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Safety of pharmacotherapy options for bulimia nervosa and binge eating disorder

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Abstract

Introduction: Eating disorders represent a set of psychiatric illnesses with lifelong complications and high relapse rates. Individuals with eating disorders are often stigmatized and clinicians have a limited set of treatment options. Pharmacotherapy has the potential to improve long term compliance and patient commitment to treatment for eating disorders.

Areas Covered: This review will examine the efficacy and safety profile of the FDA-approved medications for the treatment of bulimia nervosa (BN) and binge eating disorder (BED). This will include the evaluation of fluoxetine for BN, and lisdexamfetamine for BED. Safety information will be reviewed from randomized control trials (RCT), open label trials, and case reports.

Expert Opinion: Fluoxetine for BN and lisdexamfetamine for BED are relatively safe and well-tolerated. Despite these properties, these two medications represent a limited arsenal for the pharmacological treatment of eating disorders. Thus, more research-based strategies are needed to develop safe, effective, and more targeted therapies for eating disorders.

1. Introduction

Eating disorders, such as binge eating disorder (BED), bulimia nervosa (BN) and anorexia nervosa (AN), are a set of psychiatric illnesses that are often stigmatized as a lifestyle choice and their pathologies are frequently trivialized^{1, 2}. Indeed, clinicians with limited experience in treating eating disorders often express negative attitudes towards eating disorder patients³. In addition, eating disorders are commonly underdiagnosed⁴. Such misguided perceptions regarding patients struggling with eating disorders can adversely impact disease progression and successful treatment outcomes^{2, 3}. In the United States, there is some debate over the exact prevalence and full characterization of disordered eating pathologies in adults. However, one large-scale population based study, which is often cited, estimates the prevalence to be 0.6% for AN, 1.0% for BN, and 2.8% for BED⁵. Women are more at risk

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and midlife women have an estimated lifetime prevalence of 15.3% for an eating disorder^{5, 6}. These aspects, as well as the comorbidity of eating disorders with other psychiatric illnesses, can present challenges for the successful long term management of eating disorders.

Cognitive behavioral therapy (CBT), as well as intrapersonal therapy (IPT), are considered standard effective therapies for eating disorders⁷⁻⁹. Like other psychiatric disorders, interdisciplinary approaches for treating eating disorders are often combined with pharmacotherapy¹⁰. However, there is some debate as to whether combining CBT with pharmacotherapy improves treatment effectiveness for managing certain eating disorders or improving treatment outcomes¹¹. For AN, there is strong evidence to suggest that the addition of fluoxetine or other selective serotonin reuptake inhibitor (SSRI) antidepressants to a CBT regimen does not provide an additional therapeutic benefit beyond CBT^{12, 13}. Nonetheless, further studies are needed to determine whether antidepressants or other medications alone could be beneficial for the management of AN¹⁴. Currently, there is no FDA-approved medication for the treatment of AN. For BN and BED, however, the use of pharmacotherapy with or without psychotherapy offers the potential for more opportunities for the treatment of certain individuals. Moreover, pharmacotherapy alone could offer more avenues for successful long term management of BN or BED. One reason is convenience in treatment. That is, pharmacotherapy alone does not require intense psychotherapy training for the treating health care professional or regularly scheduled time commitment by the eating disorder patient¹⁰. In addition, pharmacotherapy can reduce the perceived stigma associated with BED and BN because other psychiatric illnesses are also conventionally treated with pharmacotherapy^{10,15,16}. While the efficacy of CBT or IPT for eating disorders can be debated, these treatment options are safe with long term adherence¹⁷. As pharmacotherapy options are being increasingly used to treat BN and BED, it becomes necessary to evaluate the safety of these available medications. This review includes the safety evaluation of the FDA-approved treatments for BN and BED, fluoxetine and lisdexamfetamine, respectively. Although there are some medications that are used “off-label” to treat eating disorders, the FDA-approved medications should be the first choice of consideration for pharmacotherapeutic options. Thus, this review is limited to FDA-approved medications for eating disorders. This evaluation will include data from randomized control trials (RCT), open label trials, and case reports.

1.1 Fluoxetine for the treatment of BN

Fluoxetine hydrochloride is a racemic mixture ($\pm$)-N-Methyl- γ -[4-(trifluoromethyl)phenoxy] benzenepropanamine hydrochloride that was developed by Eli Lilly and company in 1972 as a putative analgesic based on the serotonergic actions of the compound^{18,19}. Several *in vivo* studies revealed it had a potent antidepressant profile as a SSRI compared with other known antidepressant compounds^{18,20,21}. Fluoxetine was FDA approved for the treatment of major depressive disorder in 1987, and is also approved for obsessive compulsive disorder and acute treatment of panic disorder with or without agoraphobia²². Fluoxetine was approved for acute treatment and maintenance of BN in 1994. The effectiveness of fluoxetine to treat BN has been determined by several randomized placebo-controlled studies²³⁻²⁵. A multi-center study conducted by Fluoxetine Bulimia Nervosa

Collaborative Study Group of BN women (n = 387) assessed bingeing and vomiting frequency following an 8-week course of fluoxetine (20 mg/day and 60 mg/day) compared with placebo²³. Fluoxetine (60 mg/day) effectively reduced binge eating and vomiting episodes per week for the first 7 weeks. From the last observation carried forward analysis, fluoxetine (60 mg/day) reduced binge eating episodes by 67% and vomiting episodes by 56% from pretreatment, whereas placebo resulted in a 33% reduction in binge eating and 5% reduction in vomiting episodes. The lower dose fluoxetine (20 mg/day) only produced a significant reduction in vomiting, which was a 26% reduction from pretreatment²³.

Another multi-center study by Goldstein and colleagues evaluated fluoxetine (60 mg/day) compared with placebo over a 16-week time period in BN subjects (n= 398; 96.2% women)²⁴. Similar to the 8-week study conducted by Fluoxetine Bulimia Nervosa Collaborative Study Group of BN women²³, the 16-week fluoxetine demonstrated a significant 50% decrease in binge eating and vomiting episodes from pretreatment compared with only 18% decrease in binge eating and 21% in vomiting from pretreatment with placebo²⁴. However, when BN subjects were classified as responders (a treatment-induced reduction in binge eating and vomiting by ≥ 50%) or non-responders (a treatment-induced reduction in binge eating and vomiting by < 50%), fluoxetine was twice as effective for treating BN as placebo in responders²⁴.

The long-term maintenance of controlling BN relapse with fluoxetine (60 mg/day) was examined in a 52-week randomized trial by Romano and colleagues²⁵. Before beginning the 52-week trial, all BN subjects (n = 232) were classified as responders or non-responders after an 8-week acute treatment with fluoxetine (60 mg/day). Only responders during the 8-week pretreatment period were randomized into placebo (n = 73 females and 1 male) and fluoxetine (n = 74 females and 2 males) groups to participate in the 52-week trial²⁵. At 3 months, there was a statistically significant decrease in relapse to bulimic behaviors (or discontinuation rate) between the fluoxetine (19%) and placebo (37%) groups (p< 0.04). Similar rates between treatments were observed at 6 months and 12 month, but they were not statistically different²⁵. The effectiveness of fluoxetine for treating BN in other comparisons, such as with or without CBT and compared with other SSRI medications, have been reviewed elsewhere²⁶. Overall, these studies demonstrate that fluoxetine is effective for treating BN and can improve relapse outcomes in patients.

1.2 Pharmacokinetics and metabolism of fluoxetine

Fluoxetine undergoes N-demethylation to produce the active metabolite norfluoxetine. Following a single oral dose of fluoxetine (40 mg) in a pharmacokinetic study of 25 adult males, the maximum plasma concentration (T_{max}) of fluoxetine occurred at 5.0 ± 1.7 h and at 76.0 ± 18.1 h for norfluoxetine²⁷. The half-life ($t_{1/2}$) of fluoxetine was 3.62 ± 2.93 days (ranged from 1–13 days) and the plasma clearance (Cl_p) of fluoxetine was 93.9 to 703.5 ml/min²⁷. The $t_{1/2}$ and Cl_p of norfluoxetine was longer than fluoxetine²⁷. The $t_{1/2}$ of norfluoxetine has been estimated to be 16 days and contribute to the long-term treatment efficacy of fluoxetine²⁸. The single dose pharmacokinetics of fluoxetine or norfluoxetine were not different between subjects with impaired renal function receiving dialysis and those of healthy controls²⁷.

An assessment of plasma levels of fluoxetine and norfluoxetine after 8 weeks of treatment in BN subjects (n= 59) revealed an association with reducing bulimia pathology ($r^2 = 0.48$, $p < 0.00001$ for fluoxetine and $r^2 = 0.38$, $p < 0.00001$ for norfluoxetine)²⁹. There were no associations between plasma concentrations of fluoxetine and norfluoxetine and adverse events²⁹.

1.3. Safety profile of fluoxetine in BN

In the Fluoxetine Bulimia Nervosa Collaborative Study Group of BN women the most commonly reported adverse events was insomnia in the 20 mg fluoxetine (17.8%; 23 out of 129 subjects) and 60 mg fluoxetine (23.2%; 30 out of 129 subjects) groups that were significantly different ($p < 0.001$) from placebo (7.8%; 10 out of 129 subjects). Tremor was also reported in 20 mg fluoxetine (3.1%; 4 out of 129 subjects) and 60 mg fluoxetine (9.03%; 12 out of 129 subjects) that were significantly when compared with placebo (0%; 0 out of 129 subjects). Discontinuation in the study due to treatment-emergent adverse events (TEAE) was less than 5%²³.

In the 16-week multicenter study conducted by Goldstein and colleagues there were a several more reported adverse events with fluoxetine (60 mg) that were significantly ($p < 0.05$) different from placebo, which included insomnia (34.5% with fluoxetine vs. 18.6% with placebo), nausea (30.4% with fluoxetine vs. 12.7% with placebo) asthenia (21.3% with fluoxetine vs. 6.9% with placebo), anxiety (17.6% with fluoxetine vs. 8.8% with placebo), tremor (14.2% with fluoxetine vs. 2.0% with placebo), dizziness (12.5% with fluoxetine vs. 3.9% with placebo), yawning (12.2% with fluoxetine vs. 0% with placebo), sweating (9.5% with fluoxetine vs. 2.0% with placebo), and decreased libido (6.4% fluoxetine vs. 1.0% with placebo). Discontinuation rates caused by any TEAE were similar for fluoxetine (10.8%) compared with placebo (5.9%)²⁴.

In the 52-week randomized trial by Romano and colleagues that exclusively used responders, rhinitis was the only TEAE that was significantly different between fluoxetine (31.6%) and placebo (16.2%)²⁵. In addition, unintended pregnancy (2.6% in fluoxetine vs. 4.1% in the placebo groups) was most often cited adverse event leading to discontinuation. However, discontinuation rates were not significantly different between fluoxetine and placebo treatment groups²⁵.

Decreased libido and anorgasmia are potential TEAE associated with fluoxetine^{22,30}. Two case reports have indicated that use of cryptoheptadine, an antihistamine with serotonergic actions and often used to treat sexual dysfunction, can reverse the fluoxetine-induced suppression of bulimic symptoms³¹. Indeed, two BN patients receiving fluoxetine (60 mg/day) had resolution of anorgasmia shortly following treatment with cryptoheptadine (4 mg/day and 8 mg/day), but had a relapse or recurrent binge episodes. In both patients, cessation of bulimic symptoms was restored after the discontinuation of cryptoheptadine³¹. Cryptoheptadine was not recommended for the potential fluoxetine-associated sexual dysfunction^{30,31}.

1.4 Lisdexamfetamine dimesylate for the treatment of BED

Lisdexamfetamine dimesylate is a prodrug that has L-lysine conjugated to dextroamphetamine. The trade name for lisdexamfetamine dimesylate is Vyvanse and is manufactured by Shire Pharmaceuticals. In the United States, the FDA approved Vyvanse for the maintenance of attention deficit hyperactive disorder (ADHD) in 2007 for children (6–12 years old) and in adults in 2008. In 2015, lisdexamfetamine was approved by the FDA as the only medication available for the maintenance of moderate to severe BED. Efficacy for BED was determined by a phase II and two phase III studies^{32, 33}.

The phase II trial consisted of a multicenter randomized, placebo-controlled trial of BED subjects ($n = 260$; 81.5% female)³³. Subjects that were randomized to lisdexamfetamine underwent a 3-week forced-dose titration period that was initiated with 30 mg/day and uptitrated in increments of 20 mg/day per week (i.e., 50 mg/day or 70 mg/day). This was followed by an 8-week maintenance dose period with each group receiving a fixed single dose of lisdexamfetamine (30 mg/day, 50 mg/day or 70 mg/day). There was a significant ($p < 0.005$) reduction in binge frequency at study completion (at end of week 11) in BED subject receiving 50 mg/day (-4.1 mean binge eating/week from baseline) and 70 mg/day (-4.6 mean binge eating/week from baseline) compared with placebo (-3.3 mean binge eating/week from baseline). The 30 mg/day (-3.5 mean binge eating/week from baseline) dose of lisdexamfetamine was not different from placebo³³. The phase III trials were randomized placebo-controlled multicenter studies that had a 3-week dose optimization with an 8-week maintenance. BED subjects ($n = 383$, for study 1; $n = 390$ for study 2) received 50 mg/day or 70 mg/day lisdexamfetamine based on their tolerability during 3-week dose optimization period. At study completion (week 11–12), lisdexamfetamine resulted in a significant mean reduction in binge eating for both studies ($p < 0.001$). Specifically, binge eating days/week were reduced from baseline in lisdexamfetamine (-3.87 for study 1 and -3.92 for study 2) compared with placebo (-2.51 for study 1 and -2.26 for study 2)³².

A 12-month open label extension study of lisdexamfetamine treatment was conducted in BED subjects ($n = 599$; 87% female) from Phase II and Phase III trials³⁴. The mean duration of lisdexamfetamine exposure was 284.3 days (± 118.84 days, SD) and the optimal dosing was 29.9% for 50 mg/day and 64.9% for 70 mg/day. At week 52, subjects had 1.14 (± 2.92 , SD) binge eating days for the past 28 days with lisdexamfetamine compared with 16.68 (± 6.84 , SD) binge eating days at pre-treatment baseline³⁴.

A randomized placebo-controlled 26-week study was conducted in lisdexamfetamine responders in women with BED ($n = 275$). The determination of lisdexamfetamine responders was defined as 1 binge eating day per week for 4 consecutive weeks in a 12-week open-label screening trial. Of 418 BED subjects that began the screening trial, only 275 BED subjects were eligible for 26-week placebo controlled study. The primary endpoint was time to binge-eating relapse. The relapse rate for lisdexamfetamine was 3.7%, whereas the relapse rate was 32.1% in the placebo group. At 30 days following the 12-week open label screening (i.e., post-randomization) 24.4% of the placebo group met the criteria for relapse³⁵.

1.5 Pharmacokinetics and metabolism of lisdexamfetamine dimesylate in BED.

The clinical efficacy of lisdexamfetamine is dependent on the conversion of d-amphetamine. A time course pharmacokinetics study in adults with a clinical diagnosis of ADHD (n = 24; 66.67% were men) was conducted after 5 week treatment of lisdexamfetamine. The mean dose of lisdexamfetamine was 62.5 mg/day (± 14.2 mg/day) on the day of dosing and plasma levels of lisdexamfetamine were assessed at regular intervals at 12 hours post-dosing. Plasma levels of lisdexamfetamine peaked at 1.5 hours (T_{max}), but were undetectable 6 hours post-dosing. Based on the time course of lisdexamfetamine presence in the plasma, the C_{max} was 25.0 ng/ml and the $t_{1/2}$ was 0.5 hours. However, the lisdexamfetamine-derived amphetamine plasma levels had a T_{max} of 4.4 hours, C_{max} of 67 ng/ml and $t_{1/2}$ was 17 hours³⁶. A similar pharmacokinetic profile was observed in an older population of subjects (n=47; > 55 years old) receiving a single dose of lisdexamfetamine (50 mg)³⁷.

A reanalysis of the data from the 12-week phase III trials by McElroy and colleagues determined the time course for the efficacy of lisdexamfetamine for binge eating in BED subjects (n= 724)³⁸. Beginning on week 1, there was significant suppression ($p < 0.01$) of binge eating response in the lisdexamfetamine group. In week 1, there were 3 times more subjects in the lisdexamfetamine that had 100% reduction of binge eating episodes compared with the placebo group³⁸.

1.6. Safety profile of lisdexamfetamine dimesylate in BED

In the phase II trial discontinuation due to TEAE was 3.1% and 1.5% has serious TEAE. One subject in the 70 mg/day group died during the study and toxicological findings indicated methamphetamine overdose³³. The most commonly (> 10% of subjects) reported TEAE were dry mouth, decreased appetite, insomnia, and headache. The most common TEAE, dry mouth, was reported in 7.9% (5 out of 63 subjects) of the placebo, 33.3% (22 out of 66 subjects) of the 30 mg/day, 33.8% (22 out of 65 subjects) of the 50 mg/day, and 41.5% (27 out of 65 subjects) of the 70 mg/day groups³³. At study completion at 11 weeks, all doses of lisdexamfetamine results in body weight loss compared with placebo ($p < 0.001$). Reduction in baseline body weight subtracted from placebo groups were 3.28 ± 0.71 % for 30 mg/day, 5.2 ± 0.72 % for 50 mg/day, and 5.28 ± 0.72 % for 70 mg/day³³. There was a trend for heart rate to increase over the 11 week study, but there were no significant differences in measured hemodynamic parameters (e.g., heart rate, systolic blood pressure, and diastolic blood pressure) over the course of the phase II trial³³.

For the phase III trials, lisdexamfetamine had a similar safety and tolerability profile³². Serious TEAE and TEAE leading to discontinuation were reported at equal frequencies between placebo and lisdexamfetamine groups. Specifically, the common TEAE of dry mouth, headache, and insomnia were reported by > 10% of the subjects receiving lisdexamfetamine. At 12 weeks, there were increases in hemodynamic measures with a 4.41–6.31 bpm increase in heart rate, 0.2–1.45 mm Hg for systolic blood pressure, 1.06–1.83 mm Hg for diastolic pressure in subjects receiving lisdexamfetamine³². An Amphetamine Cessation Symptom Assessment (ACSA) was conducted at baseline (i.e., pre-treatment) at study completion at 12 weeks, and 7 days post-treatment cessation in both the placebo and lisdexamfetamine groups. Scores from ACSA were lower at study termination and 7 days

post-treatment than the baseline period in lisdexamfetamine. There were also no differences in ACSA scores in lisdexamfetamine and placebo groups at any time point, which indicates lisdexamfetamine (50 or 70 mg/day) over a 12- week time period does not result in amphetamine withdrawal symptoms³².

In the open-label 12-month extension trial of the phase II and phase III studies, 2.8% subjects (17 out of 599) subjects has a serious TEAE³⁴. Except for cholecystitis, which was reported by 3 subjects, the serious TEAE were not reported by more than one subject. The number of subjects that had TEAE that lead to study discontinuation was 9% (54 out of 599), insomnia (n = 5), anxiety (n = 4; 2 unrelated to treatment), irritability (n =4), increased blood pressure (n = 3), hypoesthesia (n =2; 1 unrelated to treatment), and rash (n=2). The other TEAE that lead to discontinuation were only reported by 1 subject. Similar to phase II and phase III trials, the common reported TEAE of dry mouth, headache, and insomnia were reported by > 10% of the subjects during the extension. Notably, upper respiratory tract infection was reported as a TEAE in 11.4% (68 out of 599) of the subjects. At the 52 weeks endpoint, there were also electrocardiogram (ECG) changes from baseline in 98.1% subjects (588 out of the 599) subjects. The greatest mean change in heart rate demonstrated on the ECG was 7.26 ± 10.21 bpm (SD) at 36 weeks and the mean change from Freiderica-corrected QT interval at 52 weeks was -2.23 ± 12.97 (SD)³⁴. A reduction in body weight from baseline was observed at week 44 (-8.21%), which was maintained until study completion³⁴.

In the 26-week time to relapse study in lisdexamfetamine responders only 2 serious TEAE in lisdexamfetamine group (both unrelated to treatment) were reported ³⁵. There was, however, an infant death reported by a subject receiving 70 mg/day dose before it was discovered she was pregnant. Dosing was immediately discontinued. At birth, the infant had 3 serious TEAE (exomphalos, limb malformation, and congenital diaphragmatic hernia). The common TEAE (5% of the subjects) and safety profiles were similar to the 52-week extensions and included dry mouth, headache, insomnia, and upper respiratory infections³⁵. During the open-label 12 week phase of the study hemodynamic parameters were elevated from the pre-treatment baseline and subjects had reduction in body weight. There were further increases in systolic blood pressure (+0.9 mm Hg), but a decrease in diastolic blood pressure (-0.35 mm Hg) and body weight (-2.86 kg) at the 26-week time point. There were no changes in heart rate comparing the 12-week open label phase and at the end of the 26-week randomization phase in the lisdexamfetamine group³⁵. At the completion of the study at 26 weeks there were also no differences in ACSA scores between the lisdexamfetamine and placebo groups³⁵.

Based on the conversion of lisdexamfetamine to amphetamine and potential for abuse and dependence, the Drug Enforcement Agency (DEA) has classified lisdexamfetamine dimesylate as a Schedule II controlled medication³⁹. The abuse potential and safety of lisdexamfetamine was compared with amphetamine and amphetamine derivative in a double-blind cross-over study (n = 36)⁴⁰. For the study, subjects were given single doses of placebo, lisdexamfetamine (50 mg, 100 mg, and 150 mg), d-amphetamine (40 mg) and diethylpropion (200 mg), a Schedule IV amphetamine derivative. Each dose was tested in 48 h period (24 h test day/ 24 h wash-out) and assessments were conducted at baseline and at

regular intervals post-dosing (11 intervals over 24 hours). Abuse potential was assessed by subjective scoring of the Liking Scale of the Drug Rating Questionnaire-Subject (DRQS), objective assessment by the Drug Rating Questionnaire-Observer (DRQO), and Addiction Research Center Inventory (ARCI)⁴⁰. For the DRQS, there was an approximate 2- fold change in scoring of lisdexamfetamine (50 mg and 100 mg compared with placebo, but these changes were not significant. Liking scoring of lisdexamfetamine was only significantly different from placebo at 150 mg dose ($p < 0.01$). In contrast, amphetamine and diethylpropion showed > 4 fold change in liking scoring from placebo ($p < 0.01$) and both medications had significantly higher scores from the 50 mg and 100 mg lisdexamfetamine ($p < 0.05$ for both)⁴⁰. Results were similar for the DRQO assessment, in that amphetamine, diethylpropion, and lisdexamfetamine (150 mg) were rated significantly higher than placebo ($p < 0.05$). One difference from the DRQS was that 100 mg lisdexamfetamine was rated significantly higher than placebo ($p < 0.05$). For the ARCI, lisdexamfetamine (100 mg and 150 mg) were significantly higher than placebo for measures of the inventory ($p < 0.05$), but the 50 mg dose was significantly lower than amphetamine ($p < 0.05$)⁴⁰. Taken together, the data suggest that at the 50 mg dose, lisdexamfetamine has low abuse potential.

Respiratory-related adverse effects, such as dry mouth, upper respiratory tract infections, and nasopharyngitis, have been reported after long-term treatment with lisdexamfetamine, but these have been reported to be mild or moderate in their severity^{34, 35, 39}. A case report of a 49- year old male details the development of high altitude pulmonary edema (HAPE) shortly after starting a regimen of lisdexamfetamine (20 mg/day) for ADHD⁴¹. Respiratory distress began after 3 days of high altitude. The case is remarkable because the male is an avid mountain climber with 27 previous high altitude excursions ($> 30,048$ m above sea level), but this was his first excursion since beginning lisdexamfetamine. Sympathomimetic amphetamine actions leading to pulmonary vasoconstriction was the suspected mechanisms of action for lisdexamfetamine-induced HAPE⁴¹.

2. Conclusion

Several obstacles exist for the treatment of eating disorders, such as BN and BED. One obstacle is patient compliance with treatment. The goal of pharmacotherapy is to improve eating disorder pathology outcomes and increase patient compliance with long-term treatment. Both FDA-approved medications, fluoxetine and lisdexamfetamine, are overall safe medications with few treatment-emergent adverse effects. The most commonly reported adverse effect in BN patients being treated with fluoxetine appears to be insomnia. Fluoxetine, however, does not have an abuse potential. Lisdexamfetamine has a few more associated adverse events, including dry mouth, headache, and insomnia. There are also increases in heart rate and blood pressure that are positively associated with longer length of treatment. Lisdexamfetamine does have an abuse potential and is a schedule II classification by the DEA. Lisdexamfetamine and fluoxetine both have a FDA pregnancy category C, which means the risks of the medication to unborn child have not been systematically studied and the risks are unknown. Nonetheless, the current pharmacotherapeutic options are safe and tolerable and do have the potential to help manage eating pathologies for some individuals.

3. Expert opinion

Currently, pharmacotherapy options for eating disorders are limited. Rather than developing novel therapeutic options, medications for other psychiatric illnesses are expanding their indications (“repurposing”) to include treatment of eating disorders. While BN and BED have benefited from repurposing existing FDA-approved medications, this approach could be potentially beneficial for finding a pharmacotherapy for AN. Specifically, olanzapine and other second generation antipsychotics have the TEAE of weight gain. Hence, there has been interest in determining whether these medications can be indicated for the weight gain of AN patients⁴². Several case reports and a few open-label trials suggested that the antipsychotic, olanzapine, has therapeutic potential pharmacotherapy for AN^{43–45}. However, in a meta-analysis of RCT of second generation antipsychotics (7 studies, n= 201) to treat AN, there were no differences in weight gain or AN symptoms with the second generation antipsychotics (4 trials olanzapine, 2 quetiapine, and 1 risperidone) compared with the placebo-treated group⁴⁶. For BN and BED, the two medications, fluoxetine and lisdexamfetamine, are generally safe and well-tolerated for certain populations. Fluoxetine has the added benefit of reducing depressive symptoms for some patients with a comorbidity of BN and major depressive disorder episodes²⁴. Attention and impulsive behaviors are also improved with lisdexamfetamine^{36, 39}. Some BN and BED patients do not reduce binge eating behaviors or related behaviors with fluoxetine or lisdexamfetamine treatment, respectively, and are classified as “non-responders”. Because there is no other FDA-approved medication for BN or BED, non-responders have to undergo CBT or other forms of psychotherapy for treatment or relapse. The single option approach for treating BN with fluoxetine or BED with lisdexamfetamine is a major limitation for advancing the use and development of pharmacotherapy options for eating disorders.

Eating disorders are often stigmatized as not being serious psychiatric disorders^{1–3}. Despite the increased mortality and increased risk of suicide associated with AN, there is still a trivialization of eating disorders.^{47, 48} Recent attempts to broaden the criteria for binge eating and to classify BED in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), has helped to shift the clinical perspective on the seriousness of eating disorders⁴⁹. The general public perspective, however, needs to be changed. The popularity of competitive speed eating, the overuse of the term “binge” by advertisers, and the focus on body image by social media contributes to an environment of endorsing disordered eating behavior. It is also important to note that the current FDA-approved medications for eating disorders fluoxetine and lisdexamfetamine were originally approved for other psychiatric disorders. As such, BN patients wonder why they are being treated with the antidepressant fluoxetine, since they do not endorse a diagnosis of depression. Likewise, BED patients wonder why they are being treated with attention-deficit medication, lisdexamfetamine. One approach that can minimize or reduce the BN or BED perspective of “repurposing” is through patient education and discussion of the mechanisms of action of the medication and how it relates to the pathology. Taken together, the reason why eating disorders are stigmatized, trivialized, and treated with “repurposed” medications, is simply because we do not have a comprehensive understanding of the neurobiology of eating disorders. Nonetheless, “repurposed medications” offer immediate benefits for the afflicted

patient. More clinical and basic science research is needed to understand the neurobiology of sustaining eating pathologies, as well as develop more specific treatments for eating disorders.

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Article highlights

- Medications for the maintenance of eating disorders, bulimia nervosa (BN) and binge eating disorder (BED), are limited.
- Fluoxetine for BN and lisdexamfetamine for BED are the only FDA-approved medications.
- Insomnia was the most common treatment-emergent adverse event (TEAE) reported with fluoxetine in BN patients.
- Dry mouth, headache, and insomnia, are the most TEAE with lisdexamfetamine in BED. Lisdexamfetamine is also a schedule II DEA controlled medication associated with elevations in heart rate and blood pressure with long term treatment.
- Both medications are generally safe and well-tolerated.
- More medications are needed to treat eating disorders, specifically anorexia nervosa and other eating pathologies.