Pharmacologic Treatment of Bulimia Nervosa: Research Findings and Practical Suggestions

by HARRISON G. POPE, JR, MD and JAMES I. HUDSON, MD

Bulimia nervosa is a syndrome characterized by compulsive eating binges that usually are followed by self-induced vomiting, laxative abuse, or other attempts to prevent weight gain. The disorder is quite common in the United States, particularly among women, and spans the entire range of socioeconomic classes. Depending on the population studied and the criteria used, between 1.3% and 10% of American women suffer from the syndrome at some time in their lives.\textsuperscript{2-4} Bulimia nervosa often is associated with serious psychiatric morbidity, particularly depression, and also with medical complications that can contribute to morbidity and even mortality.\textsuperscript{5,6} Thus, bulimia nervosa represents a significant public health problem.

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\textbf{BACKGROUND}

Little systematic study of therapeutic methods to treat bulimia nervosa was conducted until the 1980s, and most bulimic patients were treated with psychodynamic psychotherapy. However, an increasing number of recent studies have shown that bulimia nervosa may respond promptly and often completely to various antidepressant medications.

Twelve positive placebo-controlled double-blind studies of antidepressant medications in bulimia nervosa have appeared:

- five were conducted with tricyclic antidepressants,\textsuperscript{7-11}
- three with monoamine oxidase inhibitors (MAOIs),\textsuperscript{12-14}
- one with bupropion,\textsuperscript{15}
- one with nomifensine,\textsuperscript{16}
- one with trazodone,\textsuperscript{16} and
- one with fluoxetine.\textsuperscript{17}

All of these agents were found to be significantly superior to placebo,

Dr. Pope is Associate Professor of Psychiatry, Harvard Medical School and Chief, Biological Psychiatry Laboratory, Laboratories for Psychiatric Research, McLean Hospital, Belmont, Massachusetts.

Dr. Hudson is Associate Professor of Psychiatry, Harvard Medical School and Associate Chief, Biological Psychiatry Laboratory, Laboratories for Psychiatric Research, McLean Hospital, Belmont, Massachusetts.

Address reprint requests to Harrison G. Pope, Jr, MD, Biological Psychiatry Laboratory, Laboratories for Psychiatric Research, McLean Hospital, 115 Mill St, Belmont, MA 02178.
not only in reducing the frequency of eating binges, but also in measures of other aspects of the syndrome, such as depression, anxiety, obsessions about food and body weight, and other pathological attitudes toward food and eating.

Two additional controlled studies with antidepressants have produced less promising results: a study with amitriptyline\textsuperscript{18} produced only a weakly positive finding and another study with mianserin\textsuperscript{19} produced negative findings. However, a review of both of these studies suggests that inadequate doses of medication probably were used.\textsuperscript{20}

Follow-up data with antidepressants are less extensive. One study\textsuperscript{21} followed a sample of 20 bulimic patients for up to 2 years. Ten (50\%) of these patients had achieved a remission of their bulimic symptoms at the time of last follow-up. A more recent study\textsuperscript{22} found that nearly two thirds of bulimic patients treated with various antidepressants and followed for an average of one year had achieved a remission of their symptoms, provided that they tried a second or a third antidepressant if the first agent failed.

However, these optimistic findings must be tempered with a number of observations. First, as just mentioned, many bulimic patients do not respond to the first antidepressant agent tried, and often more than one agent is needed in order to find one that is satisfactory. This can be a time-consuming and difficult task, often compounded by the fact that bulimic patients are reluctant to take medications, fearing that they will be substituting a new “addiction” for their old “addiction” to food. Thus, considerable education and support on the part of the physician often are necessary.

Second, side effects often pose a problem for bulimic patients, even when the antidepressant and anti-bulimic effects of the drugs are satisfactory. With tricyclic antidepressants, anticholinergic and sedative effects often are prominent; with MAOIs, insomnia and postural hypotension are usually the most difficult problems. Indeed, in one study of phenelzine (an MAOI), 24 of 27 individuals who responded to the drug had discontinued it at long-term follow-up, primarily because of side effects.\textsuperscript{15} In another study of isocarboxazid, 11 of 18 bulimic patients discontinued the drug, again primarily because of side effects.\textsuperscript{14}

Newer antidepressants, such as trazodone, bupropion, nomifensine, and fluoxetine, have all offered the promise of fewer side effects than the more standard tricyclics and MAOIs. However, bupropion produced grand mal seizures in four bulimic patients in the course of a recent double-blind study\textsuperscript{15} and, therefore, must be considered contraindicated in bulimia nervosa until this phenomenon is explained. Nomifensine also has been eliminated from the list of choices because it has been withdrawn from the market entirely, primarily as a result of hypersensitivity reactions observed in patients treated for major depression. Trazodone and fluoxetine, however, remain as choices for treating the bulimic patient.

Finally, it should be mentioned that some bulimic patients display concomitant manic symptoms and thus probably should not be treated with antidepressants at all. Such patients sometimes respond to lithium carbonate, carbamazepine, and valproate.\textsuperscript{20} At present, data on these three agents are limited; it appears that an occasional bulimic patient will display dramatic responses to each of these three agents, but that the majority of patients do not show significant improvement.

**PRACTICAL ASPECTS OF TREATMENT**

Some patients with bulimic symptoms will consult the psychiatrist specifically for treatment of their disorder, but a large number of patients are apprehensive about revealing their symptoms. Thus, in interviewing the patient—particularly a female patient between the ages of 13 and 40—it is critical for the psychiatrist to inquire carefully about symptoms of eating disorder, because the patient may not volunteer this information.

Most bulimic patients can be treated with pharmacotherapy on an outpatient basis. If the patient has simultaneous anorexia nervosa and is severely cæ cachetic, if she displays severe electrolyte or EKG abnormalities, or if she is acutely suicidal, then inpatient treatment may be preferable.

It should be noted that antidepressant treatment should not be reserved only for those bulimic patients who are depressed. Studies with bulimic patients who do not display concomitant major depression\textsuperscript{8,13,15} have repeatedly shown that these patients respond at least as well to antidepressants as do bulimic patients with concomitant depression.

Next, it is important to educate and to reassure many bulimic patients with regard to the nature of antidepressant treatment. As mentioned earlier, some patients have the illusion that antidepressant drugs are addictive and will simply substitute another form of addiction for their “food addiction.” An explanation of the nature of antidepressant effects often will help to resolve these questions. It is important for the patient to understand that antidepressants are not “tranquilizers” or stimulants that simply will “cover over” their symptoms, but that successful antidepressant treatment leads to improvement in the underlying procc-
ocupations with food, body weight, and associated depression, rather than simply relief in the symptom of binge eating. Bulimic patients also are often apprehensive that antidepressant medications will cause them to gain weight. In practice, we have found that this is rarely the case; when relieved of the urge to binge, most bulimic patients manage to remain at about the same weight, and some actually lose weight. Finally, it is important for the patient to realize that taking antidepressant medication is not contradictory to psychotherapy and that both treatments may be conducted simultaneously.

**CHOICE OF MEDICATIONS**

Once the doctor and patient have decided to try antidepressants, we suggest starting with fluoxetine and raising the dose to 60 mg per day over the course of the first week. Although doses of only 20 mg per day have been found effective in the treatment of major depression, it has been our impression that in bulimia nervosa, a substantially larger number of patients respond to 60 mg per day. Indeed, we have treated occasional bulimic patients with doses of fluoxetine as high as 140 mg to 160 mg per day (a dose well above the upper limit of 80 mg per day recommended by the manufacturer for the treatment of major depression) and have had no problems with adverse effects at these doses. However, the physician contemplating doses of more than 60 mg per day of fluoxetine in a bulimic patient must weigh the limited amount of experience available with high doses against the potential for possible further benefit to the patient if such doses are used.

One guideline that may be helpful, if available to the physician, is to obtain fluoxetine plasma levels. These are not widely performed, but recently have become commercially available in a few localities. In our experience, it frequently has been necessary for patients to achieve a combined fluoxetine plus norfluoxetine level of about 800 ng/mL to 1000 ng/mL in order to get an optimal response. Combined levels above 1000 ng/mL have not, in our experience, offered much additional benefit. It should be remembered, however, that this experience is anecdotal and based on a small number of cases.

Fluoxetine is remarkably free of side effects in most bulimic patients, but it may cause gastrointestinal upset, particularly when the drug is initiated.

Fluoxetine is convenient to administer because its long half-life permits it to be taken on a once-daily basis. The antidepressant and antibulimic effects of fluoxetine usually take about 3 weeks to appear, although some patients may experience an improvement in bulimic symptoms more quickly.

For patients unable to tolerate fluoxetine, an alternate agent is trazodone, in doses gradually increased to between 200 mg and 600 mg at bedtime. Our group recently completed a placebo-controlled double-blind study of trazodone; in this study a majority of patients were able to tolerate 400 mg of trazodone at bedtime without difficulty. Some patients, on an open-label basis after completion of the double-blind phase of the study, were able to take even larger doses of trazodone without an undue degree of sedation.

In bulimic patients who show a partial, but not complete response to fluoxetine or to trazodone, further improvement may occasionally be gained by adding lithium carbonate to the antidepressant regimen. We generally begin with 300 mg three times daily and raise the lithium dose until plasma levels of 0.8 mEq/L to 1.0 mEq/L are obtained. If patients still show insufficient improvement after two weeks of lithium plus fluoxetine or trazodone, another antidepressant usually is required.

In bulimic patients who have failed fluoxetine or fluoxetine plus lithium, it is possible to stop either or both drugs abruptly because they are only slowly removed from the central nervous system and thus "taper themselves." Trazodone perhaps should be tapered over a few days because it is removed from the central nervous system more rapidly.

The next drug that we usually try is a tricyclic antidepressant such as desipramine or nortriptyline. Tricyclics are preferable to MAOIs at this point because severe reactions have been reported in patients receiving an MAOI immediately after the discontinuation of fluoxetine. Hence, 5 weeks should be allowed between discontinuing...
fluoxetine and initiating an MAOI. Thus, tricyclic antidepressants represent useful agents for an interim trial, with MAOIs held in reserve to be used at the 5-week point if tricyclics prove ineffective.

Perhaps because bulimic patients generally are young and tend to metabolize tricyclic antidepressants quickly, large doses of tricyclics often are needed in order to obtain therapeutic plasma levels: at least 3.5 mg/kg of body weight are often required for desipramine and about 1.5 mg/kg for nortriptyline. Plasma levels can be obtained commercially for both of these drugs in a wide number of laboratories. A level of at least 200 ng/mL is advisable for desipramine; for nortriptyline, plasma levels should be adjusted between 50 ng/mL and 140 ng/mL. It is critical to obtain plasma levels in bulimic patients; otherwise some of these patients may be subjected to an inadequate medication trial.

Other tricyclic antidepressants have been used in the treatment of bulimia nervosa with good results. However, many of these agents, such as imipramine, amitriptyline, and the tricyclic-like tetracyclic drug maprotiline frequently display more side effects than desipramine and nortriptyline. Further, plasma levels for most of these drugs, although commercially available, are not well understood and hence difficult to interpret. The exception to this problem is imipramine, for which a combined imipramine plus desipramine plasma level probably should be 200 ng/mL or higher.

If a patient has failed both an initial fluoxetine or trazodone trial and a subsequent tricyclic antidepressant trial, then MAOIs offer the best chance of success. These agents have shown robust effects in bulimic patients treated on a double-blind basis and, in our experience, are the most effective antidepressants available for bulimia nervosa. The manufacturers of MAOIs recommend a 14-day washout period between the discontinuation of tricyclic antidepressants and the beginning of MAOI therapy. However, many experienced practitioners allow a much briefer period and will administer MAOIs immediately after discontinuing tricyclics.

It might be thought that bulimic patients would be at substantial risk when taking MAOIs because they might ingest one of the foods substances that are contraindicated in conjunction with these drugs, such as aged cheese or sour cream. However, in our experience with at least 200 bulimic patients treated with MAOIs, we have not yet observed a serious hypertensive crisis. One reason for this observation may be that bulimic patients tend to binge on high-carbohydrate and easily ingested foods, such as ice cream, cookies, and baked goods, which do not contain tyramine and thus do not pose a hazard.

As with tricyclics, it appears that bulimic patients may metabolize MAOIs quickly, thus sometimes requiring larger doses than customarily used. We have frequently used doses of up to 80 mg per day of tranylcypromine or 120 mg per day of phenelzine in order to obtain a beneficial effect. Usually, the limiting point for dosage of MAOIs is postural hypotension. If hypotension becomes prominent, it is usually necessary to limit or slightly lower the dosage because tolerance rarely is acquired to this hypotension.

Another problem frequently encountered with MAOIs is insomnia. This often can be treated successfully by adding trazodone at bedtime. We have encountered no difficulties in combining MAOIs and trazodone, and we believe that in some cases the antidepressant effects of the two drugs may be synergistic. Because trazodone is a potent sedative, it often will alleviate insomnia and allow the patient to have a normal sleep-wake cycle despite taking an MAOI.

The above general strategy results in either marked improvement or remission of bulimic symptoms in a majority of patients. However, a number of patients remain who do not respond to these agents, but who may respond to other antidepressant strategies. For such cases, additional psychopharmacological approaches, similar to those used in refractory cases of major depression, occasionally may be rewarding in the hands of an experienced psychopharmacologist.

**CONCOMITANT THERAPY**

Whatever psychopharmacologic treatment is used for bulimic patients, the possibility of additional therapeutic modalities should not be neglected. Many bulimic patients, even if they are not treated with psychodynamic psychotherapy, group therapy, or behavior therapy, derive great benefit from groups for women with eating disorders. Such groups often are free or inexpensive, and may offer substantial support.

Formal psychodynamic psychotherapy, family therapy, group therapy, and behavioral therapy (especially cognitive behavioral therapy) are all widely prescribed for bulimic patients. Cognitive behavioral therapy has been shown effective for bulimic patients in controlled studies. Therefore, this modality may be particularly worthy of consideration, especially for those bulimic patients who have not shown an adequate response to pharmacologic treatment.

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