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REVIEW ARTICLE

Progress in Developing Pharmacologic Agents to Treat Bulimia Nervosa

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Abstract

This paper reviews past and current progress in developing pharmacologic agents for the treatment of individuals with bulimia nervosa (BN). We searched the literature and clinical trial registries for compounds studied in BN, the related condition, binge eating disorder (BED), and preclinical models of binge-eating behavior. Drug classes evaluated included antidepressants, antiepileptic drugs, stimulants and other medications for attention-deficit/hyperactivity disorder, opioid antagonists, and weight loss agents, among others. The only available drugs with established efficacy in BN at this time include antidepressants (especially selective serotonin reuptake inhibitors [SSRIs]) and the antiepileptic topiramate, though the efficacy of these compounds is modest at best. The only medications we found currently receiving empirical study in people with BN were fluoxetine, other serotonergic antidepressants, intranasal naloxone, lisdexamfetamine dimesylate, phentermine–topiramate combination, the antiandrogenic oral contraceptive ethinyl estradiol plus drospirenone, and prazosin. Preclinical models suggest that nociceptin receptor antagonists, the selective serotonin 5-HT2C receptor agonist lorcaserin, monoamine stabilizers, and selective orexin-1 receptor antagonists might be helpful. We found no evidence of a drug developed specifically for the treatment of individuals with BN. Future areas for research in the pharmacotherapy of BN are suggested. Importantly, until drugs are developed specifically for eating disorders, drugs developed for other conditions that are centrally acting and associated with beneficial psychotropic effects and/or reduced appetite or weight loss might be considered for repurposing in BN.

Key Points

Empirical study into the pharmacologic treatment of bulimia nervosa (BN) has substantially lagged behind that into other serious mental disorders. Indeed, only one drug (the selective serotonin reuptake inhibitor fluoxetine) has regulatory approval for the treatment of individuals with BN.

Few studies of pharmacologic agents in individuals with BN are presently ongoing.

Pharmacotherapy agents with efficacy in other conditions characterized by binge eating (e.g., binge eating disorder [BED]) or hyperphagia (e.g., Prader–Willi syndrome) should be considered for evaluation in BN, though assessment of safety will be crucial.

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1 Introduction

Bulimia nervosa (BN), characterized by recurrent binge-eating episodes and regular inappropriate compensatory weight loss behaviors, is an important public health problem. It is present in approximately 1.0% of the general worldwide adult population as a lifetime diagnosis and 0.4% as a 12-month diagnosis [1]. Among adolescents from the USA, the lifetime prevalence estimate of BN is 0.9% [2]. BN is more common in females than males, with 1.5% of adult women [3] and 1.3% of adolescent females [2] from the USA experiencing BN during their lifetime. Median age of onset of BN is late teens to early 20s in adults [1] and 12.4 years in adolescents [2]. Though a substantial proportion of individuals with BN recover over the long term, the disorder is recurrent or chronic in others [4–6].

BN is associated with substantial psychiatric and medical comorbidity, including mood, anxiety, substance use, and attention-deficit/hyperactivity (ADHD) disorders, suicidality and self-injurious behavior, dental complications, electrolyte abnormalities, obesity, and increased mortality [1, 3, 7]. BN is further associated with impairment in

role functioning, reduced health-related quality of life, and increased healthcare utilization and costs [1, 3, 8].

Though psychotherapy is viewed by many to be the treatment of choice for BN [9, 10], patients with BN often receive pharmacotherapy [11]. However, only one drug, the selective serotonin reuptake inhibitor (SSRI) fluoxetine, has regulatory approval for the treatment of BN (in the USA and other countries). Moreover, no drug has been developed specifically for the treatment of an eating disorder, which may reflect in part the limited knowledge about the pathophysiology and molecular genetics of these disorders [12–14]. New medications with novel mechanisms of action are sorely needed for the treatment of individuals with BN.

We review past and ongoing research with specific medications or medication classes in treating individuals with BN. We searched PubMed and clinical trial registries to identify medications evaluated in BN. Because we found so few, we also searched PubMed and clinical trial registries to identify drugs evaluated in patients with binge-eating disorder (BED). Although BED is a diagnostic entity distinct from BN, it is also characterized by recurrent binge-eating episodes as a core feature, the binge-eating episodes for both disorders are similarly defined in modern nosologic systems [15, 16], and there is substantial diagnostic shift between the two disorders [4]. Although not yet definitively proven, a drug that reduces binge eating in BED might also reduce binge eating in BN. Finally, we also searched PubMed for drugs evaluated in preclinical models of binge eating, though whether findings from these models generalize to individuals with BN remains unclear [17].

This search found a broad array of drugs evaluated in the treatment of BN and related conditions, including antidepressants, antiepileptic drugs, stimulants and other ADHD medications, agents with hormonal properties, and weight loss drugs, among others. We summarize these data and suggest future areas for research.

2 Antidepressants

As noted, the SSRI antidepressant fluoxetine is the only medication with regulatory approval (in the USA and other countries) for the treatment of BN. In the largest randomized controlled trial (RCT) of fluoxetine in BN, 387 women with BN were randomized to receive fluoxetine 60 mg/day, fluoxetine 20 mg/day, or placebo for 8 weeks at 13 sites [18]. Fluoxetine 60 mg/day was superior to placebo for reducing binge-eating and vomiting episodes, whereas fluoxetine 20 mg/day had an intermediate effect [18]. Fluoxetine 60 mg/day was also superior to placebo for reducing depression, carbohydrate craving, and pathological eating attitudes and behaviors. However, not all patients responded to fluoxetine. To address this issue, an open-label study is ongoing in France to evaluate the efficacy of SSRIs in 45 participants with BN according to brain serotonin profile as determined by positive emission tomography using the specific brain serotonin 5-HT1A receptor ligand [18F]MPPF (NCT02359513).

Other antidepressants beyond fluoxetine have been shown to be superior to placebo for reducing the frequency of both binge-eating and purging episodes in BN [19, 20], and guidelines have concluded that antidepressants are efficacious for BN [9, 21]. This includes SSRIs other than fluoxetine, tricyclic antidepressants, monoamine oxidase inhibitors, and atypical agents such as mianserin, trazodone, and bupropion. A 2003 meta-analysis of 19 antidepressant RCTs in people with BN showed antidepressants were modestly superior to placebo for stopping binge-eating episodes [22]. This meta-analysis showed antidepressants were also safe for treatment of BN, with the important exception of bupropion. Though efficacious for reducing binge eating and purging, this agent was associated with an increased risk of seizures [23] and is therefore contraindicated for the treatment of BN (and anorexia nervosa).

To our knowledge, three randomized, placebo-controlled, relapse-prevention trials have been undertaken with antidepressants in BN. In the first RCT, though desipramine was superior to placebo for reducing binge eating in the initial acute phase of the study, not enough patients completed the maintenance phase to determine whether the drug also had long-term efficacy [24]. In the second RCT, 72 patients with BN successfully treated with intensive inpatient psychotherapy were randomized to receive fluvoxamine ($n=33$) or placebo ($n=39$) as outpatients for 12 weeks [25]. Fluvoxamine was begun 3 weeks before hospital discharge, for a total of 15 weeks of treatment. Relapse rate was significantly lower with fluvoxamine than placebo, as evidenced by (1) 10 versus 46% deterioration on the Psychiatric Status Rating Scale for Bulimia Nervosa; (2) 111 versus 270% increase in self-reported binge-eating episodes in the last week, and (3) 50 versus 175% increase on the Structured Interview for Anorexia and Bulimia Nervosa subscale of bulimic behavior. In addition, at the end of the relapse prevention, significantly more patients in the fluvoxamine group than the placebo group reported no binge-eating episodes in the past week ($p<0.05$). However, the dropout rate was high (33%), with 14 (38%) fluvoxamine recipients and five (14%) placebo recipients stopping treatment prematurely.

In the third study, 232 outpatients with purging-type BN received single-blind treatment with fluoxetine 60 mg/day for 8 weeks; 150 (65%) met response criteria and were randomly assigned to continue fluoxetine 60 mg/day ($n=76$) or switch to placebo ($n=74$) for 52 weeks [26]. Fluoxetine-treated participants had a significantly longer time to relapse (defined as a return to baseline vomiting frequency for 2 weeks) than placebo-treated participants ($\chi^2=5.79$, $f=1$,

$p < 0.02$). In addition, endpoint analyses showed statistically significant differences favoring fluoxetine for binge-eating and vomiting episodes, obsessive-compulsive symptoms, and clinical global outcome. However, relapse rates and symptom measures increased over the trial in both treatment groups, and the attrition rate was very high, with 63 (83%) fluoxetine recipients and 68 (92%) placebo recipients stopping the study prematurely. Taken together, these studies suggest antidepressants may have some long-term efficacy in BN, but treatment discontinuation rates are high.

It is important to note that several antidepressant classes have not yet been evaluated in randomized placebo-controlled trials in individuals with BN. These include serotonin norepinephrine reuptake inhibitors (SNRIs; e.g., desvenlafaxine, duloxetine, milnacipran, and venlafaxine), norepinephrine reuptake inhibitors (NRIs; e.g., reboxetine), and novel agents such as vilazodone (an SSRI and 5-HT1A receptor partial agonist) and vortioxetine (an SSRI, 5-HT3 receptor antagonist, and 5-HT1A receptor agonist). Open-label data suggest milnacipran, reboxetine, and duloxetine may be effective in BN, including in treatment-resistant cases [27–31]. Additionally, preliminary randomized controlled data suggest duloxetine may be effective for reducing binge eating in BED [32], and an investigator-initiated trial of vortioxetine is ongoing in BED (NCT02528409). Finally, antidepressant compounds with novel mechanisms of action are in development. These include glutamatergic modulators, AVP-786 (deuterium-modified dextromethorphan hydrobromide in combination with very-low-dose quinidine sulfate), AXS-05 (dextromethorphan plus bupropion), brexanolone (a neurosteroid with possible efficacy in post-partum depression) [33], opioid modulators, cholinergic modulators (e.g., scopolamine), anti-inflammatory agents (e.g., the monoclonal antibody sirukumab), natural killer (NK)-1 receptor antagonists, vasopressin receptor antagonists, and neurogenesis enhancers [34]. If any of these compounds prove efficacious and safe for major depressive disorder, they should be considered for evaluation in BN.

Antidepressants have been studied both against and in combination with a variety of psychological interventions in BN, including cognitive behavior therapy (CBT), intensive inpatient psychotherapy, and nutritional counseling [19, 35]. Designs and results have varied, making firm conclusions difficult. In 2001, Bacaltchuk et al. [35] published a Cochrane Review of RCTs in which antidepressants were compared with psychological treatments or the combination of antidepressants with psychological treatments was compared with each treatment alone for reducing symptoms in BN and for tolerability. The main efficacy outcome was remission of bulimic symptoms. The authors had three major findings. First, remission rate for antidepressant treatment alone was 20 versus 39% for psychological treatment alone (relative risk [RR] 1.28; 95% confidence interval [CI] 0.98–1.67). In addition, withdrawal rates were higher for antidepressants alone than for psychological treatments alone (RR 2.18; 95% CI 1.09–4.35). Second, remission rate for combination antidepressant–psychological treatment was 42 versus 23% for antidepressant treatment alone (RR 1.38; 95% CI 0.98–1.93). Third, remission rate for psychological treatment alone was 36 versus 49% for combination treatment (RR 1.21; 95% CI 1.02–1.45), with higher withdrawal rates for combination treatment compared with psychological treatment alone (RR 0.57; 95% CI 0.38–0.88). The only statistically significant difference between groups was that combination therapy was superior to psychological treatment alone. The authors concluded that combined antidepressant–psychological treatment was superior to psychotherapy alone but that the number of trials might be insufficient to show combination therapy or psychotherapy alone as superior to antidepressants alone. They also concluded that psychotherapy was more acceptable to patients with BN and that the addition of antidepressants to psychotherapy reduced its acceptability. However, in an important RCT, fluoxetine was superior to placebo for reducing binge-eating behavior in patients with BN who had an inadequate response to CBT [36].

Preliminary evidence suggests dialectical behavior therapy (DBT) may be effective for BN [37]. An RCT comparing DBT alone, fluoxetine alone, and the combination in patients with BN is ongoing (NCT03455088). It is interesting to wonder whether antidepressants might differentially augment DBT versus CBT for the treatment of individuals with BN.

3 Antiepileptic Drugs

Two antiepileptic drugs—carbamazepine and topiramate—have been evaluated for the treatment of BN in RCTs. In the single RCT of carbamazepine, 16 participants with BN received carbamazepine or placebo in a crossover design [38–40]. The first six patients received 6-week intervals of placebo–carbamazepine–placebo or carbamazepine–placebo–carbamazepine over 18 weeks. The next ten patients received two 6-week intervals of placebo–carbamazepine or carbamazepine–placebo over 12 weeks. There was no significant difference in response between carbamazepine and placebo. One patient completely stopped binge eating (this patient also had bipolar disorder), one patient had a marked response, and three additional patients improved on carbamazepine compared with baseline but did not show a difference on drug compared with placebo. The other nine patients had minimal or no response.

Both published RCTs of topiramate in BN were positive. In the first study, 69 participants with BN received topiramate or placebo for 10 weeks [41, 42], with 22

(63%) of 35 topiramate recipients and 18 (53%) of 34 placebo recipients completing the trial. Topiramate (median dose 100 mg/day; range 25–400 mg/day) was superior to placebo in reducing the frequency of binge eating and purge days (days during which at least one binge-eating or purging episode occurred; $p = 0.004$). Topiramate also produced a greater reduction than placebo in measures of bulimia/uncontrollable overeating ($p = 0.005$), body dissatisfaction ($p = 0.007$), and drive for thinness ($p = 0.002$) on the Eating Disorder Inventory; measures of bulimia/food preoccupation ($p = 0.019$) and dieting ($p = 0.031$) on the Eating Attitudes Test; anxiety symptoms ($p = 0.046$); and body weight (mean decrease of 1.8 kg for topiramate vs. 0.2 kg increase for placebo; $p = 0.004$). In addition, significantly more topiramate recipients than placebo recipients reported improvement on the Patient Global Improvement scale ($p = 0.004$). The percentage of participants who achieved ≥ 50% reduction in the number of binge-eating and/or purge days was significantly greater with topiramate (52%) than with placebo (24%; $p = 0.012$). Remission rates from binge eating and purging were numerically but not significantly higher for topiramate (23%) than placebo (6%), whereas attrition rates were numerically lower for topiramate (34%) than placebo (47%). The most common side effects associated with topiramate were fatigue, flu-like symptoms, and paresthesias.

In the second study, 60 patients with BN received topiramate ($n = 30$; titrated to 250 mg/day by 6 weeks) or placebo ($n = 30$) for 10 weeks [43]. Compared with placebo, topiramate produced significant decreases in frequency of binge-eating/purging episodes (defined as a > 50% reduction; 37% for topiramate and 3% for placebo); body weight (difference in weight loss between the two groups 3.8 kg); and all scales on the 36-Item Short Form Health Survey (SF-36) (all $p < 0.001$). Five (17%) patients receiving topiramate and six (20%) patients receiving placebo left the study prematurely. All patients tolerated topiramate well.

Further supporting the possibility that topiramate reduces binge-eating behavior in BN are three positive RCTs of topiramate in individuals with BED [44–46]. Of note, the rationale leading to study of topiramate in BED was its strong association with anorexia and weight loss [44]. All drugs associated with anorexia or weight loss that have since been evaluated in BED in RCTs have produced reduced binge eating [47]. Topiramate also decreased binge-like behavior in one preclinical model of binge eating [48], though not in another [49]. Moreover, topiramate has been reported to reduce binge eating and/or purging in patients with BN with treatment-resistant illness, those with comorbid mood or personality disorders, and those receiving the drug as adjunctive therapy in combination with antidepressants, mood stabilizers, and/or antipsychotics [50–52]. Topiramate has also been reported to have decreased binge eating in a woman with BN and epilepsy [53]. However, reports also exist of patients with eating disorders misusing topiramate to promote weight loss [54, 55] as well as patients developing eating disorder symptoms after topiramate exposure [56].

Regarding other antiepileptic drugs evaluated in BN, an open-label trial in 12 patients found zonisamide reduced binge eating and purging symptoms but was associated with a high withdrawal rate (50%) [57]. This finding was consistent with an RCT showing that zonisamide produced a statistically significant reduction in binge eating in patients with BED but was associated with a high withdrawal rate due to adverse effects (27%) [58]. Valproate was effective in three hospitalized women with BN and comorbid rapid-cycling bipolar disorder that was previously inadequately responsive to lithium and antipsychotics [40, 59, 60]. All three patients showed marked improvement of both bulimic and mood symptoms. In contrast, increased binge-eating behavior in patients with BED receiving valproate have been reported [61]. Finally, lamotrigine was helpful for reducing eating disorder symptoms and mood instability in five patients with BN or eating disorder not otherwise specified (EDNOS) and co-occurring affective dysregulation [62]. However, in a 16-week RCT of lamotrigine in 51 obese patients with BED, lamotrigine and placebo were comparably effective in reducing binge eating, though lamotrigine was superior to placebo for reducing fasting levels of glucose, insulin, and triglycerides [63].

Finally, it should be noted that antiepileptic drugs with novel mechanisms have recently come to market and are in development [64]. Agents associated with anorexia or weight loss (like topiramate), in particular, should be considered for evaluation in BN [47]. This includes pharmaceutical grade cannabidiol, which behaves as a negative allosteric modulator of cannabinoid (CB) 1 receptors, is approved for Dravet and Lennox–Gastaut syndromes, and was consistently associated with decreased appetite in study subjects receiving the drug [65, 66].

4 Opioid Antagonists and Other Drugs for Addiction

The four published RCTs of opioid antagonists in the treatment of BN we located were all small and had mixed results [67–70]. In the first, 16 of 19 women with BN completed a 6-week, placebo-controlled, crossover trial of naltrexone 50 mg/day [67]. There were no significant differences in frequency of binge-eating or vomiting episodes between drug and placebo. In the second study, 28 women with BN and 41 obese patients with binge eating were randomized to receive naltrexone 100–150 mg/day, imipramine, or placebo

for 8 weeks [68]. Among all patients, there was no change in the frequency or duration of binge eating. Among the 22 patients with BN who completed the trial, naltrexone was associated with a significant reduction in binge-eating duration ($p = 0.02$) but not binge-eating frequency. In the third study, 13 patients with BN received naltrexone up to 200 mg/day or placebo in individualized crossover 6-week trials [69]. Significant reductions in binge eating, purging, urges to binge eat, and urges to purge were seen with naltrexone. In the fourth study, intravenous administration of naloxone suppressed the consumption of sweet high-fat foods in normal weight and obese women with BN ($n = 20$) but not in controls ($n = 21$) [70].

Open studies suggest some patients with BN, including those resistant to antidepressants and psychotherapy and those with type 1 diabetes mellitus, may respond to doses of naltrexone up to 400 mg/day [71]. In an investigation of standard-dose (50–100 mg/day) compared with high-dose (200–300 mg/day) naltrexone in 16 patients with antidepressant-resistant BN, participants in the standard-dose group had no significant change in frequency of binge eating or purging after 6 weeks of treatment, whereas participants in the high-dose group had significant reductions in both behaviors [72]. Similarly, there are two favorable case reports of high-dose naltrexone in individuals with BED. One was a positive on-off-on case of naltrexone monotherapy using doses of 200 and 400 mg/day [73]. The other was the successful augmentation of fluoxetine with naltrexone 100 mg/day [74]. However, three small published RCTs of opioid antagonists for binge eating in patients with BED were negative [68, 75, 76].

A phase II randomized, placebo-controlled, 24-week study of intranasal naloxone spray in 127 individuals with BED has been reported in abstract form but not yet published [77]. Intranasal naloxone 2 mg administered before each binge-eating episode up to a maximum of 4 mg/day produced a significantly greater reduction than placebo in time spent binge eating, measured as minutes per week. In addition, body mass index (BMI) decreased significantly from week 12 to week 24 among naloxone recipients.

Taken together, these data suggest BN may respond to opioid antagonists at oral doses larger than those efficacious for substance use disorders or when they are delivered intranasally. In the latter instance, plasma and/or brain drug levels may be higher than those with oral delivery given the rich vascular supply of the nasal mucosa and the avoidance of first-pass hepatic metabolism [78]. Importantly, an RCT of intranasal naloxone in BN is currently underway in the UK (EudraCT number 2016-003107-65).

We found no other RCTs evaluating anti-addiction drugs beyond opioid antagonists for BN. However, a small ($n = 40$) RCT of acamprosate in patients with BED that failed to show drug–placebo separation in the primary statistical (longitudinal) analyses showed greater improvement in binge-day frequency with drug versus placebo in a secondary (baseline to endpoint) analysis [79].

5 Drugs for Attention-Deficit Hyperactivity/Disorder (ADHD)

The only drug besides fluoxetine that has regulatory approval for treatment of an eating disorder is lisdexamfetamine dimesylate (LDX), a stimulant pro-drug converted to d-amphetamine. Specifically, LDX is approved for the treatment of moderate-to-severe BED in adults and for ADHD in children and adults. It reduces binge-eating behavior in BED patients both acutely [80, 81] and over the long term [82]. The efficacy of LDX for binge eating in BED suggests stimulants might also be efficacious for reducing binge eating in BN. Two lines of preliminary data support this possibility. First, in a double-blind, randomized, crossover trial (the only RCT of a stimulant in BN we were able to locate), eight patients with BN were given methylamphetamine or placebo intravenously followed by a test meal and separated by a 1-week interval [83]. Significantly fewer mean ± standard deviation (SD) calories were consumed after methylamphetamine (224 ± 111) than after placebo (943 ± 222; $p < 0.02$). In addition, "the frequency of bulimia" was significantly lower after methylamphetamine (zero of eight patients) than after placebo (four of eight patients; $p < 0.05$). (Of note, bulimia in this study was defined as rapid, excessive, distressful eating followed by vomiting or purgation). Second, a growing number of case reports describe the successful use of methylphenidate in treating patients with BN, including those who respond inadequately to psychotherapy and antidepressants and those with comorbid cluster B personality disorders or ADHD [84–89]. Importantly, a feasibility study of LDX is ongoing in patients with BN in Nova Scotia, Canada (NCT03397446). The aim of this open-label, 2-month trial is to gain preliminary safety and effectiveness data as well as an estimate of treatment effect of LDX in BN in hopes of informing future RCTs of stimulants in BN.

That LDX is efficacious for reducing binge eating in BED raises the question of whether nonstimulant ADHD drugs might reduce binge eating in BN. Though no such drugs have been studied in RCTs in individuals with BN, the nonstimulant ADHD drug atomoxetine, a selective norepinephrine inhibitor, has been shown to be superior to placebo for reducing binge eating in patients with BED [90]. Additionally, dasotraline is a novel norepinephrine and dopamine reuptake inhibitor being evaluated in ADHD and BED [91]. Dasotraline has been shown to be superior to placebo for reducing binge eating in individuals with BED in two RCTs that have been presented at scientific meetings but not yet published [92, 93]. However, in a preclinical study, the α-2A

adrenergic receptor agonist guanfacine increased binge-eating like behavior [94].

In addition to dasotraline, other drugs are in development for the treatment of ADHD [95]. Though many of these compounds are derivatives of methylphenidate or D-amphetamine, novel agents include a controlled-release form of the serotonin norepinephrine dopamine reuptake inhibitor mazindol [96], an extended-release formulation of metadoxine, an ion-pair salt of pyridoxine and 2-pyrrolidone-5-carboxylate [97], the 5-HT1A/1B partial agonist eltoprazine [98, 99], and the metabotropic glutamate receptor activator fasoracetam [100]. If any of these compounds reach the market, they might also be considered for evaluation in BN, especially if they are associated with decreased appetite or body weight (as are mazindol [96] and eltoprazine [99]).

6 Serotonin 5-HT3 Receptor Antagonists

Faris et al. [101] conducted a 4-week randomized, placebo-controlled trial of the potent and selective antagonist of the 5-HT3 receptor ondansetron in 26 women with severe BN. Ondansetron 4 mg ($n = 14$), which was self-administered in capsules up to six per day upon the urge to binge eat or vomit, was associated with a significantly greater decrease in frequency of binge eating/vomiting episodes ($p < 0.001$) and with a significant increase in normal meals consumed ($p < 0.03$) compared with placebo ($n = 12$). Ondansetron was also associated with significant improvement in the time spent engaging in bulimic behaviors ($p < 0.05$). There was no difference in weight change between groups. Despite the positive findings of this RCT, we were unable to locate any other RCTs of ondansetron or other 5-HT3 receptor antagonists in the treatment of patients with BN (or BED).

7 Weight-Loss Drugs

Centrally active weight-loss drugs have received some attention in the treatment of BN and BED, probably because of the phenomenological similarities between binge eating and increased hunger and/or reduced satiety [47] as well as the strong relationship of both disorders with obesity [1]. This includes studies of drugs removed from the market for safety concerns as well as available weight-loss agents [102].

Regarding drugs that are no longer available, three RCTs of fenfluramine or its isomer dexfenfluramine were conducted in individuals with BN. In one study, fenfluramine was compared with desipramine in a 15-week randomized, placebo-controlled crossover trial in 22 patients with BN [103]. Both drugs reduced the frequency of binge-eating and vomiting episodes, but a numerically greater proportion of patients responded to fenfluramine than to desipramine. In another study, 42 patients with BN were randomized to receive dexfenfluramine or placebo for 12 weeks [104]. Dexfenfluramine produced significantly greater decreases in binge eating and self-induced vomiting than placebo. In the third trial, dexfenfluramine plus CBT was not superior to placebo plus CBT in reducing bulimic or depressive symptoms in 43 women with BN [105]. Dexfenfluramine was also superior to placebo for decreasing binge-eating episodes in one RCT in 28 severely obese women with BED [106]. The SNRI sibutramine produced greater reductions in binge-eating episodes than placebo in three RCTs in patients with BED [107–109]. In addition, the CB1 receptor agonist rimonabant was superior to placebo for decreasing binge eating in one RCT in 289 obese patients with BED [110]. Further evidence that these drugs may reduce binge eating comes from reports of their decreasing binge-like eating in preclinical models [48, 111, 112].

Importantly, available centrally active weight-loss agents are receiving some attention in the treatment of BN and BED. A randomized, placebo-controlled crossover study of phentermine-topiramate combination in 22 participants with BN or BED is ongoing (NCT02553824) [113]. RCTs of bupropion–naltrexone combination (NCT02317744; NCT03539900) and the glucagon-like peptide (GLP)-1 agonist liraglutide 3 mg daily (NCT03279731) are ongoing in individuals with BED. Indeed, open-label reports have described obese patients with BED displaying reductions in binge-eating behavior (and weight loss) in response to treatment with phentermine–topiramate combination [114], bupropion–naltrexone combination [115, 116], and liraglutide 1.8 mg daily [117]. Of note, liraglutide is indicated for type 2 diabetes mellitus at 1.8 mg daily and for weight loss at 3 mg daily [118].

A number of centrally active weight-loss agents are in development; those that come to market might be considered for evaluation in BN (and BED). These agents include GLP-1 receptor analogs other than liraglutide (such as semaglutide and orally active equivalents), the melanocortin-4 receptor agonist setmelanotide, dual-action GLP-1/glucagon receptor agonists (such as oxyntomodulin), the neuropeptide Y antagonist velneperit, amylin mimetics, methionine aminopeptidase-2 inhibitors, combination zonisamide–bupropion, and the serotonin norepinephrine dopamine reuptake inhibitor tesofensine [119, 120].

RCTs of the peripherally active lipase inhibitor orlistat in obese individuals with BED suggest this drug may produce weight loss in such individuals, but its effects on binge-eating behavior have been mixed [121, 122]. It is thus important to note that misuse of orlistat by patients with eating disorders, including those with BN, has been reported [123–126]. These observations suggest peripherally acting weight-loss agents might not be efficacious for BN and might even be associated with the risk of misuse by patients with BN.

8 Hormonal Treatments

Several agents with hormonal properties have received preliminary attention in the treatment of individuals with BN. In a single-dose, placebo-controlled, crossover study, 34 patients with BN, along with 35 patients with anorexia nervosa and 33 healthy control subjects, received intravenous oxytocin 40 IU followed by an emotion recognition task and an apple juice drink [127]. In healthy controls, oxytocin enhanced emotional sensitivity but had no impact on calorie consumption. Patients with anorexia nervosa showed no response on either outcome. In contrast, patients with BN displayed enhanced emotion recognition and a decrease in 24-h caloric consumption. However, whether these findings would generalize to binge-eating behavior remains unknown.

In another study, 46 women with BN were randomized to the antiandrogenic compound flutamide, the SSRI citalopram, flutamide plus citalopram, or placebo for 3 months [128]. Final flutamide and citalopram doses were 500 mg/day and 40 mg/day, respectively. All three active drug groups had superior improvement on a self-rated global assessment of symptom intensity as compared with the placebo group. A comparison of all flutamide recipients versus placebo recipients showed significant reductions in global ratings ($p = 0.03$) and binge eating ($p = 0.02$) but not vomiting. Compared with the placebo group, binge eating was significantly reduced only in the group receiving flutamide plus citalopram ($p = 0.04$); vomiting was not significantly decreased in any group.

In an open-label study, the effects of an antiandrogenic oral contraceptive (drospirenone plus ethinyl estradiol) were evaluated in 21 women with BN and 17 age- and BMI-matched controls [129]. Before treatment, women with BN had a higher frequency of menstrual disturbances, higher acne and hirsutism scores, and higher levels of testosterone but lower meal-related cholecystokinin (CCK) secretion than controls. After 3 months of treatment, meal-related hunger and gastric distention were decreased in women with BN. Meal-related CCK secretion was unchanged in women with BN but decreased in control women. Testosterone and free testosterone were decreased in patients and controls. Frequency of self-induced vomiting decreased during treatment ($p < 0.05$), but binge eating and weight phobia were not significantly changed. Compared with nonresponders, the six (29%) responders had significantly higher levels of total and free testosterone, binge eating, and self-induced vomiting at baseline but lower levels of weight phobia. Reduced frequency of vomiting correlated with reduced testosterone levels ($r = 0.50$, $p < 0.05$). The authors concluded that antiandrogenic oral contraceptives might be a treatment strategy for women with BN and hyperandrogenic symptoms. Importantly, an RCT of this antiandrogenic oral contraceptive in women with BN is ongoing in Sweden (EudraCT number 2011-006099-38).

Finally, a randomized, placebo-controlled trial in 93 women with BN found no effect with spironolactone, a diuretic with mineralocorticoid and aldosterone antagonistic properties [130].

9 Prokinetic Agents

In light of research suggesting an association between BN and gastrointestinal dysfunction, 29 individuals with BN were randomized to receive the prokinetic agent erythromycin up to 500 mg three times daily or placebo for 6 weeks [131]. Treatment with erythromycin showed no beneficial clinical effect: weekly mean ± SD binge-eating/vomit frequencies were 11.4 ± 10.7/11.3 ± 10.9 for patients receiving erythromycin and 7.2 ± 4.1/7.6 ± 4.4 for those receiving placebo.

10 Lithium

In an RCT in 91 patients with BN, lithium (mean level 0.62 mEq/L) was not superior to placebo in decreasing binge-eating episodes [132]. Importantly, there were no serious adverse events. By contrast, case reports have described successful treatment with lithium in patients with BN and comorbid bipolar disorder [133].

11 Antipsychotics

We found no published or ongoing RCTs of antipsychotics in the treatment of individuals with BN. Although the successful use of aripiprazole in the treatment of patients with BN has been described [134, 135], there are also reports of second-generation antipsychotics inducing or exacerbating BN symptoms in patients receiving the drugs for mood or psychotic disorders [136–139].

12 Other Medications

The antispasmodic agent baclofen, a γ-aminobutyric acid (GABA) B receptor agonist sometimes used to treat addictions, reduced binge-like eating of pure fat in one preclinical model [140] but did not reduce binge-like eating in another [49]. In an open-label trial in seven patients with BN ($n = 3$) or BED ($n = 4$), baclofen 60 mg/day for 10 weeks reduced binge eating in five participants (two with BN) [141]. By contrast, a woman with an alcohol use disorder and BN found that alcohol craving but not food craving responded

to high-dose baclofen [142]. In one small crossover RCT in 12 individuals with binge eating, participants were randomized to receive baclofen titrated to 60 mg/day for 48 days followed by placebo for 48 days, or the reverse [143]. Relative to placebo, baclofen produced a small but statistically significant reduction in binge eating frequency and a small but statistically significant increase in depressive symptoms. Of note, patients with BED who do not respond to baclofen 60 mg daily may respond to higher doses up to 180 mg daily [144]. However, such doses of baclofen have been associated with toxicity [145].

Our group conducted a 12-week, open-label trial of N-acetyl cysteine (NAC) in patients with BN [146] because an RCT showed that NAC reduced trichotillomania symptoms (which share some phenomenological overlap with BN symptoms) and was well tolerated [147]. However, we stopped the study after none of the first eight patients responded to NAC and six (75%) patients discontinued the compound prematurely.

BN is often comorbid with post-traumatic stress disorder (PTSD) [148], and the α-1 adrenergic receptor inverse agonist prazosin has been shown to reduce nightmares in patients with PTSD in some [149] but not all studies of PTSD [150]. A small crossover trial evaluating prazosin in ten patients with BN with nightmares due to PTSD is ongoing (NCT02382848). Change in BN symptoms is a secondary outcome.

Several small open-label trials have evaluated (albeit not in patients with BN) the glutamate-modulating agent memantine [151, 152] and the narcolepsy medication sodium oxybate [153] and found reduced binge-eating episodes in patients with BED.

13 Medications Only Evaluated in Preclinical Models of Binge Eating

Several medications have been evaluated only in preclinical models of binge eating. In these studies, the nociceptin receptor antagonist LY2940094 [154], the monoamine stabilizer (−)-OSU6162 [155], the selective 5-HT2C receptor agonist weight-loss agent lorcaserin [111], a GLP-1–estrogen conjugate [156], and selective orexin-1 receptor antagonists [157, 158] all reduced binge-like eating behavior. In contrast, the benzodiazepine midazolam increased high fat intake [48] and guanfacine increased binge-like eating [94].

14 Conclusions

Research into the pharmacotherapy of BN has substantially lagged behind that into most other serious psychiatric disorders. Indeed, only one medication has regulatory approval for the treatment of BN, no drug has been specifically developed for the treatment of BN, relatively few drugs have been studied in BN (Table 1), and we located only seven ongoing medication trials in individuals with BN (Table 2). Moreover, many of the published pharmacotherapy studies in BN have limitations, including small sample size, inadequate power to detect effects, and unclear generalizability of findings to real-world clinical situations.

Some preliminary conclusions about the state of BN pharmacotherapy can nonetheless be made. Substantial evidence indicates SSRIs and antidepressants from several other classes are modestly efficacious for BN acutely and possibly over the long term [22]. Though antidepressants

Table 1 Qualitative overview of compounds evaluated in randomized controlled trials in individuals with bulimia nervosa or binge eating disorder

Drug	Efficacy in BN	Ongoing study in BN	Efficacy in BED	Ongoing study in BED
Fluoxetine	+++	Yes	++	No
Other ADs	+++	No	+++	Yes
Topiramate	+++	No	+++	No
Zonisamide	+	No	++	No
Lamotrigine	+	No	−	No
Lisdexamfetamine dimesylate	ND	Yes	+++	No
Atomoxetine	ND	No	++	No
Dasotraline	ND	No	+++	Yes
Naltrexone/naloxone	+/−	Yes	+/−	No
Erythromycin	−	No	ND	No

ADs antidepressants, *BED* binge eating disorder, *BN* bulimia nervosa, *ND* no data, *RCTs* randomized controlled trials, +++ indicates two or more positive RCTs, ++ indicates one positive RCT, + indicates positive open-label study or case reports, +/− indicates that data are largely mixed, − indicates only negative controlled data

Table 2 Pharmacotherapy studies ongoing in individuals with bulimia nervosa

Compound	Registration #	Study description
Lisdexamfetamine dimesylate	NCT03397446	Open-label, 2-month trial of lisdexamfetamine in adults with BN
Drospirenone–ethinyl estradiol combination	EudraCT 2011-006099-38	Randomized, double-blind, placebo-controlled, 3-month study of the effects of drospirenone ethinyl estradiol (an antiandrogenic oral contraceptive) on eating behavior in women with BN
Intranasal naloxone	EudraCT 2016-003107-65	Randomized, double-blind, placebo-controlled trial of intranasal naloxone in women with BN
Phentermine–topiramate combination	NCT02553824	Randomized, double-blind, placebo-controlled crossover trial in individuals with BN or BED
Fluoxetine	NCT03455088	Randomized trial comparing DBT alone, fluoxetine alone, and the combination in individuals with BN
Prazosin	NCT023822848	Randomized, double-blind, placebo-controlled trial of prazosin in patients with BN experiencing nightmares due to PTSD
SSRIs	NCT02359513	Evaluation of the efficacy of serotonergic antidepressants in BN according to brain serotonin profile determined by positron emission tomography with [18F] MPPF

BED binge eating disorder, *BN* bulimia nervosa, *DBT* dialectical behavior therapy, *PTSD* post-traumatic stress disorder, *SSRIs* selective serotonin reuptake inhibitors

probably do not enhance the efficacy of CBT for BN, RCTs have shown that fluoxetine may be used effectively in the primary care setting and when response to psychotherapy is inadequate [36, 159]. An important RCT is ongoing to see whether the SSRI fluoxetine enhances the efficacy of DBT in patients with BN (NCT03455088).

Substantial evidence suggests that the antiepileptic drug topiramate may also be efficacious for BN [41–43], though the amount of supporting evidence is much smaller than that for antidepressants. The considerable amount of double-blind, placebo-controlled data showing that LDX reduces binge-eating behavior in BED suggests this agent (and maybe other stimulants) might be efficacious for individuals with BN, a possibility supported by a growing number of positive case reports of stimulants in patients with BN. Of course, the safety of stimulants in individuals with BN will need to be carefully assessed. An ongoing RCT of intranasal naloxone in women with BN (EudraCT number 2016-003107-65) will hopefully help clarify the role opioid antagonists may have in treating BN. Further RCTs of 5-HT3 receptor antagonists in BN are needed to see whether the one small positive study of ondansetron [101] can be replicated. Extremely preliminary data suggest RCTs of oxytocin and antiandrogenic compounds in individuals with BN may also be fruitful. Preclinical models suggest nociceptin receptor antagonists, lorcaserin, monoamine stabilizers, and selective orexin-1 receptor antagonists may have therapeutic effects in binge-eating behavior. Finally, some medications appear to be ineffective for BN (e.g., lithium, prokinetics, and spironolactone) or may even exacerbate it (second-generation antipsychotics), though further research is needed.

14.1 Future Directions

Further pharmacotherapy research into BN is greatly needed at many levels. At a basic level, greater understanding of the pathophysiology and genetic architecture of BN is needed, and preclinical models of binge eating need further refinement and development, especially regarding which models are most predictive of medication response in individuals with BN. At a clinical level, and similar to what has been done in other major mental disorders, RCTs are needed that explore strategies where medications are optimized, switched, augmented, or combined. Thus, studies of topiramate in combination with antidepressants or psychological treatments would be important in patients with treatment-resistant or chronic forms of BN, as has been reported for BED [46, 160]. In addition, studies are needed in patients with BN who have clinically important comorbidities, such as major depressive disorder, bipolar disorder, anxiety disorders, substance use disorders, and self-injurious behavior [161], as well as patients with co-occurring obesity and obesity-related medical conditions (e.g., diabetes).

Perhaps most importantly, new efficacious compounds need to be identified for treating individuals with BN. Available drugs that hold promise for BN and merit evaluation in RCTs include stimulants and the nonstimulant ADHD medication atomoxetine; SNRIs and newer antidepressants (e.g., vilozidone and vortioxetine); the antiepileptic drugs zonisamide and cannabidiol; and drugs approved for long-term

weight loss, including the 5-HT2C receptor antagonist lorcaserin, naltrexone–bupropion combination, phentermine–topiramate combination, and liraglutide 3 mg daily [118]. For most compounds, especially those associated with weight loss, both abuse liability and effects on body weight will need to be carefully monitored. Fortunately, a trial of phentermine–topiramate combination is ongoing in individuals with BN or BED (NCT02553824), as are trials of bupropion–naltrexone combination (NCT02317744; NCT03539900) and liraglutide 3 mg/day (NCT02379731) in individuals with BED.

Novel compounds that might be repurposed for BN include some of those in development for other conditions, such as ADHD, mood disorders, addiction, obesity, and epilepsy. Thus, preliminary data suggest the norepinephrine-dopamine reuptake inhibitor dasotraline is efficacious in individuals with BED [92, 93]. Agents being developed for depression that might be repurposed for BN include glutamatergic modulators, AVP-786 (deuterium-modified dextromethorphan hydrobromide in combination with very-low-dose quinidine sulfate), AXS-05 (dextromethorphan plus bupropion), brexanolone, and serotonin-norepinephrine-dopamine (triple) reuptake inhibitors, among others [34]. Brexanolone is an interesting treatment option because BN and BED are associated with symptoms of post-partum depression in adult women [162], and—like post-partum depression—BN is associated with abnormal neurosteroid levels [163]. Compounds being developed for obesity that might have therapeutic effects in BN include triple reuptake inhibitors (e.g., tesofensine), GLP-1 receptor agonists beyond liraglutide (e.g., semaglutide), melanocortin-4 receptor agonists (setmelanotide), dual-action GLP-1/glucagon receptor agonists, neuropeptide Y5 receptor inhibitors, leptin receptor agonists (metreleptin), cannabinoid receptor antagonists beyond rimonabant; and the combination of bupropion with zonisamide [119]. Combination zonisamide–bupropion might be a particularly interesting option for individuals with BN, given bupropion's efficacy in BN [23] and zonisamide's antiepileptic activity and efficacy in BED [58].

Yet other drugs that might be repurposed for BN include those in development for human conditions characterized by hyperphagia, such as Prader–Willi syndrome and hypothalamic obesity [164]. Examples of latter compounds include the K ATP agonist diazoxide choline (NCT03440814; NCT02034071), the melanocortin-4 receptor agonist setmelanotide (NCT02311673), the combination of tesofensine and metoprolol (NCT03149445), and GLWL-01 (which reduces circulating levels of acetylated ghrelin) (NCT03274856).

Finally, for pharmacotherapy research in BN to truly advance, it will need to be made a national and global priority. Such an advance will require collaborations among academia, the pharmaceutical industry, and governmental agencies. One goal would be to foster public–private partnership programs devoted to developing potential therapeutic compounds specifically targeting BN, as has been done by the National Institute of Mental Health for mood, anxiety, and psychotic disorders [165]. Another goal would be to form a network of sites devoted to conducting RCTs in BN similar to the networks that have been successful in conducting RCTs in mood and psychotic disorders [166–168].

In sum, pharmacotherapy has an important role in the management of BN, especially in patients who refuse or are unresponsive to psychotherapy, patients with comorbid psychiatric or medical disorders, and those with chronic or intractable BN. However, the available pharmacotherapeutic armamentarium and its supporting evidence base for BN are far from adequate. Further study is needed to clarify which available agents might be most useful for which BN patient subgroups and to identify agents with novel mechanisms of action in BN. In particular, rational drug discovery devoted to BN needs to occur. In the meantime, current and future medications with psychotropic benefits and/or effects on appetite and weight might be considered as potential therapeutic agents that may be repurposed for this condition.

Compliance with Ethical Standards

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Ethical Approval All procedures performed in studies involving human participants, to the best of our knowledge, were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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