Pharmacotherapy for Patients With Eating Disorders

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Anorexia nervosa, bulimia nervosa and binge-eating disorder remain challenging disorders for the practicing psychiatrist. While psychopharmacological agents play an important role in the overall treatment of eating disorders, current empirical evidence does not support their sole use. A recipe consisting of evidence-based psychopharmacological agents together with evidence-based psychotherapeutic approaches is usually required for a successful outcome.

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 QTc 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-HT₂-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 anti-anxiety, 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-HT₃ 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 binging 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 binging is reduced by the SSRIs fluoxetine (Arnold et al., 2002), fluvoxamine (Hudson et al., 1998), sertraline (Zoloff) (McElroy et al., 2000) and citalopram (Celexa) (McElroy et al., 2003b). Recent results indicate that sibutramine (Meridia) significantly reduces binge eating and weight in BED in comparison to placebo (Appolinario et al., 2003). Finally, a randomized control trial found the anticonvulsant topiramate to be effective in reducing binge eating as well as weight (McElroy et al., 2003a).

**Conclusions**

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

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