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Original Investigation

Efficacy and Safety of Lisdexamfetamine for Treatment of Adults With Moderate to Severe Binge-Eating Disorder
A Randomized Clinical Trial

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IMPORTANCE Binge-eating disorder (BED), a public health problem associated with psychopathological symptoms and obesity and possibly with metabolic syndrome, lacks approved pharmacotherapies.

OBJECTIVE To examine the efficacy and safety of lisdexamfetamine dimesylate, a dextroamphetamine prodrug, to treat moderate to severe BED.

DESIGN, SETTING, AND PARTICIPANTS We performed a randomized, double-blind, parallel-group, forced dose titration, placebo-controlled clinical trial at 30 sites from May 10, 2011, through January 30, 2012. Safety and intention-to-treat analyses included 259 and 255 adults with BED, respectively.

INTERVENTIONS Lisdexamfetamine dimesylate at dosages of 30, 50, or 70 mg/d or placebo were provided to study participants (1:1:1:1). Dosages were titrated across 3 weeks and maintained for 8 weeks. We followed up participants for a mean (SD) of 7 (2) days after the last dose.

MAIN OUTCOMES AND MEASURES We assessed the change in binge-eating (BE) behaviors measured as days per week (baseline to week 11) with a mixed-effects model using transformed log (BE days per week) + 1. Secondary measures included BE cessation for 4 weeks. Safety assessments included treatment-emergent adverse events, vital signs, and change in weight.

RESULTS At week 11, log-transformed BE days per week decreased with the 50-mg/d (least squares [LS] mean [SE] change, −1.49 [0.066]; $P = .008$) and 70-mg/d (LS mean [SE] change, −1.57 [0.067]; $P < .001$) treatment groups but not the 30-mg/d treatment group (LS mean [SE] change, −1.24 [0.067]; $P = .88$) compared with the placebo group. Nontransformed mean (SD) days per week decreased for placebo and the 30-, 50-, and 70-mg/d treatment groups by −3.3 (2.04), −3.5 (1.95), −4.1 (1.52), and −4.1 (1.57), respectively. The percentage of participants achieving 4-week BE cessation was lower with the placebo group (21.3%) compared with the 50-mg/d (42.2% [$P = .01$]) and 70-mg/d (50.0% [$P < .001$]) treatment groups. The incidence of any treatment-emergent adverse events was 58.7% for the placebo group and 84.7% for the combined treatment group. In the treatment groups, 1.5% of participants had serious treatment-emergent adverse effects. Events with a frequency of at least 5% and changes in heart rate were generally consistent with the known safety profile. The mean (SD) change in body weight was −0.1 (3.09), −3.1 (3.64), −4.9 (4.43), −4.9 (3.93), and −4.3 (4.09) kg for the placebo group, the 30-, 50-, and 70-mg/d treatment groups, and the combined treatment groups, respectively ($P < .001$ for each dose vs placebo group comparison in post hoc analysis).

CONCLUSIONS AND RELEVANCE The 50- and 70-mg/d treatment groups demonstrated efficacy compared with the placebo group in decreased BE days, BE cessation, and global improvement. The safety profile was generally consistent with previous findings in adults with attention-deficit/hyperactivity disorder. Further investigation of lisdexamfetamine in BED is ongoing.

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Binge-eating disorder (BED) is gaining recognition as a serious public health problem.[1-5] Binge-eating disorder is associated with obesity and psychiatric comorbidities, including depression, and may be predictive of metabolic syndrome.[1,2,6] Many patients are undertreated despite functional impairments and personal and social difficulties leading to a poor quality of life.[1,4,6,7] Binge-eating disorder is characterized by recurrent episodes of excessive food consumption accompanied by a sense of loss of control (binge eating [BE]) and psychological distress but without the inappropriate compensatory weight-loss behaviors of bulimia nervosa.[6,8] In the *DSM-5,* BED is an official diagnosis,[8] which will likely raise clinical awareness.[9,10]

Cognitive behavioral therapy and/or interpersonal psychotherapy reduces BE behavior, even in patients with severe symptoms and psychopathological features, but implementation has not been widespread, and not all patients respond adequately.[11,12] Antidepressants, including tricyclic agents, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors, reduce the frequency of BE behavior but fail to have substantial weight-loss effects.[3,13,14] Treatment with the antiobesity agent sibutramine hydrochloride demonstrated some efficacy in clinical trials; however, safety concerns led to market withdrawal.[3,14-16] Antiepileptics also have been studied for BED, although they are associated with high rates of discontinuation.[3,17,18] The most extensively studied antiepileptic for BED, topiramate, has efficacy in BE and weight loss, but its use is limited by effects on cognition.[19] At present, no pharmacologic treatments for BED are approved by the US Food and Drug Administration.[3] Additional clinical trials are needed to identify effective pharmacotherapies.

Pathologic overeating may be related to dysfunction of the dopamine (DA) and norepinephrine systems, as evidenced by genetic and pharmacologic findings and animal models.[20-25] Food stimulation generates abnormal DA responses in obese individuals,[26,27] and methylphenidate-mediated inhibition of DA transport leads to greater increases of DA levels within the caudate in obese individuals with BED compared with those without BED.[27]

Agents, such as dextroamphetamine, that inhibit reuptake of DA and norepinephrine and elicit release of monoamine neurotransmitters[28] may alter pathologic BE and be feasible treatment options for BED. Clinical trials designed to assess psychostimulants in adults with BED are needed. Lisdexamfetamine dimesylate is a dextroamphetamine prodrug approved for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children, adolescents, and adults.[29] The aim of the present study was to examine the efficacy and safety of lisdexamfetamine vs placebo in adults with moderate to severe BED, as indicated by at least 3 BE days per week for the 2 weeks before the baseline visit.

Methods

The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice, all local ethical and legal requirements, and the World Medical Assembly (Declaration of Helsinki). The study protocol and procedures were submitted and approved by each site's institutional review board or independent ethics committee. Written informed consent was required for study participation.

This multicenter, randomized, double-blind, parallel-group, forced dose titration, placebo-controlled clinical trial was initiated at 31 US sites and conducted at 28 from May 10, 2011, through January 30, 2012. The median number of enrolled participants per site was 10 (range, 2-22). The overall study duration for each participant was 14 weeks; treatment was administered for 11 weeks. Study sites included clinical research centers, university-affiliated clinics, and psychiatric practices. The study was initiated at a large number of sites in anticipation of recruitment difficulties given that individuals in the population with BED often are not well recognized in clinical settings. Subsequent to study completion, 1 investigator came under investigation for reasons unrelated to this study. Lacking information on the purpose or scope of the investigation, we deemed it prudent to drop this investigator's site from our analyses.

Adults (aged 18-55 years) who met the *DSM-IV-TR* diagnostic criteria[30] for BED were eligible. The diagnosis was confirmed using the eating disorders module (module H) of the Structural Clinical Interview for *DSM-IV-TR* Axis I Disorders[31] and the Eating Disorder Examination Questionnaire.[32] Additional eligibility criteria included a body mass index of at least 25 and no greater than 45 (calculated as weight in kilograms divided by height in meters squared).

Exclusion criteria included current bulimia nervosa, anorexia nervosa, ADHD, or another psychiatric disorder; a lifetime history of bipolar disorder or psychosis or other conditions that may confound efficacy and safety assessments; a total Montgomery-Åsberg Depression Rating Scale (MADRS)[33] score of at least 18 at screening or baseline visits; psychological or weight-loss interventions initiated within 3 months of screening; use of a psychostimulant within the prior 6 months; and a personal or family history of cardiovascular disease that could increase vulnerability to the sympathomimetic effects of psychostimulants. Any adult with a recent history of suspected substance abuse or a lifetime history of psychostimulant abuse and/or dependence was excluded. Prior (within the past 30 days) or current therapy with investigational compounds, sedatives, anxiolytics, antipsychotics, antidepressants, norepinephrine reuptake inhibitors, sedative hypnotics, benzodiazepines, antihistamines (centrally and peripherally acting), herbal preparations, over-the-counter medications, and weight-reducing agents and prior (within the past 60 days) or current therapy with psychostimulants was prohibited. Nicotine dependence was not exclusionary.

Participants were randomized (1:1:1:1) to receive placebo or 30, 50, or 70 mg/d of lisdexamfetamine dimesylate (treatment groups) using an interactive voice-response system/interactive web-response system. The study blind was maintained by overencapsulation, making placebo and active treatments appear identical in size, weight, shape, and color. The placebo capsule included components similar to those of

the lisdexamfetamine capsule, with the exception of the exclusion of the active ingredient and the inclusion of croscarmellose. The 3-week forced-dose titration period was followed by an 8-week dose-maintenance period. Once-daily oral doses for participants assigned to 30-, 50-, or 70-mg/d treatment groups were initiated at the 30-mg/d dosage and titrated weekly in increments of 20 mg/d to the assigned dosage. Dosage changes and reductions were not permitted during the maintenance period; participants could discontinue treatment if they experienced intolerance.

Efficacy

The primary efficacy measure was the number of BE days per week based on clinician interview and confirmation of identified BE episodes in self-reported BE diaries. The primary efficacy end point was the change from baseline to week 11 on the log-transformed scale (BE days per week) + 1. Clinician raters needed to be credentialed and have experience and training to ensure the rigor, validity, and consistency of the ratings. Training of investigator raters was provided by an expert in the field of BED (S.L.M.) to allow for assessment standardization. Training included, but was not limited to, the *DSM-IV-TR* criteria for BED, description of core BED symptoms, daily BE diary content, participant diary completion instructions, completion content, and completion interpretation. At an investigators' meeting, training included psychiatric evaluation of adults with BED based on the *DSM-IV-TR*, Structural Clinical Interview for *DSM-IV-TR* Axis I Disorders (module H), the Mini International Neuropsychiatric Interview Plus,[34] and a review of the Eating Disorder Examination Questionnaire.

Secondary efficacy measures included the number of BE episodes per week, 1-week BE episode response status, and 4-week cessation from BE (free from BE episodes). The Clinical Global Impressions–Improvement Scale (CGI-I)[35] rated global improvement of symptoms over time; results were dichotomized as improved (CGI-I ratings of 1 or 2 [very much/much improved]) or not improved (CGI-I ratings of 3-7). The self-reported Eating Inventory, also known as the Three-Factor Eating Questionnaire (TFEQ),[36] with demonstrated sensitivity in BED trials, assessed 3 eating behavior factors (cognitive restraint of eating, emotionally based disinhibition of eating, and perceived hunger); for BED, increased scores for the cognitive restraint factor indicate improvement, whereas decreased scores for the disinhibition and perceived hunger factors indicate improvement. Another measure, the self-reported Binge Eating Scale,[37] assessed behavioral, affective, and attitudinal components of BE. The Yale-Brown Obsessive Compulsive Scale modified for BE (YBOCS-BE)[38] measured obsessiveness of BE thoughts and compulsiveness of BE behaviors. In addition, version 11 of the Barratt Impulsiveness Scale (BIS-11),[39] a self-reported scale, measured impulsiveness. Score decreases on the Binge Eating Scale, YBOCS-BE, and BIS-11 indicate improvement. Version 2 of the 12-Item Short Form Health Survey (SF-12),[40] a general measurement, assessed participant-perceived quality of life, with score increases indicating improvement. Additional secondary measures included the MADRS,[33] which rated severity of depression symptoms, and the Hamilton Anxiety Rating Scale,[41] which assessed anxiety.

Safety and Tolerability

Safety assessments included treatment-emergent adverse events (TEAEs), the Columbia–Suicide Severity Rating Scale,[42] vital signs, electrocardiography, weight, and laboratory test results (biochemistry, hematologic analysis, and urinalysis). Urine drug testing was conducted at screening, at baseline, and at the investigators' discretion. Weight was recorded using a calibrated scale while the participants were not wearing shoes, rounded to the nearest 0.5 pounds, and converted to kilograms (to convert, multiply by 0.45) for data reporting.

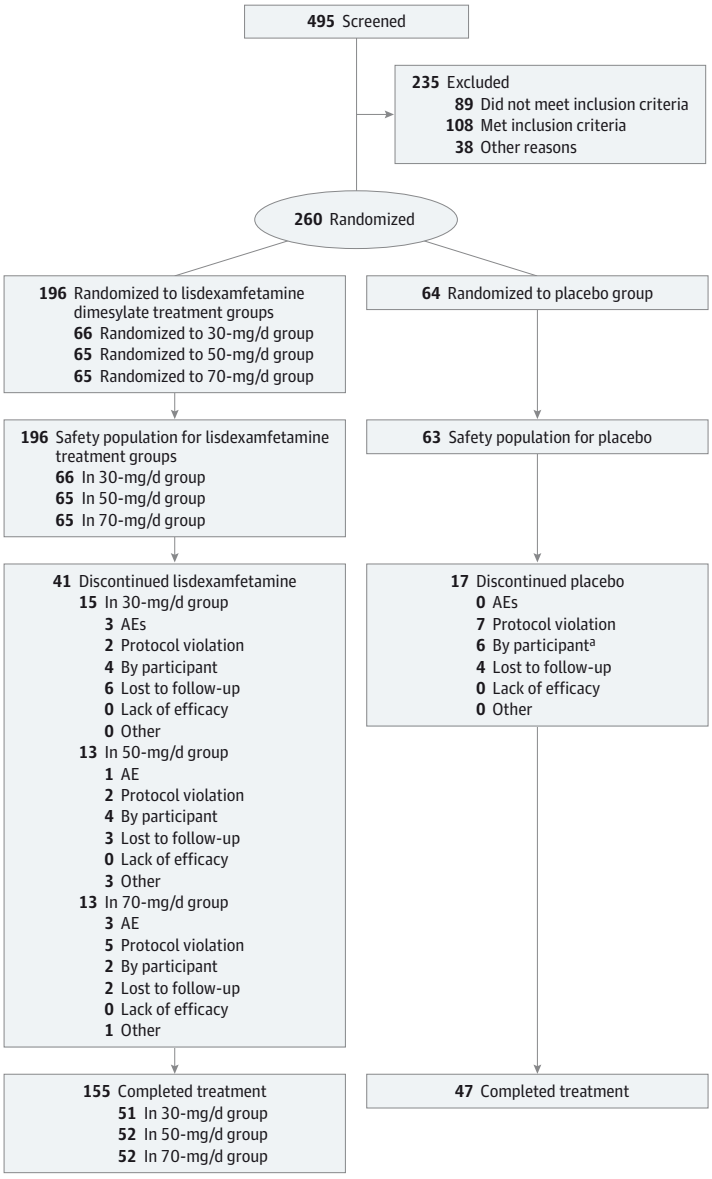
Statistical Analysis

For statistical analysis, the full-analysis set was defined as all participants who took at least 1 dose of the study drug and had at least 1 postbaseline primary efficacy assessment. The safety-analysis set was defined as all randomized participants who took at least 1 dose of the study drug and completed at least 1 follow-up safety assessment. Intergroup comparisons used a mixed-effects model for repeated measures, including fixed factors for treatment and visit, the interaction of treatment and visit, a covariate of the log-transformation ([baseline number of BE days per week] + 1), and the interaction of the baseline covariate and visit using visit as a categorical variable. Study site was not included as a factor because we had no a priori reason to suspect additional explanatory value of site owing to the use of standardized criteria and training across sites. Mixed-effects models for repeated measures estimated differences from placebo in the change from baseline of the log-transformed scale ([BE days per week] + 1) at week 11 (primary end point). Based on previous experience,[18,43] log-transformation was planned to reduce skewness. A hierarchical testing procedure in descending order of lisdexamfetamine dosage was used for pairwise testing between lisdexamfetamine dosages and placebo on the primary end point because we hypothesized that higher lisdexamfetamine dosages would be more likely than lower dosages to be efficacious. We also analyzed changes from baseline in log-transformed BE episodes, TFEQ factor scores, and YBOCS-BE total score to week 11 using the mixed-effects model for repeated measures. Binge-eating episode response rates at 1 week and BE cessation at 4 weeks were analyzed by the Cochran-Mantel-Haenszel test using a modified ridit score with individual treatment arm vs placebo. Pairwise χ^2 statistical tests evaluated dichotomized CGI-I ratings at week 11 or early termination for placebo vs each treatment group.

For 80% power to compare the change from baseline in BE days per week on the log-transformed scale, assuming a true effect size of 0.6 between any treatment group and the placebo group, 45 participants who completed treatment were needed in each treatment group based on a 2-sided 2-group *t* test at the .05 level of significance. Treatment groups of approximately 65 participants were selected, assuming that 30% would not complete the double-blind treatment phase. Double-blind randomization to treatment was assigned by an interactive voice-response system/interactive web-response system designed for this study.

At each double-blind treatment visit, the remaining pills were counted, and a treatment adherence rate was calcu-

Figure 1. Participant Disposition



AE indicates adverse event.

[a] One participant randomized to placebo did not provide postbaseline safety assessment data and was not included in the safety population.

lated based on the number of pills not returned divided by the number of days. Participants were considered adherent to treatment if the calculated rate ranged from 80% to 120% inclusive. Participants who had taken 80% to 100% of the investigational product given, as assessed by the investigator, were considered adherent for study management purposes.

Results

Disposition and Demographics

Of 260 enrolled participants, 255 were included in the efficacy analyses and 259 in the safety analyses (**Figure 1**). Fifty-eight participants did not complete the study (17 in the placebo group: 15 in the 30-mg/d treatment group and 13 each in the 50-mg/d and 70-mg/d treatment groups). Seven participants withdrew because of TEAEs (all in the treatment groups) and none for lack of efficacy; no participant discontinued because of weight loss. Of the 259 participants in the safety population, 257 had an adherence rate within the 80% to 120% range. Two participants did not meet this criterion. One participant (in the 30-mg/d treatment group) had a rate less than 80%, and another (in the 70-mg/d treatment group) had a rate of 144.44%. This adherence rate beyond the specified range (>120%) was related to the a priori method for calculation of adherence but, based on medical review, was not a safety issue related to misuse of the investigational product. Demographics and baseline characteristics, including mean number of BE days per week, are shown in **Table 1**.

Table 1. Demographics and Baseline Characteristics, Safety-Analysis Set

Characteristic[a]	Placebo Group (n = 63)	Lisdexamfetamine Dimesylate Treatment Group				All Participants (N = 259)
		30 mg/d (n = 66)	50 mg/d (n = 65)	70 mg/d (n = 65)	All Dosages (n = 196)	
Age, mean (SD), y	38.0 (10.30)	38.4 (11.14)	39.6 (9.32)	38.6 (10.01)	38.9 (10.15)	38.7 (10.17)
Age, y, No. (%)						
<40	35 (55.6)	35 (53.0)	30 (46.2)	34 (52.3)	99 (50.5)	134 (51.7)
≥40	28 (44.4)	31 (47.0)	35 (53.8)	31 (47.7)	97 (49.5)	125 (48.3)
Sex, No. (%)						
Male	14 (22.2)	9 (13.6)	15 (23.1)	10 (15.4)	34 (17.3)	48 (18.5)
Female	49 (77.8)	57 (86.4)	50 (76.9)	55 (84.6)	162 (82.7)	211 (81.5)
Ethnicity, No. (%)[b]						
Hispanic/Latino	5 (7.9)	7 (10.6)	7 (10.8)	10 (15.4)	24 (12.2)	29 (11.2)
Non-Hispanic/non-Latino	58 (92.1)	59 (89.4)	58 (89.2)	55 (84.6)	172 (87.8)	230 (88.8)
Race, No. (%)[b]						
White	52 (82.5)	48 (72.7)	53 (81.5)	49 (75.4)	150 (76.5)	202 (78.0)
Nonwhite	11 (17.5)	18 (27.3)	12 (18.5)	16 (24.6)	46 (23.5)	57 (22.0)
Black/African American	9 (14.3)	15 (22.7)	10 (15.4)	12 (18.5)	37 (18.9)	46 (17.8)
Asian	2 (3.2)	1 (1.5)	0	1 (1.5)	2 (1.0)	4 (1.5)
Native American/Alaskan native	0	0	1 (1.5)	2 (3.1)	3 (1.5)	3 (1.2)
Other	0	2 (3.0)	1 (1.5)	1 (1.5)	4 (2.0)	4 (1.5)
Weight, mean (SD), kg	96.8 (17.28)	98.5 (18.65)	100.6 (18.84)	98.4 (16.70)	99.2 (18.03)	98.6 (17.85)
Height, mean (SD), m	1.68 (0.081)	1.67 (0.094)	1.69 (0.079)	1.68 (0.089)	1.68 (0.088)	1.68 (0.086)
BMI, mean (SD)	34.3 (5.31)	35.0 (5.39)	35.2 (5.73)	35.0 (4.82)	35.1 (5.30)	34.9 (5.30)
BMI category, No. (%)						
Overweight (≥25 to <30)	14 (22.2)	14 (21.2)	16 (24.6)	14 (21.5)	44 (22.4)	58 (22.4)
Obese (≥30 to <40)	39 (61.9)	39 (59.1)	33 (50.8)	41 (63.1)	113 (57.7)	152 (58.7)
Severely obese (≥40)	10 (15.9)	13 (19.7)	16 (24.6)	10 (15.4)	39 (19.9)	49 (18.9)
Baseline CGI-S illness present[c]						
Normal, not at all	0	0	0	0	NA	NA
Borderline mental	0	0	0	1 (1.6)	NA	NA
Mild	1 (1.6)	0	2 (3.1)	1 (1.6)	NA	NA
Moderate	35 (56.5)	36 (54.5)	38 (59.4)	27 (42.9)	NA	NA
Marked	18 (29.0)	20 (30.3)	19 (29.7)	30 (47.6)	NA	NA
Severe	7 (11.3)	8 (12.1)	4 (6.3)	4 (6.3)	NA	NA
Among the most extreme	1 (1.6)	2 (3.0)	1 (1.6)	0	NA	NA
Baseline MADRS score, mean (SD)[c]	3.4 (3.39)	2.9 (3.02)	3.6 (3.29)	3.7 (3.94)	NA	NA
Baseline HAM-A score, mean (SD)[c]	2.5 (3.01)	2.3 (2.32)	2.3 (2.60)	2.5 (3.22)	NA	NA

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CGI-S, Clinical Global Impressions–Severity; HAM-A, Hamilton Anxiety Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; NA, not applicable.

[a] Baseline value for a characteristic is reported from the baseline visit or the last visit before randomization.

[b] Self-described ethnicity and race are reported for the participants' demographic profile.

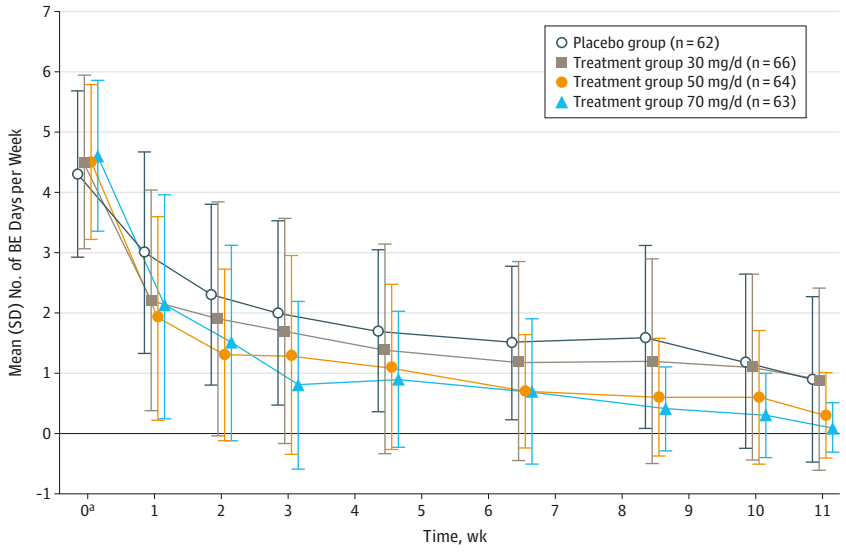
[c] Full-analysis set includes 62 in the placebo group, 66 in the 30-mg/d treatment group, 64 in the 50-mg/d treatment group, and 63 in the 70-mg/d treatment group.

Efficacy

The change in the number of BE days per week from baseline through week 11 for all treatment groups is shown in **Figure 2**. The mean (SD) changes from baseline to week 11 or early termination in nontransformed BE days per week for the placebo and the 30-, 50-, and 70-mg/d treatment groups were −3.3 (2.04), −3.5 (1.95), −4.1 (1.52), and −4.1 (1.57), respectively. The primary efficacy end point (least squares [LS] mean change from baseline to week 11 on log-transformed BE days per week) was significantly decreased in the 50- and 70-mg/d treatment groups but not in the 30-mg/d treatment group compared with the placebo group (**Table 2**).

The LS mean change from baseline to week 11 of log-transformed BE episodes per week was significantly decreased for the 50- and 70-mg/d treatment groups (Table 2). At week 11 or early termination, the 1-week response status was improved in the 50- and 70-mg/d treatment groups compared with the placebo group, and the 4-week BE cessation response status was improved in the 50- and 70-mg/d treatment groups compared with the placebo group (Table 2).

Figure 2. Nontransformed Weekly Binge-Eating (BE) Days at Baseline and Through Week 11



Includes full-analysis set of 255 participants.

[a] Baseline is the number of BE days experienced in the 7 days before the baseline visit.

Greater proportions of participants receiving lisdexamfetamine were rated improved (CGI-I rating, 1 or 2) compared with those receiving placebo at week 11 or early termination (Table 2). At baseline, mean TFEQ scores for the cognitive restraint factor were in the low to normal range (0-10). Scores were in the clinical (≥12) and high (9-11) ranges for the disinhibition and hunger factors, respectively (Table 2). At week 11, LS mean scores on all 3 TFEQ factors in the 70-mg/d treatment group and 2 of the 3 TFEQ factors (not cognitive restraint) in the 50-mg/d treatment group significantly improved compared with the placebo group (Table 2). At baseline, mean Binge Eating Scale scores were in the severe range (≥27) and demonstrated greater improvement at week 11 in all the treatment groups compared with the placebo group (Table 2). At baseline, mean YBOCS-BE total scores were in the moderate range (16-23); the LS mean total scores for this measure improved in all treatment groups compared with the placebo group at week 11 (Table 2). As additional secondary efficacy measures, significant improvement in the LS mean BIS-11 total score was found in the 70-mg/d treatment group compared with the placebo group (Table 2). The SF-12 Physical and Mental Health Component Summary aggregate scores were comparable at baseline across treatment groups. The change in the LS mean score for the aggregate Mental Health Component Summary was not significantly different between any treatment group and the placebo group. Moreover, the aggregate change in the LS mean score for the SF-12 Physical Health Component Summary was significant only for the 70-mg/d treatment group compared with the placebo group and not for the other treatment groups (Table 2). Baseline mean MADRS and Hamilton Anxiety Rating Scale symptom scores indicated that depression and anxiety symptoms were low across all groups; none of the changes in the LS mean scores for the MADRS and Hamilton Anxiety Rating Scale across the treatment groups were significantly different from those of the placebo group at week 11 (Table 2).

Safety

The frequency of TEAEs is summarized in **Table 3**. In the placebo group, no discontinuations owing to TEAEs, no serious TEAEs, and no deaths occurred. Among the 196 participants receiving lisdexamfetamine, 6 (3.1%) discontinued treatment owing to TEAEs and 3 (1.5%) had serious TEAEs. One participant (in the 70-mg/d treatment group) died because of toxicology findings consistent with a methamphetamine overdose. During screening, the participant denied a history of substance abuse, and results of drug tests during the study were negative. However, postmortem toxicologic analysis found methamphetamine/amphetamine levels consistent with methamphetamine overdose. The study investigator did not consider this death to be related to the study drug. Two other serious TEAEs (acute pancreatitis and appendicitis) occurred in participants in the 30-mg/d treatment group and were considered unrelated to the study drug. According to scores on the Columbia-Suicide Severity Rating Scale, no participant had suicidal ideation, thoughts, or attempts during treatment. Mean heart rate tended to increase from baseline to week 11 or early termination with lisdexamfetamine treatment (Table 3). No comparable trends were observed with systolic or diastolic blood pressure (Table 3). Also, no clinically meaningful trends were observed for clinical laboratory results or electrocardiography interval data.

Participants' mean weight in the treatment groups decreased with treatment; the placebo group experienced no mean weight change. The mean (SD) change in body weight was −0.1 (3.09), −3.1 (3.64), −4.9 (4.43), −4.9 (3.93), and −4.3 (4.09) kg for the placebo group; the 30-, 50-, and 70-mg/d treatment groups; and the combined treatment groups, respectively. In a post hoc analysis, the percentage of reduction in body weight was greater for all treatment groups compared with the placebo group at week 11 (all, $P < .001$). In addition, the LS mean (SE) differences compared with the placebo group in the percentage of reduction in body weight

Table 2. Efficacy Measures

Variable	Placebo Group (n = 62)	Lisdexamfetamine Dimesylate Treatment Group 30 mg/d (n = 66)	50 mg/d (n = 64)	70 mg/d (n = 63)
Primary Efficacy Variable				
Nontransformed, mean (SD) , BE days[a]				
Baseline	4.3 (1.38)	4.5 (1.44)	4.5 (1.28)	4.6 (1.25)
Week 11 or ET change	1.1 (1.45)	1.0 (1.69)	0.4 (0.86)	0.5 (1.25)
Log-transformed, LS, mean (SE), BE days[b]				
Week 11 or ET change[c]	−1.23 (0.069)	−1.24 (0.067)	−1.49 (0.066)	−1.57 (0.067)
Week 11 difference[d]	NA	−0.01 (0.096)	−0.26 (0.096)	−0.35 (0.096)
P value	NA	.88	.008	<.001
Secondary Efficacy Variable				
BE episodes (week 11)				
Nontransformed, mean (SD)[a]				
Baseline	5.2 (2.13)	5.8 (3.03)	5.6 (2.75)	5.6 (2.43)
Week 11 or ET	1.1 (1.55)	1.2 (2.13)	0.5 (1.01)	0.5 (1.34)
Log-transformed LS, mean (SE)[b]				
Change[c]	−1.36 (0.072)	−1.37 (0.070)	−1.62 (0.069)	−1.71 (0.070)
Difference (treatment − placebo)[d]	NA	−0.01 (0.100)	−0.27 (0.100)	−0.35 (0.100)
P value	NA	.89	.009	<.001
1-wk BE response (week 11) LOCF, % of participants				
1-wk Cessation (100% reduction)	37.1	42.4	51.6	55.6
Marked response (75%-<100% reduction)	24.2	30.3	37.5	36.5
Moderate response (50%-<75% reduction)	21.0	12.1	6.3	1.6
Negative/minimal response (<50% reduction)	17.7	15.2	4.7	6.3
P value	NA	.33	.006	.002
4-wk BE response (week 11)				
Cessation (100% reduction), % of participants	21.3	34.9	42.2	50.0
P value	NA	.09	.01	<.001
CGI-I score				
Improved at week 11/ET, %	64.5	84.6	90.6	93.7
P value	NA	.009	<.001	<.001
TFEQ score				
Cognitive restraint of eating				
Baseline, mean (SD)	6.4 (4.05)	7.2 (4.01)	7.1 (4.60)	8.2 (4.54)
LS change, mean (SE)[c]	2.5 (0.65)	4.4 (0.62)	3.8 (0.61)	4.3 (0.62)
Difference in LS, mean (SE)[d]	NA	1.9 (0.89)	1.3 (0.89)	1.8 (0.90)
P value	NA	.04	.14	.046
Disinhibition of eating				
Baseline, mean (SD)	13.1 (2.33)	13.2 (2.26)	13.0 (2.36)	12.9 (2.49)
LS change, mean (SE)[c]	−3.8 (0.58)	−5.6 (0.56)	−6.3 (0.55)	−7.2 (0.56)
Difference in LS, mean (SE)[d]	NA	−1.8 (0.80)	−2.5 (0.80)	−3.4 (0.80)
P value	NA	.03	.002	<.001
Perceived hunger				
Baseline, mean (SD)	11.5 (2.43)	10.3 (3.19)	10.3 (3.03)	10.4 (3.53)
LS change, mean (SE)[c]	−3.3 (0.58)	−5.3 (0.56)	−6.0 (0.55)	−7.8 (0.56)
Difference in LS, mean (SE)[d]	NA	−2.0 (0.81)	−2.7 (0.81)	−4.5 (0.81)
P value	NA	.02	<.001	<.001
BES total score				
Baseline, mean (SD)	27.0 (8.62)	28.5 (7.16)	27.4 (7.22)	30.3 (7.47)
LS change, mean (SE)[c]	−12.2 (1.28)	−16.1 (1.25)	−17.6 (1.24)	−20.6 (1.24)
Difference in LS, mean (SE)[d]	NA	−3.9 (1.79)	−5.4 (1.78)	−8.5 (1.79)
P value	NA	.03	.002	<.001

(continued)

Table 2. Efficacy Measures (continued)

Variable	Placebo Group (n = 62)	Lisdexamfetamine Dimesylate Treatment Group 30 mg/d (n = 66)	50 mg/d (n = 64)	70 mg/d (n = 63)
YBOCS-BE total score				
Baseline, mean (SD)	20.9 (4.61)	20.7 (4.87)	19.5 (5.19)	19.8 (5.48)
LS change, mean (SE)[c]	−12.0 (0.87)	−15.0 (0.84)	−15.3 (0.83)	−17.0 (0.83)
Difference in LS, mean (SE)[d]	NA	−2.97 (1.203)	−3.25 (1.204)	−4.93 (1.202)
P value	NA	.01	.008	<.001
BIS-11 total score				
Baseline, mean (SD)	63.1 (13.22)	61.8 (10.70)	61.0 (9.84)	61.4 (12.69)
LS change, mean (SE)[c]	−3.1 (1.09)	−5.8 (1.05)	−5.2 (1.05)	−6.9 (1.05)
Difference in LS, mean (SE)[d]	NA	−2.7 (1.52)	−2.1 (1.51)	−3.7 (1.51)
P value	NA	.08	.17	.02
SF-12 Aggregate Physical Health Component Summary score				
Baseline, mean (SD)	49.54 (7.875)	48.83 (7.264)	49.16 (9.114)	48.99 (7.386)
LS change, mean (SE)[c]	1.3 (0.78)	2.6 (0.75)	2.4 (0.74)	3.9 (0.75)
Difference in LS, mean (SE)[d]	NA	1.3 (1.08)	1.1 (1.07)	2.5 (1.08)
P value	NA	.25	.31	.02
SF-12 Aggregate Mental Health Component Summary score				
Baseline, mean (SD)	48.74 (10.241)	49.12 (9.485)	46.74 (9.594)	48.62 (9.969)
LS change, mean (SE)[c]	4.9 (1.03)	5.0 (1.00)	5.5 (0.99)	4.9 (1.00)
Difference in LS, mean (SE)[d]	NA	0.1 (1.44)	0.6 (1.43)	0.0 (1.43)
P value	NA	.96	.65	.98
MADRS score				
Baseline, mean (SD)	3.4 (3.39)	2.9 (3.02)	3.6 (3.29)	3.7 (3.94)
LS change, mean (SE)[c]	−1.7 (0.35)	−1.9 (0.34)	−1.3 (0.33)	−1.6 (0.33)
Difference in LS, mean (SE)[d]	NA	−0.15 (0.484)	0.49 (0.480)	0.14 (0.480)
P value	NA	.75	.31	.77
HAM-A score				
Baseline, mean (SD)	2.5 (3.01)	2.3 (2.32)	2.3 (2.60)	2.5 (3.22)
LS change, mean (SE)[c]	−1.5 (0.30)	−0.9 (0.29)	−1.1 (0.29)	−0.6 (0.29)
Difference in LS, mean (SE)[d]	NA	0.53 (0.417)	0.40 (0.415)	0.81 (0.414)
P value	NA	.20	.33	.05

Abbreviations: BE, binge eating; BES, Binge Eating Scale; BIS-11, Barratt Impulsiveness Scale, version 11; ET, early termination; HAM-A, Hamilton Anxiety Rating Scale; LOCF, last observation carried forward; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; NA, not applicable; SF-12, 12-Item Short Form Health Survey (version 2); TFEQ, Three-Factor Eating Questionnaire; YBOCS-BE, Yale-Brown Obsessive Compulsive Scale modified for BE.

[a] Nontransformed data were summarized using the LOCF at week 11 or ET.

[b] Transformed data analysis used mixed-effects model for repeated measures and therefore analyzed data as baseline vs week 11.

[c] Change is from baseline to week 11.

[d] Difference is calculated as treatment − placebo.

at week 11 for the 30-, 50-, and 70-mg treatment groups were 3.268% (0.7197%), 5.179% (0.7214%), and 5.282% (0.7229%), respectively.

Discussion

In the primary analysis of this study of adults with moderate to severe BED, lisdexamfetamine dimesylate treatment with 50 and 70 mg/d, but not 30 mg/d, demonstrated a significant decrease (compared with placebo) in weekly BE days per week at week 11. Similarly, BE episodes decreased in the 50- and 70-mg/d treatment groups. The 1-week BE episode response status was improved in the 50- and 70-mg/d treatment groups, and a greater proportion of participants achieved 4-week cessation of BE episodes and global improvement of symptom severity with all lisdexamfetamine dosages. Participant-reported BE symptoms and clinician-rated BE obsessive-compulsive features were improved with all lisdexamfetamine dosages. Together, these findings provide substantial preliminary evidence that lisdexamfetamine may be effective for treatment of moderate to severe BED, which is consistent with its effect on DA and norepinephrine neurotransmitters and a potential effect on abnormal eating behaviors. Potential confounding effects due to depressive or anxiety symptoms are unlikely to have contributed to these effects given that the MADRS and Hamilton Anxiety Rating Scale scores were low at baseline and did not change during the study. Similarly, potential confounding effects due to ADHD symptoms are unlikely because comorbid ADHD was a criterion for exclusion.

Other drug classes and agents as well as psychological therapy have demonstrated efficacy in treating various aspects of BED, including BE frequency, BE response status, metabolic and medical markers, and global symptom severity.[17,18,43-49] However, no direct comparisons were conducted in the present study. Comparative studies of active treatments for BED are lacking and would be needed to determine the relative efficacy among treatments, including lisdexamfetamine.

Table 3. Safety Parameters: Adverse Events and Vital Signs[a]

	Placebo Group (n = 63)	Lisdexamfetamine Dimesylate Treatment Group			
		30 mg/d (n = 66)	50 mg/d (n = 65)	70 mg/d (n = 65)	All (n = 196)
TEAEs, No. (%)[b]					
Any	37 (58.7)	57 (86.4)	56 (86.2)	53 (81.5)	166 (84.7)
Dry mouth	5 (7.9)	22 (33.3)	22 (33.8)	27 (41.5)	71 (36.2)
Decreased appetite	4 (6.3)	17 (25.8)	13 (20.0)	12 (18.5)	42 (21.4)
Insomnia	1 (1.6)	7 (10.6)	10 (15.4)	9 (13.8)	26 (13.3)
Headache	6 (9.5)	9 (13.6)	9 (13.8)	5 (7.7)	23 (11.7)
Nausea	0	5 (7.6)	6 (9.2)	4 (6.2)	15 (7.7)
Constipation	1 (1.6)	6 (9.1)	3 (4.6)	5 (7.7)	14 (7.1)
Nasopharyngitis	2 (3.2)	8 (12.1)	1 (1.5)	3 (4.6)	12 (6.1)
Weight decrease	1 (1.6)	2 (3.0)	4 (6.2)	6 (9.2)	12 (6.1)
Irritability	4 (6.3)	5 (7.6)	3 (4.6)	3 (4.6)	11 (5.6)
Diarrhea	0	4 (6.1)	5 (7.7)	1 (1.5)	10 (5.1)
Anxiety	0	4 (6.1)	4 (6.2)	1 (1.5)	9 (4.6)
Feeling jittery	0	1 (1.5)	3 (4.6)	5 (7.7)	9 (4.6)
Palpitations	0	4 (6.1)	2 (3.1)	3 (4.6)	9 (4.6)
Upper respiratory tract infection	4 (6.3)	1 (1.5)	3 (4.6)	5 (7.7)	9 (4.6)
Sleep disorder	0	1 (1.5)	3 (4.6)	4 (6.2)	8 (4.1)
Vital signs, mean (SD)					
SBP, mm Hg					
Baseline	119.7 (8.51)	121.7 (10.38)	119.6 (9.87)	117.7 (9.51)	119.7 (10.01)
Change from baseline to week 11 or ET	-1.5 (8.41)	-1.1 (10.39)	-0.1 (8.63)	1.6 (10.40)	0.1 (9.85)
DBP, mm Hg					
Baseline	77.3 (7.47)	79.1 (6.64)	78.0 (8.28)	77.1 (6.39)	78.0 (7.16)
Change from baseline to week 11 or ET	-0.5 (6.80)	-1.3 (7.65)	0.4 (6.91)	-1.2 (7.36)	-0.7 (7.32)
Heart rate, bpm					
Baseline	69.9 (7.78)	72.9 (9.65)	72.0 (10.39)	71.6 (8.99)	72.2 (9.66)
Change from baseline to week 11 or ET	1.0 (8.10)	2.3 (9.16)	4.2 (12.63)	5.0 (12.65)	3.8 (11.57)
Weight, kg					
Baseline	96.8 (17.28)	98.5 (18.65)	100.6 (18.84)	98.4 (16.70)	99.2 (18.03)
Change from baseline to week 11 or ET	−0.1 (3.09)	−3.1 (3.64)	−4.9 (4.43)	−4.9 (3.93)	−4.3 (4.09)

Abbreviations: DBP, diastolic blood pressure; ET, early termination; SBP, systolic blood pressure; TEAEs, treatment-emergent adverse events.

[a] Includes the safety-analysis set.

[b] Indicates any TEAEs with a reported frequency of at least 5% in any group, per the *Medical Dictionary for Regulatory Activities*, version 11.1, preferred term (under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH]; MedDRA trademark is owned by the International Federation of Pharmaceutical Manufacturers & Associations on behalf of the ICH). Participants were counted once per preferred term, per dose level.

Weight, in this study, was assessed as a safety variable. A post hoc analysis suggested that lisdexamfetamine treatment may result in weight decreases relative to placebo, but no participant discontinued the study owing to weight loss. Being overweight and being obese are acknowledged to be important medical issues for a significant proportion of patients with BED. As such, prospective studies are ongoing that, in addition to the effects on core features of BED (ie, BE behavior), will provide important data regarding the short- and long-term weight changes associated with lisdexamfetamine treatment in individuals with BED.

The safety profile of lisdexamfetamine was generally consistent with that seen in studies of lisdexamfetamine in adults with ADHD in the types and frequency of adverse effects.[50-52] In the present study, small mean increases in heart rate were noted with lisdexamfetamine treatment, consistent with other studies of psychostimulants.[50,51] Discontinuation owing to lack of efficacy (none) and adverse events (7 of 259 participants) was comparable with results of selective serotonin reuptake inhibitor studies and somewhat lower than that seen in topiramate trials.[13,17,49]

One participant died during the study. Postmortem toxicology analysis reported that methamphetamine/amphetamine levels were consistent with a methamphetamine overdose. This was, to our knowledge, the first such report of a methamphetamine overdose during the course of a lisdexamfetamine clinical trial, because no previous publications of lisdexamfetamine clinical trials across multiple indications have reported methamphetamine overdose.[50,51,53-60] Although available data suggest an increased likelihood of comorbid alcohol and other substance use disorders among patients with BED,[1,5] the data do not support a correlation between eating disorders and the licit or illicit use of stimulants.[61] However, like other amphetamine-based medications, lisdexamfetamine is a schedule II controlled substance with a black box warning that notes the potential for

abuse and dependence.[62] To help physicians monitor for potential misuse, most states have prescription drug monitoring programs, which can be effective in reducing prescription drug misuse.[63]

This study has several limitations. Most participants were female, white, non-Hispanic/non-Latino, and overweight or obese (based on body mass index). Participants with comorbid illnesses (eg, cardiovascular or psychiatric conditions) were excluded, limiting the generalizability of these findings to all adult patients with BED.[1,6,16,64] Although the lifetime prevalence of mood disorders in individuals with BED is approximately 50%[1,65,66] and the prevalence of depressive symptoms in this study was very low, individuals with current Axis I disorders were excluded intentionally to limit potential confounding factors and to allow for an assessment of the effect of lisdexamfetamine specifically on BE behavior. The short study duration may have limited separation from placebo on the aggregate SF-12 physical and mental functioning measures and may limit conclusions about the long-term efficacy and safety of lisdexamfetamine. Assessment and calculation of BE days and episodes relied on diary reports by participants, which were reviewed and verified by an experienced and trained clinical investigator to ensure the accuracy of the reported BE episodes. However, because divergence between participant and physician reports were not measured formally, the level of potential discrepancies between participant and investigator reports is not known. In addition, conclusions on the large numbers of secondary end points in this study should be drawn with caution because such analyses were not subject to multiplicity adjustment. Subjective differences related to participant-reported outcomes may have occurred during data collection; therefore, the potential for variability and magnitude of the differences should be considered when evaluating the results.

Conclusions

This study supports further assessment of lisdexamfetamine as a treatment option for decreasing BE behavior and the BE-associated obsessive and compulsive features in adults with moderate to severe BED. Increased efficacy with increasing dosages of lisdexamfetamine suggests a dose-response relationship. In this cohort of adults, the lisdexamfetamine safety profile was generally consistent with findings in adults with ADHD.[50-52] Confirmation of these findings in ongoing clinical trials may result in improved pharmacologic treatment for moderate to severe BED.

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