

Review Paper
Examen critique

Psychopharmacotherapy of anorexia nervosa, bulimia nervosa and binge-eating disorder

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Pharmacotherapy for anorexia nervosa is considered to be of limited efficacy. However, many studies suffer methodological limitations, and the utility of newer drugs in the treatment of anorexia has not been examined yet. Although there have been more fruitful investigations on the efficacy of medication in the management of bulimia nervosa, there are still many unresolved issues regarding the optimal management of partial remission during the acute treatment phase and the intensity and duration of pharmacotherapy to achieve optimal prophylaxis. Selective serotonin reuptake inhibitors (SSRIs) control the binge urges in binge-eating disorder, but more trials are required to investigate the utility of SSRIs and other agents in maintenance treatment. We review the current status of psychopharmacotherapy for anorexia nervosa, bulimia nervosa and binge-eating disorder and evaluate the merits of newer agents in the treatment of these disorders.

On considère que la pharmacothérapie est d'une efficacité limitée contre l'anorexie nerveuse. Beaucoup d'études comportent toutefois des limites méthodologiques et l'on n'a pas encore étudié l'utilité de nouveaux médicaments dans le traitement de l'anorexie. Même s'il y a eu des études plus fructueuses sur l'efficacité des médicaments dans la prise en charge de la boulimie nerveuse, de nombreuses questions demeurent encore sans réponse au sujet de la prise en charge optimale d'une rémission partielle au cours de la phase de traitement aigu, ainsi que de l'intensité et de la durée de la pharmacothérapie nécessaire pour obtenir une prophylaxie optimale. Les inhibiteurs sélectifs du recaptage de la sérotonine (ISRS) contrôlent les épisodes de frénésie alimentaire dans les cas de troubles d'alimentation excessive, mais d'autres études s'imposent pour analyser l'utilité des ISRS et d'autres agents dans un traitement de maintien. Nous passons en revue la situation actuelle de la pharmacothérapie contre l'anorexie nerveuse, la boulimie nerveuse et le trouble d'alimentation excessive et nous évaluons les avantages des nouveaux agents dans le traitement de ces troubles.

It is a reflection of both the refractory nature of eating disorders and the increasing number of biological investigations that virtually every class of psychotropic medication has been tested in the treatment of eating disorders. The main reason drug therapy was consid-

ered to treat patients with eating disorders was the resemblance and comorbidity between some symptoms of eating disorders and other symptoms or conditions known to respond to pharmacotherapy, such as affective disorders, obsessive-compulsive disorder and

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other anxiety disorders, and delusional disorder.¹⁻⁴

There was considerable enthusiasm about the benefit of pharmacotherapy for both anorexia nervosa and bulimia nervosa until a few years ago. However, the approach of treating anorexia nervosa with medication that is efficacious for phenomenologically similar conditions has proven to be simplistic, and to date, no drug or class of drugs has emerged as an effective agent to treat patients with this disorder.⁴ Also, attempts to regulate hunger and satiety through pharmacological modulation of neurotransmitter and neuropeptide mechanisms have only been of short-term benefit. However, in light of the severe nature of anorexia nervosa and the scarcity of optimal nonpharmacologic treatment approaches, research in this area should not be abandoned, particularly as "new generation" agents become available.

In contrast to the rather limited efficacy of pharmacotherapy for anorexia nervosa, there have been more fruitful investigations of the utility of medication in the management of bulimia nervosa.^{5,6} Even so, an optimal pharmacotherapeutic treatment strategy for bulimia nervosa has yet to be defined because, in many patients, sometimes more than 2 or 3 medication trials are necessary to improve symptoms, and with current regimens, most patients do not achieve full remission.⁴ In addition, questions regarding treatment duration, continuation and maintenance pharmacotherapy and the role of medication when combined with nonpharmacologic treatment modalities remain unanswered.

Binge-eating disorder is a syndrome that has received attention only within the last decade. Because of some phenomenological overlap between bulimia nervosa and binge-eating disorder, it is not surprising that treatment attempts have been derived from those that have been successful for bulimia nervosa. Evidence suggests that drug therapies that have proven efficacious in the treatment of bulimia nervosa are also helpful in treating patients with binge-eating disorder.⁷ In addition, binge-eating disorder is often comorbid with depressive disorders;⁸⁻¹⁰ obesity and binge eating are reported to cause depression in some people because of the serious stigmatization associated with both conditions in Western culture.¹¹ Thus, the few studies on pharmacotherapy for patients with binge-eating disorder have, by and large, focused on treatment with antidepressants.¹²⁻¹⁸

This paper reviews the current status of psychopharmacotherapy for patients with anorexia nervosa, bulimia nervosa and binge-eating disorder and evaluates the

merits of newer pharmacological agents in the treatment of these disorders.

Anorexia nervosa

Description

Anorexia nervosa affects an estimated 0.3% to 0.7% of women. It is characterized by the refusal to maintain a minimally normal body weight and the fear of weight gain, even in the face of increasing cachexia. Patients with anorexia nervosa exhibit a significant disturbance in the perception of body shape and size. The disorder may be further categorized into restricting and binge-eating/purging subtypes. The stereotypical presentation of its phenomenology, gender distribution and course point to a biological etiology, with cultural influences playing only a modifying role.

Antipsychotics

Patients with anorexia nervosa were once treated with antipsychotics because it was argued that their preoccupation with shape and weight resembled a delusion.¹⁹ The advantages of chlorpromazine, used to treat patients with anorexia nervosa for 30 years after its introduction into psychopharmacology, (25 mg to 100 mg an hour before meals, and often with insulin) were thought to include anxiolytic, sedative and weight-promoting effects. However, the initial enthusiasm was short-lived because of considerable side effects.²⁰ In addition, if weight gain was not paralleled by an attitudinal change and improvement in eating behaviour, it was usually not permanent. Thus, the idea of treating anorexia nervosa with chlorpromazine was abandoned, and there is no reason to recommend its use today.

In the double-blind, placebo-controlled studies on the use of pimozide²¹ and sulphiride²² in the treatment of anorexia nervosa neither drug significantly improved any of the core features of the disorder.

No studies have been performed on the newer antipsychotic agents because there does not appear to be any justification for their use in the treatment of anorexia nervosa.

Anxiolytics

Although there have been no controlled trials on the use of benzodiazepines in the treatment of anorexia nervosa,

these agents may be useful in reducing anxiety, a common symptom in those suffering from anorexia nervosa.²³ Anxiety is particularly severe when therapeutic efforts are made to counteract the pursuit of thinness and ritualistic behaviours around eating. In addition, patients with anorexia nervosa are reported to be at high risk for developing anxiety disorders later in life.²⁴

To facilitate eating without causing too much sedation, short-acting benzodiazepines such as lorazepam may be administered in low doses (e.g., 0.5 mg) before mealtimes or in situations where anxiety is particularly severe. However, treatment with these drugs should be limited to a maximum of 4 weeks, especially in patients with the binge-eating/purging subtype of anorexia, who have a higher risk of substance abuse and dependence than those with the restricting subtype.²⁵ Despite their merits in the acute treatment of anorexia nervosa, benzodiazepines are used sparingly in clinical settings. This may be because psychotherapy, accompanied by nutritional and behavioural approaches to healthy eating and weight gain, is considered the most promising treatment, at least for less-severely ill patients.^{26–28} In addition, many patients are young, and benzodiazepine treatment, which carries the potential of abuse, is considered a risk.

Surprisingly, there have been no systematic studies on the use of the non-benzodiazepine anxiolytic buspirone. There is one case report on the augmentation of sertraline with buspirone in a patient with anorexia nervosa and concomitant obsessive–compulsive disorder and premenstrual dysphoria.²⁹ In this patient, compulsive and dysphoric symptoms improved dramatically when buspirone was added, but no mention was made of an improvement in anorexic symptoms. However, there is no reason buspirone should not be evaluated for the treatment of anorexia nervosa in systematic trials. It carries none of the risks of conventional benzodiazepines, and although it is not suitable for the treatment of acute anxiety, it may reduce general anxiety in these patients, facilitate inpatient treatment and prevent relapse.

Tricyclic antidepressants

In the 1970s, several investigators focused on the presence of depressive symptoms in patients with anorexia nervosa; for several years there was a debate about the “variant of affective disorder” hypothesis.³⁰ The use of tricyclic antidepressants seemed appropriate for

patients with anorexia nervosa because, in depressed patients, tricyclics not only alleviated mood symptoms, but also led to considerable weight gain and an increase in appetite. However, most studies reported only minimal significant evidence for the efficacy of tricyclic antidepressants in promoting weight gain, improving attitudes toward eating and ultimate outcome in the treatment of anorexia nervosa.^{31–34} It should be noted however, that, in 2 studies,^{31,34} the antidepressant doses used were below those used to treat depression, and in 1 study,³¹ patients received additional behavioural therapy, which may have masked drug benefits. In addition, the number of patients in these studies was small.

In light of the symptom overlap between anorexia nervosa and depression and the increased prevalence of mood disorders in relatives of those suffering from anorexia nervosa, it is surprising that tricyclic antidepressants do not seem to be of much benefit. It appears that depression is a feature secondary to the core anorexic symptoms and that improvement of depression does not positively influence eating attitude and behaviour. Weight gain in patients with anorexia nervosa treated with tricyclic antidepressants is more a side effect of the medication and may not be permanent. However, the lack of adequately powered, multicentre, controlled trials and the low dosages of tricyclic antidepressants used in most studies limits any final conclusions about the efficacy of tricyclics.

Selective serotonin reuptake inhibitors

As with tricyclic antidepressants, treatment with selective serotonin reuptake inhibitors (SSRIs) is based on the findings that patients with anorexia nervosa frequently exhibit depressive symptoms and that the symptom profile of the disorder shows some similarity to obsessive–compulsive disorder, as evidenced by high scores on obsessive–compulsive disorder rating scales and frequent obsessions with symmetry and order.³⁵

In addition, dysfunction of the serotonergic system has been postulated as one of the etiological factors in anorexia nervosa.⁴ There is considerable evidence that when underweight, patients with anorexia nervosa have significantly lower basal concentrations of the serotonin (5-HT) metabolite 5-hydroxyindolacetic (5-HIAA) in cerebrospinal fluid (CSF) than healthy controls,^{36,37} as well as a blunted plasma prolactin response to drugs with 5-HT activity.³⁸ Low levels of estrogen, often

observed in patients with anorexia nervosa,^{39,40} are also reported to thwart central serotonergic activity.⁴⁰ These findings suggest reduced serotonergic activity that could be a state-related phenomenon because dieting is known to reduce the availability of tryptophan, the precursor of serotonin.⁴¹ In long-term weight-restored patients with anorexia nervosa, CSF concentrations of 5-HIAA are reported to be elevated.^{41,42} This elevation may explain some of the pathology that frequently persists after weight recovery in some patients such as perfectionism, harm avoidance and behavioural overcontrol.⁴¹

Despite the biological evidence for serotonergic dysfunction in the etiology of anorexia nervosa, the therapeutic use of SSRIs remains controversial. There have been 2 published open trials of fluoxetine.^{43,44} In one,⁴³ 29 of 31 patients with anorexia nervosa who had gained weight with fluoxetine therapy maintained their weight at or above 85% of average body weight. Fluoxetine treatment also reduced depression, obsessive-compulsive symptoms and anxiety. In the other study,⁴⁴ all 6 patients with chronic refractory anorexia treated with fluoxetine gained weight. There is also a case report that supports these findings.⁴⁵ In contrast, however, Ferguson and colleagues⁴⁶ reported that SSRI treatment had no effect on clinical symptoms in 24 underweight malnourished patients with anorexia.

There are 2 double-blind, placebo-controlled trials of fluoxetine in the acute treatment of anorexia nervosa^{47,48} and 1 trial assessing its utility in the post-hospital course of weight-restored patients with the restricting subtype of anorexia nervosa.⁴⁹ Kaye⁴⁷ reported a good response to fluoxetine in 10 of 16 patients with anorexia; there were only 3 responders in the placebo group. In this study, fluoxetine treatment was not initiated until after the patients' weight had been restored to near-normal levels. Obsessive and compulsive symptoms were successfully reduced during treatment with fluoxetine.

It has been argued that treatment with SSRIs should be initiated *after* nutritional improvement for 2 reasons. Tryptophan depletion caused by food restriction may inhibit the therapeutic effects of fluoxetine because tryptophan depletion limits serotonin production and is reported to reverse the effects of SSRIs in depressed patients.^{50,51} In addition, food restriction is also known to reduce 5-HT synthesis and down-regulate 5-HT receptor density in the brain.^{52,53}

Attia et al⁴⁸ assessed the clinical outcomes of 31 acutely ill women with anorexia nervosa who were treated

with an average dose of 60 mg fluoxetine over a 7-week period. All patients also received extensive psychotherapy and participated in a structured behavioural program. Compared to placebo, fluoxetine conferred no additional benefit to the inpatient treatment of the patients with anorexia. Again, fluoxetine efficacy may have been impaired by nutritional factors.

In a prospective 24-month naturalistic, longitudinal follow-up study on 33 patients with restricting anorexia nervosa who were receiving an average dosage of 34 mg fluoxetine per day, Strober et al⁴⁹ found that fluoxetine had no significant effect on the maintenance of target weight, the risk of sustained weight loss or other clinical measures of outcome. Of note is that all patients received weekly psychotherapy and medication had been started after 1 month of initial nutritional stabilization during inpatient treatment. However, the average dose of fluoxetine was rather low. Fluoxetine might still be of benefit at higher doses or to those who do not receive extensive outpatient psychotherapy.

Bergh and colleagues⁵⁴ caution against the use of SSRIs to treat anorexia nervosa; they reported that 8 of 30 patients treated with citalopram had an alarming drop in body weight by a mean of 5.4 kg. They argued that serotonin inhibits food intake, thus explaining the efficacy of SSRIs in treating obese patients and patients with bulimia. The formal investigation of the issue —whether treatment of anorexia nervosa with SSRIs actually decreases body weight or increases weight and improves core anorexic symptoms — however, is not ethical. Clinicians and researchers should therefore monitor patients' weight closely when using these agents.

In view of the many unresolved issues concerning the use of SSRIs to treat patients with anorexia nervosa and the dieting-related factors that might impair SSRI function, there is a need for more carefully designed studies to investigate the efficacy of fluoxetine and other SSRIs (e.g., fluvoxamine, sertraline, paroxetine, citalopram) in the treatment of anorexia nervosa. Such studies should also focus on subgroups of patients with anorexia nervosa including those of the binge-eating/purging subtype, those with prominent depressive symptoms, obsessive thinking or severe ritualistic behaviour around food, and those for whom psychotherapy is of no particular benefit.

Antidepressant drugs influencing monoamine systems

Significant decreases of CSF homovanillic acid levels

reported for underweight patients with anorexia nervosa suggest a disturbance in dopamine metabolism.⁵⁵⁻⁵⁷ Because levels normalize after weight is restored, dopaminergic disturbance is interpreted as a state phenomenon. Dysfunction of the dopaminergic system, however, is associated with symptoms such as the inability to experience motivation and reward and with motor hyperactivity,^{58,59} a core symptom of anorexia nervosa that increases with the level of starvation. Decreased dopamine turnover may thus perpetuate symptoms of anorexia nervosa.

In light of these findings, it is unfortunate that the potential role of bupropion has not been investigated in patients with anorexia nervosa. This may be because of unexplained seizures in patients with bulimia nervosa treated with this agent.⁶⁰ The clinical relevance of increased locomotor activity and decreased appetite in animal studies of bupropion⁶¹ and of decreased appetite in depressed patients receiving bupropion⁶² should be assessed in larger treatment trials.

Disturbances in the metabolism of norepinephrine also seem to contribute to either the development or maintenance of anorexia nervosa. Pirke and others^{55,57,63,64} have found that noradrenergic activity seems to be either normal or reduced in patients with anorexia nervosa and decreased in long-term weight-recovered patients (~20 months).⁵⁵ Norepinephrine dysfunction is associated with depressed mood, vegetative dysregulation and disturbances in energy and drive,⁶³ all of which are symptoms of acute anorexia nervosa, and some of which may persist beyond weight restoration. With the availability of the antidepressant reboxetine, a selective norepinephrine reuptake inhibitor, there is an opportunity to evaluate its role in anorexia nervosa.

Moreover, in light of the availability of antidepressants that act on both 5-HT and norepinephrine, it is surprising that no trials have been conducted using medications such as venlafaxine or mirtazapine. These drugs may be particularly useful in the treatment of anorexia nervosa because of their mild side-effect profile and their potential to alleviate symptoms of anxiety.⁶⁵

Mood stabilizers

There is 1 case report⁶⁶ and a 4-week, double-blind, parallel group study of 8 patients⁶⁷ on the use of lithium to treat patients with anorexia nervosa. Lithium led to weight gain in all patients; however, this is not surprising, because weight gain is one of the most common

side effects of lithium.⁶⁸ There was no mention if other core symptoms of anorexia improved with lithium treatment, and no follow-up was done to determine if the weight gain was maintained.

A patient with anorexia nervosa of the binge eating/purging subtype of anorexia was treated unsuccessfully with carbamazepine for 6 months.⁶⁹ This patient, after attempting suicide by ingesting 7500 mg of acetaminophen, developed fulminant hepatic failure and required a liver transplant, possibly due to increased acetaminophen toxicity resulting from carbamazepine and the fasting-related acceleration of the P450 mixed oxidase system. In another case report,⁷⁰ a patient with anorexia nervosa and concomitant seizure disorder was effectively treated with valproate; the drug improved both the seizures and the core anorexic symptoms.

Nevertheless, because there is not enough evidence demonstrating the benefits of mood stabilizing medications to patients with anorexia nervosa, their use in the treatment of anorexia nervosa is not recommended.

Bulimia nervosa

Description

Bulimia nervosa is characterized by repeated episodes of binge eating, followed by inappropriate compensatory behaviours to prevent weight gain. Patients are usually of normal weight, but their perception of body shape and size is distorted. The disorder predominantly occurs in women — between 1.7% and 2.5% of women are affected. As is the case with anorexia nervosa, the etiology of the disorder is unknown. Although cultural factors seem to play a bigger role in bulimia than in anorexia nervosa, some biological vulnerability is also suggested.

Tricyclic antidepressants

Two studies on the use of imipramine^{71,72} for the treatment of patients with bulimia report a 30% abstinence rate from binge eating within 6 weeks and an improvement in the “antibulimic” effect after 16 weeks of treatment. No association was found between severity of depressive symptoms and response to imipramine. However, in 2 other studies^{73,74} imipramine was not well tolerated and was associated with a high relapse rate.

Desipramine was found to be more effective than placebo in reducing binge-eating and purging behav-

our, independent of depressive symptoms, in dosages ranging from 100 to 350 mg/day administered over 6–32 weeks.^{15,75–78} However, in 1 study,⁷⁶ the majority of responders had relapsed at 6-month follow up. Although desipramine was better tolerated than imipramine, cardiovascular side effects were quite frequent. Desipramine seemed to be most effective at reducing core bulimic symptoms and associated affective symptoms when combined with psychotherapy.

Amitriptyline was also evaluated in the treatment of bulimia nervosa at a dosage of 150 mg/day;⁷⁹ the drug was not found to be superior to placebo. These results should be interpreted with caution, however, because the dose was low, the trial duration was only 8 weeks and behavioural therapy was performed concurrently.

In summary, although some tricyclic antidepressants may be of some benefit in the treatment of bulimia nervosa, their use cannot be recommended because of the side-effect profile and a lack of long-term efficacy.

Selective serotonin reuptake inhibitors

Among the SSRIs, fluoxetine, which has been shown to interrupt the binge-eating/purging cycle, is the most rigorously studied for the treatment of bulimia nervosa.^{80–82} Goldbloom and Olmsted⁸² reported that short-term treatment with fluoxetine was associated with attitudinal and behavioural changes in patients with bulimia nervosa that were independent of the depressive symptoms. The dosage of fluoxetine shown to be superior to placebo and to be tolerated with minimal side effects in a large placebo-controlled trial involving 387 patients is 60 mg/day.⁸⁰ Similar to the tricyclic antidepressants, fluoxetine was effective in reducing binge eating and purging, even in the absence of depressive symptoms.⁸³ This and the preferential effectiveness of the 60 mg/day dosage, suggest that the mechanism of action of antidepressants in patients with bulimia nervosa may be different from that in patients with depression.

There have been several studies on the combination of psychotherapy and fluoxetine for the treatment of patients with bulimia nervosa.^{84–87} With the exception of 1 study,⁸⁶ all trials were placebo-controlled. The results are somewhat inconsistent — in 2 studies, no difference was found between cognitive behavioural therapy and medication,^{85,86} whereas 2 other studies reported that cognitive behavioural therapy, nutritional counselling and other psychotherapeutic interventions were superior to medication alone.^{84,87} However, in the latter study,

after 20 weeks, there were no differences in outcome measures between the group who had received fluoxetine and those who had received placebo or cognitive behavioural therapy.

Agras⁸⁸ suggests fluoxetine treatment be continued for at least 6 months to minimize relapse risk. Unfortunately, because of the a lack of data, no definite recommendations regarding the use of fluoxetine in continuation and maintenance treatment of bulimia nervosa can be made. Fichter et al⁸⁹ conducted a double-blind placebo-controlled study to evaluate the role of fluvoxamine in preventing relapse in 72 patients with bulimia nervosa and found that, despite a high drop-out rate, fluvoxamine was effective in reducing the recurrence of binge-eating and purging behaviour. Another 8-week open trial of fluvoxamine (50–150 mg/day) in 20 patients with bulimia nervosa⁹⁰ suggested the drug was a safe and effective treatment for bulimia nervosa and that it not only reduced binge eating and purging, but also improved attitudes toward eating and body image.

Sertraline⁹¹ and paroxetine⁹² have been reported to improve core symptoms of bulimia nervosa, suggesting that both drugs should be tested in larger trials. To our knowledge, neither drug has been systematically evaluated in the treatment of bulimia nervosa.

Patients with bulimia nervosa alternate between extremes of dieting and binge eating with purging, and they often show extreme mood swings. It has been suggested that patients with bulimia may suffer from a modulatory 5-HT defect,⁴⁰ which leads to an inability to adequately respond to stress or stimuli (e.g., food) and to appropriately modulate affective states and impulses. It has been proposed that women with bulimia nervosa may have a dysregulated vulnerable 5-HT system that responds to dietary manipulation and that binge eating and dieting may serve to self-regulate 5-HT activity in the brain.^{93,94} In this model, dieting or binge eating alters tryptophan levels in the brain which then leads to changes in 5-HT synthesis and availability.^{40,95} In support of this hypothesis, studies have found that patients with bulimia nervosa exhibit mood lability, increased dysphoria and tend to overeat when subjected to tryptophan depletion;⁹⁶ they also exhibit blunted cortisol and prolactin responses after meta-chlorophenylpiperazine challenge.⁹⁷ Although these findings and hypotheses may be rather simplistic to explain the complex nature of bulimia nervosa, they do account for the efficacy of SSRIs in the treatment of bulimia ner-

vosa; they fail to explain why SSRIs also work in the absence of mood symptoms, however.⁸⁷

The data on SSRI treatment of bulimia nervosa suggest that core symptoms of the disorder respond to this class of medication. It is particularly noteworthy that the most impressive evidence of the “antibulimic” effect of fluoxetine comes from the only large multicentre SSRI trial,⁸⁰ urging that equally large studies be performed with other SSRIs.

Antidepressant drugs influencing monoamine systems

The rationale behind the use of monoamine oxidase inhibitors (MAOIs) in the treatment of bulimia nervosa was that patients with this disorder often exhibit symptoms resembling atypical depression,⁹⁸ including prominent anxiety, hyperphagia and hypersomnia, which are reported to respond well to MAOIs.⁹⁹

Although the traditional MAOIs (i.e. phenelzine and isocarboxazid) reduced the frequency of binge eating, their side effects led to frequent drop outs during acute treatment and at follow up.^{100–102} In addition, traditional MAOIs cannot be recommended as first-line treatments because of dietary restraints required in their use that may be hard for patients with bulimia to follow.

Kennedy et al¹⁰³ found that the reversible inhibitor of monoamine oxidase-A brofaromine (175 mg/day) reduced binge eating in patients with bulimia nervosa over an 8-week period. However, the response rate to placebo was almost as high, and frequent physician visits may have contributed to the positive trial outcome. To date, brofaromine is not available for clinical use in Canada.

Surprisingly, moclobemide, also a reversible inhibitor of monoamine oxidase-A with established antidepressant efficacy, available in Europe, Canada and Australia but not in the United States, does not appear to have been evaluated for the treatment of bulimia nervosa.

Horne et al⁶⁰ conducted the only multicentre placebo-controlled trial of bupropion treatment of non-depressed patients with bulimia nervosa. Although bupropion in moderate doses markedly decreased binge eating and purging and was generally well tolerated, 4 patients experienced grand mal seizures, and this could not be explained satisfactorily. The seizure rate with bupropion, within the therapeutic range, in patients with major depression does not exceed rates with SSRIs and other novel antidepressants.¹⁰⁴ Nevertheless, the use of bupropion is not recommended for

bulimia nervosa unless it is combined with anticonvulsant medication.

Despite evidence of a dysfunctional norepinephrine system in patients with bulimia,¹⁰⁵ the norepinephrine and serotonin reuptake inhibitors and the selective norepinephrine reuptake inhibitors, which include nefazodone, venlafaxine, mirtazapine and reboxetine, have not been evaluated in the treatment of bulimia nervosa.

Anxiolytics

There are no controlled trials of the efficacy of benzodiazepines in the treatment of bulimia nervosa and because of comorbid substance abuse disorder in many of these patients, the use of benzodiazepines should be limited. In addition, there is no biological basis for a direct antibulimic effect of anxiolytics. However, because of frequent comorbid anxiety disorders in patients with bulimia nervosa,¹⁰⁶ treatment with the non-benzodiazepine buspirone may be of benefit to a subgroup of patients. Waller et al¹⁰⁷ investigated impulsivity and neuroendocrine response to buspirone challenge in 6 patients with bulimia nervosa and found evidence for a blunted cortisol response. However, their report is not a treatment trial and anxiety was not assessed. Thus, the role of buspirone in bulimia nervosa requires further evaluation.

Mood stabilizers

The use of anticonvulsants dates back to observations of EEG abnormalities in patients with bulimia nervosa and subsequent treatment with phenytoin.¹⁰⁸ Of note is that 7 of the 19 patients treated with for binge eating in one study had EEG abnormalities — a finding that could not be explained, but is of particular interest given the bupropion-related link to seizures.

The frequent mood swings and the impulse dysregulation in patients with bulimia nervosa led to trials with the mood stabilizer lithium and the anticonvulsant carbamazepine. Lithium failed to exhibit any “antibulimic” efficacy when given to 91 patients with bulimia in one study.¹⁰⁹ A double-blind, placebo-controlled trial with carbamazepine was conducted with 16 patients with bulimia nervosa without significant benefit to the majority of patients.¹¹⁰ There are no controlled trials of the other mood-stabilizing agents (e.g., valproate, lamotrigine, gabapentin), but judging from results of lithium and carbamazepine trials, their use should be limit-

ed to patients with bulimia nervosa who have a comorbid bipolar mood disorder.¹¹¹

Other medications

In a 4-week trial assessing the efficacy of ipsapirone, a 5-HT_{1A} agonist, in 17 patients with bulimia nervosa¹¹² the drug was well tolerated and binge eating and purging were markedly diminished in two-thirds of the patients after 1 week. After 4 weeks, the mean frequency of binges was reduced by 81%. At this time, data are too scarce to recommend ipsapirone for the treatment of bulimia nervosa. Other medications in this class including flesinoxan, flibanserin and gepirone (which is not currently available) may be considered in the future.

Binge-eating disorder

Description

Binge-eating disorder is characterized by persistent and frequent episodes of binge eating that are not accompanied by the regular compensatory behaviours required for the diagnosis of bulimia nervosa. Binge-eating disorder is associated with significant psychiatric morbidity and with obesity. It is frequently seen outside of psychiatric settings and is particularly common among overweight individuals seeking treatment.

Tricyclic antidepressants

There is 1 placebo-controlled study on imipramine in the treatment of 33 patients with binge-eating disorder¹² and another placebo-controlled study on the efficacy of desipramine in 23 patients with non-purging bulimia nervosa,¹⁵ a condition similar to binge-eating disorder. Alger et al¹² found no difference between imipramine, naltrexone and placebo in reducing binge frequency after 8 weeks of treatment. However, the placebo response rate in this study was exceptionally high (70% median decrease in frequency of binges), rendering the drug treatment results difficult to interpret. McCann and Agras,¹⁵ found that desipramine was superior to placebo in reducing binge-eating episodes, stress-related binge eating and hunger and in increasing dietary restraint. In another study by Agras and colleagues,¹¹³ in which patients who had completed 12 weeks of cognitive behavioural therapy received either open-label desipramine plus weight-loss treatment or

weight-loss treatment alone, the patients treated with desipramine reported more weight loss.

The data on the treatment of binge-eating disorder with tricyclic antidepressants are relatively scarce and suggest that these drugs may be somewhat helpful in the short term in reducing binge-eating episodes. Final recommendations with regard to dosing and duration of treatment cannot be made at this point, however.

Selective serotonin reuptake inhibitors

The only randomized, double-blind, placebo-controlled trial on SSRI treatment of binge-eating disorder¹⁷ comprised 85 patients treated with flexible doses of fluvoxamine (50–300 mg) for a period of 9 weeks. Compared with placebo, fluvoxamine was associated with a reduction of binge-eating episodes and body mass indices and with an improvement on clinical global outcome measures. No differences were found between placebo and fluvoxamine on change in depressive symptomatology. Adverse effects occurred in 10% or more of fluvoxamine-treated patients (e.g., insomnia, nausea, abnormal dreams), which was higher than the adverse effects reported in the placebo group. However, no serious medical side effects and no changes in clinical laboratory values were observed.

Another double-blind, placebo-controlled trial, conducted by Marcus et al,¹⁴ assessed the utility of long-term fluoxetine administration as a weight-loss method for the obese. In this study, the obese population was divided into binge eaters and non-binge eaters. All patients received behavioural therapy for 52 weeks, and half of each group was also treated with fluoxetine (60 mg/day). Although there was no significant difference in treatment outcome between binge eaters and non-binge eaters, the groups that received combination therapy lost significantly more weight than the groups treated with behavioural therapy and placebo.

De Zwaan et al¹³ assessed 64 obese patients and estimated that 22 of these patients (34.4%) fulfilled the criteria for binge-eating disorder (excluding the frequency criterion). All patients were randomly assigned to 1 of 4 treatment modalities, comprising either fluvoxamine or placebo in combination with nutritional management or cognitive behavioural therapy. Fluvoxamine was of no additional benefit to binge eaters with regard to weight loss.

Two small open label studies, 1 of fluvoxamine¹¹⁴ and the other of paroxetine,¹⁶ for the treatment of binge-

eating disorder suggest that both drugs may be effective at reducing binge eating. In an open trial on the efficacy of fluoxetine and phentermine, a dopamine-releasing agent, combined with cognitive behavioural therapy for patients with binge-eating disorder,¹⁸ the combination of either drug with cognitive behavioural therapy proved superior to treatment with cognitive behavioural therapy alone in reducing binge eating and improving mood symptoms and body image.

It appears that SSRIs are full of short-term promise in the treatment of patients with binge-eating disorder, but there is not enough data to support their benefit in the long-term treatment of this disorder. Their mechanism of action in binge-eating disorder remains uncertain, and information is too scarce to define specific indications for the use of SSRIs in these patients. In light of the fact that there are no controlled trials of any psychotherapeutic intervention in binge-eating disorder, as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, treatment with SSRIs should be initiated in conjunction with psychotherapeutic measures until such studies are available. For treatment with fluoxetine, average doses required seem to be as high as they are for bulimia nervosa; however, no dose recommendations can be made for other SSRIs until more studies have been conducted.

Other drugs

d-Fenfluramine, an appetite suppressant with serotonergic properties,¹¹⁵ was successful in the acute treatment of binge-eating disorder, but failed to show any benefit at 4-month follow-up. The drug was withdrawn from the market in 1997 because of an increased rate of valvular abnormalities.¹¹⁶ Naltrexone, an opiate antagonist,¹¹⁷ in combination with fluoxetine or psychotherapy was shown to be somewhat beneficial in reducing binge eating, suggesting that opiate blockade may be considered in the clinical management of binge-eating disorder. Sibutramine, which blocks reuptake of both serotonin and norepinephrine, has recently been approved as a weight loss agent. Venlafaxine, which has a similar mechanism of action, however, has not been used to treat patients binge-eating disorder.

Conclusions

Pharmacotherapy of eating disorders should ideally target 3 domains: (1) the remission of core symptoms

during acute treatment, (2) the prevention of relapse in the post-acute phase, and (3) the protection of biologically vulnerable patients against recurrences of the disorder over the long-term or lifetime course.

To reach these goals, medication trials should focus more on the underlying biological disturbances and clinical symptoms of eating disorders, than on implementing treatment strategies that have been previously tested in disorders that share some phenomenological overlap. In addition, the influence of nutritional factors unique to the eating disorders should be considered in the timing of pharmacological treatment studies.

The increasing evidence for biological factors as the preeminent causal determinants in the etiopathogenesis of the eating disorders and the important role of these factors in the reinforcement of symptomatology should encourage investigators to perform adequately powered trials on the well-established and "new generation" agents that may target the pathophysiological abnormalities of the eating disorders more specifically.

Finally, to address the optimal intensity and duration of various pharmacotherapies, as well as how to best integrate pharmacological and nonpharmacologic treatment modalities for all treatment phases, large comparative treatment trials must be conducted.

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