recovered from AN had continued core ED symptoms, such as a drive for thinness, and significant psychopathology related to eating habits. Similarly, people who have recovered from BN continue to be overly concerned with body shape and weight, display abnormal eating behaviors, and report dysphoric mood (14-17). Recovered AN and BN women have increased perfectionism; their most common obsessional target symptoms are the need for symmetry and ordering/arranging. Considered together, these residual behaviors can be characterized as over-concerns with body image and thinness, obsessionality with symmetry, exactness, and perfectionism, and dysphoric/negative affect. In general, pathologic eating behavior and malnutrition appears to exaggerate the magnitude of these concerns. Thus, the intensity of these symptoms is less after recovery but the content of these concerns remains unchanged. The persistence of these symptoms after recovery raise the possibility that the disturbances are premorbid traits that contribute to the pathogenesis of AN and BN.

PHARMACOLOGIC TREATMENT OF ANOREXIA NERVOSA

Most medication trials in AN have been conducted with inpatients in an attempt to accelerate restoration of weight. Some studies also examined the impact of medication on mood or anorectic attitudes. A wide variety of psychoactive medications, such as L-dopa (18), phenoxybenzamine (19), diphenylhydantoin (20,21), stimulants (22), and naloxone (23), have been administered to people with anorexia nervosa in open, uncontrolled trials. In many of these trials, medications have been claimed to be beneficial, but none of these observations has been confirmed under double-blind, controlled conditions.

Few studies of medication using rigorous double-blind placebo-controlled trials have been reported in patients with AN. In contrast to the positive claims from open trials, results from double-blind trials have been limited, for the most part. Double-blind studies, at most, report marginal success in treatment of specific problems such as improving the rate of weight gain during refeeding, and disturbed attitudes toward food and body image, depression, or gastrointestinal discomfort.

One problem with determining the efficacy of pharmacotherapy in AN is that often medications have been given in association with other therapies. Thus, it may be unclear whether it was the medication or therapy that resulted in improvement. Furthermore, the primary criterion for improvement has often been weight gain, not a normalization of thinking and reduction in fears of being fat. It is important to emphasize that treatment in structured settings, such as inpatient units, even without medication, succeeds in restoring the weight of over 85% of underweight patients (24). Thus, it may be difficult to prove that an active medication is effective in such a setting. However, relapse within 1 year after successful inpatient weight restoration is very common (25). For example, the Maudsley study (26) reported that only 23% of the patients had a good outcome at 1 year after discharge despite intensive outpatient individual or family therapy.

Controlled trials of the neuroleptics pimozide (27) and sulpiride (28) have suggested limited effects in accelerating weight gain or altering anorectic attitudes for some patients for part of the study, but overall drug effect was marginal. Recently, there has been clinical interest in "atypical" neuroleptics for AN because of their notoriety for causing weight gain in other patient populations (29). A recent case report suggested that olanzapine administration was associated with weight gain and maintenance as well as reduced agitation and resistance to treatment in 2 women with AN (30). Several drugs have been tested because of anecdotal reports of their effects on stimulating appetite. Tetrahydrocannabinol (THC) was not useful and, in fact, may have been detrimental because it increased dysphoria in some patients (31). Clonidine was also found to have no therapeutic effect on increasing weight restoration as compared to placebo (32), even with doses that affected hemodynamic parameters.

When underweight, patients with anorexia nervosa have delayed gastric emptying (33), which improves with refeeding. Still, delayed gastric emptying could perpetuate the disorder in some patients by limiting the quantity of food that may be comfortably eaten. Most studies of prokinetic drugs in AN have been limited to parenteral preparations or experiments with small uncontrolled groups of patients (34–36). In a controlled trial, cisapride (37) was no better than placebo in improving gastric emptying, although some subjective measures of distress during meals and measures of hunger improved more in the group on cisapride.

In summary, these medication trials have been of short duration and focused on whether medication produces additive benefit to an established treatment program. Few follow-up studies have examined whether medication treatment produces lasting benefit. A new generation of studies has begun to focus on whether medication can prevent relapse after patients leave to a structured treatment setting.

Use of Antidepressants in AN

There has been controversy as to whether AN and major depressive disorders share a common diathesis; however, critical examination of clinical phenomenology, family history, antidepressant response, biological correlates, course and outcome, and epidemiology yield limited support for this hypothesis (38–40). Still, the high frequency of mood disturbances associated with this disorder resulted in trials of drugs such as amitriptyline (41–43), and lithium (44). Neither medication appears to significantly improve mood compared with the effects of placebo.

For more that 50 years (45), investigators have suggested that AN shares similarities with obsessive-compulsive disorder (OCD). In fact, patients with AN have a high prevalence of obsessive-compulsive symptoms or disorders (46–48), as well other anxiety disorders (49). More over, adult women with OCD have an increased incidence of prior AN (50). Individuals with a past history of AN display evidence of increased serotonin (51) activity that persists after long-term weight recovery. In addition, women who recover from AN continue to have modest, but significant, increases in nega-

tive mood, obsessionality, perfectionism, and core eating disorder symptoms. Similarly (10), personality characteristics associated with AN, such as introversion, self-denial, limited spontaneity, and a stereotyped thinking style, may also persist after weight recovery. Studies in humans and animals suggest that serotonin activity is related to behavioral inhibition. Together, these data raise the possibility that increased CSF 5-HIAA could be associated with inhibition and an obsessive need with exactness and perfectionism. A disturbance of this neurotransmitter system has been implicated in OCD (52) and only serotonin-specific medication has been found to be useful in treating OCD.

There are suggestions that medications that affect the serotonin system may impact the clinical characteristics of patients with AN. Initial reports on cyproheptadine, a drug that is thought to act on the serotonergic and histaminergic system (53), indicated that it might have beneficial effects on weight gain, mood, and attitude in some patients (54, 55). Cyproheptadine data from comparison trials with amitriptyline and placebo found cyproheptadine to significantly improve weight gain in the restricting subtype of AN, whereas amitriptyline was more effective in those patients with bulimic behavior (56).

Several groups (57,58) reported that an open trial of fluoxetine, a highly specific serotonin reuptake inhibitor might help patients with AN gain and/or maintain a healthy body weight. Recently, the Pittsburgh group reported a double-blind placebo-controlled trial of fluoxetine in 35 patients with restrictor-type AN (59). Subjects were started on fluoxetine after they achieved weight restoration (approximately 90% of ideal body weight) during a hospitalization. Patients were randomly assigned to fluoxetine (N=16) or placebo (N=19) after inpatient weight-restoration and then were followed as outpatients for 1 year. After 1 year of outpatient follow-up, 10 of 16 (63%) subjects had a good

outcome on fluoxetine, whereas only three of 19 (16%) had a good outcome on placebo (P = .006) (Fig. 116.1). Aside from improved outcome, fluoxetine administration was associated with a significant reduction in obsessions and compulsions and a trend toward a reduction in depression. These data suggest that fluoxetine may help prevent relapse in some patients with AN.

It is important to note that SSRIs appear to have little effect on reducing symptoms and preventing hospitalization in malnourished, underweight anorexics (60,61). Women with AN, when malnourished and underweight, have reduced plasma tryptophan availability (62) and reduced CSF 5-HIAA (63), the major metabolite of serotonin in the brain. In addition, low estrogen values during the malnourished state may reduce serotonin activity by effects on gene expression for serotonin receptors (64) or the serotonin transporter (65). SSRIs are dependent on neuronal release of serotonin for their action. If malnourished patients have compromised release of serotonin from presynaptic neuronal storage sites and reduced synaptic serotonin concentrations, then a clinically meaningful response to an SSRI might not occur (66). The possibility that fluoxetine is only effective for patients after weight restoration is supported by the fact that a change of serotonin activity is associated with weight gain. For example, CSF 5-HIAA levels are low in underweight anorexics, normal in short-term weight-restored anorexics, and elevated in long-term weight-restored anorexics (67). If CSF 5-HIAA levels accurately reflect CNS serotonin activity, then these data imply that a substantial increase in serotonin activity occurs after weight gain.

The use of serotonin-specific medications in the treatment of AN is promising but many questions remain. First, only one double-blind placebo-controlled study has been completed in a relatively small number of restrictor-type patients. Thus, it will be important to replicate this work

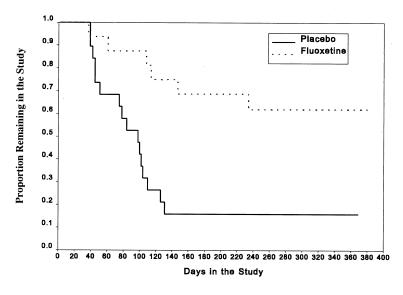


FIGURE 116.1. Survival of subjects with anorexia nervosa treated with fluoxetine or placebo.

in a larger group of patients. Second, more data are needed to determine if there are differential effects in the restricting of binge eating/purging subtypes of AN. Third, it needs to be determined whether certain features are especially responsive to serotonin-specific medications: core anorexic symptoms, depression, anxiety, obsessionality, or eating behavior.

Guidelines for Clinical Treatment

The first line of treatment for underweight patients with AN should be refeeding and weight restoration. As noted, although difficult, most patients will gain weight in a structured eating disorders treatment program without the use of medication. Weight gain alone tends to reduce exaggerated obsessionality and dysphoric mood in many patients (68). There is limited evidence that fluoxetine and possibly other serotonergic medications help prevent relapse after weight restoration. It is important to emphasize that some physiologic and cognitive alterations persist for months after achieving goal weight, including increased energy needs, menstrual disturbances, several neurotransmitter disturbances, urges to engage in disordered eating patterns, and body image distortions. Thus, treatment should continue for at least 3 to 6 months after achieving goal weight, preferably until there is resumption of menstrual periods, normalization of caloric needs, remediation of any physical complications, and sufficient remission of pathologic eating and body-image distortions so that daily activities are not disturbed. We strongly support use of the recent American Psychiatric Association (APA) guidelines for eating disorders (69), which describe comprehensive treatment of AN.

PHARMACOLOGIC TREATMENT OF BN

As summarized in Neuropsychopharmacology, the Fourth Generation of Progress, a substantial body of work was published during the 1980s and early 1990s demonstrating that antidepressants are more effective than placebo in the treatment of BN (70). In 1996, the FDA approved the use of fluoxetine (71,72) for this disorder, the only medication to receive such an official indication to date. Although the notion of using antidepressants for BN emerged because of the high frequency of symptoms of depression and anxiety, the utility of antidepressants does not appear confined to patients with concurrent major depression, suggesting that these medications may exert their effects, at least in part, via alterations in the neural systems underlying the control of appetite. The notion that antidepressants may be useful in BN via mechanisms other than those that are responsible for their antidepressant activity is also suggested by the observations that a higher daily dose of fluoxetine (60 mg per day) appears superior to the standard antidepressant dose (20 mg per day) in the treatment of BN and that the onset

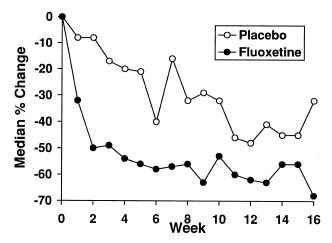


FIGURE 116.2. Median percentage change in the number of binge-eating episodes among patients with bulimia nervosa receiving fluoxetine or placebo.

of benefit from antidepressant treatment typically is quite rapid (Fig. 116.2).

No trials have been published in which the efficacy of one antidepressant is compared directly to that of another. In the absence of such data, although virtually all classes of antidepressants appear superior to placebo in reducing binge frequency, SSRIs are generally preferred because of their relatively benign side-effect profile; however, aside from fluoxetine, only fluvoxamine has been formally examined in BN. Fichter and colleagues reported a study of novel design in which patients were randomly assigned to fluvoxamine or placebo following successful completion of inpatient treatment (73). Although fluvoxamine was associated with a dropout rate of 38% over 19 weeks compared to 14% on placebo, the active drug was superior to placebo in reducing the re-emergence of bulimic behaviors and attitudes. In light of these results, it is surprising that a large European trial has been reported to find no difference between the response to fluvoxamine and placebo in the initial treatment of outpatients with bulimia (Freeman, personal communication, 1999). Thus, although most clinicians expect sertraline, paroxetine, citalopram, and venlafaxine to be useful, the efficacy and ideal dose of SSRIs other than fluoxetine for the treatment of BN have not been established.

Since the clear recognition of bulimia as a syndrome in 1979, effective psychotherapeutic approaches, have also been developed, most of which utilize cognitive behavioral therapy (CBT). CBT is generally believed to be more effective than a single course of an antidepressant medication (69). This fact, coupled with reasonable evidence of sustained benefit following CBT and the reluctance of many patients to take psychotropic medications, has led to CBTs being generally considered the treatment of first choice for BN. Several studies have examined whether it is beneficial

to combine psychological treatment with antidepressant medication.

The earliest studies of the combination of medication and psychotherapy utilized tricyclic antidepressants. Mitchell and associates (74) found that imipramine was associated with a greater reduction in measures of anxiety and depression than was placebo when combined with an intensive group psychotherapy program; however, imipramine did not augment the impact of the psychological treatment on the salient behavioral symptom, binge eating. Agras and colleagues (75) compared five treatments for BN: individual CBT alone, desipramine alone for 16 or 24 weeks, and CBT plus desipramine for either 16 or 24 weeks. As was also true of the study of Mitchell and colleagues, Agras and coworkers reported that the outcome of psychological treatment alone was clearly superior to that of a course of tricyclic antidepressant. There were a few hints of a small advantage for the combination of medication and CBT, but these were not impressive. Leitenberg and co-workers (76) attempted to compare CBT to a course of desipramine and to a combination, but terminated the study prematurely because of a high dropout rate, primarily caused by medication side effects.

More recent studies have examined the potential advantages of combining an SSRI (fluoxetine) and psychological treatment. The Columbia group has reported the results of a study that compared two forms of individual psychological treatment (CBT and supportive psychotherapy) combined either with placebo or a two-stage medication intervention (77). Patients assigned to receive active medication received desipramine; if desipramine was either ineffective or intolerable, the medication was changed to fluoxetine under double-blind conditions. In this study, CBT was clearly superior to supportive psychotherapy in reducing the key behavioral symptoms of BN. In addition, compared to placebo, active medication added modestly but significantly to improvement in binge eating and depression.

Goldbloom and colleagues (78) compared individual CBT to a course of fluoxetine and the combination. Unfortunately, interpretation of the results is limited by a high dropout rate, which resulted in few significant differences among the three treatments. Beumont and colleagues (79) reported a comparison of fluoxetine versus placebo when combined with nutritional counseling, which presumably included many elements of CBT. The nutritional counseling program was impressively effective, and at the conclusion of treatment, there were no significant differences between the fluoxetine and placebo groups in binge frequency; however, the fluoxetine-treated group exhibited less dietary restraint and fewer concerns about body shape and weight.

Combined, these data suggest that adding medication to structured psychological treatment for BN does provide added benefit, but of small magnitude. Clinically, guidelines to identify patients who are particularly likely to benefit from one treatment approach or another would be extremely useful. Unfortunately, attempts to identify such predictors of treatment response have been impressively unsuccessful. Because those patients who derive the greatest benefit from treatment typically exhibit an early response (80), it may useful to initiate treatment with CBT, for example, and to add another intervention such as medication if the initial response is not satisfactory. Recent data demonstrate that medication can be useful for patients who do not respond adequately to psychological treatment or who relapse following the end of treatment (18).

Despite the progress in developing treatment approaches for bulimia in the last 20 years, a major current problem is the absence of treatments of established efficacy other than CBT and antidepressant medication. Even in the best hands, only about 50% of patients achieve remission with these treatments, and a significant number relapse following the conclusion of the initial intervention. Clinicians and investigators have considered the use of other psychotropic medications that are believed to reduce appetite, such as topiramate, but no controlled data are available to date about its utility in BN. Recently, Faris and associates (82) have reported that the antiemetic medication ondansetron, a 5-HT3 antagonist, was more effective than placebo during a 4-week trial in reducing binge eating and vomiting in a group of chronically and severely ill bulimic patients. More data regarding the side effects of ondansetron and its impact on psychological features of the disorder are required to assess the clinical utility of this agent, but the exploration of novel medication interventions for BN is overdue.

PHARMACOLOGIC TREATMENT OF BINGE EATING DISORDER

During the development of DSM-IV, interest grew in defining another eating disorder characterized by frequent binge eating but without the recurrent use of inappropriate compensatory behavior required for the diagnosis of BN. Out of these discussions, criteria for binge eating disorder (BED) evolved, and were included in an appendix of DSM-IV as a criteria set for further study. Significant interest in the characteristics and treatment of BED has since developed, and the results of several psychopharmacologic interventions have been published. Although obesity is not required by the criteria for BED suggested in DSM-IV, the studies to date have generally focused on overweight or obese individuals.

Even before the delineation of BED, McCann and Agras (83) reported that desipramine was superior to placebo in reducing binge frequency among a group of "nonpurging bulimics." Most of the participants were overweight, but neither desipramine nor placebo was associated with significant weight loss in this short-term study. In contrast, Mar-

cus and associates (84) found that when combined with a behavioral weight loss program, fluoxetine was associated with greater weight loss than was placebo during a 1-year study of obese binge eaters; unfortunately, information on binge frequency was not obtained. In contrast, Alger and colleagues (85) reported that neither imipramine nor nal-trexone was more effective than placebo in reducing binge frequency or weight in obese binge eaters.

More recently, studies have focused on patients meeting the criteria of DSM-IV for BED and have examined serotonergic agents. Stunkard and co-workers (86) found that the appetite suppressant *d*-fenfluramine, which has since been withdrawn from the market, was more effective than placebo among 28 obese women with BED in reducing binge frequency; however, surprisingly, not in promoting weight loss. Nevertheless, fluvoxamine compared with placebo was associated with significant reductions in both binge frequency and body mass index among 85 patients with BED (87).

Obesity is a major and growing public health problem in the industrialized world in general and the United States in particular. Approximately one-third of obese individuals presenting to weight loss clinics meet diagnostic criteria for BED; therefore, effective treatments for this disorder may be of widespread clinical utility. Research conducted to date suggests that pharmacotherapy may play a role, but a number of important issues are unresolved. Individuals with BED have disturbances in eating behavior by definition, and are typically overweight and exhibit symptoms of anxiety and depression in clinical samples. Effective interventions should lead to improvements in all three spheres. Yet, it is surprising that the response of these presumably related symptoms to medication is at least somewhat inconsistent, so that patients may report a decrease in binge frequency but no change in weight. A major problem in the development of effective treatment strategies is an impressively high response of binge eating to nonspecific interventions, including placebo. In part for this reason, the effects of medication treatment have been modest in size. Furthermore, the impact of medication in BED appears to fade rapidly once medication has been discontinued. These issues leave the role of pharmacotherapy for BED currently unresolved, and underline the need for additional research, including studies to examine the potential benefits of combining medication with psychological treatment, especially CBT.

REFERENCES

- Halmi KA, Eckert E, Marchi P. Comorbidity of psychiatric diagnoses in anorexia nervosa. Arch Gen Psychiatry 1991;48(8): 712–718.
- Hsu LKG, Sobkiewicz TA. Bulimia nervosa: a four-to six-year followup-study. Psychol Med 1989;19:1035–1038.

- 3. Schweiger U, Fitcher M. Eating disorders: clinical presentation, classification and aetiological models. In: Jimerson D, Kaye WH, eds. *Bailliere's clinical psychiatry international practice and research, eating disorders.* London: Balliere's Tindall, 1997:199–216.
- 4. Garner DM. Pathogenesis of anorexia nervosa. *Lancet* 1993;341: 1631–1635.
- Treasure J, Campbell I. The case for biology in aetiology of anorexia nervosa. *Psychol Med* 1994;24(1):3–8.
- Garner DM, Garfinkel PE, O'Shaughnessy M. The validity of the distinction between bulimia with and without anorexia nervosa. Am J Psychiatry 1985;142(5):581–587.
- Strober M, Salkin B, Burroughs J, et al. Validity of the bulimiarestricter distinction in anorexia nervosa: parental personality characteristics and family psychiatric morbidity. *J Nerve Ment Dis* 1982;170(6):345–351.
- Casper RC. Personality features of women with good outcome from restricting anorexia nervosa. *Psychosom Med* 1990;52(2): 156–170.
- O'Dwyer AM, Lucey JV, Russell GF. Serotonin activity in anorexia nervosa after long-term weight restoration: response to d-fenfluramine challenge. Psychol Med 1996;26(2):353–359.
- Srinivasagam NM, Kaye WH, Plotnicov KH, et al. Persistent perfectionism, symmetry, and exactness after long-term recovery from anorexia nervosa. Am J Psychiatry 1995;152(11): 1630–1634.
- 11. Strober M. Personality and symptomatological features in young, nonchronic anorexia nervosa patients. *J Psychosom Res* 1980; 24(6):353–359.
- Vitousek K, Manke F. Personality variables and disorders in anorexia nervosa and bulimia nervosa. J Abnorm Psychol 1994; 103(1):137–147.
- 13. Keel PK, Mitchell JE. Outcome in bulimia nervosa. *Am J Psychiatry* 1997;154(3):313–321.
- 14. Čollings S, King M. Ten-year follow-up of 50 patients with bulimia nervosa. *Br J Psychiatry* 1994;164:80–87.
- 15. Johnson-Sabine E, Reiss D, Dayson D. Bulimia nervosa: a 5-year follow-up study. *Psychol Med* 1992;22:951–959.
- 16. Kaye WH, Greeno CG, Moss H, et al. Alterations in serotonin activity and psychiatric symptomatology after recovery from bulimia nervosa. *Arch Gen Psychiatry* 1998;55:927–935.
- Norring CE, Sohlberg SS. Outcome, recovery, relapse and mortality across six years in patients with clinical eating disorders. *Psychiatr Scand* 1993;87(6):437–444.
- Johanson AJ, Knorr N J. L-Dopa as treatment for anorexia nervosa. In: Vigersky RA, ed. *Anorexia nervosa*. New York: Raven Press, 1977:363–372.
- 19. Redmond DE, Swann A, Heninger GR. Phenoxybenzamine in anorexia nervosa. *Lancet* 1976;2:397.
- Green RS, Rau JH. Treatment of compulsive eating disturbances with anticonvulsant medication. Am J Psychol 1974;131: 428–432.
- Green RS, Rau JH. The use of diphenylhydantoin in compulsive eating disorders: further studies in anorexia nervosa. In: Vigersky RA, ed. *Anorexia nervosa*. New York: Raven Press, 1977: 377–385.
- 22. Wulliemier JF, Rossel F, Sinclair K. La therapie comportementale de l'anorexia. *J Psychsom Res* 1975;19:267–272.
- Moore R, Mills İH, Forster A. Naloxone in the treatment of anorexia nervosa: effect on weight gain and lipolysis. J Roy Soc Med 1981;74:129–131.
- Halmi KA. Anorexia nervosa. In: Kaplan HI, Freedman AM, Sadock RJ, eds. Comprehensive textbook of psychiatry, vol 2, 3rd ed. Baltimore: Williams & Wilkins, 1980.
- 25. Hsu LKG. The treatment of anorexia nervosa. Am J Psychiatry 1986;143:573-581.

- Russell GFM, Szmukler GI, Dare C, et al. An evaluation of family therapy in anorexia nervosa and bulimia nervosa. Arch Gen Psychiatry 1987;44:1047–1056.
- Vandereychken W, Pierlott R. Pimozide combined with behavior therapy in the short-term treatment of anorexia nervosa. *Acta Psych Scand* 1982;66:445–450.
- Vandereychken W. Neuroleptics in the short-term treatment of anorexia nervosa: a double-blind, placebo controlled study with sulpiride. *Br J Psychol* 1984;144:288–292.
- Casey DE. Side effect profiles of new antipsychotics. J Clin Psychol 1996;57(S11):38–45.
- 30. La Via MC, Gray N, Kaye WH. Case reports of olanzapine treatment of anorexia nervosa. *Int J Eating Dis* 2000;27(3): 363–366.
- Gross H, Ebert MH, Faden VB. A double-blind trial of delta-9-tetrahydrocannabinol in primary anorexia nervosa. *J Clin Psy*chopharmacol 1983;3:165–171.
- Casper RC, Schlemmer RF, Javaid JI. A placebo-controlled, crossover study of oral clonidine in acute anorexia nervosa. *Psychol Res* 1987;20:249–260.
- Szmukler GI, Young GP, Lichenstein M, et al. A serial study of gastric emptying in anorexia and bulimia nervosa. Aust NZ J Med 1990;20:220–225.
- Domstad PA, Shih WJ, Humphries L, et al. Radionuclide gastric emptying studies in patients with anorexia nervosa. J Nucl Med 1987;28:816–819.
- 35. Russell DM, Freedman ML, Feiglin DH, et al. Delayed gastric emptying and improvement with domperidone in a patient with anorexia nervosa. *Am J Psychiatry* 1983;140:1235–1236.
- Saleh JW, Lebwohl P. Metoclopramide-induced gastric emptying in patients with anorexia nervosa. Am J Gastroenterol 1980;74: 127–132.
- 37. Stacher G, Bergmann H, Wiesnagrotzki S, et al. Intravenous cisapride accelerates delayed gastric emptying and increases antral contraction amplitude in patients with primary anorexia nervosa. *Gastroenterology* 1987;92:1000–1006.
- 38. Strober M, Katz JL. Depression in the eating disorders: a review and analysis of descriptive, family, and biological findings. In: Garner DM, Garfinkel PE, eds. *Diagnostic issues in anorexia nervosa and bulimia nervosa*. New York: Brunner/Mazel, 1988.
- 39. Rothenberg A. Differential diagnosis of anorexia nervosa and depressive illness: a review of 11 studies. *Comp Psychiatry* 1988; 29:427–432.
- 40. Swift WJ, Andrews D, Barklage NE. The relationship between affective disorder and eating disorders: a review of the literature. *Am J Psychol* 1986;143:290–299.
- Moore R. Amitriptyline therapy in anorexia nervosa. Am J Psychol 1977;13:1303–1304.
- Needlemen HL, Waber D. The use of amitriptyline in anorexia nervosa. In: Vigersky RA, ed. *Anorexia nervosa*. New York: Raven Press, 1977.
- Beiberman J, Herzog DB, Rivinus TM, et al. Amitriptyline in the treatment of anorexia nervosa: a double-blind placebo-controlled study. J Clin Psychopharmacol 1985;5:10–16.
- Gross HA, Ebert MH, Faden VB, et al. A double-blind controlled trial of lithium carbonate in primary anorexia nervosa. *J Clin Psychopharmacol* 1981;1:376–381.
- 45. Kaye WH, Weltzin T, Hsu LKG. Anorexia nervosa. In: Hollander E, ed. *Obssessive-compulsive related disorders*. Washington, DC: American Psychiatric Press, 1993:49–70.
- Strober M. Personality and symptomatological features in young, nonchronic anorexia nervosa patients. J Psychosom Res 1980;24: 353–359.
- 47. Hudson JI, Pope HG, Jonas JM, et al. Phenomenologic relationship of eating disorders to major affective disorder. *Psychiatry Res* 1983;9:345–354.

- 48. Solyom LS, Freeman RJ, Miles JE. A comparative psychometric study of anorexia nervosa and obsessive neurosis. *Can J Psychiatry* 1982;27:282–286.
- Toner BB, Garfinkel PE, Garner DM. Long term follow-up of anorexia nervosa. *Psychosom Med* 1986;48:520–529.
- Kasvikis YG, Tsakiris F, Marks IM. Past history of anorexia nervosa in women with obsessive compulsive disorder. *Int J Eating Dis* 1986;5:1069–1075.
- Kaye WH, Gwirtsman HE, George DT, et al. Altered serotonin activity in anorexia nervosa after long-term weight restoration. Arch Gen Psychol 1991;48:556–562.
- Zohar J, Insel TR. Obsessive-compulsive disorder: psychobiological approaches to diagnosis, treatment, and pathophysiology. *Biol Psychiatry* 1987;22:667–687.
- Stone CA, Wenger HC, Ludden CT. Antiserotonin-antihistamine properties of cyproheptadine. *J Pharmacol Exp Ther* 1961; 131:73–81.
- Goldberg SC, Halmi KA, Eckert ED. Cyproheptatadine in anorexia nervosa. Br J Psychiatry 1979;134:67–70.
- Halmi KA, Eckert E, Falk JR. Cyproheptadine for anorexia nervosa. *Lancet* 1982;1:1357–1358.
- Halmi KA, Eckert ED, LaDu, TJ, et al. Anorexia nervosa: treatment efficacy of cyproheptadine and amitriptyline. Arch Gen Psychiatry 1986;43:177–181.
- Gwirtsman HE, Guze BH, Yager J, et al. Fluoxetine treatment of anorexia nervosa: an open clinical trial. *J Clin Psychiatry* 1990; 51:378–382.
- Kaye WH, Weltzin TE, Hsu LKG, et al. An open trial of fluoxetine in patients with anorexia nervosa. J Clin Psychol 1991;52: 464–471.
- Kaye WH, Hsu LKG, Weltzin TE, et al. Double-blind placebocontrolled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 2001;49(7): 644–652.
- Ferguson CP, La Via MC, Crossan PJ, et al. Are SSRIs effective in underweight anorexia nervosa? *Int J Eating Dis* 1999;25(1): 11–17.
- Attia E, Haiman C, Walsh BT, et al. Does fluoxetine augment the inpatient treatment of anorexia nervosa? Am J Psychiatry 1998; 155(4):548–551.
- 62. Schweiger V, Warnoff M, Pahl J, et al. Effects of carbohydrate and protein meals on plasma large neutral amino acids, glucose and insulin plasma levels of anorectic patients. *Metabolism* 1986; 35(2):938–943.
- Kaye WH, Gwirtsman HE, George DT, et al. CSF 5-HIAA concentrations in anorexia nervosa: reduced values in underweight subjects normalize after weight gain. *Biol Psychiatry* 1988; 23(1):102–105.
- 64. Fink G, Summner BEH. Oestrogen and mental state. *Nature* 1996;383:306.
- McQueen JK, Wilson H, Dow RC, et al. Oestradiol-17 Beta increases serotonin transporter (SERT) binding sites and SERT mRNA expression in discrete regions of female rat brain. J Physiol (Lond) 1996;495:114.
- Tollesson GD. Selective serotonin reuptake inhibitors. In: Schatzberg AF, Memeroff CB, eds. *Textbook of psychopharmacology*. Washington, DC: American Psychiatric Press, 1995.
- Kaye WH, Ebert MH, Raleigh M, et al. Abnormalities in CNS monoamine metabolism in anorexia nervosa. *Arch Gen Psychiatry* 1984;41(4):350–355.
- 68. Pollice C, Kaye WH, Greeno CG, et al. Relationship of depression, anxiety, and obsessionality to state of illness in anorexia nervosa. *Int J Eating Dis* 1997;21:367–376.
- 69. American Psychiatric Association. Practice guideline for the treatment of patients with eating disorders (revision). *Am J Psychiatry* 2000;157:139.

- Walsh BT, Devlin M. Psychopharmacology of anorexia nervosa, bulimia nervosa, and binge eating. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology: the fourth generation of progress.* New York: Raven Press, 1993.
- Flouxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa: a multicenter, placebocontrolled, double-blind trial. Arch Gen Psychiatry 1992;49: 139–147.
- 72. Goldstein DJ, Wilson MC, Thompson VL, et al. Long-term fluoxetine treatment of bulimia nervosa. *Br J Psychiatry* 1995; 166:660–666.
- Fichter MM, Kruger R, Rief W, et al. Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating—specific psychopathology. *J Clin Psychopharmacol* 1996;16:9–18.
- 74. Mitchell JE, Pyle RL, Eckert ED, et al. A comparison study of antidepressants and structured group psychotherapy in the treatment of bulimia nervosa. *Arch Gen Psych* 1990;47:149–157.
- Agras WS, Arnow B, Schneider JA, et al. Pharmacologic and cognitive-behavioral treatment for bulimia nervosa: a controlled comparison. Am J Psychiatry 1992;49:82–87.
- 76. Leitenberg H, Rosen JC, Wolf J, et al. Comparison of cognitive-behavior therapy and desipramine in the treatment of bulimia nervosa. *Behav Res Ther* 1994;32:37–45.
- 77. Walsh BT, Wilson GT, Loeb KL, et al. Medication and psychotherapy in the treatment of bulimia nervosa. *Am J Psychiatry* 1997;154:523–531.
- 78. Goldbloom DS, Olmsted MP, Davis R, et al. A randomized controlled trial of fluoxetine and cognitive behavioral therapy for bulimia nervosa: short-term outcome. *Behav Res Ther* 1997;9: 803–811.

- 79. Beumont PJV, Russel JD, Touyz SW, et al. Intensive nutritional counseling in bulimia nervosa: a role for supplementation with fluoxetine? *Aust NZ J Psychiatry* 1997;31:514–524.
- 80. Wilson GT, Loeb KL, Walsh BT, et al. Psychological versus pharmacological treatments of bulimia nervosa: predictors and processes of change. *J Consult Clin Psychol* 1999;67:451–459.
- Walsh BT, Agras WS, Devlin M, et al. Fluoxetine for bulimia nervosa following poor response to psychotherapy. Am J Psychiatry 2000;157(8):1332–1334.
- 82. Faris PL, Kim SW, Meller WJ, et al. Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia. *Lancet* 2000;355(9206)792–797.
- 83. McCann UD, Agras WS. Successful treatment of nonpurging bulimia nervosa with desipramine: a double-blind, placebo-controlled study. *Am J Psychiatry* 1990;147:1509–1513.
- 84. Marcus MD, Wing RR, Ewing L, et al. A double-blind, placebocontrolled trial of fluoxetine plus behavior modification in the treatment of obese binge eaters and non-binge eaters. *Am J Psychiatry* 1990;147:876–881.
- 85. Alger SA, Schwalberg MD, Bigaouette JM, et al. Effect of a tricyclic antidepressant and opiate antagonist on binge-eating in normoweight bulimic and obese, binge-eating subjects. *Am J Clin Nutr* 1991;53:865–871.
- 86. Stunkard A, Berkowitz R, Tanrikut C, et al. *d*-Fenfluramine treatment of binge eating disorder. *Am J Psychiatry* 1996;153: 1455–1459.
- 87. Hudson JI, McElroy SL, Raymond NC, et al. Fluvoxamine in the treatment of binge-eating disorder: a multicenter placebocontrolled, double-blind trial. *Am J Psychiatry* 1998;155: 1756–1762.