Lisdexamfetamine for Adults with Binge Eating Disorder

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Citation

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Abstract

Binge eating disorder is a poorly-understood condition with significant physical and psychological comorbidity. Norepinephrine and dopamine dysregulation is implicated in its etiology. Treatment is comprised of psychotherapy and pharmacotherapy with serotonin reuptake inhibitors or anticonvulsants. Lisdexamfetamine is a stimulant which modulates concentrations of norepinephrine and dopamine and was recently approved to treat adults with moderate to severe binge eating disorder. It reduced the frequency of binge eating in short-term studies, and was generally well tolerated. Clinicians should screen for abuse and dependence potential prior to and during treatment, and monitor for adverse effects such as changes in mood, blood pressure or pulse increase, or vasculopathy. Lisdexamfetamine appears to be a promising treatment for adults with binge eating disorder, but longer trials are needed to assess long-term efficacy and safety.

INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition defines binge eating disorder (BED) as consuming an amount of food in a discrete period of time that is definitely larger than what most people would eat in a similar amount of time under similar circumstances, and patients feel they lack control over eating.1 These episodes are marked by at least three of the following: Eating more rapidly than normal, eating until feeling uncomfortably full, eating large amounts of food when not feeling physically hungry, eating alone because of embarrassment by the amount of food consumed, or feeling disgusted with oneself, depressed, or guilty after overeating. The episodes occur, on average, at least once a week for three months in the absence of inappropriate compensatory behaviors and do not occur solely during the course of bulimia nervosa or anorexia nervosa. Severity is classified according to the number of binge eating episodes per week: mild (1-3), moderate (4–7), severe (8-13), or extreme (≥14).

BED has a lifetime prevalence of 1.9 percent and a 12-month prevalence of 0.8 percent, and is more common in women than men, with the median age of onset of approximately 23 years.2 Comorbid psychopathology is common, with 79% of individuals having a lifetime history of at least one other psychiatric disorder, most commonly specific or social phobia, unipolar depression, posttraumatic stress disorder, and alcohol use disorder.3 Although the pathophysiology is not fully elucidated, neuroimaging studies of patients with BED have identified dysregulated, low concentrations of dopamine and norepinephrine which modulate each other.4,5

Psychotherapy is recommended as a first-line treatment for BED.6,7 However, it may not be feasible for some patients due to therapist unavailability, limited financial resources, or time constraints. A review noted that many patients with BED are overweight, and there is limited evidence that psychotherapy results in weight loss.8 For these patients, pharmacotherapy with or without psychotherapy may be indicated. There are a limited number of medications that have shown efficacy in treating BED, as assessed by reduced frequency of binge episodes. A meta-analysis found that serotonin reuptake inhibitors (SRI) were effective and well-tolerated, and the anticonvulsant topiramate demonstrated efficacy.9 For patients who have not responded to or tolerated the above agents, lisdexamfetamine (Vyvanse, Shire) may be an appropriate option.

Although lisdexamfetamine is approved to treat Attention Deficit Hyperactivity Disorder (ADHD), the Food and Drug Administration (FDA) approved it in January 2015 for the treatment of moderate to severe BED in adults. This article reviews mechanism of action, efficacy, adverse effects, dosing, administration, absorption, distribution, metabolism,

excretion, drug-drug interactions, contraindications, FDA warnings, and precautions. A search of MedLine and clinical trials database (clinicaltrials.gov) was conducted for lisdexamfetamine to identify the efficacy and safety trials presented to the FDA for approval.

EFFICACY AND SAFETY

Lisdexamfetamine is a prodrug of dextroamphetamine, which blocks norepinephrine and dopamine reuptake into the presynaptic neuron and increases their concentrations in the synapse. By modulating these neurotransmitters, it decreases the frequency of binge eating. Efficacy and safety were assessed in one Phase 2 and two Phase 3 trials (Table 1). In the Phase 2 trial, adults with BED were randomized to receive either placebo or 30, 50, or 70 mg daily of lisdexamfetamine.10 The primary outcome measure was the number of binge-eating days per week as assessed by clinician interview and confirmed by patient report. Patients in the 50 and 70 mg treatment groups (but not 30 mg) reported a significant decrease in the number of binge eating days compared to those in the placebo group. In the two Phase 3 trials, the treatment groups were started at 30 mg and could be titrated to 70 mg as indicated, with one decrease to 50 mg allowed if needed.11 Patients in all treatment groups reported a significant decrease in the number of binge eating days compared to those in the placebo group.

In all studies, treatment groups experienced weight reduction, but this significance is uncertain. There was also a decrease in triglyceride levels among the treatment groups, but the significance of this is unknown because pre-treatment levels were within normal limits.8

Lisdexamfetamine was generally well-tolerated, with adverse effects including dry mouth, anorexia, insomnia, headache, constipation, jitteriness, nausea, irritability, and fatigue.8,10,11 However, the discontinuation rate was low.

Table 1

Studies of lisdexamfetamine for BED

Study	Study Design	Duration in weeks	*N*	Doses (mg)
McElroy et al.[10]	Randomized, double-blind, placebo-controlled	11	259	30, 50, or 70
McElroy et al.[11]	Randomized, double-blind, placebo-controlled	12	379	50 or 70
McElroy et al.[11]	Randomized, double-blind, placebo-controlled	12	366	50 or 70

DOSING AND METABOLISM

According to the package insert, lisdexamfetamine is available in 10, 20, 30, 40, 50, 60, and 70 mg capsules.12 The recommended starting dose is 30 mg/day, titrated in increments of 20 mg at approximately weekly intervals to achieve the recommended target dose of 50-70 mg/day (maximum dose is 70 mg/day). It is taken by mouth with or without food in the morning to avoid potential for insomnia. The contents may be swallowed whole in the capsule or mixed with yogurt or liquids. Upon ingestion, lisdexamfetamine is rapidly absorbed from the gastrointestinal tract. It is converted to dextroamphetamine and l-lysine primarily by hydrolysis by red blood cells and does not undergo metabolism by cytochrome P450 enzymes.12 The Tmax of lisdexamfetamine was approximately 1 hour, with its dextroamphetamine metabolite reaching Tmax at 3.5 hours. When lisdexamfetamine is coadministered with food, the Tmax is prolonged by approximately 1 hour. Lisdexamfetamine and dextroamphetamine demonstrate linear pharmacokinetics. There was no accumulation of lisdexamfetamine or dextroamphetamine at steady state in healthy adults. Unpublished studies of radioactively-labeled lisdexamphetamine found that metabolites are primarily excreted in the urine, with 42% of the dose related to amphetamine.12

Due to its metabolism by hydrolysis, lisdexamfetamine exhibits no interactions with any drugs metabolized by CYP 450 isozymes and requires no dose adjustments. Acidifying agents decrease the half-life and alkalinizing agents increase the half-life of amphetamine, so prescribers should respectively increase or decrease the dose as clinically indicated.12 Patients with severe renal impairment should not receive more than 50 mg/day, and the maximum dose is 30 mg/day in those with end-stage renal disease. Lisdexamfetamine is not dialyzable.12

CONTRAINDICATIONS AND WARNINGS

Lisdexamfetamine is contraindicated in patients with a known hypersensitivity to amphetamine products or in patients receiving a monoamine oxidase inhibitor (MAOI), or who have received an MAOI dose within 2 weeks.12 In adults, there is a warning for potential abuse, dependence, sudden death, stroke, myocardial infarction, increase in blood pressure and heart rate, mental status changes, and peripheral vasculopathy.12 It is not indicated and should not be prescribed for weight loss or either mild or extreme BED.

PRECAUTIONS

Due to potential for abuse and dependence, lisdexamfetamine is a controlled Schedule II drug in the United States, and clinicians should assess the risk of abuse prior to prescribing and monitor for abuse and dependence during treatment. Clinicians are discouraged from prescribing it to patients with structural cardiac abnormalities, cardiomyopathy, serious arrhythmia, or coronary artery disease.12 Clinicians should monitor blood pressure and pulse, and weigh benefits and risks before prescribing to patients with hypertension. Prescribers should evaluate for symptoms of psychosis or mania prior to prescribing, and observe for digital changes during treatment due to vasculopathy risk. Clinicians should discontinue lisdexamfetamine if binge eating does not improve. They should counsel patients that because lisdexamfetamine affects the central nervous system, patients should determine how the medication affects them prior to operating vehicles or heavy machinery.

Due to the risk of placental constriction and hypoperfusion, premature delivery, low birth weight, and withdrawal symptoms in neonates of mothers dependent on amphetamines, lisdexamfetamine is classified as a Category C drug and should be given to pregnant women only if the benefit of continuing the drug and negative consequences of discontinuation outweigh the above risks.12 Clinicians should discontinue lisdexamfetamine if possible in nursing mothers , unless the benefit from continuing the medication outweighs the risk of transmission to the infant in breastmilk.

CONCLUSION

Binge eating disorder is a condition with significant morbidity, and limited treatment options include psychotherapy, SRIs, and anticonvulsants. Lisdexamfetamine is the only FDA-approved medication to treat BED. It has demonstrated efficacy and tolerability in clinical trials, and while it appears to be a promising treatment for clinicians treating patients with BED, pending trials will determine long term efficacy and safety.

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