# The Use of Selective Serotonin Reuptake Inhibitors in Eating Disorders

# Laurel E. S. Mayer, M.D., and B. Timothy Walsh, M.D.

The introduction of selective serotonin reuptake inhibitors (SSRIs), which are, in general, safer and more easily tolerated than conventional antidepressants, has had a profound effect on the treatment of affective illnesses and obsessive-compulsive disorder (OCD). A number of symptoms associated with eating disorders overlap those of depression and OCD, suggesting a theoretical and practical case for evaluating the SSRIs in the treatment of anorexia nervosa, bulimia nervosa, binge-eating disorder, and obesity. Despite the expectations for SSRIs in the treatment of eating disorders, clinical investigations have yielded mixed results. In this paper, results from clinical studies of SSRIs (with and without concomitant psychotherapy) in the treatment of anorexia and bulimia nervosa, binge eating disorder, and obesity are reviewed, directions for future research are suggested, and practical recommendations for the clinician are provided. *(J Clin Psychiatry 1998;59[suppl 15]:28–34)* 

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The introduction of the selective serotonin reuptake inhibitors (SSRIs) has revolutionized the practice of psychopharmacology. Although not devoid of side effects, they are often less dangerous and better tolerated than their predecessors. Their efficacy in the treatment of psychiatric disorders such as depression and obsessivecompulsive disorder is now well established. Because of the frequent overlap in symptoms between these disorders and eating disorders, the utility of SSRIs in the treatment of eating disorders is of substantial clinical and theoretical interest. This paper reviews the clinical studies of the SSRIs for the treatment of the eating disorders (anorexia nervosa, bulimia nervosa, and binge-eating disorder) and obesity.

There is substantial uncertainty regarding the role of medication in the therapy of eating disorders. Results of clinical trials of medication in the treatment of anorexia nervosa and obesity have been generally disheartening, and work with SSRIs in binge-eating disorder is just beginning. The efficacy of antidepressant agents in studies of the treatment of bulimia nervosa has been much more encouraging. However, because forms of short-term, focused psychotherapy are at least equally effective and may

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Reprint requests to: Laurel E. S. Mayer, M.D., New York State Psychiatric Institute, 722 West 168th Street, Unit 98, New York, NY 10032. have superior long-term benefits, the precise role of medication in the treatment of bulimia nervosa requires further study. Additionally, despite the fact that anorexia nervosa and bulimia nervosa typically have their onset during adolescence, clinical trials have focused entirely on adults. The utility and safety of SSRIs in pediatric populations have yet to be addressed.

# ANOREXIA NERVOSA

Anorexia nervosa is a psychiatric illness that predominantly affects adolescent girls and young women. It is associated with distorted perceptions about shape and body image, leaving the teenager or young adult thinking she is fat and disgusting. In the most severe cases, the relentless cycle of dieting and weight loss can result in death.

The American Psychiatric Association (APA) Practice Guideline for Eating Disorders<sup>1</sup> recommends a multidisciplinary approach for the treatment of anorexia nervosa. The primary interventions are family and individual psychotherapies, incorporating a major cognitive-behavioral component, and with pharmacotherapy often used as an adjunct.<sup>2</sup> Although basic and clinical research has greatly contributed to our knowledge about various neurotransmitter and neuroendocrine disturbances associated with starvation, the etiology of anorexia nervosa remains unknown. Therefore, despite recent advances, behavioral and psychosocial treatments remain the standard, and the search for effective pharmacologic interventions actively continues.

### **Antidepressant Medication**

Patients with anorexia nervosa often present with symptoms consistent with major depressive disorder (in-

From the Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, N.Y. Supported in part by grants MH-38355, MH-42206, and

cluding depressed mood, low energy, and poor concentration) and obsessive-compulsive disorder (such as extensive food-related rituals and obsessional preoccupations with weight and shape). These observations have prompted trials of the efficacy of SSRIs in the treatment of anorexia nervosa. Although there is little evidence that the efficacy of one SSRI is superior to another, controlled studies regarding use of SSRIs in the treatment of anorexia nervosa have used fluoxetine exclusively. Ferguson<sup>3</sup> reported that fluoxetine treatment was successful for a woman with anorexia nervosa who had previously developed significant side effects to other antidepressants, and thus been difficult to treat. In an open trial of fluoxetine, Gwirtsman and colleagues<sup>4</sup> described 6 patients with anorexia nervosa who all showed improvement in depressive symptoms and an increase in weight. Our own group at Columbia<sup>5</sup> has recently completed what we believe to be the only placebo-controlled trial of fluoxetine among underweight patients with anorexia nervosa. Analysis of these data suggests that the impact of fluoxetine, provided in the context of a behaviorally oriented inpatient program, was disappointing.

More encouraging findings regarding the utility of fluoxetine in the treatment of anorexia nervosa come from research with a slightly different focus. Most controlled studies of medication for anorexia nervosa have concentrated on the weight gain phase of treatment, usually in hospitalized patients participating in a structured, behav ioral program. Such programs are effective in helping patients gain weight, and thus make detecting a supplementary benefit of medication more difficult. However, the subsequent phase of treatment, the weight maintenance phase, which occurs in the less structured outpatient setting, is quite challenging, and typically is associated with a substantial rate of relapse. There are hints that fluoxetine might be helpful during this phase. A preliminary report of Kaye and colleagues<sup>6</sup> describes the course of 35 patients, all of whom met criteria for anorexia nervosa, restricting subtype, and who had successfully completed an inpatient hospitalization. They were randomly assigned to either fluoxetine or placebo and discharged to the community for continuing psychosocial care. The fluoxetine-treated patients were better able to maintain their weight and had a significantly lower rate of relapse than those receiving placebo. On the other hand, a naturalistic follow-up study by Strober et al.<sup>7</sup> suggested little benefit from fluoxetine. Data from 33 patients who had received fluoxetine during and after a successful inpatient hospitalization were compared with data from 33 historical control patients who had not received medication. Follow-up outpatient treatment, although not standardized, included at least weekly psychotherapy, with the addition of family therapy and dietary counseling as needed. Assessments were made during face-to-face interviews performed by the research staff at 6-month intervals for 2 years' duration. No patient was

lost to follow-up, and compliance with medication was high, with only 4 patients discontinuing medication by the end of the second year follow-up visit. Overall, the authors found no significant difference between the fluoxetinetreated and control groups on measures of compensatory behaviors, need for rehospitalization, and tendency to drop below target weight. Although interpretation of these data is limited due to the naturalistic design of this study, they cannot be summarily dismissed. Thus, whether treatment with fluoxetine is helpful in preventing relapse remains an active and important question for further research. There have been no controlled trials of other SSRIs in the treatment of anorexia nervosa. Whether the alternative agents in this class offer significant benefit, either to the underweight patient with anorexia nervosa or as a preventative measure against relapse for those who have regained weight, remains an open question. In addition, there is substantial clinical and biological heterogeneity among patients with anorexia nervosa. It is possible that only patients with specific, as yet unidentified characteristics respond to pharmacologic intervention. Thus, trials conducted including patients with a variety of characteristics may obscure the benefits of the medication. It may be helpful, in future studies, to focus on subgroups, such as patients with the restricting or binge/purge subtypes, patients with short duration of illness, or, as previously described, patients who have already attained a certain level of weight restoration.6

# **BULIMIA NERVOSA**

The development of pharmacologic treatments for bulimia nervosa has been much more successful than for anorexia nervosa. Several factors have presumably contributed to this difference. The higher prevalence of bulimia nervosa, compared with that of anorexia nervosa, eases recruitment into clinical trials. Secondly, the medical condition of patients with bulimia nervosa is typically much less precarious, which allows more patients to be treated on an outpatient basis, thereby reducing the cost of clinical trials. In addition, it is possible that the more normal physiologic state of patients with bulimia may be necessary for the therapeutic impact of antidepressant medications.

# **Antidepressant Medication**

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The antidepressant medications, in general, have been shown repeatedly to be effective in curbing the bingepurge cycle,<sup>8-16</sup> and the SSRIs are no exception. Again, fluoxetine is the most rigorously studied,<sup>17,18</sup> although case reports and open trials of sertraline,<sup>19</sup> fluvoxamine,<sup>20,21</sup> and paroxetine<sup>22</sup> exist.

Because of the high frequency of depressive symptoms seen in bulimia nervosa, it was plausible that the effective dose for bulimia nervosa would be identical to that for depression. A single study of fluoxetine directly addressed this issue.<sup>17</sup> In this large trial (N = 387), one group of 129 patients with bulimia nervosa was randomly assigned to receive the "standard" dose of 20 mg/day of fluoxetine, a second group of 129 patients received 60 mg/day, and a third group of 129 received placebo. The results showed that 20 mg/day of fluoxetine was, at most, marginally superior to placebo. On the other hand, 60 mg/day of fluoxetine in bulimia nervosa have generally used 60 mg/day, which is usually tolerated with minimal side effects.

There is further evidence of a divergence between depression and bulimia nervosa. Although depressive symptoms and bulimia tend to co-occur, the presence of depressive symptoms does not predict the degree of improvement in bulimic symptoms with antidepressant treatment<sup>8,10,15</sup>; that is, the eating disorder symptoms of patients with bulimia nervosa who are depressed do not respond more dramatically to antidepressant medication than do those of patients with bulimia nervosa who are not depressed. These data, and the preferential effectiveness of the 60 mg/day dose of fluoxetine, suggest that the mechanism of action of antidepressants in bulimia nervosa may be different than that in depression.

It should be noted that the pharmacologic studies of bulimia nervosa have, for the most part, been restricted to normal weight, adult women who purge through vomiting, and the results may not be generalizable to other populations including men, overweight patients, or patients with bulimia nervosa who use alternate methods of compensation such as fasting or exercise.

# **Medication and Psychotherapy**

Compelling data have emerged in the last decade demonstrating that focused forms of short-term psychotherapy, particularly cognitive behavioral therapy (CBT), are effective in the treatment of bulimia nervosa.23 The existence of effective forms of both pharmacotherapy and psychotherapy has complicated therapeutic recommendations, particularly because many important clinical questions cannot be directly answered with the data available. For example, concerns regarding the comparative efficacy of medication and psychotherapy and, especially, regarding the long-term outcome of medication treatment leave the precise place of antidepressant medication in the treatment of bulimia nervosa unclear. The studies that have compared medication and psychotherapy and evaluated the potential benefits of combined treatment have yielded somewhat inconsistent results. Several studies have been published comparing the combination of focused psychotherapy and fluoxetine.

Fichter and colleagues,<sup>24</sup> in Germany, examined the effect of fluoxetine (60 mg/day) compared with placebo in a population of patients hospitalized for bulimia nervosa who were actively engaged in a program of intensive behavioral psychotherapy. The authors found no significant

difference between the fluoxetine and placebo groups and suggested that a "ceiling effect" may have limited the power of the study to detect a benefit from medication; that is, the intensive inpatient psychotherapy was so effective that no additional medication effect could be observed.

An interesting study by the same group examined the value of fluvoxamine in preventing relapse following inpatient treatment.<sup>25</sup> In a double-blind, placebo-controlled study, 72 patients completing inpatient psychotherapy treatment for bulimia nervosa were randomly assigned to receive 12 weeks of outpatient fluvoxamine or placebo treatment. Despite a high dropout rate in the fluvoxamine-treated group, both intent-to-treat and completer analyses showed active medication to have a significant effect in reducing return of binge purge behavior.

Goldbloom et al.<sup>26</sup> conducted a 16-week, randomized trial of individual CBT, fluoxetine, and the combination in 76 women with bulimia nervosa. All groups improved over the course of the study, and intent-to-treat analysis yielded no statistically significant differences in outcome. Completer analysis showed a significantly lower subjective binge frequency in the CBT-treated group compared with the group that received fluoxetine alone. Interpretation of these data is limited by the absence of placebo and control groups and by a surprisingly high dropout rate (43%). It is uncertain whether the absence of differences in outcomes reflects similar treatment effects (that is, that fluoxetine treatment is equivalent to CBT, and that the combination is no better than either alone) or limited power to detect group differences.

Beumont et al.27 conducted a randomized, placebocontrolled trial of intensive nutritional counseling combined with fluoxetine. In an 8-week trial, with follow-up at 12 and 20 weeks, they compared 60 mg of fluoxetine with placebo in 67 patients receiving weekly nutritional counseling. Both the active medication and placebo groups showed substantial improvement over the course of the study. During active treatment, fluoxetine was superior to placebo only on measures of dietary restraint, weight concern, and shape concern. Although there were suggestions that bulimic symptoms reemerged after fluoxetine was discontinued, the fluoxetine- and placebo-treated groups had statistically similar levels of behavioral symptoms both at end of treatment and at follow-up. While this study suggests that fluoxetine does not dramatically add to the benefit of nutritional counseling, the rate of improvement from nutritional counseling was quite impressive with 61.5% of patients reporting no binge eating episodes during the last week of active treatment. This impressive degree of improvement may have limited the ability to detect any benefit from medication.

Our group recently published the results of a placebocontrolled trial designed to compare 2 forms of psychotherapy for bulimia nervosa (individual CBT and individual supportive psychotherapy) and to examine the benefit of combining medication with psychotherapy.<sup>28</sup> The medication intervention was unique in that it was 2-stage: patients randomly assigned to receive active medication were first treated with desipramine; if they could not tolerate this medication, or did not show sufficient improvement, they were switched to fluoxetine. The study was large (120 patients were randomized) and placebocontrolled. The short-term results clearly document that CBT was superior to supportive psychotherapy and also indicate that the 2-stage medication intervention modestly but significantly augmented the effect of psychotherapy. It was also of interest that the group of patients receiving only medication had an outcome on most measures similar to that of patients receiving CBT and placebo.

Although the results of these trials are by no means entirely consistent, they emphasize that, in most patients, the symptoms of bulimia nervosa respond both to structured psychotherapeutic interventions and to antidepressant medication. There are hints that combining medication and psychotherapy may confer some additional benefit, at least in the short-term, but hard evidence for superiority of combined treatment is limited. The most convincing data come from our own study in which the effects of psychotherapy were not as dramatic as reported from other centers. Conceivably, it is easier to detect the additive benefit of medication in a population of patients relatively resistant to the effects of psychotherapy.

It is safe to conclude that we have at least 3 effective treatment strategies to employ in the treatment of bulimia nervosa: CBT alone, antidepressant medication alone, and combination therapy. Pressing questions for clinical research are how to match patients with treatments and what interventions are useful for the significant number of patients who fail to respond to these established treatments.

#### **BINGE-EATING DISORDER**

Binge-eating disorder is a newly proposed diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), Appendix B: Criteria Sets and Axes Provided for Further Clinical Study. Bingeeating disorder is characterized by repeated episodes of the consumption of a large quantity of food associated with feelings of loss of control (similar to bulimia nervosa), but without the inappropriate compensatory measures such as vomiting, laxative abuse, fasting, or excessive exercise that follow binges in bulimia nervosa. Other similarities to bulimia nervosa include marked concern with body image, shape, and weight, <sup>29-31</sup> and a high prevalence of mood symptoms including depression, worthlessness, and low self-esteem. Although the diagnostic criteria for binge-eating disorder do not require the presence of obesity, most patients presenting with these symptoms are overweight. The number of controlled treatment trials for binge-eating disorder is limited, and the number of clinical trials investigating the efficacy of pharmacotherapy for this disorder is fewer still. Preliminary results regarding the efficacy of SSRIs in the treatment of binge-eating disorder are mixed.

De Zwaan et al.<sup>32</sup> examined a group of 64 obese patients, recruited specifically for complaints of "emotional problems" to attempt to better characterize the subpopulation of binge eating. Although "emotional problems" were not defined, they recruited 64 overweight women and randomly assigned them to 1 of 4 treatment conditions: CBT and fluvoxamine, CBT and placebo, dietary management and fluvoxamine, or dietary management and placebo. They conservatively estimate that roughly 22% of their sample met DSM-IV criteria for binge-eating disorder (disregarding the frequency criteria). Fluvoxamine (100 mg/day) did not seem to confer additional benefit to those with binge eating in terms of weight loss.

Prats et al.<sup>33</sup> conducted a 16-week open clinical trial in 9 patients of the efficacy of paroxetine on binge frequency. Preliminary results suggested a significant reduction in binge eating. However, these results are difficult to interpret as the cohort included patients with both binge-eating disorder and bulimia nervosa.

An open clinical trial by Devlin<sup>34</sup> attempted to assess the efficacy of phentermine and fluoxetine for binge eating when used in conjunction with CBT. Although a more complete data analysis is currently in progress, preliminary results suggest that phentermine, fluoxetine, and CBT might be more helpful than CBT alone in decreasing binge frequency and weight and improving mood and body image symptoms in the short-term (less than 6 months). However, recommendations regarding long-term efficacy and safety remain premature, and given the recent concerns regarding phentermine and dexfenfluramine, it would be prudent to await completion of data analysis and the results of controlled trials before arriving at clinical recommendations.

The only randomized, double-blind, placebo-controlled trial of an SSRI specifically focusing on binge-eating disorder to date is that of Hudson et al.<sup>35</sup> which examined fluvoxamine. A preliminary report indicates that fluvoxamine was of benefit in reducing binge frequency.

One additional, double-blind, placebo-controlled trial has relevant information. In the context of a multisite trial of the long-term efficacy of fluoxetine for weight loss in the obese, Marcus et al.<sup>36</sup> further divided their obese population into binge and nonbinge eaters. All patients received 52 weeks of behavioral treatment, while half also received fluoxetine (60 mg per day). At the end of 1 year, those subjects who had received both fluoxetine and behavioral modification had lost significantly more weight than those receiving placebo and behavioral modification, but there was no significant difference between binge and nonbinge eaters.

Thus, although there are a number of clinical similarities between binge-eating disorder and bulimia nervosa, and although a few open trials suggest clinical utility of the SSRIs for promoting weight loss and reducing binge frequency, convincing data regarding the use of SSRIs in binge-eating disorder have not yet been published.

# OBESITY

Although obesity is primarily considered a medical disorder, interest in this condition on the part of psychiatry appears to have increased in recent years. Obesity results when energy intake exceeds energy expenditure over an extended period and carries with it many serious medical complications such as diabetes mellitus and hypertension. Although dieting and exercise are clearly effective in producing short-term weight loss, long-term maintenance of this loss is very difficult for most individuals. Whereas the treatment of depression with tricyclic antidepressants was often associated with significant weight gain, the initial clinical trials of SSRIs in depression suggested it sometimes had a more welcome side effect: weight loss. This observation, along with the known role of serotonin in the regulation of appetite, led to trials of SSRIs as a pharmacologic treatment for obesity.

A decade ago, Ferguson and Feighner<sup>37</sup> enthusiastically reported preliminary data suggesting fluoxetine to be equivalent to benzphetamine and superior to placebo as an appetite suppressant. A 6-week, double-blind trial of fluoxetine (60 mg per day) in 23 obese, nondepressed women by Pijl et al.<sup>38</sup> reported significant weight loss in the fluoxetine-treated group  $(3.6 \pm 0.5 \text{ kg vs. } 0.3 \pm 0.5 \text{ kg})$ kg). Levine et al.<sup>39</sup> conducted a similar, but larger study. An 8-week, randomized, placebo-controlled, double-blind trial of fluoxetine (60 mg) evaluated weight loss in 120 nondepressed, obese subjects. As early as the first week of the study, the fluoxetine-treated group showed significantly greater weight loss compared with placebo, a finding that persisted for the duration of the trial. The degree of weight loss was correlated with initial weight; that is, the greater the degree of obesity at baseline, the larger the amount of weight lost while taking the drug. Overall, fluoxetine was well tolerated, the only significant side effect being asthenia. A second, large study was designed to evaluate the relationship between the dose of fluoxetine and weight loss.<sup>40</sup> Six hundred fifty-five patients were randomly assigned to 5 groups and treated for 8 weeks either with placebo or with 10 mg, 20 mg, 40 mg, or 60 mg of fluoxetine. Findings supported a dose-dependent relationship, with those receiving the highest dose of fluoxetine showing the greatest amount of weight loss. This result contrasts with studies of fluoxetine for major depression in which adverse side effects outweighed the beneficial mood effects at higher doses, leading to the recommendation of 20 mg/day as the standard dose for depression.

Although these studies provided new and potentially exciting information regarding the utility of fluoxetine for obesity, they were limited by the relatively brief duration of treatment. Thus, a large (N = 458), multisite study was designed to assess the effect of fluoxetine on weight loss over 1 year.41 The results were interesting, albeit discouraging. The fluoxetine-treated group showed significantly greater weight loss than the placebo group for the first 20 weeks. After week 20, however, those who received fluoxetine began to regain weight, despite continued treatment with active medication. Overall, although both the fluoxetine and the placebo groups ended the study at weights less than baseline values, there were no significant differences between the groups at the end of the 1-year period. The reasons for this weight gain remain unclear. Possibilities include development of tolerance to the drug (a concept that may be worth pursuing, given the observation that some depressed patients treated with fluoxetine seem to lose the antidepressant effect over time). Another explanation offered related to a decrease in the frequency of visits which occurred after the first 8 weeks of treatment. Whatever the reason, fluoxetine appears to be a successful short-term weight loss treatment, but its long-term efficacy is not established.

Two of the sites published their own results from this large trial. Darga et al.<sup>42</sup> added dietary counseling to both groups. This added intervention, however, did not appear to augment the weight loss effect of fluoxetine, nor prevent weight regain. However, the results (mentioned above) of Marcus et al.<sup>36</sup> portray a slightly different picture. In addition to receiving fluoxetine or placebo, all patients at this site received behavioral modification counseling and were encouraged to restrict their caloric intake and to exercise. Unlike the results at the other sites, at the end of 1 year, there was a significant difference in weight between the drug- and placebo-treated groups. The patients receiving fluoxetine lost an average of 13.9 kg over the course of the year, whereas the placebo group gained 0.6 kg (p < .004) (this analysis was based only on the 21 patients who completed the entire year). This study leaves open the possibility that a combination of fluoxetine with more intensive behavioral treatment might assist longterm weight loss.

An examination of another SSRI, citalopram, for obesity was disappointing. Szkudlarek and Elsborg<sup>43</sup> randomly assigned 72 severely obese patients to either citalopram or placebo. All patients also received instruction in the consumption of a low-calorie diet. Over the succeeding 3 months, both the citalopram and the placebo groups lost between 5 and 10 lb. However, citalopram provided no significant additional benefit compared with placebo.

Wadden et al.<sup>44</sup> were interested in the potential utility of an SSRI in maintaining weight loss. Specifically, these investigators examined the utility of sertraline in preventing weight regain following a very low-calorie diet. Fifty-three women who had lost at least 10% of their initial weight during a very low-calorie diet in the prior 26 weeks were randomly assigned to receive either 200 mg of sertraline or placebo for 1 year. During the initial 6 weeks of the study, those patients receiving sertraline continued to lose weight, while those receiving placebo began to gain weight. However, this difference promptly disappeared, and, at the end of 1 year, both groups had regained similar amounts of weight, and there was no significant difference between the sertraline- and placebotreated groups,

# PRACTICAL RECOMMENDATIONS

#### Anorexia Nervosa 🗸

As reviewed above, no pharmacologic agent has been established to be of benefit in the treatment of anorexia nervosa. The mainstay of treatment is an eclectic approach, including psychological, nutritional, and behavioral elements aimed at restoring body weight and normalizing the distorted thinking concerning food, body shape, and weight. In addition, for children and adolescents with this disorder, involvement of the family in treatment is essential.

Antidepressant medications may be considered when evidence of a significant mood disturbance or of OCD persists or emerges after weight restoration. Because of its side effect profile, extensive experience in the treatment of bulimia nervosa, and more limited experience in anorexia nervosa, fluoxetine is probably the preferred agent. Treatment may be initiated at 10 to 20 mg/day. If target symptoms include OCD, higher doses (e.g., 60 mg/day) should be employed and can be reached for most patients over 1 to 2 weeks. The limited data available suggest that fluoxetine can be used safely for patients with anorexia nervosa, but the physiologic disturbances associated with this disorder merit careful monitoring of medication side effects and interactions. It is likely that other SSRIs have similar effects, but there is very limited information concerning their use in anorexia nervosa.

### **Bulimia** Nervosa

The major pharmacologic intervention to consider for patients with bulimia nervosa is the use of an antidepressant. Because it has been extensively studied and because information concerning the effective dose is available, fluoxetine should be considered the drug of first choice. The preferred dose is 60 mg/day; most patients of normal weight with bulimia nervosa can be started immediately on this amount or can increase from 20 to 60 mg/day over the course of a week. Side effects are rarely a major problem. Anecdotal information suggests that other SSRIs are probably also effective and should be considered if the use of fluoxetine is complicated by the need for other medications with which it may interact.

#### **Binge-Eating Disorder**

Data are too limited to support a recommendation for a specific course of pharmacologic treatment for bingeeating disorder with any confidence. The utility of SSRIs in bulimia nervosa suggests that these agents also may be useful for binge-eating disorder. On the other hand, the discouraging outcome of most long-term studies of SSRIs for obesity may portend difficulties with such agents among obese individuals with binge-eating problems. More work is clearly needed.

#### Obesity

There is enormous clinical and economic interest in the development of an effective and safe pharmacologic intervention for obesity. The SSRIs, while full of short-term promise, appear unable to sustain weight loss in the longterm. It is of some interest that sibutramine, which has just been approved for marketing in the treatment of obesity, combines the blockade of serotonin reuptake with reuptake blockade of norepinephrine. This development offers hope that medications related to the currently available SSRIs will eventually prove to be useful adjuncts in the treatment of obesity.

*Drug names:* citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac), fluoxamine (Luvox), paroxetine (Paxil), phentermine (Regitine), sertraline (Zoloft), sibutramine (Meridia).

#### REFERENCES

- 1. American Psychiatric Association. Practice Guideline for Eating Disorders. Am J Psychiatry 1993;150:212–228
- Garner DM, Garfinkel PE, eds. Handbook of Treatment for Eating Disorders. New York, NY: Guilford Press; 1997
- Ferguson JM, Treatment of an anorexia nervosa patient with fluoxetine [letter]. Am J Psychiatry 1987;144:1239
- Gwirtsman HE, Guze BH, Yager J, et al. Fluoxetine treatment of anorexia nervosa: an open clinical trial. J Clin Psychiatry 1990;51:378–382
- Attia E, Haiman C, Walsh BT, et al. Does fluoxetine augment the inpatient treatment of anorexia nervosa? Am J Psychiatry 1998;155:548–551
- Kaye WH, Weltzin TE, Hsu G, et al. Relapse prevention with fluoxetine in anorexia nervosa: a double-blind placebo-controlled study. In: New Research Program and Abstracts of the 150th Annual Meeting of the American Psychiatric Association; May 21, 1997; San Diego, Calif. Abstract NR405:178
- Strober M, Freeman R, DeAntonio M, et al. Does adjunctive fluoxetine influence the post-hospital course of anorexia nervosa? a 24-month prospective, longitudinal follow-up and comparison with historical controls. Psychopharmacol Bull 1997;33:425–431
- Agras WS, Dorian B, Kirkley BG, et al. Imipramine in the treatment of bulimia: a double-blind controlled study. Int J Eat Disord 1987;6:29–38
- Horne RL, Ferguson JM, Pope HG Jr, et al. Treatment of bulimia with bupropion: a multicenter controlled trial. J Clin Psychiatry 1988;49:262–266
- Hughes PL, Wells LA, Cunningham CJ, et al. Treating bulimia with desipramine: a double-blind, placebo-controlled study. Arch Gen Psychiatry 1986;43:182–186
- Mitchell JE, Groat R. A placebo-controlled, double-blind trial of amitriptyline in bulimia. J Clin Psychopharmacol 1984;4:186–193
- Pope HG Jr, Hudson JI, Jonas JM, et al. Bulimia treated with imipramine: a placebo-controlled, double-blind study. Am J Psychiatry 1983;140: 554–558
- Pope HG Jr, Keck PE Jr, McElroy SL, et al. A placebo-controlled study of trazodone in bulimia nervosa. J Clin Psychopharmacol 1989;9:254–259
- 14. Sabine EJ, Yonace A, Farrington AJ, et al. Bulimia nervosa: a placebo con-

trolled double-blind therapeutic trial of mianserin. Br J Clin Pharmacol 1983;15(suppl 2):195S-202S

- 15. Walsh BT, Gladis M, Roose SP, et al. Phenelzine vs placebo in 50 patients with bulimia. Arch Gen Psychiatry 1988;45:471-475
- 16. Walsh BT, Hadigan CM, Devlin MJ, et al. Long-term outcome of antidepressant treatment for bulimia nervosa. Am J Psychiatry 1991;148: 1206-1212
- 17. Fluoxetine Bulimia Nervosa Collaborative Study Group. Fluoxetine in the treatment of bulimia nervosa: a multicenter, placebo-controlled, doubleblind trial. Arch Gen Psychiatry 1992;49:139-147
- 18. Goldstein DJ, Wilson MG, Thompson VL, et al. Fluoxetine Bulimia Nervosa Collaborative Study Group. Long-term fluoxetine treatment of bulimia nervosa. Br J Psychiatry 1995;166:660-666
- 19. Roberts JM, Lydiard RB. Sertraline in the treatment of bulimia nervosa [letter]. Am J Psychiatry 1993;150:1753
- 20. Spigset O, Pleym H, Case report of successful treatment of bulimia nervosa with fluvoxamine [letter]. Pharmacopsychiatry 1991;24:180
- 21. Ayuso-Gutierrez JL, Palazon M, Ayuso-Mateos JL. Open trial of fluvoxamine in the treatment of bulimia nervosa. Int J Eat Disord 1994;15: 245 - 249
- 22. Pigott TA, Sunderland BA, Horn L, et al. A pilot study of paroxetine in the treatment of patients with bulimia nervosa. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 7, 1996; New York, NY. Abstract NR416:181
- 23. Wilson GT, Fairburn CG, Agras WS. Cognitive-behavioral therapy for bulimia nervosa. In: Garner DM, Garfinkel PE, eds. Handbook of Treatment for Eating Disorders. New York, NY: Guilford Press; 1997:67-93
- 24. Fichter MM, Leibl K, Rief W, et al. Fluoxetine versus placebo: a doubleblind study with bulimic inpatients undergoing intensive psychotherapy. Pharmacopsychiatry 1991;24:1-7
- 25. Fichter MM, Kruger R, Rief W, et al. Fluvoxamine in prevention of relapse in bulimia nervosa: effects on eating-specific psychopathology. J Clin Psychopharmacol 1996:16:9-18
- 26. Goldbloom DS, Olmsted M, Davis R, et al. A randomized controlled trial of fluoxetine and cognitive behavioral therapy for bulimia nervosa: shortterm outcome. Behav Res Ther 1997;35:803-811
- 27. Beumont PJ, Russell JD, Touyz SW, et al. Intensive nutritional counselling in bulimia nervosa: a role for supplementation with fluoxetine? Aust N ZJ Psychiatry 1997;31:514-524
- 28. Walsh BT, Wilson GT, Loeb KL, et al. Medication and psychotherapy in the treatment of bulimia nervosa. Am J Psychiatry 1997;154:523-531
- 29. Spitzer RL, Devlin MJ, Walsh BT, et al. Binge eating disorder: a multisite field trial for the diagnostic criteria. Int J Eat Disord 1992;11:191-203

- 30. Spitzer RL, Yanovski S, Wadden T, et al. Binge eating disorder: its further validation in a multisite study. Int J Eat Disord 1993;13:137-153
- 31. Wilson GT, Nonas CA, Rosenblum GD. Assessment of binge eating in obese patients. Int J Eat Disord 1993:13:25-33
- 32. de Zwaan M, Nutzinger DO, Schoenbeck G. Binge eating in overweight women. Compr Psychiatry 1992;33:256-261
- 33. Prats M, Diez-Quevedo C, Avila C, et al. Paroxetine treatment for bulimia nervosa and binge eating disorder. Presented at the International Conference on Eating Disorders; 1994; New York, NY
- 34. Devlin MJ. Treatment of binge eating disorder with psychotherapy and medication. Proceedings of the 7th International Conference on Eating Disorders; April 26-28, 1996; New York, NY
- Hudson JI, McElroy SL, Raymond NC, et al. Fluvoxamine treatment of 35 binge-eating disorder: a multicenter, placebo-controlled trial. In: New Research Program and Abstracts of the 147th Annual Meeting of the American Psychiatric Association; May 26, 1994; Philadelphia, Pa. Abstract NR620.218
- 36. Marcus MD, Wing RR, Ewing L, et al. A double-blind, placebo-controlled trial of fluoxetine plus behavior modification in the treatment of obese binge-eaters and non-binge eaters. Am J Psychiatry 1990;147:876-881
- Ferguson JM, Feighner JP. Fluoxetine-induced weight loss in overweight 37 non-depressed humans. Int J Obes 1987;11(suppl 3):163-170
- 38. Pijl H, Koppeschaar HP, Willekens FL, et al. Effect of serotonin re-uptake inhibition by fluoxetine on body weight and spontaneous food choice in obesity. Int J Obes 1991;15:237-242
- 39. Levine LR, Rosenblatt S, Bosomworth J. Use of a serotonin re-uptake inhibitor, fluoxetine, in the treatment of obesity. Int J Obes 1987;11(suppl 3):185-190
- 40. Levine LR, Enas GG, Thompson WL, et al. Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: a dose-response study (with a commentary by Michael Weintraub). Int J Obes 1989;13: 635-645
- 41. Goldstein DJ, Rampey AH Jr, Enas GG, et al. Fluoxetine: a randomized clinical trial in the treatment of obesity. Int J Obes Relat Metab Disord 1994:18:129-135
- 42. Darga LL, Carroll-Michals L, Botsford SJ, et al. Fluoxetine's effect on weight loss in obese subjects. Am J Clin Nutr 1991;54:321-325
- 43. Szkudlarek J, Elsborg L. Treatment of severe obesity with a highly selective serotonin re-uptake inhibitor as a supplement to a low-calorie diet. Int J Obes Relat Metab Disord 1993;17:681-683
- 44. Wadden TA, Bartlett SJ, Foster GD, et al. Sertraline and relapse prevention training following treatment by very-low-calorie diet: a controlled clinical trial, Obes Res 1995;3:549-557

