Pharmacological Treatment of Bulimia Nervosa

May 01, 2008 | Eating Disorders [1], Addiction [2], Major Depressive Disorder [3], Opioid Related Disorders [4]

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Bulimia nervosa is a disorder with a complex cause. The disorder is most commonly seen in women, generally with onset in adolescence.

Bulimia nervosa (BN) is a disorder with a complex cause. The disorder is most commonly seen in women, generally with onset in adolescence. It is characterized by binge eating (consumption of an unusually large amount of food accompanied by feeling a loss of control), inappropriate compensatory measures to prevent weight gain (including purging by vomiting, abuse of laxatives and diuretics, strict dieting, and excessive exercise), obsessive fears of being fat, and negative self-evaluation influenced largely by body shape and weight. BN is often associated with anxiety, depression, obsessionality, substance abuse, and poor impulse control.

Antidepressants are the mainstay of pharmacological treatment for BN. In the 1980s and early 1990s they were established as more effective than placebo in treating BN in double-blind, placebo-controlled trials that tested a variety of medication classes, including tricyclic antidepressants, monoamine oxidase inhibitors, and more recently, SSRIs. Success was most commonly measured by a decrease in the number of bingeing and purging episodes, and although the studies varied widely, many patients achieved short-term reductions of 50% to 75% in one or both areas. Much less attention has been focused on whether antidepressants are as useful in reducing mood and impulse control problems often comorbid with BN.

While the observed reductions in eating-disordered behaviors were significant, it is important to realize that many patients who responded to medication continued to binge and purge at a frequency that still met criteria for a diagnosis of BN at the end of the studies. Only a minority of patients attained remission of the bingeing and purging symptoms.

Another caveat concerns the clinical applicability of trial data, because some have estimated that one-third to one-half of patients who present for treatment of BN would have been excluded from treatment studies because of accompanying substance abuse, personality disorders, current or earlier use of psychotropic medication, and other factors.

**SSRIs**

With their relatively benign adverse-effect profiles, SSRIs are the first-line pharmacological treatment of BN. Fluoxetine is the most studied of the antidepressants in this country, and the only medication approved by the FDA for treatment of BN. The indication was granted in 1996, after 2 large, multicenter, controlled trials convincingly demonstrated that fluoxetine was more efficacious than placebo for treatment of BN.

The first, an 8-week study that included nearly 400 patients, showed a response at a relatively high dosage of 60 mg/d, while a dosage of 20 mg/d was no different from placebo. The second trial, with a duration of 16 weeks, revealed that a starting dosage of 60 mg/d was generally well tolerated in this patient population.

Trials with other SSRIs have been scant. Several conducted with fluvoxamine had problems with tolerability and mixed results regarding efficacy. In a large randomized trial involving 267 patients, fluvoxamine was no better than placebo for short- or long-term (1 year) treatment of outpatients with BN. The investigators acknowledged that the dosage range of 50 to 300 mg/d may have been too low to show a treatment effect with this illness; however, titration to higher doses may have led to even more adverse events. Overall, there is little evidence for the use of fluvoxamine as an SSRI of choice for the treatment of BN.
Results with sertraline have been more promising, although the results of only one small randomized trial with 20 patients have been reported. Of interest, significant improvement versus placebo occurred with only 100 mg/d, in contrast with the relatively high doses required for fluoxetine. The reason for this finding is unknown, but replication on a larger scale would be beneficial.

Little work has been undertaken in controlled trials to compare various SSRIs for BN. One randomized controlled trial of 6 weeks' duration that involved 91 inpatients was designed to explore a genetic basis for drug response. No such basis was elucidated, but the authors reported that fluoxetine, fluvoxamine, citalopram, and paroxetine were all superior to placebo. Findings from a smaller controlled study in which patients were randomized to either citalopram or fluoxetine indicate that both groups had significant improvement in eating psychopathology.

Other antidepressants
Success with the SSRIs lends support to the theory of altered serotonin activity in BN. Nonetheless, neurotransmitter dysregulation in the disorder is more complex, and it has been known for some time that the noradrenergic system is implicated as well. In a study by Kruger and Kennedy, some tricyclic antidepressants with prominent noradrenergic effects, including desipramine and imipramine, were shown to reduce binge eating and purging.

This class of drugs may be associated with greater adverse effects in BN and thus these drugs are rarely used. However, it is surprising that no controlled trials have been conducted with the newer generation noradrenergic antidepressants. Small open trials in Austria and Italy used reboxetine, a selective noradrenaline reuptake inhibitor not available in the United States. Results showed a decrease in binging and purging symptoms as well as other psychological variables.

There are no reports of venlafaxine as a treatment for BN; however, a retrospective review found some efficacy for this serotonin-norepinephrine reuptake inhibitor (SNRI) in patients with the related condition of binge-eating disorder. The other currently prescribed SNRI, duloxetine, has appeared in a single case report of treatment-refractory BN, in which the patient achieved remission of binging and purging symptoms on a high dosage of 120 mg/d. Clearly, controlled trials are needed to assess the efficacy of SNRIs for treating BN.

Bupropion is another antidepressant worth mentioning. In 1988, the immediate-release formulation was found to be effective in reducing BN symptoms in a controlled study; however, 4 of 69 patients who received the drug had generalized seizures, resulting in its contraindication by the FDA for use in eating disorders. Subsequently, the investigators of the study reported doing an intensive examination of the patients who had experienced seizures. They found no common features in these patients' medical histories, laboratory results, concomitant medication use, or other variables that might explain predisposition to seizure, and concluded that the increased incidence of seizures could not be explained. Although no study has attempted to replicate these findings using the lower doses and longer-acting forms of the drug more commonly prescribed today, clinicians in the eating disorders field generally avoid using bupropion when treating patients with BN.

Antidepressants were initially proposed for treatment of BN because of the frequent accompanying mood symptoms of these patients. However, such medications also have proved helpful in patients with BN without comorbid anxiety and depressive disorders; they appear to independently target symptoms of binge eating, purging, and preoccupation with shape and weight. This result, along with a generally more rapid onset of action and, for fluoxetine, a higher dosage requirement than is seen with treatment of depression, suggests that drug action for BN symptoms may occur by a different mechanism, perhaps relating in part to underlying variance in the serotonergic abnormalities found in BN patients versus those with major depression. Such a possibility has led to case reports and small trials of novel medications, most notably topiramate and ondansetron.

Topiramate
The anticonvulsant topiramate has been linked to appetite suppression and weight loss, and interest in its use in BN followed suggestions of efficacy in patients with binge eating disorder. Results from the first randomized, double-blind, placebo-controlled trial of topiramate in BN were reported in
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Published on Psychiatric Times
(http://www.psychiatrictimes.com)

2003. The 10-week trial of 69 patients began with a dosage of 25 mg/d titrated to a maximum of 400 mg/d (median 100 mg/d). Topiramate was found to be more efficacious than placebo in decreasing frequency of bingeing and purging behaviors (to a similar degree as that seen in antidepressant trials) and in improving other psychological measures, including anxiety, self-esteem, eating attitudes, and body image. Adverse events were generally mild to moderate, resolved with time or dose reduction, and did not usually lead to withdrawal from the study.27,28 A 10-week controlled trial in 2004 found similar results with regard to reductions in bingeing and purging behaviors, and a decrease in weight was reported in the topiramate group.

There was an unusually low dropout rate among the 60 participants, possibly because the study enrolled only patients with moderate BN, or because the dose was increased slowly and remained relatively low (25 to 250 mg/d).29 Despite the report that there were few intolerable adverse effects in these small studies, adverse reactions to topiramate are common in clinical psychiatric practice, which tends to limit its use.

**Ondansetron**

Another novel agent proposed for treatment of BN is the antiemetic ondansetron, a selective 5-HT3 antagonist approved for the prevention of nausea and vomiting in cancer patients undergoing chemotherapy or radiation treatment. It targets serotonin release from enterochromaffin cells in the gut that may cause the symptoms by stimulating afferent branches of the vagus nerve and thereby initiating the vomiting reflex. One group of investigators has postulated that an escalating cycle of bingeing and purging behaviors in chronic BN results at least in part from a desensitization in the threshold for activation of vagal afferent fibers, with dysregulation of satiety mechanisms.30 The results of a randomized, double-blind trial of 25 patients with severe, chronic BN showed that ondansetron was more effective than placebo in reducing binge eating and purging by vomiting during a 4-week period.31 Past criticisms of potential ondansetron use have included expense and short half-life. While the drug is now available as a generic, the problem of multiple daily dosing still remains. If an extended-release version of ondansetron becomes available, larger and longer studies that include an assessment of the impact on psychological features of BN could be of interest.

**Other medications**

A few other medications have been studied in a limited number of small trials. Endogenous opioids are believed to be involved in the regulation of food intake, and the opioid antagonist naltrexone attracted attention in the late 1980s after it was observed to decrease appetite in some patients recently detoxified from opioid dependence. Unfortunately, when subsequently tested in patients with BN, the standard naltrexone doses used in addiction were found ineffective. There appeared to be some efficacy in open-label studies at 200 to 300 mg/d, but because this dosage is high enough to raise concerns of liver toxicity, naltrexone is not recommended.32-35

Lithium carbonate was no more effective than placebo for symptoms of BN in one controlled trial. Mean plasma concentrations at the low end of the usual therapeutic range may have affected outcome36; nonetheless, lithium use entails a potential toxicity risk for patients who continue purging. Carbamazepine did not prove beneficial in an early controlled trial with 6 patients.37

A future direction of research may involve the atypical antipsychotics, which have not been formally studied for use in BN. Interest in this medication class stems from preliminary data that show efficacy in some patients with anorexia nervosa, as well as reports of efficacy when used as an augmenting agent in depression and anxiety disorders.38-43

At the University of California San Diego Center for Eating Disorders Treatment and Research, we occasionally use low-dose atypical antipsychotics to augment antidepressants in some of our patients who have more chronic and severe BN and whose disorder has proved refractory to the established treatments (typically, these patients also have not achieved remission of comorbid depression or anxiety on various antidepressants). These patients often are also of relatively low weight and display the rigid, restrictive thought processes more typical of patients with anorexia nervosa.

While case reports and small open trials of anorexia nervosa, mostly with inpatients, have focused...
on olanzepine, quetiapine, and risperidone, in consideration that the weight gain sometimes attributed to these medications may benefit emaciated patients, we have found use of these particular medications in our BN outpatients to be problematic. Even in cases where patients accept the need to attain a higher target weight, fear of uncontrolled weight gain prevents most patients from agreeing to a medication trial, and those who do rarely remain adherent. In addition, some investigators have expressed concern that these medications, especially olanzapine, might exacerbate binge eating symptoms in patients with eating disorders.  

We have had more success in starting patients on the generally weight-neutral antipsychotics aripiprazole and ziprasidone. Our patients who find these medications helpful describe a reduction in distress around eating, more willingness to attempt their prescribed meal plans, fewer obsessional thoughts about food, exercise, weight, and body image, and less tendency to dwell on these thoughts when they do occur. For some, reductions in binging, purging, and restrictive eating behaviors have been demonstrated clinically. Mood tends to improve as well. However, it must be emphasized that without trial data, use of the atypical antipsychotics in BN remains experimental. Any desired benefit must be weighed against potential adverse effects, including the unlikely but possible risk of tardive dyskinesia.

**Long-term pharmacological management**

There are minimal controlled trial data on long-term efficacy of pharmacotherapy for BN. A relatively large study designed to isolate long-term potential benefits of antidepressant medication, conducted in 2002, was hampered by significant rates of attrition in both study drug and placebo arms. The trial began with 232 patients who received an 8-week course of fluoxetine, 60 mg/d, under single-blind treatment conditions. Of this group, 150 patients were considered responders (ie, a 50% or greater decrease in weekly vomiting episodes), and were randomly assigned to continued fluoxetine treatment or placebo for a 1-year double-blind relapse prevention phase. Findings included a lower rate of relapse for the fluoxetine group, but the investigators noted a worsening on all measures of efficacy over time. They concluded that pharmacotherapy alone may not be adequate treatment after acute response for most patients. Perhaps even more concerning was a less than 20% acute-phase remission rate in this study. This result, which is described as consistent with data from other trials, reveals that the vast majority of responders were still bingeing and purging at the beginning of maintenance therapy, which indicates that the idea of relapse prevention may be dubious for most trial participants.

**Pharmacological management of BN in adolescents**

It should be mentioned that data regarding pharmacological treatment of BN have been gathered almost exclusively from adult patients. One small open trial of fluoxetine in adolescents with BN suggested it was useful and well tolerated, but in general, clinicians are left to extrapolate from the adult trial literature in treating young patients. Because of the physical and psychological morbidity and risk of chronicity when BN remains poorly treated, we tend to use the same criteria in initiating SSRIs in adolescents, with the full informed consent of both patients and their parents.

**Treatment combining medication and psychotherapy**

At least 6 controlled trials have assessed direct comparisons of outcome for patients with BN treated with psychotherapy, pharmacotherapy, or a combination. In general, results showed a greater decrease in the frequency of binging and purging episodes with cognitive-behavioral therapy than with antidepressant medication when each was used alone. With treatments used in combination, the results to date have been mixed. Although several trials indicate that medication conferred no significant benefit beyond that achieved with psychotherapy, on balance, study results slightly favored the addition of medication to psychotherapy for many patients. In the clinical community, there is a consensus that an approach including both psychotherapy and medication is worth considering in most cases.

**Future directions**

Psychotropic medications, especially the SSRIs, are helpful for some patients with BN, at least in the short term. More than a decade has elapsed since the FDA approved fluoxetine for use in adult patients with BN, and few notable developments in medication management have taken place since
that time. The extent of efficacy of SSRIs and other medications has been questioned since relatively few individuals abstain from binge eating and purging behaviors, and relapse during treatment is common. Medications that have received some attention but are in need of further investigation include the SNRIs, topiramate, and possibly ondansetron. Augmentation of antidepressants also has not been investigated, and the atypical antipsychotics should be studied for this use.

References:

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