

Anorexia and Bulimia Nervosa: Neurobiology and Pharmacotherapy

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This review provides an overview of some neurobiological factors that may contribute to the development and maintenance of eating disorders, and the psychopharmacological treatment of anorexia and bulimia nervosa. Various metabolic, physiologic, and neuroendocrine disturbances are associated with bulimia and anorexia nervosa, but it is often not clear whether they represent state or trait markers of the disorders. While most patients with bulimia nervosa who receive appropriate pharmacotherapy will experience significant short-term improvement, there is a substantial rate of relapse during long-term continuation treatment with medication. Strategies that appear to improve long-term outcome in bulimia nervosa include combination treatment with cognitive-behavioral therapy (CBT) and changing to an alternative antidepressant medication. The role for medication treatment in anorexia nervosa remains very limited, although the SSRI antidepressant fluoxetine may have a limited role in long-term treatment of anorexia.

Severe body-image distortion, an enhanced concern about physical appearance, and an extreme fear of obesity or weight gain are prominent features of anorexia nervosa and bulimia nervosa. Cultural standards and social expectations appear to have some role in shaping vulnerability for developing eating disorders such as anorexia nervosa or bulimia nervosa (Brownell, 1991). Developmental and personality factors have also been implicated in the development of eating disorders (Vitousek & Manke, 1994). Most studies suggest that individuals who develop eating disorders have evidence of more psychopathology, such as the presence of personality disorders, than control subjects (Casper, Scheller, & Kushner, 1991), and others have suggested that eating disorders arise as a "pathological solution to a developmental conflict" (Brownell, 1991; Vitousek & Manke, 1994).

Biological alterations are also implicated in the expression and maintenance of the irregular feeding behaviors and attitudes toward weight regulation that occur in eating disorders (Morley & Blundell, 1988). Bulimia ner-

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vosa often initially emerges during an episode of dieting, regardless of the presence of actual weight loss (Herzog, Keller, & Lavori, 1991). This finding suggests that intermittent caloric restriction and/or recurrent, restrained eating behaviors may be more important than an actual change in weight in the pathophysiology of bulimia. Although many bulimics exhibit evidence of impaired satiety, binge episodes usually emerge relatively late in the development of bulimia nervosa (Halmi & Sunday, 1991). Recurrent dieting behaviors such as restrained eating are inevitably present in the prodromal phase of bulimia (Halmi & Sunday).

Since anorexics are by definition severely underweight, a plethora of biological abnormalities exist. However, many of the altered biological measures identified can at least in part arise from a state of starvation. For example, the presence of sufficient weight loss by itself can elicit amenorrhea in the absence of additional physiological or psychological factors. Since anorexia and bulimia nervosa are both characterized by malnutrition and disordered eating patterns, the biological aberrations that occur can represent either a primary abnormality or a secondary consequence of the underlying disease process.

Given all of these issues, it is not surprising that anorexia and bulimia nervosa are generally considered complex psychiatric disorders that arise from a confluence of psychosocial and biological factors. This review will provide an overview of (a) some of the neurobiological findings that may contribute to the development and maintenance of eating disorders and (b) the psychopharmacological treatment of anorexia and bulimia nervosa.

Anorexia and Bulimia Nervosa: Neurobiological Findings

The pathological eating behaviors exhibited in anorexia and bulimia nervosa are associated with a variety of metabolic, physiologic, and neuroendocrine disturbances (Morley & Blundell, 1988). Conducting research in subjects who have successfully recovered from an eating disorder and who have normalized their eating behaviors is one strategy that has been utilized in an attempt to differentiate disease "state" versus "trait" markers. The presumed absence of confounding nutritional influences in recovered anorexic or bulimic women increases the possibility that any persistent psychobiological abnormalities will represent trait rather than state markers. However, this approach is not devoid of problems. Recovered eating disordered subjects exhibit persistent cognitive distortions concerning body shape and weight and often continue to engage in episodic, abnormal eating patterns even after long-term recovery. Often they also continue to endorse dysphoric mood. Moreover, a history of anorexia or bulimia nervosa appears to convey an increased risk for subsequent affective and anxiety disorders (Fallon, Walsh, Sadik, Saoud, & Lukasik, 1991). Recovered anorexics and bulimics also have elevated scores on obsessional measures such as "perfectionism" and "need for symmetry" or "ordering and arranging" behaviors. The residual symptoms most often encountered in recovered subjects with past histories of anorexia or bulimia

nervosa can be classified into three main constellations: (a) overconcern with body image and thinness; (b) obsessive worries about symmetry, exactness, and perfectionism; and (c) dysphoric or negative affect. These same features are present and greatly magnified during the active phase of anorexia or bulimia nervosa. Recovery from the acute eating disorder appears to attenuate, but not eradicate, these features. The persistence of these features into the recovery phases raises the possibility that they may represent premorbid traits.

A growing understanding of the mediation and modulation of appetitive behaviors has raised the question of whether eating disorders may arise from neurotransmitter and/or neuroendocrine dysfunction. Evidence of significant alterations in noradrenergic, serotonergic, and opioid system function has been reported in subjects with anorexia nervosa and in subjects with bulimia nervosa (Fava, Copeland, Schweiger, & Herzog, 1989). However, it is not known whether the abnormalities identified represent an intrinsic abnormality, a secondary consequence of dietary and nutritional abnormalities, or a permissive factor that increases the occurrence and maintenance of eating disorders.

Monoamines

Monoamines such as norepinephrine, serotonin, and dopamine are critical neurotransmitters within the brain. These neurotransmitters are involved in the modulation of feeding behaviors, mood, and neuroendocrine function. Serotonin and norepinephrine are particularly important in modulating appetitive behaviors. Data from animal models suggest that the neurotransmitter serotonin inhibits eating behaviors, whereas the neurotransmitter norepinephrine activates eating behaviors. These effects are most likely mediated through noradrenergic (α -2) receptors located within the hypothalamus of the brain. Kaye and Weltzin (1991) have speculated that binge-eating behavior may arise from "overactivity of the hypothalamic alpha-noradrenergic system, an underactivity of hypothalamic serotonergic systems, or a combination of both defects" (p. 46). That is, bulimia nervosa may result from a fundamental disturbance in monoamine function within the brain that in turn triggers the pathological eating behaviors. Again, it is unclear whether the monoamine disturbances identified reflect an intrinsic defect (trait phenomena) or a secondary consequence (state phenomena) of the pathological processes manifested in eating disorders. Regardless, available data suggest that once the monoamine dysregulation emerges, it is likely to be sustained. Abnormalities in noradrenergic and serotonergic systems have been identified in subjects with anorexia and bulimia nervosa.

Results from most studies conducted with bulimic subjects suggest that central and peripheral norepinephrine activity is reduced (Pirke, 1996). Reduced norepinephrine function in bulimia nervosa is consistent with both animal and human data indicating that starvation and restrained eating trigger down-regulation of the norepinephrine system. The exact mechanism of this effect has not been established, but animal data suggest that caloric restriction is a potent suppressor of central and peripheral norepinephrine turnover (Lie-

bowitz, 1986). Although limited data are available concerning norepinephrine activity and function after recovery in eating disordered subjects, reduced concentrations of plasma and CSF norepinephrine or MHPG, norepinephrine's major metabolite has been reported (Pirke).

Kaye, Gwirtsman, Brewerton, George, and Wurtman (1988), in a series of studies, investigated the potential association between noradrenergic tone and binge/purge behavior in normal-weight bulimic subjects. After consumption of a large meal, the bulimic subjects had significant increases in plasma norepinephrine concentrations (peak and duration) in comparison to the normal control subjects. After several days of abstinence from bingeing and vomiting, the bulimic subjects had similar baseline peripheral and central (CSF MHPG) norepinephrine levels as the control subjects. However, after 30 days of abstinence from bingeing and vomiting, both central (CSF) and peripheral norepinephrine levels were significantly lower than control subjects. Paired comparisons (subject's norepinephrine level at admission versus subject's norepinephrine level after 30 days of abstinence) were also completed and revealed that central and peripheral norepinephrine responses to the test meal were substantially reduced after abstinence in each subject. These findings suggest that abnormally low norepinephrine concentrations and tone may emerge in bulimic subjects during periods of abstinence from bingeing and purging. The bulimic subjects who were experiencing amenorrhea were noted to have lower CSF norepinephrine levels than the menstruating, bulimic subjects at baseline and during abstinence, suggesting that a noradrenergic disturbance may contribute to the frequent incidence of amenorrhea in bulimic women (Kaye et al.).

Considerable evidence also exists of dysregulation of serotonergic processes in bulimia nervosa. Patients with active bulimia nervosa demonstrate evidence of decreased CSF serotonin activity in comparison to age- and sex-matched controls (Kaye et al., 1998). However, after long-term recovery from bulimia, females have elevated CSF concentrations of the serotonin metabolite, 5-HIAA, in comparison to control subjects. This finding of persistent abnormalities in serotonin function provides support for the contention that serotonin dysregulation represents a state rather than trait phenomenon in bulimia nervosa.

Personality features such as harm avoidance, drive for thinness, perfectionism, and excessive desire for symmetry and exactness have been linked to elevated central serotonin (CSF 5-HIAA) activity. Bulimia nervosa is a psychiatric illness characterized by extremes—whether in affect or in behavior. This clinical feature, coupled with the finding that serotonergic activity is relatively low during active bulimia and then persistently high during recovery, is consistent with the assumption that the serotonin system in bulimia nervosa is inherently unstable and poorly modulated. Certain characteristics, such as dietary restraint, dysphoric mood, and obsessional traits like harm avoidance, perfectionism, and exactness, may be associated with a state of relatively increased serotonin activity that occurs during the abstinent phase of bulimia.

In contrast, periods of dietary restraint could induce rapid depletion and subsequent reductions in central serotonergic activity. The presence of an inherent defect in modulating serotonin function may increase susceptibility for bulimia by impairing the ability to appropriately respond to stress or other stimuli. A recent model proposes that bulimics may engage in bingeing and purging behaviors as a means of self-regulating serotonergic activity. That is, the changes in plasma tryptophan elicited by dietary extremes may serve as a crude means of self-manipulating the functional activity of central serotonin.

In contrast to bulimic subjects, patients with anorexia nervosa demonstrate elevated indices of central serotonin activity in comparison to age- and sex-matched control subjects. The elevated central serotonin activity persists into the recovery phase of anorexia nervosa. Some investigators have speculated that these continued elevations in CSF 5-HIAA may account for the persistence of obsessive-compulsive personality traits and residual disturbances in eating behaviors in recovered anorexic subjects (Kaye et al., 1998).

Neuroendocrine Findings

Neuropeptides are hormone-like substances that are used as neurotransmitters in the CNS. Neuropeptides include adrenocorticotrophic hormone (ACTH), corticotrophic releasing hormone (CRH), arginine vasopressin (AVP), cholecystokinin (CCK), opioid peptides, neuropeptide Y (NPY), and peptide YY (PYY). Subjects with anorexia or bulimia nervosa often demonstrate evidence of abnormal neuropeptide activity or neuroendocrine function. Growth hormone disturbances, dysregulation of fluid balance, autonomic instability, and reductions in metabolic function have all been reported in anorexic and bulimic subjects (Kaye, 1992). Some of these abnormalities may represent state rather than trait-related phenomena, since they tend to normalize with clinical recovery from the eating disorder (Kaye).

Recently, research has focused on the possibility that intrinsic abnormalities in neuropeptide function may serve as the primary basis for the disturbances in neuroendocrine function that have been identified in anorexia and bulimia nervosa. Neuropeptides play an important role in modulating feeding behaviors. The mechanisms responsible for controlling food intake involve a complicated interplay between peripheral (taste, gastrointestinal peptides, vagal afferent nerves) and central nervous system neuropeptides and/or monoamines. Data from animal studies indicate that the opioid neuropeptides NPY and PYY are involved in the regulation of the rate and duration of eating, as well as meal size and selection of macronutrient content (Leibowitz, 1986). With these issues in mind, it is not surprising that a number of alterations in neuropeptide concentrations have been identified in eating disorders.

Anorexics, and, at times, bulimics, typically exhibit many of the features common to a starvation state, including reduced concentrations of triiodothyronine (T-3) and TSH plasma levels in the low, normal range (Casper, Pandey, Jaspán, & Rubenstein, 1988). Other starvation effects frequently present in anorexia nervosa include severe reductions in metabolic rate, impaired glu-

cose tolerance, hypercarotemia, hypercholesterolemia, and reduced levels of serum transferrin.

CCK is a neuropeptide with a variety of peripheral and CNS actions. CCK is secreted by the gastrointestinal (GI) tract in response to food intake and is thought to contribute to satiety. Reduced CCK secretion and decreased central (CSF) CCK concentrations have been reported in bulimic females. In fact, some investigators have suggested that bulimics may binge in order to provoke enough CCK release to achieve satiety (Geraciotti & Liddle, 1988).

AVP, a neuropeptide secreted from the posterior pituitary gland, is important in the regulation of learning, memory, and water diuresis. Vasopressin administration delays extinction of active shock avoidance in rat models (Demitrack et al., 1992). This finding has led to speculation that AVP may modulate processes underlying memory consolidation. Interestingly, elevated concentrations of CSF vasopressin, in comparison to control subjects, has been reported in subjects with obsessive-compulsive disorder (OCD), anorexia nervosa, and bulimia nervosa, respectively, in preliminary studies (Demitrack, 1992). Subjects with OCD, anorexia nervosa, and bulimia nervosa, respectively, have also demonstrated evidence of altered peripheral vasopressin responses during challenge studies with hypertonic saline administration (Demitrack et al., 1992). Based upon these findings, Demitrack et al. (1989) have speculated that elevated vasopressin activity may enhance the expression of "obsessional" features and may also form the basis for the shared phenomenological features between OCD, anorexia, and bulimia nervosa.

Peptide YY (PYY) is a neuropeptide that is a potent stimulant of feeding in experimental models. Bulimic patients have increased cerebrospinal fluid concentrations of peptide YY. Kaye and Weltzin (1991) have suggested that elevated central PYY activity may be responsible for the powerful and uncontrollable urge to binge in bulimics. Data from animal studies (Leibowitz, 1986) suggest that opioid agonists generally increase feeding, and opioid antagonists, in turn, decrease food intake. This finding raises the possibility that altered endogenous opioid activity might also contribute to the pathological feeding behaviors seen in eating disorders. There is some support for this hypothesis since reduced concentrations of CSF opioid activity have been reported in anorexic subjects (Morley, Levine, Yim, & Lowry, 1983).

In summary, a wealth of biological abnormalities has been identified in both anorexia and bulimia nervosa. However, most of these alterations are likely to reflect the effects of severe caloric restriction on either a prolonged (anorexia) or an episodic (bulimia) basis. Besides leading to extensive speculation, many of the identified abnormalities have also become the focus for proposed treatment strategies. Unfortunately, few if any treatment strategies that have targeted presumed etiological mechanisms have proven to be particularly beneficial in the treatment of anorexia or bulimia nervosa. These issues will be reviewed in more detail in the treatment section.

Pharmacotherapy of Bulimia Nervosa

Since most estimates suggest that bulimia nervosa is at least 8 to 10 times more common than anorexia nervosa, it is not surprising that considerably more information is available about successful treatment options for bulimia. Most evidence suggests that pharmacotherapy represents an important component in the treatment of bulimia nervosa. Bulimic symptoms are significantly improved by (a) tricyclic antidepressants (TCAs) such as imipramine and desipramine; (b) monoamine oxidase-inhibitors (MAOIs) such as isocarboxazid and phenelzine; (c) atypical antidepressants such as trazodone and mianserin; (d) selective serotonin reuptake inhibiting antidepressants (SSRIs); and (e) alternative medications such as d-fenfluramine. Antibulimic effects appear to be independent of antidepressant effects in most studies. Despite extensive reports of the short-term efficacy of medication for bulimia, relatively little is known about a number of essential issues. These issues will be reviewed in this section.

Tricyclic Antidepressants

Early trials conducted in bulimia research involved TCAs. The primary pharmacological effect of TCAs is to block the reuptake of serotonin and norepinephrine within the synapse. However, they also have multiple interactions with other receptors. These additional pharmacological effects are responsible for mediating many of the side effects commonly encountered with TCAs including sedation, fatigue, tachycardia, cardiac palpitations, constipation, dizziness, sweating, and orthostatic hypotension. Since electrolyte disturbances are not entirely uncommon in bulimic patients, TCA-induced changes in cardiac rate or conduction time can have particularly serious implications. TCAs are also frequently associated with substantial weight gain. Though the exact mechanism of the weight gain is not known, data from animal models suggest that TCAs directly facilitate appetite, which is, at least in part, mediated by effects upon histamine within the hypothalamus (Alger, Schwalberg, & Bigaouette, 1991).

In one of the first controlled studies conducted in bulimia, 6 weeks of the TCA imipramine (200 mg/day) was significantly more effective than placebo (Agras, Dorian, & Kirkley, 1987). In fact, the number of binge and purge episodes was reduced by 70% in the imipramine-treated group of bulimics, whereas the binge and purge frequency was unchanged in the placebo-treated bulimics (Agras et al.). Mitchell and colleagues (1989) also reported significantly more improvement with imipramine (200 to 300 mg/day) than placebo in another study. Longer treatment (16 weeks) with imipramine (up to 300 mg/day) was associated with even greater reductions in bulimia in a third controlled trial of imipramine for bulimia (Agras et al., 1987).

Imipramine was reported to be ineffective for bulimia in one controlled study (Pope, Hudson, & Jonas, 1983). However, only bulimic subjects who also met criteria for comorbid atypical depression were included in this study that compared imipramine or phenelzine to placebo administration. Phenelzine

demonstrated superior antibulimic and antidepressant effects to imipramine. In fact, similar changes in bulimic and depressive symptoms occurred between imipramine and placebo during the study (Pope et al.). Since TCAs, in general, are less effective than MAOIs for atypical depressive symptoms, it is difficult to extrapolate from these results.

The efficacy of imipramine in the long-term treatment of bulimia has also been investigated. A large group of bulimic subjects ($N = 68$) was treated with either imipramine treatment alone, intensive group psychotherapy (plus placebo), or combined treatment with imipramine plus intensive group psychotherapy in the first phase of the study. Subjects who responded during the acute phase of the study (47%) were then eligible for entry into a 4-month maintenance phase. Relapse was considerable (30%) during the maintenance phase. Interestingly, the bulimics who received group psychotherapy alone or group psychotherapy plus imipramine were much less likely to relapse than those treated with imipramine alone (Pyle, Mitchell, Eckert, & Hatsukami, 1990). These results suggest that imipramine and group therapy substantially improves bulimic symptoms during acute treatment, but that relapse is not uncommon over the next 2 to 4 months. Particularly discouraging is the finding that medication (imipramine) alone was significantly less effective than group therapy in protecting against relapse during maintenance treatment for bulimia.

Desipramine has been the most extensively investigated TCA in the treatment of bulimia. Placebo-controlled trials have consistently demonstrated that desipramine treatment is significantly better than placebo in reducing bulimic symptoms (Barlow, Blouin, & Blouin, 1988). Hughes and colleagues (1986) conducted the initial treatment trial of desipramine in bulimia. After 6 weeks, binge frequency was reduced more than 90% in the desipramine group (200 mg/day), whereas bingeing increased by 19% in the placebo group. Moreover, more than two-thirds of the desipramine-treated bulimics achieved full remission by Week 10 of the study. In another controlled study, desipramine (150 mg/day) was compared to the serotonin-releasing agent fenfluramine (60 mg/day) in bulimic subjects. Desipramine demonstrated superiority to placebo on a number of efficacy measures, including weekly binge and purge frequency. Interestingly, there was no correlation between the antibulimic and antidepressant effects associated with either desipramine or fenfluramine during this study.

Desipramine also appears to be effective in nonpurging bulimics. In a 12-week controlled study of nonpurging bulimics, binge eating was significantly less in the desipramine-treated (63%) than placebo (16% increase) group. Remission in bulimic symptoms was four times more likely with desipramine than placebo administration in the same study (McCann & Agras, 1990). In the largest study ($N = 80$) reported to date, bulimics treated with desipramine for 8 weeks had a much greater improvement in binge frequency (47% decrease) than those receiving placebo (7% increase; Barlow et al., 1988). Blouin and colleagues (1989) attempted to identify potential prognostic indi-

cators for antibulimic response with desipramine in another study. Response to desipramine was associated with a greater frequency of baseline purge episodes or a lower baseline score on the bulimia subscale of the Eating Disorder Inventory (EDI). Again, no correlation was found between the antibulimic and antidepressant effects associated with desipramine treatment during the study.

Although Walsh, Hadigan, and Wong's (1992) large desipramine study revealed marked benefit during the acute phase of treatment, less than one-third of the desipramine-treated subjects maintained their response during an additional 16-week maintenance phase (Agras, Rossiter, & Arnow, 1992). These findings suggest that while desipramine may be effective in the acute treatment of bulimia, the long-term efficacy appears to be limited. Cardiovascular parameters were also examined during the study in the bulimics under 30 years of age ($n = 13$) who received desipramine. Significant increases in blood pressure and significant reductions in cardiac rate variability occurred in the desipramine-treated bulimics. This may represent a potentially important finding since similar cardiovascular effects have been associated with an increased risk of cardiac arrhythmia (Walsh et al., 1992).

In contrast to imipramine and desipramine, the TCA amitriptyline appears to lack significant efficacy in the treatment of bulimia. Two separate, controlled trials have failed to demonstrate significant differences in antibulimic effects between amitriptyline (100 to 150 mg/day) and placebo administration (Edelbroek, Zitman, & Knoppert-van der Klein, 1987; Mitchell & Groat, 1984). However, the placebo-response rate was fairly high in both of these studies, which may have limited the ability to detect a significant drug-placebo difference.

In summary, imipramine and desipramine have demonstrated consistent antibulimic effects in short-term, controlled trials, whereas amitriptyline may be ineffective for bulimia. A considerable number of dropouts occurred during the studies, and there is some evidence that cardiac effects of the TCAs may be problematic. A number of case reports have suggested that other TCAs such as nortriptyline and clomipramine may also be effective in the treatment of bulimia, but controlled trials are currently absent (Pope et al., 1985). Although limited data are available concerning long-term efficacy of the TCAs in bulimia, results are discouraging. TCAs also have considerable side effects and serious toxicity in overdose. Ingestion of 5 of 7 days of a routine TCA dose can be a potentially fatal amount. Since impulsive behavior frequently accompanies bulimia nervosa, the potential toxicity of TCAs represents an important issue. TCA-associated weight gain can also be particularly troublesome. Bulimic patients are particularly fearful of gaining weight and frequently resist taking medications that might further contribute to weight gain or obesity. These factors suggest that TCAs are not first-line medications for bulimia.

MAOI Antidepressants

The primary pharmacological action of the MAOI is to inhibit the enzyme, monoamine oxidase, that is responsible for degradation of the neurotransmit-

ters serotonin, norepinephrine, and dopamine. Since nonselective MAOIs block both MAO-A and MAO-B, a low tyramine diet is required to avoid hypertensive reactions. Serious, sometimes fatal, reactions can also occur when some medications are co-administered with an MAOI. Such prohibited medications are widely available and include many sinus, cough, and cold remedies, commonly used anesthetics, and other antidepressants. In addition to these constraints, MAOI therapy is further limited by the occurrence of side effects. Frequent MAOI-related side effects include severe orthostatic hypotension, insomnia, tremor, and weight gain. Newer MAOIs are more selective and selectively block either MAO-A or MAO-B. As a result, selective MAOIs such as brofaramine do not require dietary restrictions, have few drug interactions, and are better tolerated than the traditional, nonselective MAOIs.

Traditional MAOIs such as phenelzine and isocarboxazid have also been investigated in bulimia. In 24 patients comorbid for atypical depression and bulimia, the MAOI phenelzine (mean dose, 75 mg/day) was associated with significant reductions in bulimic and depressive symptoms (Rothschild, Quitkin, & Quitkin, 1994). Since imipramine was no better than placebo in reducing bulimic or depressive symptoms during the same study, these results suggest that phenelzine may be a better choice for bulimic patients who also have atypical depression.

Walsh, Gladis, and Roose (1988) conducted a placebo-controlled study of phenelzine (60 to 90 mg/day) in bulimia. Phenelzine was superior to placebo in both reduction of binge frequency (64% vs. 5%) and in the number of patients achieving remission at 8 weeks (35% vs. 4%). Unfortunately, 6-month follow-up data revealed that every one of the initial phenelzine responders relapsed within the follow-up period. Most disconcerting were results from a 2-to-9-year follow-up of the same patients conducted by Fallon and colleagues (1991). They found that serious hypertensive episodes had occurred in 20% (3/15) of the phenelzine-treated bulimics, including one that proved to be fatal.

In contrast to results from an initial open trial (Stewart, Walsh, & Wright, 1984), the MAOI isocarboxazid (60 mg/day) was significantly more effective than placebo administration in reducing binge and purge episodes in bulimic patients. Isocarboxazid, however, was poorly tolerated during the study; over half of the subjects experienced side effects and many discontinued. At 1-year follow-up more than 60% of the bulimics had discontinued the drug due to side effects (Stewart et al.). Several case reports have suggested that the MAOI tranlylcypromine is effective for bulimia (McElroy, Keck, & Pope, 1989; Pope et al., 1983). In a small open trial ($n = 12$) conducted for bulimia, tranlylcypromine (40 to 60 mg/day) markedly improved symptoms in 2 out of 12 of the patients who had failed other medications (Stewart et al., 1984). Two cases of spontaneous hypertensive reactions have also been reported with tranlylcypromine treatment in bulimic patients (Keck, Pope, & Nierenberg, 1989). Although the mechanism of these reactions is unknown, Keck

and colleagues reported some results in terms of the acute cardiovascular response to a single dose of an MAOI in bulimic subjects that may help to explain these reactions. Significant but asymptomatic increases in systolic and diastolic blood pressure were noted after administration of a single MAOI dose. Given these reports, it is not surprising that controlled trials of tranlycypromine for bulimia have not been pursued.

Brofaromine, a selective inhibitor of MAO-A, is not commercially available in the U.S. but offers some advantages over the nonselective MAOIs. For example, dietary constraints are not required. However, in the only controlled trial reported to date, brofaromine was only modestly effective and, surprisingly, only marginally tolerable in the treatment of 38 patients with bulimia (Kennedy, Goldbloom, & Ralevsky, 1993). Given all of these factors, MAOIs have limited utility in the treatment of bulimia. They should be considered, however, for patients with bulimia who do not respond to first-line therapies.

Other Antidepressants

Several other antidepressant medications have been investigated in the treatment of bulimia nervosa. An open-label, flexible-dose study with the atypical antidepressant trazodone was conducted in bulimia ($N = 10$). After approximately 7 weeks of trazodone treatment, significant reductions in the frequency of binge and purge episodes were noted (Opler & Mickley, 1986). Hudson, Pope, Keck, and McElroy (1989) conducted a double-blind study of trazodone versus placebo in bulimic females ($N = 42$). Trazodone was superior to placebo in reducing the frequency of binge and purge episodes and was well tolerated throughout the 6-week treatment period. Follow-up conducted 9 to 19 months after completion of the study revealed that 72% of the bulimic subjects remained improved. Moreover, complete symptom remission was reported in 18% of the bulimic subjects.

Bupropion was superior to placebo in a placebo-controlled, multicenter trial conducted for bulimia ($N = 81$). Unfortunately, the 6% prevalence rate for seizures in the bulimic subjects during the 8-week study precludes routine use of bupropion for bulimia (Horne, Ferguson, & Pope, 1988). The antidepressant nomifensine has also been reported to be effective for bulimia in both an open and a controlled trial. However, it has been withdrawn from the market due to serious side toxic reactions. Mianserin, another atypical antidepressant, was no more effective than placebo in a controlled trial conducted in 50 patients with bulimia (Sabine, Yonace, & Farrington, 1983).

SSRIs

As discussed, an extensive body of research indicates that the neurotransmitter serotonin plays an important role in mediating satiety and appetite. Since SSRIs selectively target serotonin and are associated with a favorable side effect and toxicity profile, they represent a particularly promising treatment for bulimia.

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The earliest reports concerning SSRI antidepressants in the treatment of

bulimia involved the use of fluoxetine. A number of open studies of fluoxetine alone, or in combination with behavioral therapy, reported very encouraging results (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992; Freeman & Hampson, 1987; Goldstein, Wilson, & Thompson, 1995; Solyom, Solyom, & Ledwidge, 1990). Some reports even suggested that fluoxetine treatment was beneficial in bulimic patients who had previously failed to respond to other antidepressant medications (Agras, Rossiter, & Arnow, 1991, 1994; Mitchell et al., 1989).

Fluoxetine has subsequently been the most extensively investigated of the SSRIs in the treatment of bulimia. Moreover, fluoxetine remains the only medication in the U.S. that is FDA-approved for the indication of treatment of bulimia nervosa. Approval of fluoxetine in the treatment of bulimia was based primarily on data obtained from two large, multicenter, placebo-controlled trials of fluoxetine in subjects who met *DSM-III-R* criteria for bulimia nervosa. In the first study ($N = 387$), fluoxetine (20 mg/day or 60 mg/day) was compared to placebo administration in an 8-week, fixed-dose design (Fluoxetine Bulimia Nervosa Collaborative Study Group, 1992). The 60-mg/day fluoxetine-treated group, in comparison to the placebo-treated group, had significantly less binge (67% vs. 33% reduction) and purge (56% vs. 5% reduction) episodes per week. Although fluoxetine at 20 mg/day was significantly better than placebo in reducing purge (29% vs. 5%) episodes, reductions in binge episodes were not statistically different from placebo administration. Fluoxetine treatment was also associated with significant improvement in depressive symptoms, complaints of carbohydrate craving, and distorted attitudes and behaviors about eating. These effects were more robust at the higher than lower dose of fluoxetine. Although side effects tended to occur more often in the fluoxetine than placebo-treated groups, dropouts due to side effects were similar between the three treatment groups. The most common side effects encountered with the fluoxetine-treated group were insomnia, nausea, asthenia, and tremor.

A second multicenter, placebo-controlled study ($N = 389$) also demonstrated that fluoxetine (60 mg/day) was effective and well tolerated in the treatment of bulimia (Goldstein et al., 1995). Compared with placebo, 60 mg of fluoxetine resulted in significantly greater improvements in binge (50% vs. 18% reduction) and purge (50% vs. 21% reduction) episodes. Again, fluoxetine was well tolerated during the study and medication-related side effects were only slightly more likely in the fluoxetine than placebo-treated group of bulimic subjects (Goldstein et al.). A subsequent analysis of the data from the two multicenter studies also examined the potential association between changes in behavior versus cognition during the study. Reductions in bulimic behaviors were significantly associated with the likelihood of improvement in the distorted cognitions associated with bulimia. Interestingly, the presence of depression at baseline did not enhance the likelihood that the distorted cognitions related to bulimia would improve (Solyom et al., 1990). Fluoxetine appears to be well tolerated and exceptionally safe in the treatment of

bulimia nervosa. In fact, some data suggest that fluoxetine may have some beneficial effects in terms of cardiac vagal tone. Rissanen, Nauukkarinen, Virkkunen, Rawlings, and Linnoila (1998) systematically examined cardiac vagal tone in women with bulimia nervosa before and after treatment with fluoxetine. Prior to fluoxetine treatment, the bulimic subjects exhibited evidence of increased cardiac vagal tone at rest, in comparison to control subjects. However, fluoxetine treatment was associated with normalization of the elevated resting cardiac vagal tone. This represents a potentially important finding since treatment with the TCA desipramine for bulimic symptoms has been associated with quite opposite, and potentially deleterious, cardiac effects. These data suggest that fluoxetine treatment in bulimia may actually convey some protective effects in terms of reducing the risk of potential cardiac arrhythmias.

A few initial case reports suggested that fluoxetine treatment for bulimia might be associated with increased suicidal or aggressive behavior. However, subsequent large-scale research efforts have failed to support any connection between fluoxetine treatment and the emergence of suicidal or violent behavior (Wheadon, Rampey, & Thompson, 1992). In fact, examination of the entire database from controlled clinical trials conducted with fluoxetine in non-mood disorder patients such as bulimia ($N = 4,959$) reported much different conclusions. Overall, suicide attempts were very rare and no completed suicides were reported during any of the multicenter, non-mood disorder, fluoxetine treatment trials. There was also no evidence of treatment differences in the rate of suicide attempts or emergence of suicidal ideation. That is, similar rates for suicide attempts or ideation were found in the fluoxetine, TCA, and placebo-treatment groups during these studies.

A subsequent analysis of the data from the double-blind, placebo-controlled trials of fluoxetine in bulimia nervosa ($N = 785$) was also conducted to examine suicidality. Suicidal ideation emerged in 3% of the bulimic subjects, but only 1% of the bulimic subjects actually attempted, and none completed, suicide during these studies. In fact, a smaller percentage of fluoxetine-treated (2.0%) than placebo-treated (3.8%) patients experienced the emergence of substantial suicidal ideation during the study. Indeed, suicidal ideation was more likely to improve in the fluoxetine-treated than the placebo-treated group of bulimic subjects during the study (Wheadon et al., 1992). A meta-analysis of the Fluoxetine Clinical Trial Database ($N = 3,992$) was also performed to address the possible association of fluoxetine with violence or aggression. Significantly fewer fluoxetine-treated (0.15%) than placebo-treated (0.65%) patients experienced events suggestive of aggressive or violent behavior (increased hostility, antisocial behavior, etc.). A relative risk analysis revealed that aggressive or violent actions were four times more likely to occur during placebo than fluoxetine treatment (Wheadon et al.).

Patients with bulimia nervosa frequently report a history of childhood abuse. Results from one study ($N = 30$) suggest that patients with bulimia

who report childhood physical abuse may be more likely to have a significant improvement in depressive symptoms with fluoxetine treatment than those without such histories. However, no relationship was demonstrated between a history of childhood abuse and improvement or changes in bingeing or purging behaviors (McCarthy, Goff, & Baer, 1994). The SSRI antidepressant fluvoxamine has also been investigated in the treatment of bulimia nervosa. In one of the first reports, 8 weeks of treatment with open-label fluvoxamine (50 to 150 mg/day) resulted in significant decreases in binge and purge episodes in 20 bulimic subjects (Ayuso-Gutierrez, Palazone, & Ayuso-Mateos, 1994). Although 9 (45%) of the bulimic patients complained of mild side effects, particularly daytime somnolence (25%) or insomnia (15%), none discontinued treatment secondary to adverse effects. Fluvoxamine (100 to 200 mg/day) was also investigated as a treatment in a small pilot study involving non-purging, binge-eating obese subjects ($n = 10$) and obese subjects with bulimia nervosa ($n = 6$). Although the bulimic group had significant reductions in hunger, no significant improvement in binge and purge frequency occurred during the study. Surprisingly, the nonpurging group did experience significant benefits. They lost significant weight and had substantial reductions in binge frequency, anxiety levels, and distorted attitudes about food (Gardiner, Freeman, & Jesinger, 1993).

Fichter, Kruger, and Rieg (1996), however, recently reported results from a double-blind placebo-controlled study that examined fluvoxamine's potential utility in prevention of relapse in bulimia. Their study involved 72 patients with bulimia nervosa and was conducted in two phases over a 15-week period. In the initial phase, fluvoxamine was initiated and titrated to a therapeutic range on an inpatient basis over a 2-to-3-week period. Fluvoxamine was then continued on an outpatient basis for 12 more weeks in the second phase of the study. Fluvoxamine was found to be effective in preventing relapse of bulimic symptoms as measured by a clinician global assessment of illness severity. There was also a positive statistical trend toward maintenance of improvement in depressive symptoms and improvement in a self-report measure of general psychopathology associated with fluvoxamine treatment. Interestingly, self-report measures of obsessive-compulsive traits, but not of perfectionism, were also significantly improved with fluvoxamine in the study (Fichter et al.). No controlled studies have been reported with other SSRI antidepressants such as paroxetine, sertraline, or citalopram. Given the substantial amount of information supporting its efficacy and safety in the treatment of bulimia, fluoxetine is generally considered first-line pharmacotherapy for bulimia nervosa. There is also some evidence that fluvoxamine is effective in bulimia, but further controlled data are needed (Spigset & Pley, 1991). A few case reports have suggested that sertraline may also be useful in treating bulimia nervosa (Roberts & Lydiard, 1993). Although controlled data concerning the remainder of the SSRIs in the treatment of bulimia are lacking, their primary pharmacological effects are similar to fluoxetine, so it is likely that they will also possess antibulimic effects.

Alternative Medications

In an initial open-label study, naltrexone (doses up to 300 mg/day) was reported to substantially reduce binge and purge episodes in a group ($n = 13$) of previously treatment-refractory bulimic subjects (Jonas & Gold, 1986). However, subsequent results with controlled studies of the opiate antagonists in the treatment of bulimia have been largely disappointing.

Mitchell and colleagues conducted two separate controlled trials with opiate antagonists in bulimia (Mitchell, Christenson, & Jenninger, 1988; Mitchell, Laine, & Morley, 1986). In the first study, naltrexone reportedly reduced caloric intake during binges but the binge episodes persisted. In the second study, naltrexone was no more effective than placebo in reducing binge and purge frequency in bulimic ($n = 16$) females. Negative results were also reported from an 8-week double-blind crossover trial comparing naltrexone (120 mg/day) to placebo in bulimic subjects (Igoin-Apfelbaum & Apfelbaum, 1987).

Two other studies conducted in bulimia with opiate antagonists reported some positive effects. Modest improvement in bulimia was noted after 6-week controlled trial of high-dose (200 to 300 mg/day) naltrexone in 16 subjects (Jonas & Gold, 1988). An 8-week placebo-controlled trial compared the opiate antagonist naltrexone with imipramine in a group of obese binge eaters ($n = 33$) and a group of bulimics ($n = 22$). Naltrexone (100 to 150 mg/day) produced a significant reduction in binge duration in the bulimic group, whereas imipramine significantly reduced binge duration in the obese binge eaters. Although binge frequency was reduced after naltrexone and imipramine treatment, a strong placebo effect also occurred, and this appeared to effectively nullify any statistical difference between the three treatment groups in the obese binge eaters. These results suggest that naltrexone may have some modest antibinge effects, but relatively high doses may be necessary (Alger et al., 1991).

The anticonvulsant carbamazepine was ineffective in 5 out of 6 bulimic subjects in a double-blind, placebo-controlled crossover study (Kaplan, Garfinkel, & Darby, 1983). A few controlled trials were also conducted with serotonin releasers *d*, *l*-fenfluramine, and *d*-fenfluramine prior to their withdrawal from the commercial market. In two controlled studies, *d*-fenfluramine was no different than placebo in reducing bulimic symptoms (Russell, Checkley, & Feldman, 1988; Stunkard, Berkowitz, & Tanrikut, 1996). However, a placebo-controlled, crossover comparison of *d*, *l*-fenfluramine and desipramine reported that *d*, *l*-fenfluramine was more effective than placebo in reducing binge and purge episodes (Fahy, Eisler, & Russell, 1993).

Case reports have also suggested that other medications may also benefit bulimic patients. Such medications include anxiolytic (ipsapirone, alprazolam) and antiemetic (ondansetron) medication as well as the testosterone antagonist flutamide. Although intriguing, further research is clearly needed before any conclusions can be reached concerning these agents in bulimia.

Maintenance Pharmacotherapy

Although most (60% to 80%) bulimic patients treated with antidepressant medication will experience clinically relevant symptom reduction, estimates suggest that only 1 out of 4 will attain short-term remission. Particularly disheartening is the finding that one-third of the bulimic patients who achieve remission will relapse despite continuation of the medication. Fortunately, there is some evidence that substituting an alternative antidepressant when the initial medication begins to fail improves outcome during long-term maintenance therapy of bulimia nervosa.

There is also some evidence that a second antidepressant trial should be considered in patients with bulimia nervosa who fail to respond to an initial antidepressant trial. Mitchell and colleagues (1989) conducted a small open-label investigation to determine the rate of response to a second antidepressant (primarily fluoxetine or an MAOI) in a group of bulimic patients who had failed an initial imipramine trial. Interestingly, almost half (47%) of the subjects experienced a complete remission of symptoms when treated with a second antidepressant (Mitchell et al.). These results suggest that a substantial portion of bulimic patients who do not respond to an initial antidepressant will respond during treatment with an alternative antidepressant.

Similar results supporting the importance of sequential antidepressant treatment in bulimia nervosa were also noted in another study. Pope and colleagues (1983) assessed outcome in a group of bulimic patients ($n = 20$) who had initially participated in an imipramine trial for bulimia. During the 2-year follow-up period, the vast majority of patients (95%) experienced at least partial improvement and 50% reported complete remission in their bulimic symptoms during the follow-up period of observation. However, two to four medication trials were often required to achieve the level of improvement reported during the study (Pope et al.).

Combined Treatment

Numerous controlled treatment trials have demonstrated that cognitive-behavioral therapy (CBT) is an effective treatment for bulimia nervosa. In fact, a substantial wealth of evidence suggests that CBT may be the most effective treatment for bulimia in terms of symptom reduction and relapse prevention. Goldbloom et al. (1997) randomly assigned bulimic females ($N = 76$) to three treatment cells: (a) fluoxetine, (b) CBT, or (c) fluoxetine plus CBT. After 16 weeks of treatment, the combined treatment group and the CBT-treated group were significantly better than the fluoxetine-treated group in terms of bulimic symptoms. There was no statistically significant advantage for the combined treatment group over the group receiving CBT alone. Walsh et al. (1997) conducted a large ($N = 120$) placebo-controlled comparison of three different treatment modalities and two combined treatment regimens in bulimic subjects. The bulimic subjects were randomly assigned to (a) CBT alone, (b) supportive psychotherapy alone, (c) medication alone, (d) CBT plus medication, or (e) supportive psychotherapy plus medication.

The results suggested that CBT was superior to supportive psychotherapy and CBT plus medication was superior to medication alone. However, there was no advantage of supportive psychotherapy plus medication over medication alone.

Mitchell et al. (1989) reported a 12-week study that compared three active treatments to placebo in bulimic patients. The bulimics were randomly assigned to either (a) imipramine alone, (b) imipramine combined with intensive group psychotherapy, (c) placebo combined with intensive group psychotherapy, or (d) placebo. All three active treatment groups had significant improvements in bulimic and depressive symptoms relative to the group assigned to placebo. However, there was no significant advantage in the combined active treatment group over the medication alone or group therapy alone groups. Agras and colleagues (1994) compared 1-year outcome in bulimic patients that received treatment with either 16 weeks of desipramine, 24 weeks of CBT, or 24 weeks of medication plus CBT. Both the combined (medication + CBT) treatment group and the CBT-treated group were significantly better than medication alone in reducing binge episodes. The broadest gains were associated with the combined 24-week treatment regimen during this study.

Results from the controlled comparisons of treatment modalities in bulimia suggest that (a) medication treatment alone for bulimia nervosa is significantly less effective than CBT alone; and (b) combined treatment with medication and CBT is superior to medication treatment alone in bulimia. Most of these studies also suggest that combining CBT and medication may not offer clear advantages over CBT alone. These findings, along with the evidence that benefits associated with a medication may diminish over time, suggest that CBT should always be considered when pharmacotherapy is used for the treatment of bulimia. Adjunctive CBT should also be investigated for relapse prevention whenever medication discontinuation is being considered. The optimal sequence for combining medication and CBT has not been established, but medication is usually initiated first.

Interestingly, there is no apparent connection in therapeutic response between bulimic versus depressive symptomatology. That is, antidepressant medication appears effective for bulimia even in the absence of substantial depressive or anxiety symptoms. Moreover, the presence or severity of depressive symptoms does not have a substantial impact on subsequent response in bulimic patients.

Pharmacotherapy of Anorexia Nervosa

At this time, the role of pharmacotherapy remains limited at best in the treatment of anorexia nervosa. Studies reporting positive results with medication treatment for anorexia nervosa have frequently lacked controlled designs and yielded, at best, incremental improvement. This is particularly striking in the treatment of low-weight anorexia, where, even in the context of limited objectives such as enhanced weight gain, results with medication treatment

have been dismal. Recent results support a potential role for medication in the recovery phase of anorexia nervosa. These and related issues will be reviewed in this section.

Most medication studies conducted in anorexia have focused on underlying mechanisms conceptualized as important in the development and/or perpetuation of anorexia nervosa. That is, medication strategies for anorexia nervosa have primarily been based upon the treatment of anorexia as (a) a manifestation of an underlying psychotic, depressive, or obsessional state and/or (b) a disturbance of appetite regulation or satiety. Unfortunately, none of these treatment tactics has proven particularly beneficial in the acute phase of anorexia.

Neuroleptic Medication

Anorexics often exhibit distorted body image and a frantic pursuit of weight loss through prolonged starvation. Moreover, individuals without pre-existing psychiatric illness often develop psychotic symptoms and perseverative behaviors during periods of prolonged starvation or severe caloric restriction. In addition to potentially attenuating any underlying psychosis or delusional thinking, neuroleptic treatment has long been associated with increased appetite and weight gain in the treatment of traditional psychotic conditions. Initial reports suggested improved weight gain during treatment with typical neuroleptic medications such as chlorpromazine in anorexics. However, seizures and other substantial neuroleptic-related side effects were also common. Therefore, the poor tolerability and potential toxicity of the typical neuroleptics appear to outweigh any modest benefits that might occur in anorexics. Recent controlled studies utilizing newer neuroleptics such as pimozide and sulpiride, respectively, were no more effective than placebo in promoting weight gain in low-weight anorexics (Vandereycken, 1984; Vandereycken & Pierloot, 1982). Therefore, the current consensus is that there is little if any justification for the use of neuroleptic medication in anorexia nervosa at this time.

Antidepressant Medication

Several lines of evidence support a strong association between anorexia nervosa and depressive disorders. Many signs of depression, including blunted mood, irritability, excessive guilt, ruminatory anxiety, anhedonia, social withdrawal, and neurovegetative symptoms such as sleep and appetite disturbance, weight loss, and impaired concentration, are frequently present in anorexia nervosa. Although many of these symptoms may also arise from starvation, it is interesting to note that patients afflicted with anorexia nervosa have a greatly elevated lifetime risk for depression and related mood disorders. Evidence from family studies also provides some data supporting a potential familial or genetic link between anorexia nervosa and depressive disorders. Several studies have demonstrated that the biological relatives of anorectics have elevated rates of lifetime depressive disorders. These find-

ings, coupled with the frequent association of antidepressants with weight gain, have led to multiple studies with antidepressant medication in anorexia nervosa.

The potential impact of antidepressant medication on weight gain in low-weight anorexics has been investigated in several studies. Treatment with TCAs such as amitriptyline and MAOIs such as phenelzine have historically been associated with complaints of enhanced appetite, increased carbohydrate and caloric consumption, and considerable weight gain in depressed patients (Walsh et al., 1988). Decreases in basal metabolic rate and potent antihistaminic effects are often implicated in TCA- or MAOI-induced weight gain. Lithium has antidepressant properties and is also frequently associated with weight gain in patients with mood disorders; this effect may result from lithium's potent antithyroid effects. With these issues in mind, TCAs, MAOIs, and lithium have all been investigated in the acute phase of anorexia treatment. Unfortunately none of these medications has been effective in enhancing weight gain or reducing anorexic behaviors during the acute phase of anorexia nervosa. In the largest controlled study to date ($N = 72$), amitriptyline was no better than placebo in promoting weight gain and recovery in a group of low-weight anorexics (Halmi, Eckert, & LaDu, 1986). Amitriptyline was also ineffective in another study conducted by Biederman and colleagues (1985). Amitriptyline was poorly tolerated by the anorexics during both of these studies. MAOIs have also been advocated as potential treatments for anorexia, but results have been no more encouraging than with the TCAs. Lithium has also been investigated as a potential therapeutic agent for anorexia nervosa. In the largest study to date, no benefits were associated with lithium therapy in 16 patients with anorexia (Gross, Ebert, & Faden, 1981). Therefore, TCA, MAOI, and lithium therapy do not appear to be indicated in the acute treatment of anorexia nervosa.

Antiobsessional Medication

The focal preoccupation with body weight and appearance seen in anorexia nervosa has also been compared to the excessive, repetitive obsessions and ritualistic behaviors that characterize OCD. In addition to the phenomenological similarities between anorexia nervosa and OCD, there is also evidence of substantial comorbidity as well as possible familial and/or genetic links. Results from several studies indicate that individuals who manifest anorexia nervosa also have an elevated lifetime risk for developing OCD. In fact, Halmi and colleagues (1986) reported that the biological mothers of anorexic compared to control subjects were significantly more likely to meet criteria for OCD. These findings, combined with evidence of serotonin dysregulation in both OCD and anorexia nervosa, have resulted in considerable speculation that anorexia nervosa may represent an OCD spectrum disorder. With these issues in mind, several investigators have researched the potential utility of antiobsessional agents in the treatment of anorexia nervosa.

Initial investigations focused on the use of clomipramine for patients with anorexia nervosa (Crisp, Lacey, & Crutchfield, 1987). In comparison to other

TCAs, clomipramine has the most potent serotonin-enhancing properties. These serotonergic effects are considered to be the basis for clomipramine's therapeutic efficacy in OCD, whereas other TCAs lack efficacy in OCD. In the largest study reported to date, low-dose clomipramine (50 mg/day) was not effective in 16 patients with anorexia (Crisp et al.). Clomipramine was also associated with substantial side effects and, in general, poorly tolerated by most of the anorexic patients.

Besides clomipramine, SSRIs are the only other medications that demonstrate consistent efficacy in the treatment of OCD. Fortunately, the side effects commonly encountered with SSRIs are much more benign than those associated with clomipramine. Several studies have investigated the potential utility of fluoxetine in the treatment of anorexia nervosa. Two separate, open-label studies have reported that low-weight anorexics treated with fluoxetine have an enhanced chance of sustaining weight gain during the maintenance and recovery phases of anorexia (Gwirstman et al., 1990; Kaye, Weltzin, Hsu, & Bulik, 1991). Kaye and colleagues conducted the first controlled trial of fluoxetine in weight-recovered, restrictor-type anorexics ($N = 35$). The anorectic patients randomized to fluoxetine treatment were significantly more likely to maintain their weight during the recovery phase than those randomized to placebo administration. These results are very encouraging, but further studies are clearly needed before the use of SSRI medication in anorexia nervosa can be recommended on a routine basis.

Prokinetic Gastrointestinal (GI) Medications

Numerous studies conducted in anorexics have revealed evidence of impaired GI function, particularly delayed gastric emptying. Since anorexics inevitably complain of increased satiety, feeling "bloated," and chronic abdominal distention even in the absence of objective findings, several investigators have conducted studies with medications primarily indicated for GI disorders as potential adjunctive treatments for anorexia. Open studies have suggested that prokinetic medications such as domperidone (Russell et al., 1983; Stacher et al., 1986), bethanecol (Dubois, Gross, & Ebert, 1980), and metoclopramide (Saleh & Lebwohl, 1980) may enhance gastric emptying in anorexic patients, but placebo-controlled trials are absent. Two separate placebo-controlled trials have been conducted in anorexics with the gastric motility agent, cisapride (Stacher, Abutzi-Wentzel, & Wiesnagrotzki, 1993). The results with cisapride have been mixed and any benefits noted have been very modest (Szmukler et al., 1995). In the first report, cisapride failed to demonstrate benefit over placebo in reducing either complaints of bloating or in promoting weight gain in anorexic subjects (Stacher et al., 1993). A subsequent study reported less complaints of bloating or abdominal distention in the cisapride-treated than placebo-treated group of anorexic subjects (Szmukler, Young, & Miller, 1995). However, there was no significant correlation between improvement in subjective complaints of abdominal distention and actual measures of gastric emptying indices. Although further studies of this

approach appear worthwhile, prokinetic agents do not appear to have a major role in the treatment of anorexia nervosa at this time.

Appetite Stimulators

Since anorexia is also characterized by refusal to eat or marked reductions in caloric ingestion, appetite dysregulation or impaired satiety have long been postulated. Yet, most evidence suggests that anorexics do not have reduced appetite unless the starvation state is particularly prolonged. Instead, anorexia is typically characterized by severe dietary restraint despite persistent appetite. Anorexics appear to gain internal reinforcement and satisfaction from their ability to resist the appetitive drive. Nonetheless, appetite-stimulating agents have been extensively investigated in the treatment of anorexia nervosa. In one particularly novel study, anorexics were treated with tetrahydrocannabinol (THC), a well-recognized and potent stimulator of appetite, and the anxiolytic diazepam in a crossover design. Neither THC nor diazepam was of benefit in enhancing eating or weight gain (Gross, Ebert, & Faden, 1983). Moreover, the study was prematurely terminated due to the emergence of severe dysphoric mood in a number of the anorexics during the diazepam phase of the study. The adrenergic blocker clonidine has also been unsuccessfully used in low-weight anorexics as a potential appetite stimulator (Casper, Schlemmer, & Javaid, 1987).

Opiate Antagonists

The state of starvation is often accompanied by marked elevations in endogenous opioids including endorphins. Opiate dysregulation has been implicated in the pathophysiology of anorexia nervosa. Several investigators have speculated that increased opioid concentrations act as a potent and "addicting" stimulus to maintain starvation in individuals afflicted with anorexia nervosa (Marrazzi, Bacon, & Kinzie, 1995). In fact, several case reports and open studies suggest that the potent opiate antagonist naltrexone might represent a useful treatment strategy for anorexia nervosa (Marrazzi et al.). Results of a recent double-blind, placebo-controlled, crossover study revealed that naltrexone had a modest advantage over placebo in a group of patients with anorexia nervosa. A small, although statistically significant, greater increase in weight gain was noted in the naltrexone versus placebo-treated anorexic patients (Marrazzi et al.). Given the lack of robust findings in positive, controlled studies with opiate antagonists in the treatment of anorexia nervosa, their role in anorexia treatment remains speculative.

Alternative Medication Strategies

There is some evidence that the antihistamine cyproheptadine might have some benefits in the restrictor subtype of anorexia nervosa. Halmi and colleagues (1986) reported that restricting anorexics had improved weight gain when treated with cyproheptadine (mean 3.3 mg/day). However, anorexics with the bingeing subtype actually were reported to have a worse outcome

when treated with cyproheptadine in the same study. Unfortunately, two subsequent controlled studies of cyproheptadine failed to replicate the initial positive results reported (Goldberg, Halmi, & Eckert, 1979). The relatively low dose of cyproheptadine used in the later studies (Vigersky & Loriaux, 1977) may have contributed to the lack of response. Cyproheptadine was well tolerated in all of these reports. Interestingly, a controlled study of zinc gluconate (100 mg/day) supplementation in low-weight anorexics ($N = 5$) reported some promising results (Birmingham, Goldner, & Bakan, 1994). The anorexic patients gained significantly more weight when they received the supplemental zinc in comparison to placebo during the study.

With these results in mind, there is very limited evidence that any form of pharmacotherapy has a significant impact on the course of anorexia during the low-weight phase. Administration of neuroleptic medication, MAOI antidepressants, TCAs, lithium, or clonidine has failed to demonstrate significant benefit in patients with low-weight anorexia nervosa. There may be some benefit associated with cyproheptadine in the acute treatment of the restrictor subtype of anorexia, but evidence is very limited. If initial encouraging results are replicated, supplementation with zinc may have some role in enhancing weight gain on at least a modest basis in the acute phase of anorexic treatment. Prokinetic agents may also provide some benefit as adjunctive agents for delayed gastric emptying or prominent complaints of bloating in the acute phase of anorexia. Perhaps most promising is the recent data suggesting a role for fluoxetine in the treatment of anorexia nervosa. Although fluoxetine treatment appears to have little impact on the course of anorexia during the acute, low-weight phase, it is well tolerated and it may impart some protective effects in the maintenance phase of anorexia (Attia, Haiman, & Walsh, 1998). While initial results are encouraging, further studies are necessary before fluoxetine's potential utility in relapse prevention can be established. It is unclear whether other SSRIs will have similar effects in the treatment of anorexia nervosa. Widespread clinical experience with SSRIs in the treatment of other disorders such as OCD, panic disorder, and depression confirm that each SSRI has a similar, broad spectrum of efficacy. Therefore other SSRIs may well possess similar therapeutic effects in anorexia nervosa.

Conclusions

SSRI antidepressants, particularly fluoxetine, should be considered first-line pharmacotherapy for the treatment of bulimia nervosa. Other antidepressant medications, including TCAs, MAOIs, and atypical antidepressants, are also efficacious for bulimia, but they are generally associated with more frequent side effects and greater potential toxicity in comparison to the SSRI antidepressants. While most patients with bulimia nervosa who receive appropriate pharmacotherapy will experience significant short-term improvement, there is a substantial rate of relapse during long-term continuation treatment with medication. Strategies that appear to improve long-term out-

come in bulimia nervosa include changing to an alternative antidepressant medication during symptom exacerbation or recurrence and combination treatment with CBT and medication. Although systematic studies are lacking, clinical consensus suggests that CBT may also have a role in reducing the risk of relapse during discontinuation of medication treatment.

The role for medication treatment in anorexia nervosa remains very limited. Many medications, including neuroleptics, antidepressants (TCAs, MAOIs, SSRIs, and atypical agents), lithium, appetite enhancers, opiate antagonists, and prokinetic agents, have been systematically investigated in anorexia nervosa. Yet no medication has demonstrated consistent evidence of benefit in terms of enhancing weight gain or accelerating recovery during the low-weight phase of anorexia. In addition, TCAs and neuroleptic medications may have potentially dangerous side effects in low-weight anorexics. However, the SSRI fluoxetine may have a limited role in long-term treatment of anorexia. Although preliminary and awaiting replication, some data suggest that fluoxetine treatment in the acute phase may convey some beneficial or protective effects in terms of weight maintenance during the long-term recovery phase of anorexia. Further research is clearly needed to clarify these initial promising results and to identify new pharmacological treatment strategies that may prove to be beneficial in anorexia nervosa.

References

- Agras, W. S., Dorian, B., & Kirkley, B. G. (1987). Imipramine in the treatment of bulimia: A double-blind controlled study. *International Journal of Eating Disorders*, 6, 29-38.
- Agras, W. S., Rossiter, E. M., & Arnow, B. (1991). Pharmacologic and cognitive-behavioral treatment for bulimia nervosa: A controlled comparison. *American Journal of Psychiatry*, 149, 325-333.
- Agras, S. A., Rossiter, E. M., & Arnow, B. (1992). Pharmacological and cognitive-behavioral treatment for bulimia nervosa: A controlled comparison. *American Journal of Psychiatry*, 149, 82-87.
- Agras, W. S., Rossiter, E. M., & Arnow, B. (1994). One-year follow-up of psychosocial and pharmacological treatments for bulimia nervosa. *Journal of Clinical Psychiatry*, 55, 179-183.
- Alger, S. A., Schwalberg, M. D., & Bigaouette, J. M. (1991). Effect of tricyclic antidepressant and opiate antagonist on binge-eating behavior in normal-weight bulimic and obese, binge eating subjects. *American Journal of Clinical Nutrition*, 53, 865-871.
- Attia, E., Haiman, C., & Walsh, B. T. (1998). Does fluoxetine augment the inpatient treatment of anorexia nervosa? *American Journal of Psychiatry*, 155, 144-151.
- Ayuso-Gutierrez, J. L., Palazone, M., & Ayuso-Mateos, J. L. (1994). Open-trial of fluvoxamine in the treatment of bulimia nervosa. *International Journal of Eating Disorders*, 15, 245-249.
- Barlow, J., Blouin, J., & Blouin, A. (1988). Treatment of bulimia with desipramine: A double-blind crossover study. *Canadian Journal of Psychiatry*, 33, 129-133.
- Biederman, J., Herzog, D. B., Rivinus, T. M., Harper, G. P., Ferber, R. A., Rosenbaum, J. F., Harmatz, J. S., Tondor, F. R., Orsulak, P., & Schildkraut, J. J. (1985). Amitriptyline in the treatment of anorexia nervosa: A double blind, placebo controlled study. *Journal of Clinical Psychopharmacology*, 5, 10-16.
- Birmingham, C. L., Goldner, F. M., & Bakan, R. (1994). Controlled trial of zinc supplementation in anorexia nervosa. *International Journal of Eating Disorders*, 15, 251-255.