SPECIAL REPORT

Pharmacotherapy for Patients With Eating Disorders

by Timothy D. Brewerton, M.D.

Psychiatric Times •May 2004 •Vol. XXI •Issue 6

Eating disorders, including anorexia nervosa (AN), bulimia nervosa (BN) and binge-eating disorder (BED), remain one of the most complex and clinically challenging groups of mental disorders in our nomenclature. There are no easy solutions, and the bottom line of this article is that pharmacological agents are not the primary treatment of choice. Although a number of agents have been found in randomized controlled trials to be beneficial, they are by and large insufficient as stand-alone treatments. Space does not allow a comprehensive overview of this topic, but the reader is referred to a recent review by Steinglass and Walsh (2004). In addition, the revised American Psychiatric Association practice guidelines for the treatment of eating disorders (APA, 2000) and the recently released National Institute of Clinical Excellence (NICE) Guidelines (2004) are useful resources regarding the use of drug therapy within the context of a comprehensive treatment approach.

Anorexia Nervosa

No pharmacological agents have ever been shown in double-blind, placebo-controlled trials to significantly improve AN when given outside a structured, inpatient program. Food remains the "drug of choice" for this population, for reasons that will be elaborated below. Of course, administering food in the interest of weight restoration is much easier said than done, given the profound denial and resistance typical of this disorder. There are a handful of drugs found to be statistically better than placebo in randomized controlled trials, but there is little clinical significance of these findings. Lithium (Eskalith, Lithobid) was shown in one controlled trial to be statistically better than placebo in a small group of patients being treated at the National Institute of Mental Health on an intensive, highly structured, specialized treatment unit (Gross et al., 1981). However, the effect was small, and eating disorder specialists generally deem the potential risks of lithium treatment in this population to be far greater than the possible benefits, largely due to the danger of lithium toxicity secondary to dehydration and electrolyte imbalances from starvation, compulsive exercising and/or purging. Another study found amitriptyline (Elavil) statistically better than placebo for patients who are both bulimic and anorexic, while cyproheptadine (Periactin) was better for restricting anorexia (Halmi et al., 1986). However, other studies have had mixed results.

Although the use of antidepressant medications in AN seems theoretically sound, the results from randomized controlled trials have been dismal. In addition, the cardiac effects of tricyclic antidepressants include prolongation of the QT_C interval, which can already be prolonged in patients with AN, a setup for sudden death. Selective serotonin reuptake inhibitors might seem applicable given their safety profile and usefulness in major depression and obsessive-compulsive disorder, as well as the profound central serotonergic disturbances reported in AN (Brewerton, 1995; Brewerton and Jimerson, 1996). Fluoxetine (Prozac) has been shown to have absolutely no effect on weight, body image, anxiety or mood in low-weight patients with AN (Attia et al., 1998). However, once patients are weight-recovered, one controlled trial indicated that relapse (which is common) can be significantly reduced with fluoxetine in comparison to placebo, presumably due to its antiobsessional effects (Kaye et al., 2001).

It is essential for the clinician to understand that the reason fluoxetine, or any monoamine reuptake inhibitor, cannot work in low-weight patients is because central 5-HT levels are profoundly depleted in these individuals as a direct result of starvation and weight loss (Brewerton, 1995; Brewerton and Jimerson, 1996; Kaye et al., 1988). The effectiveness of SSRIs depends not only on having sufficient central 5-HT available for release and reuptake-inhibition, but also on essential amino acid precursor (l-tryptophan) availability (via a balanced meal plan) to allow continued 5-HT-synthesis following weight recovery. This is well-established as a result of many tryptophan-depletion studies.

There is excitement in the field about the possibility of using olanzapine (Zyprexa) and other atypical antipsychotics in low-weight patients with AN. Olanzapine acts in part via postsynaptic 5-HT_2-antagonism, so it bypasses the presynaptic apparatus altogether and does not depend on l-tryptophan availability. Olanzapine's propensity toward enhanced appetite and weight gain, as well as its antianxiety, antiobsessional and antidepressant properties, makes it theoretically an excellent drug for AN, especially the restricting subtype. It also increases sleep and decreases motor activity, thereby conserving energy expenditure. Open trials and case reports are promising (La Via et al., 2000; Malina et al., 2003; Powers et al., 2002), but no controlled trials have been completed as of yet. Adult patients often resist or refuse to take olanzapine because of its weight gain and soporific effects; however, in children and adolescents, parents can ensure compliance. Very low doses are usually sufficient to attain the desired effect (i.e., 0.625 mg/day to 5.0 mg/day). There are no long-term follow-up data, but once weight restoration is achieved, olanzapine can be tapered and usually stopped as fluoxetine "kicks in" for prophylaxis. If needed, a very low dose of a relatively weight-neutral atypical antipsychotic agent, such as quetiapine (Seroquel), ziprasidone (Geodon) or aripiprazole (Abilify) may be a helpful adjunct as recovery progresses, especially when there is significant comorbidity. However, this remains speculative and untested, and most patients do not need continued antipsychotic treatment following full weight recovery. The propensity for olanzapine and other atypical antipsychotics to induce hyperglycemia, diabetes mellitus and extrapyramidal side effects certainly requires monitoring and caution, but their use must be weighed against the significant psychiatric and medical morbidity and mortality associated with AN.

Bulimia Nervosa

Although cognitive-behavioral therapy (CBT) is the most empirically validated treatment for BN (APA, 2000; NICE, 2004), several randomized control trials attest to the effectiveness of antidepressant medications in reducing binge and purge frequencies in patients with BN (Steinglass and Walsh, 2004). Such antibulimic effects have been shown in several studies to be independent of the drugs' antidepressant effects per se. In general, these studies have several limitations, including short duration (generally six to eight weeks) and exclusion of patients with major, yet common, comorbidities (e.g., mood/anxiety/substance use disorders, suicidality or parasuicidality). Both imipramine (Tofranil) (Mitchell et al., 1990) and desipramine (Norpramin) have been found to be effective in short-term, randomized controlled trials. Unlike treatment for major depression or anxiety disorders, one cannot generalize from one SSRI to another because not all of them have been studied in BN, and available evidence suggests that they are not equally effective. The only SSRIs that have been seriously studied in BN using randomized controlled trials are fluoxetine and fluvoxamine (Luvox). Fluoxetine at 60 mg/day, but not 20 mg/day, was superior to placebo in reducing both binge and purge frequencies (Romano et al., 2002), so it is important that clinicians treating BN realize that higher doses (40 mg/day to 80 mg/day) are generally required for an effective antibulimic response (similar to OCD). On the other hand, fluvoxamine has not been found to be statistically different from placebo in European randomized controlled trials (unpublished data), although it may help in relapse prevention (Fichter et al., 1996).

There are no known studies using non-SSRI newer generation agents such as nefazodone (Serzone), mirtazapine (Remeron) and venlafaxine (Effexor), except bupropion (Wellbutrin). Although bupropion has been found to be effective in one randomized controlled trial to reduce bingeing and purging frequency (Horne et al., 1988), the risk of seizures far outweighs its potential benefits, therefore its use in AN or BN is contraindicated.

There is one randomized controlled trial using ondansetron (Zofran), a potent 5-HT_3 antagonist and antiemetic indicated in the treatment of chemotherapy-induced nausea and vomiting in patients with cancer (Faris et al., 2000). Ondansetron was found to be effective in reducing bingeing and purging when compared to placebo. Although this agent is very costly, it is worth considering in refractory and/or severe cases.

The anticonvulsant topiramate (Topamax) has been recently reported to be effective in reducing binge and purge frequencies in comparison to placebo (Hoopes et al., 2003). However, bothersome side effects such as paresthesias, impaired mentation, metabolic acidosis and oligohydrosis may lessen its usefulness. It appears to be an ideal adjunct treatment to other mood stabilizers in patients with BN who are also overweight or obese and have comorbid bipolar disorder and/or migraine.

Naltrexone (ReVia) is a possible adjunct in patients who are refractory to SSRIs, especially in those with comorbid alcoholism and/or self-injurious behaviors. Although naltrexone was no better than placebo in one randomized controlled trial in BN (Mitchell

et al., 1989), a double-blind, placebo-controlled crossover study in patients with AN or BN showed it to significantly reduce bingeing and purging (Marrazzi et al., 1995).

Binge-Eating Disorder

Like in BN, CBT has been demonstrated in randomized controlled trials to be the treatment of choice for BED. In two unpublished controlled studies comparing CBT and fluoxetine, CBT was superior with or without fluoxetine (Devlin, 2002; Grilo et al., 2002). Cognitive-behavioral therapy has also been combined with fluvoxamine with better results (Ricca et al., 2001). Nevertheless, randomized controlled trials suggest that bingeing is reduced by the SSRIs fluoxetine (Arnold et al., 2002), fluvoxamine (Hudson et al., 1998), sertraline (Zoloft) (McElroy et al., 2000) and citalopram (Celexa) (McElroy et al., 2003b). Recent results indicate that sibutramine (Meridia) significantly reduces binge eating and weight in BED in comparison to placebo (Appolinario et al., 2003). Finally, a randomized control trial found the anticonvulsant topiramate to be effective in reducing binge eating as well as weight (McElroy et al., 2003a).

Conclusions

Without weight restoration in AN, antidepressants are essentially useless for this condition, while olanzapine shows some promise in open studies. There is a strong case for the use of fluoxetine as an adjunct in the treatment of BN, but remission rates are low in comparison to the effects of CBT. Other SSRIs may be helpful for BED, while topiramate appears to be effective in both BN and BED. Despite its expense, ondansetron can be useful in refractory BN, as can naltrexone with or without SSRIs.

Dr. Brewerton is clinical professor of psychiatry and behavioral sciences at the Medical University of South Carolina and is in private practice in the Charleston area.

References

APA Work Group on Eating Disorders (2000), Practice guideline for the treatment of patients with eating disorders (revision). Am J Psychiatry 157(suppl 1):1-39.

Appolinario JC, Bacaltchuk J, Sichieri R et al. (2003), A randomized, double-blind, placebo-controlled study of sibutramine in the treatment of binge-eating disorder. Arch Gen Psychiatry 60(11):1109-1116.

Arnold LM, McElroy SL, Hudson JI et al. (2002), A placebo-controlled, randomized trial of fluoxetine in the treatment of binge-eating disorder. J Clin Psychiatry 63(11):1028-1033.

Attia E, Haiman C, Walsh BT, Flater SR (1998), Does fluoxetine augment the inpatient treatment of anorexia nervosa? Am J Psychiatry 155(4):548-551.

Brewerton TD (1995), Toward a unified theory of serotonin dysregulation in eating and related disorders. Psychoneuroendocrinology 20(6):561-590.

Brewerton TD, Jimerson DC (1996), Studies of serotonin function in anorexia nervosa. Psychiatry Res 62(1):31-42.

Devlin MJ (2002), Psychotherapy and medication for binge eating disorder. Presented at the Academy for Eating Disorders 2002 International Conference on Eating Disorders and Clinical Teaching Day. Boston; April 25-28.

Faris PL, Kim SW, Meller WH et al. (2000), Effect of decreasing afferent vagal activity with ondansetron on symptoms of bulimia nervosa: a double-blind trial. Lancet 355(9206):792-797.

Fichter MM, Kruger R, Rief W et al. (1996), Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. J Clin Psychopharmacol 16(1):9-18.

Grilo CM, Masheb RM, Heninger G, Wilson GT (2002), Controlled comparison of cognitive behavioral therapy and fluoxetine for binge eating disorder. No. 1624. Presented at the 2002 International Conference on Eating Disorders. Boston; April 28.

Gross HA, Ebert MH, Faden VB et al. (1981), A double-blind controlled trial of lithium carbonate in primary anorexia nervosa. J Clin Psychopharmacol 1(6):376-381.

Halmi KA, Eckert E, LaDu TJ, Cohen J (1986), Anorexia nervosa. Treatment efficacy of cyproheptadine and amitriptyline. Arch Gen Psychiatry 43(2):177-181.

Hoopes SP, Reimherr FW, Hedges DW et al. (2003), Treatment of bulimia nervosa with topiramate in a randomized, double-blind, placebo-controlled trial, Part 1: improvement in binge and purge measures. J Clin Psychiatry 64(11):1335-1341.

Horne RL, Ferguson JM, Pope HG et al. (1988), Treatment of bulimia with bupropion: a multicenter controlled trial. J Clin Psychiatry 49(7):262-266.

Hudson JI, McElroy SL, Raymond NC et al. (1998), Fluvoxamine in the treatment of binge-eating disorder: a multicenter placebo-controlled, double-blind trial. Am J Psychiatry 155(12):1756-1762.

Kaye WH, Gwirtsman HE, George DT et al. (1988), CSF 5-HIAA concentrations in anorexia nervosa: reduced values in underweight subjects normalize after weight gain. Biol Psychiatry 23(1):102-105.

Kaye WH, Nagata T, Weltzin TE et al. (2001), Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. Biol Psychiatry 49(7):644-652.

La Via MC, Gray N, Kaye WH (2000), Case reports of olanzapine treatment of anorexia nervosa. Int J Eat Disord 27(3):363-366.

Malina A, Gaskill J, McConaha C et al. (2003), Olanzapine treatment of anorexia nervosa: a retrospective study. Int J Eat Disord 33(2):234-237.

Marrazzi M, Bacon JP, Kinzie J, Luby ED (1995), Naltrexone use in the treatment of anorexia nervosa and bulimia nervosa. Intl J Clin Psychopharmacol 10(3):163-172.

McElroy SL, Arnold LM, Shapira NA et al. (2003a), Topiramate in the treatment of binge eating disorder associated with obesity: a randomized, placebo-controlled trial. [Published erratum Am J Psychiatry 160(3):612.] Am J Psychiatry 160(2):255-261.

McElroy SL, Casuto LS, Nelson EB et al. (2000), Placebo-controlled trial of sertraline in the treatment of binge eating disorder. Am J Psychiatry 157(6):1004-1006.

McElroy SL, Hudson JI, Malhotra S et al. (2003b), Citalopram in the treatment of binge-eating disorder: a placebo-controlled trial. J Clin Psychiatry 64(7):807-813.

Mitchell JE, Christenson G, Jennings J et al. (1989), A placebo-controlled, double-blind crossover study of naltrexone hydrochloride in outpatients with normal weight bulimia. J Clin Psychopharmacol 9(2):94-97.

Mitchell JE, Pyle RL, Eckert ED et al. (1990), A comparison study of antidepressants and structured intensive group therapy in the treatment of bulimia nervosa. Arch Gen Psychiatry 47(2):149-157.

NICE (2004), Eating disorders: anorexia nervosa, bulimia nervosa and related eating disorders. Available at: www.nice.org.uk/pdf/cg009publicinfoenglish.pdf. Accessed March 29.

Powers PS, Santana CA, Bannon YS (2002), Olanzapine in the treatment of anorexia nervosa: an open label trial. Int J Eat Disord 32(2):146-154.

Ricca V, Mannucci E, Mezzani B et al. (2001), Fluoxetine and fluvoxamine combined with individual cognitive-behaviour therapy in binge eating disorder: a one-year follow-up study. Psychother Psychosom 70(6):298-306.

Romano SJ, Halmi KA, Sarkar NP et al. (2002), A placebo-controlled study of fluoxetine in continued treatment of bulimia nervosa after successful acute fluoxetine treatment. Am J Psychiatry 159(1):96-102 [see comments].

Steinglass JE, Walsh BT (2004), Psychopharmacology of anorexia nervosa, bulimia nervosa, and binge eating disorder. In: Clinical Handbook of Eating Disorders: An Integrated Approach, Brewerton TD, ed. New York: Marcel Dekker, Inc., pp489-508.