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Biological Therapies for Eating Disorders

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Abstract

Objective—To provide a comprehensive review of pharmacotherapy and other biological treatments for eating disorders.

Method—Literature on this topic was systematically reviewed.

Results—The bulimia nervosa literature underscores the utility of antidepressants, particularly SSRIs, in improving the symptoms of the disorder. The literature on binge eating disorder supports efficacy on reduction in binge eating frequency for a variety of compounds. However, such compounds have only modest effects on weight. Certain antiepileptic agents such as topiramate, if tolerated, are probably more useful in terms of weight loss. The number of controlled trials in patients with anorexia nervosa in particular has been quite small, and recent meta-analyses show disappointing results using atypical antipsychotics in anorexia nervosa.

Discussion—The pharmacological treatment of eating disorders remains an underdeveloped field although drug therapy clearly plays a role in the treatment of those with bulimia nervosa and binge eating disorder. Other biological therapies have not been adequately studied.

Keywords

anorexia nervosa; bulimia nervosa; binge eating disorder; pharmacotherapy; drug treatment

The purpose of this review is to briefly summarize the extant literature on the biological therapies for bulimia nervosa, binge eating disorder and anorexia nervosa. Several other recent reviews have also summarized the literature in this area and may be of interest to readers^{1,2}.

Pharmacotherapy of Bulimia Nervosa

Several important issues are involved in considering pharmacotherapy for bulimia nervosa (BN). First, as will be seen, the evidence in this area is limited. Many of the reports in the

literature have been case reports, case series, and open label non-randomized studies. Double-blind randomized controlled trials have been modest in number, particularly in recent years. Most of the trials have utilized antidepressants, in particular the selective serotonin reuptake inhibitors (SSRIs). Indeed the SSRI fluoxetine is the only drug that carries a Food and Drug Administration (FDA) indication for the treatment of BN³. The most frequently studied group of agents are the SSRI antidepressants (fluoxetine - twelve trials, fluvoxamine - three trials, sertraline – one trial and citalopram - one trial) followed by the tricyclic antidepressants (TCAs: desipramine - four trials, imipramine – one trial, and amitriptyline - one trial). Two trials of reversible monoamine oxidase-A inhibitors (MAOI-A) have been reported (brofaromine and moclobemide). Lastly, the serotonin-2 receptor antagonist trazodone (in two trials) has been investigated, as has the serotonin and dopamine reuptake inhibitor bupropion (in one trial). It is important to note that bupropion is contraindicated for the treatment of BN and AN due to its seizure risk. Non-antidepressants have included the serotonin-3 receptor antagonist, ondansetron (one trial), the anticonvulsant topiramate (two trials), the serotonin augmenting agent fenfluramine, which is no longer on the market (one trial), and the androgen antagonist flutamide which was studied in combination with citalopram (see Table 1). Unfortunately, rates of achieving complete remission (abstinence from binge eating and purging) are often not reported.

Controlled Trials

Twenty nine double-blind, placebo controlled trials were reviewed and the type of drug, level of response and abstinence rates are summarized in Table 1. Twelve of the trials had a multisite design and ten of those reported a positive therapeutic effect. The seventeen single site studies reported positive therapeutic effects in eleven of the trials.

The outcome of BN treatment has often been considered unsatisfactory⁴. Also, abstinence has not been a frequent topic of research in this area. Indeed, an important question is what constitutes complete “remission” in patients with BN? Is it abstinence from binge eating and purging alone, or should it include a reduction of specific rating scale scores to a level which represents an absence of all symptoms? Bacaltchuk & Hay⁵ reported abstinence rates of less than 20% from the pooled results of 24 studies comparing drug to placebo. Such abstinence rates are not encouraging. Upon reflection, there could be a great many reasons for this. This finding could reflect the poor efficacy of the treatments available, both psychotherapy and medications, and the complexity of the illness. Adherence to treatment also could have a major impact on the achievement of abstinence, as do dropout rates. To some extent this may represent problems among participants in understanding the mechanisms of action and reasons for certain treatment recommendations, which speaks to the need for a more complete discussion of such issues in the clinical setting⁶. In contrast, the affective disorder literature supports pursuing a goal of remission of all symptoms of depression. Those who don't achieve complete remission have been shown to have a poorer prognosis, with an increase likelihood of recurrences of depressive episodes and progression to chronic refractory depression⁷⁻⁹. Very little has been reported concerning the outcomes for those who are abstinent versus those who are responders yet still symptomatic among those with BN.

Maintenance Treatment

Walsh and colleagues¹⁰ conducted a trial that involved a combination of a direct comparison of desipramine versus placebo in an eight week trial. Those who responded to desipramine (50% reduction from their baseline two week binge eating frequency), progressed into a sixteen week maintenance phase. Less than half of the patients met the entry criteria for the maintenance phase of treatment. Twenty nine percent of those who did enter the maintenance phase relapsed over the next four months. While desipramine was demonstrated to have acute efficacy for the treatment of BN compared to placebo, intent to treat analysis did not demonstrate a robust response using this drug as a maintenance treatment.

Fichter and colleagues¹¹ performed a placebo-controlled double-blind outpatient relapse-prevention study. Inpatients were treated with behavioral psychotherapy. Those who were rated on the clinical global impression-severity scale as only moderately ill or better could move on to the outpatient relapse-prevention phase of the study. This 12 week phase of the study compared fluvoxamine vs. placebo in preventing relapse utilizing intent to treat analysis. Fluvoxamine had a significant effect in preventing relapse. However, 33% of the randomized participants dropped out of treatment or were discontinued by the investigators due to low fluvoxamine plasma levels. The overall attrition in the fluvoxamine group was 51%.

Romano and colleagues¹² conducted the longest maintenance trial to date, of 52 weeks. After treatment with open label fluoxetine 60 mg/day for eight weeks patients who responded to treatment by exhibiting a decrease 50% from baseline in the frequency of vomiting episodes for the last 2 weeks of the open label phase were eligible for randomization to fluoxetine or placebo. Patients who experienced a return to baseline vomiting frequency persisting for 2 consecutive weeks were considered to have relapsed. The intent to treat analysis of this trial supported the superiority of fluoxetine over placebo for maintenance treatment. However it is difficult to interpret these results considering the dropout rate for the two groups, (fluoxetine = 83%, placebo = 92%). The problem of continuation with therapy clearly has an impact on maintenance treatment and ultimately on the abstinence rate.

Adherence to Medication Treatment

One factor in patient dropouts is the adverse reactions to medications. Reported adverse reactions in BN patients receiving antidepressants include nausea, dizziness, sedation, fatigue insomnia, dry mouth, constipation, palpitations, sexual dysfunction, tremors and increases in pulse rate, declining systolic and diastolic blood pressures and orthostatic hypotension. Weight gain can occur with antidepressants and may pose a problem with those who have a fear of weight gain. Word finding difficulties, difficulty with concentration and paresthesias have been reported with topiramate treatment of BN patients. Most of the adverse effects are reported to be transient and well tolerated in controlled studies as in the small trial reported by Milano (et al. 2004)¹³.

Most of the BN studies are associated with significant dropout rates from both psychotherapy and medication treatments. The causes of patients leaving treatment are many, with the tolerability of the medication presumed to be a major cause. However, in the case of the Romano et al.¹², study, which had the highest dropout rate of all the trials, a minority cited adverse reactions as the cause (fluoxetine 6% and placebo 4%). The most common causes related to leaving the study included illness relapse (fluoxetine 29%, placebo 29%) and patient decision (fluoxetine 27% placebo 32%). As mentioned earlier, to some extent this may reflect individual patient's lack of understanding concerning the reasons for the clinician to recommend pharmacotherapy⁶. A more detailed evaluation of the reasons for leaving studies would be helpful to understand the dropout rates and the compliance issues in clinical practice. This information could assist in the design of pharmacotherapy treatments which would be more patient friendly.

Augmentation, Switching and Combination Treatment

When a patient fails to respond to the initial pharmacotherapy several alternative courses of action can be attempted. They include: 1) switching to a new agent and discontinuing the initial drug; 2) adding on a new drug and continuing the original medication; and, 3) adding an augmenting drug to the initial medication. The difference between an added medication and an augmentation drug is that the added drug is known to be effective in the treatment of the condition and the augmenter medication is a treatment that is not usually used to treat the condition as a single agent. The augmenter is presumed to have effects that may complement the initial treatment. An example of an augmentation treatment would be the addition of lithium to antidepressant treatment in a patient with major depressive disorder. An example of additive treatment would be the addition of an antidepressant such as desipramine (a norepinephrine agent) to an SSRI agent (although one must manage the drug interaction with this combination). In this case both drugs are antidepressants while the former example of augmentation utilizes lithium.

No trials reviewed had a component of augmentation. However, combination therapy has been used in a variety of studies with only one trial reporting that the combination of medication and psychotherapy produced results that were significantly better than single treatments¹⁴. Switching treatments is also infrequent^{10, 14, 15}. Walsh et al.¹⁰ in an intent to treat analysis reported fifteen patients who did not respond to desipramine who were switched to the MAOI phenelzine – 10 patients, or fluoxetine – 5 patients. After 10 weeks of treatment 13 patients' binge eating frequency was reduced by 67% and 3 patients were in remission. The other switching trials consisted of beginning treatment with fluoxetine and having nonresponders switch to desipramine. Unfortunately no data were reported as to the effectiveness of this technique. In general the combination treatments were not notably beneficial, and the results of the medication switching trials are unclear. These trials have small data sets, in part caused by participant dropout.

The intent to treat data that are available support the efficacy of pharmacotherapy in the treatment of BN. While Cognitive Behavior Therapy (CBT) remains the treatment of choice it is not always available in all treatment settings. Therefore pharmacotherapy would be appropriate. In addition antidepressant treatment may benefit comorbid affective symptoms

although the presence of depression is not required for antidepressant efficacy. It is important to note that the therapeutic dose of fluoxetine is 60 mg/d, three times the typical antidepressant dose. For the other agents most of the studies used doses consistent with their FDA indications; we found no reports of using higher doses for the non-fluoxetine studies.

If one is to attempt to improve abstinence rates and improve outcome in BN, perhaps the most essential problem is the poor adherence to treatment, be it psychotherapy or pharmacotherapy. Without improved adherence it will be extremely difficult to produce meaningful data regarding the other areas of concern. Alternative treatments in patients that do not respond to a first trial have not been explored to a sufficient degree. Trials evaluating combination therapy, switching treatments and augmentation techniques require specific protocols to effectively evaluate potential for efficacy. Innovative exploration may eventually result in unique agents or methods of treatment that would be beneficial in improving the treatment of those with BN.

Lastly, studies exploring pharmacotherapy in children and adolescents with BN are sparse. Most of the drugs do not have data on treating this group even for their primary indication. Fluoxetine however, has an indication for use in children and adolescents diagnosed with depression, and is well tolerated. In light of the evidence for fluoxetine in treating adults with BN and its use in pediatric depression, it is reasonable to include it in the treatment of child and adolescent BN.

Pharmacotherapy of Binge Eating Disorder

Trials addressing what we now label binge eating disorder began before the diagnostic criteria were in the nomenclature, but became more specific as the criteria evolved. Also, given the association between BED and overweight/obesity, many trials have included such patients, and other trials have focused on such patients. For that reason we will briefly address weight loss in the published trials.

Tricyclic Antidepressants

There are a few studies that systematically examine the utility of TCAs in this population, or related populations. One paper examined the effects of desipramine in non-purging BN patients, many of whom would have met the current criteria for BED, and found superiority for the active drug over placebo in terms of reduction in frequency of binge eating. All the subsequent trials using TCAs involved comparisons other than or in addition to placebo; one involved a comparison with naltrexone. Imipramine did result in decreased binge eating frequency in “obese binge eaters”, while naltrexone seemed to have more effect in patients with BN. Of note, the TCA trials in general did not result in substantial weight loss in participants who were overweight or obese at baseline. The pharmacotherapy trials are summarized in Table 2.

SSRI Antidepressants

Several of the available agents have been studied, including citalopram, escitalopram, fluvoxamine, and sertraline.^{15–21} While the results have varied somewhat, in general it can be concluded that SSRIs are reasonably effective agents in suppressing, albeit rarely

eliminating, binge eating behavior. These agents are generally well tolerated, as in the treatment of individuals with other diagnoses. However, the amount of weight loss was usually modest at best.

Relative to trials including other interventions such as CBT, Marcus et al.²² found additional benefit in adding fluoxetine to behavior modification for the treatment of individuals with BED. However, Ricca et al.²³ did not find additional benefit with fluoxetine or fluvoxamine over individual CBT, and Devlin et al.²⁴ found benefit in depression with fluoxetine but not binge eating frequency.

Serotonin–Norepinephrine Reuptake Inhibitors and Norepinephrine Reuptake Inhibitors

McElroy et al.²⁵ found benefit for atomoxetine in reduction of binge eating frequency and weight compared to placebo. One study by Silveria et al.²⁶ examined the effectiveness of reboxetine in this group of patients, again finding benefits in reduction of weight and scores on the Binge Eating Scale, as well as on a measure of clinical global improvement. Also, Guerdjikova et al.²⁷ found evidence of improvement in depressive symptoms in BED patients using duloxetine. As in the SSRI studies, the weight loss was usually modest.

Sibutramine and d-fenfluramine

Sibutramine is no longer on the market in the United States because of toxicity concerns. However, several studies found benefit in terms of binge eating frequency reduction and weight loss while the drug was still available. An early study by Stunkard et al.²⁸ found a reduction in the binge eating episodes per week with d-fenfluramine, but again this compound is no longer marketed because of concerns regarding cardiovascular toxicity.

Orlistat

This lipase inhibitor has been used in several trials in individuals with BED primarily targeting weight loss rather than binge eating frequency. Positive effects have been found in terms of weight loss in both adolescents and adults with this disorder.

Anti-epileptics

The anti-epileptic agent topiramate, which has been shown to have significant weight loss properties in patients with epilepsy and in obesity, has been used experimentally now in a number of trials in individuals with BED. The results have generally been positive in terms of reduction in binge eating episodes and of weight loss, many times involving weight reductions in excess of what is seen with many pharmacological interventions^{29–31}. Also, trials using zonisamide have been reported, again with positive results on binge eating frequency and again with substantial weight loss^{32–24}.

Pharmacotherapy of Anorexia Nervosa

The treatment literature in anorexia nervosa (AN) consists of relatively few controlled pharmacotherapy studies in comparison to BN and BED. Controlled studies have generally shown a lack of efficacy for pharmacological interventions. Historically, TCAs and first-generation antipsychotics were examined, which yielded mixed results. More recently,

studies evaluating SSRIs and second-generation antipsychotics have produced mixed, though predominantly negative results. Several additional medications have been examined which are not clinically useful in the treatment of AN at the present time. The controlled medication trials, by medication class, will be reviewed. Additionally, there have been numerous uncontrolled trials of various psychotropic and miscellaneous agents in the treatment of AN. These trials are beyond the scope of this review and have been discussed elsewhere³⁵. Pharmacotherapy studies in AN typically enroll either acutely ill patients with the goal of weight regain, or recruit weight restored patients with the goal of weight maintenance.

Tricyclic Antidepressants

In the 1980's, the TCAs amitriptyline^{36,37} and clomipramine³⁸ were examined for their ability to stimulate weight gain. The majority of patients in these trials were inpatients. Concomitant with the study-related antidepressant therapy, these patients were also generally treated with psychosocial or psychotherapeutic interventions along with dietary support to promote weight regain. TCAs generally failed to accelerate weight regain in these trials. Clomipramine appeared to increase hunger and calorie consumption early in treatment, but did not alter outcome. Amitriptyline did not produce significant improvement in weight regain or depressive symptoms, but did result in significant adverse effects, including diaphoresis, drowsiness, dry mouth, and hypotension³⁶. These trials were relatively short in duration (ranging from approximately one to two months) and may have been insufficient in duration to fully realize any antidepressant potential from these drugs.

SSRI Antidepressants

Following the demonstration of efficacy with fluoxetine in the treatment of BN, fluoxetine was studied in one controlled brief inpatient treatment study and in two outpatient treatment studies of one year in duration to promote weight maintenance in AN. Attia and colleagues³⁹ randomized 33 inpatients in a seven week trial to a maximum of 60 mg of fluoxetine versus placebo. Patients also received CBT and a prescribed number of kilocalories per day. There were no differences observed between the fluoxetine and placebo groups on weight gain or mood, although the drug was well tolerated. Kaye and colleagues⁴⁰ performed the first of two maintenance trials of fluoxetine in AN. This study enrolled 39 outpatients who were assessed for 52 weeks. Patients were randomized to fluoxetine (doses varied widely) or placebo. In this trial, psychotherapy was optional. After one year, the majority of patients remained on fluoxetine (10/16) whereas the majority discontinued placebo (3/19 remaining on placebo at one year). In this study, fluoxetine treated patients had higher weights and decreased core eating disorder symptoms at one year in comparison with patients treated with placebo. Most recently, Walsh and colleagues⁴¹ completed a larger maintenance treatment trial which included 49 patients who were randomized to a target dose of 60 mg of fluoxetine and 44 who were randomized to placebo. This trial, which thoroughly investigated the efficacy of fluoxetine for relapse prevention in AN, found no difference between drug and placebo on time-to-relapse or on depressive symptoms. Collectively, the available data suggest that fluoxetine is not efficacious for the treatment of AN.

Antipsychotics

The first generation antipsychotics pimozide and sulpiride were studied by Vandereycken and colleagues^{42,43} for the short-term treatment of AN. Neither of these drugs improved outcome significantly in AN inpatients. Researchers became interested in the second-generation antipsychotics (SGAs) for the treatment of AN in the late 1990's owing to their improved tolerability and weight-promoting effects. It was also observed that the distorted thinking that accompanies AN resembles the delusional thinking that occurs in psychotic illness⁴⁴. Numerous uncontrolled trials and case reports preceded several controlled trials which have now been published in this area. The efficacy of SGA treatment for AN was recently reviewed⁴⁵ and was also the subject of two recent meta-analyses^{46,47}. Overall, the evidence shows that antipsychotics do not improve weight significantly. Various atypical antipsychotics can also lead to significant side effects in some patients, including extrapyramidal side effects, hyperprolactinemia, type II diabetes, hyperlipidemia, QTc prolongations, and others. At the present time, the available data do not support a role for SGAs in the treatment of AN, although the existing evidence base consists of relatively small studies. Larger controlled studies may illuminate predictors of treatment response or identify subgroups of patients who may benefit from SGA treatment.

Overall, pharmacological treatment of AN has been disappointing. The antidepressants and antipsychotics appeared promising in early clinical trials, and larger trials have since shown a lack of efficacy for both classes of medications. Future research is needed to identify efficacious pharmacotherapy for AN. A very small percentage of the available psychotropic agents have been explored in clinical trials in AN. Novel pharmacological agents targeting hormonal systems in the control of appetite and food intake may also play a role in the treatment of AN in the future.

Other Biological Therapies

The Use of the Mandometer

Bergh, Södersten and colleagues have developed a device which they call the Mandometer that provides patients with feedback on their rate of eating^{48–52}. In several publications these investigators have reported that providing patients with such feedback can either accelerate or decelerate the rate of eating behavior, increasing the rate in those who eat too slowly, while decelerating it in those who eat too quickly. They believe that this can be very useful in training patients with AN to increase their rate of eating and those with obesity, and presumably BED, to decelerate their rate of eating. This program is now available in several countries including the Netherlands, Australia and the U.S. However, van Elburg and colleagues⁵³ found no benefit for this approach over treatment as usual.

Light Therapy

The worsening of mood and eating disorder symptoms during the winter months, similar to what is seen in patients with seasonal affective disorders has been reported among some patients with BN. Because of this, Lam and colleagues⁵⁴ conducted an experiment to determine the effects of early morning light therapy using bright white lights versus dim red lights in a counter-balanced cross-over design administered for two weeks. The outcome of

the bright white light condition was superior to the dim red light condition on mood and eating outcome measures. There was a particularly positive effect in those with “seasonal” bulimic symptoms. These authors subsequently reported an open trial of light therapy for women with comorbid seasonal affective disorder and BN, again finding evidence of symptom improvement, although complete cessation of binge eating was uncommon⁵⁵. Blouin and colleagues⁵⁶ also studied the effect of light therapy on food intake and affective symptoms in BN patients in a double-blind study, but found that bright white light was not superior to a dim light source over a one week period in terms of binge eating frequency. Braun and colleagues⁵⁵ also compared bright light treatment to a dim red light condition, finding superior benefit for the bright light condition.

Repetitive Transcranial Magnetic Simulation

Although research in this area is in its infancy, repetitive transcranial magnetic stimulation (rTMS) is now being studied in patients with eating disorders. Walpoth et al.⁵⁶ randomized 14 women with BN to three weeks of active treatment with rTMS or to a sham stimulation condition. The average number of binge eating episodes per day declined significantly between baseline and end-of-treatment in both groups, with no significant differences. Van den Eynde and colleagues⁵⁷ administered single rTMS sessions to individuals with AN and found subjectively that the patients’ experiences of their eating disorder, including the urge to restrict and feelings of fullness, improved.

Summary

The available literature suggests a prominent role for pharmacotherapy in the treatment of BN and BED. BN improves with a variety of treatment agents, although in general clinicians have favored SSRIs, and fluoxetine is the only FDA approved drug for this indication and is commonly used. It is well tolerated at a dosage of 60 mg each day. Relative to BED, the binge eating symptoms appear to respond to several agents. In many situations, SSRIs work well and are tolerated well. However, for the overweight or obese, weight loss is usually modest at best with these compounds. Certain antiepileptic drugs such as topiramate are useful in suppressing binge eating and inducing weight loss. In individuals with AN, atypical antipsychotics may be useful during the weight gain phase, but the evidence here is limited. Clearly new directions in pharmacotherapy should be pursued. Other approaches for these disorders, such as the use of the Mandometer, light therapy, and rTMS, should be considered experimental and not recommended in the care of patients.

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Table 1

Pharmacotherapy for Bulimia Nervosa

Class	Drug	Response	
		Binge Eating	Abstinence (%)
TCA's	Amitriptyline	0	Not reported
	Imipramine	++	Not reported
	Desipramine	++	14.5
SSRIs	Fluoxetine	++	17.9
	Fluvoxamine	++	Not reported
	Citalopram	0	Not reported
MAO-Is	Brofaromine	+/-	31.5
	Moclobemide	0	0.0
5-HT ₂ antagonists	Trazodone	++	10.0
* AD Other Classes	Bupropion **	++	30.0
Anti-Epileptics	Topiramate	++	22.6
Other Classes	Ondansetron	++	Not reported
	Lithium	0	17.0
	Flutamide	++	Not reported

* AD-antidepressants,

** Bupropion contraindicated due to risk of seizures.

Table 2

Pharmacotherapy for Binge Eating Disorder

Class	Drug	Responses	
		Binge-eating	Weight Loss
<u>Tricyclics</u>	Imipramine	++	+/-
	Desipramine	++	+/-
<u>SSRIs</u>	Citalopram	++	+
	S-citalopram	++	+
	Fluvoxamine	++	+
	Sertraline	++	+
	Atomoxetine	++	+
<u>SNRIs/NRIs</u>	Venlafaxine	++	+
	Duloxetine	++	+
	Orlistat	+/-	++
<u>Anti-Epileptics</u>	Topiramate	++	+++
	Zonisamide	++	+++
<u>Other Classes</u> *	Baclofen	+	-
	Na Oxybate	+	+
	Lamotrigine	-	+
	Acamprosate	-	-

* None of these have been adequately studied.