Clinical Characteristics and Treatment Response to Lisdexamfetamine Dimesylate Versus Placebo in Adults With Binge Eating Disorder:

Analysis by Gender and Age

Susan G. Kornstein, MD[a,*]; Caleb Bliss, PhD[b]; Judith Kando, PharmD, BCPP[c,‡]; and Manisha Madhoo, MD[c]

ABSTRACT

Objective: To describe clinical characteristics and lisdexamfetamine dimesylate (LDX) treatment effects, based on gender and age, in adults diagnosed with moderate to severe binge eating disorder (BED).

Methods: Adults diagnosed with *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*–defined BED of moderate to severe severity were randomized to 12 weeks of dose-optimized LDX (50 or 70 mg) or placebo in 2 studies (conducted from November 26, 2012, to September 25, 2013 [study 1] and from November 26, 2012, to September 20, 2013 [study 2]). These post hoc analyses pooled data by gender (men vs women) and age (< 40 vs ≥ 40 years) across studies; reported *P* values are nominal (descriptive and unadjusted).

Results: The pooled safety analysis and full analysis sets included 745 and 724 participants, respectively (men, n = 105 and n = 97; women, n = 640 and n = 627; < 40 years, n = 398 and n = 386; ≥ 40 years, n = 347 and n = 338). Across subgroups, most participants had a body mass index ≥ 30 kg/m^2 (63.0%–75.5%). The mean baseline number of binge eating days/wk was comparable across gender (4.6–4.7) and age (4.6–4.9), as was Yale-Brown Obsessive Compulsive Scale modified for Binge Eating (Y-BOCS-BE) total score (gender, 20.42–21.70; age, 21.40–21.63). Least squares mean (95% CI) treatment differences nominally favored LDX in all subgroups (all $P < .001$) for changes from baseline in binge eating days/wk at weeks 11–12 and in Y-BOCS-BE total score at week 12; no interactions by gender or age were reported. Consistent with the overall profile of LDX, across all subgroups LDX was associated with higher frequencies of treatment-emergent adverse events than placebo and with increases in blood pressure and pulse.

Conclusions: Across gender and age, participants exhibited comparable clinical characteristics and responses to dose-optimized LDX compared with placebo.

Trial Registration: ClinicalTrials.gov identifiers: NCT01718483 and NCT01718509

J Clin Psychiatry 2019;80(2):18m12378

To cite: Kornstein SG, Bliss C, Kando J, et al. Clinical characteristics and treatment response to lisdexamfetamine dimesylate versus placebo in adults with binge eating disorder: analysis by gender and age. *J Clin Psychiatry.* 2019;80(2):18m12378.

To share: https://doi.org/10.4088/JCP.18m12378

[a]Department of Psychiatry and Institute for Women's Health, Virginia Commonwealth University, Richmond, Virginia

[b]Biostatistics, Shire, Lexington, Massachussetts, a member of the Takeda group of companies

[c]Global Medical Affairs, Shire, Lexington, Massachussetts, a member of the Takeda group of companies

‡Dr Kando is now an employee of Tris Pharma and is no longer affiliated with Shire.

**Corresponding author:* Susan G. Kornstein, MD, Department of Psychiatry and Institute for Women's Health, Virginia Commonwealth University, PO Box 980710, Richmond, VA 23298-0710 (susan.kornstein@vcuhealth.org).

Lisdexamfetamine dimesylate (LDX) is approved for the treatment of adults diagnosed with moderate to severe binge eating disorder (BED) and for individuals ≥ 6 years old diagnosed with attention-deficit/hyperactivity disorder (ADHD) in the United States[1] and other countries. The efficacy, safety, and tolerability of LDX in adults with BED have been assessed in several phase 3 studies.[2–5] In 2 identically designed, 12-week, placebo-controlled trials, LDX resulted in clinically meaningful and statistically superior reductions in binge eating (BE) days per week (primary endpoint) compared with placebo in adults diagnosed with protocol-defined moderate to severe BED.[3] In these studies, LDX also produced statistically significant improvements on multiple key secondary efficacy endpoints, including the dichotomized Clinical Global Impressions–Improvement (CGI-I) scale and the Yale-Brown Obsessive Compulsive Scale modified for Binge Eating (Y-BOCS-BE).[3] Across studies,[2–5] the safety and tolerability of LDX were similar to its established profile in ADHD.[1]

Multiple studies have reported that BED is more common in women than men and in younger than older individuals.[6–8] Furthermore, women diagnosed with BED experience greater body image dissatisfaction than men diagnosed with BED.[9] Although previous studies have not examined the effects of gender or age on treatment response to pharmacotherapy for BED, it has been reported that younger age and female gender are moderators of treatment response to pharmacotherapy in adults diagnosed with BED.[10] Furthermore, published reports indicate that the efficacy of and tolerability to pharmacotherapy in other psychiatric disorders[11–16] and neurophysiological activity in response to suppression of hunger in healthy adults[17] can differ by gender. Taken together, these observations suggest that examination of clinical characteristics and treatment responses as a function of gender and age may further our understanding of BED and identify factors impacting the clinical outcomes of pharmacotherapy. Additionally, they emphasize the importance of assessing clinical study results by age and gender and not assuming treatment response equivalency across age and gender.

The objectives of the current post hoc analyses were to examine clinical characteristics, LDX treatment responses, and the safety and tolerability of LDX as a

Clinical Points

- Binge eating disorder (BED) is more common among women than men and among younger than older individuals, but knowledge of age and gender influences on BED outcomes is limited.
- To advance clinical understanding, characteristics and treatment responses by gender and age were assessed from lisdexamfetamine BED studies.
- Comparable clinical characteristics and lisdexamfetamine treatment responses were observed across ages and genders.

function of gender (men vs women) and age (< 40 vs ≥ 40 years). Age was dichotomized as < 40 years versus ≥ 40 years in an attempt to differentiate women who are likely to be premenopausal from those who may be perimenopausal or postmenopausal.[18] These analyses were conducted using pooled data from 2 identically designed LDX studies; the primary findings from these studies have already been published.[3]

METHODS

Study Design

The data for these pooled, post hoc analyses were derived from 2 randomized, placebo-controlled, 12-week studies (NCT01718483 [study 1], conducted from November 26, 2012, to September 25, 2013; NCT01718509 [study 2], conducted from November 26, 2012, to September 20, 2013). Study protocols were approved by ethics committees, and the studies were conducted in accordance with International Council for Harmonization Good Clinical Practice and the principles of the Declaration of Helsinki. Participants provided written informed consent before entering either study.

Each study included a 2- to 4-week screening phase, a 12-week double-blind treatment phase (dose optimization, 4 weeks; dose maintenance, 8 weeks), and a 1-week follow-up phase. After screening, eligible participants were randomly assigned (1:1) to once-daily LDX or placebo; treatments were identical in appearance. Treatment was initiated at 30 mg LDX during week 1, titrated to 50 mg LDX at week 2, and increased to 70 mg LDX during week 3 based on tolerability and clinical need. A single dose reduction to 50 mg LDX was allowed during week 3 if tolerability was poor, but no further changes were permitted. The optimized LDX dose (50 or 70 mg) at the end of week 3 was maintained for the remainder of the study (weeks 4–12). Participants requiring a dose reduction during the maintenance phase were discontinued. A follow-up visit occurred 1 week after the final treatment visit (week 12/early termination [ET]).

Participants

Eligible participants were men or women (aged 18–55 years) meeting *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*), *Fourth Edition, Text Revision* (*DSM-IV-TR*) BED criteria, confirmed by the eating disorders module of the Structured Clinical Interview for the *DSM-IV-TR* Axis I Disorders (SCID-I)[19] and the Eating Disorder Examination-Questionnaire. Participants were required to have protocol-defined moderate to severe BED (≥ 3 BE days/wk during the 14 days before baseline and Clinical Global Impressions–Severity [CGI-S][20] scores ≥ 4 at screening and baseline), and a body mass index (BMI) ranging from 18 to 45 kg/m^2.

Key exclusion criteria included current diagnoses of anorexia nervosa or bulimia nervosa (based on the SCID-I eating disorders module); comorbid Axis I or Axis II psychiatric disorders controlled with prohibited medications or uncontrolled and associated with significant symptoms (those exhibiting mild mood or anxiety symptoms that did not meet diagnostic criteria, did not require treatment based on the investigator's assessment, and did not confound efficacy or safety assessments in the opinion of the examining investigator could be included); pregnancy; psychotherapy or weight loss support for BED (≤ 3 months of screening); psychostimulant use for BED (≤ 6 months of screening); being considered a suicide risk, having previously attempted suicide, or currently demonstrating active suicidal ideation; a lifetime history of psychosis, mania, hypomania, dementia, or ADHD; a history of cardiovascular conditions; moderate or severe hypertension, resting average sitting systolic blood pressure (SBP) > 139 mm Hg, or average diastolic blood pressure (DBP) > 89 mm Hg at screening or baseline; lifetime history of amphetamine or stimulant abuse; recent substance abuse or dependence history; and intolerance or hypersensitivity to LDX or related compounds.

Endpoints

Efficacy. The prespecified primary efficacy endpoint in both studies was change from baseline in BE days/wk at weeks 11–12 based on daily self-report diaries that were reviewed and approved by study investigators. BE diaries were examined at all study visits except screening. Prespecified key secondary endpoints included improvement on the dichotomized CGI-I at week 12/ET and change from baseline in Y-BOCS-BE total score at week 12. The CGI-I[20] measured changes in clinical severity relative to baseline (range, 1 [very much improved] to 7 [very much worse]) and was assessed from the perspective of BED symptoms at each postbaseline visit. The Y-BOCS-BE is a 10-item clinician-rated scale (0 [no symptoms] to 4 [extreme symptoms]) for BED that measures the obsessiveness of BE thoughts and compulsiveness of BE behaviors[21]; total scores range from 0 to 40. The Y-BOCS-BE was assessed at baseline and weeks 4, 8, and 12. The Y-BOCS-BE demonstrates high internal consistency, with a Cronbach α of 0.81 at baseline, and good construct validity in relation to the Three-Factor Eating Questionnaire and the Binge Eating Scale.[21]

Safety and tolerability. The safety and tolerability endpoints examined in these post hoc analyses included adverse events (AEs) and vital signs (SBP, DBP, and pulse), both of which were assessed at all study visits.

Table 1. Baseline Demographics and Clinical Characteristics, Pooled Safety Analysis Set

	Placebo	LDX	Overall	Placebo	LDX	Overall	Nominal *P* Value[a]
	Men			Women			
n	56	49	105	316	324	640	
Age, mean ± SD, y	40.36 ± 9.838	36.45 ± 10.332	38.53 ± 10.212	37.76 ± 10.123	38.04 ± 10.201	37.90 ± 10.156	.556
Gender, n (%)							NA
Male	56 (100)	49 (100)	105 (100)	0	0	0	
Female	0	0	0	316 (100)	324 (100)	640 (100)	
Identified race, n (%)							.382
White	36 (64.3)	36 (73.5)	72 (68.6)	245 (77.5)	244 (75.3)	489 (76.4)	
Black/African American	15 (26.8)	10 (20.4)	25 (23.8)	46 (14.6)	66 (20.4)	112 (17.5)	
Native Hawaiian/Other Pacific Islander	0	0	0	1 (0.3)	4 (1.2)	5 (0.8)	
Asian	3 (5.4)	1 (2.0)	4 (3.8)	6 (1.9)	5 (1.5)	11 (1.7)	
American Indian/Alaska Native	0	1 (2.0)	1 (1.0)	6 (1.9)	1 (0.3)	7 (1.1)	
Multiple	2 (3.6)	1 (2.0)	3 (2.9)	12 (3.8)	3 (0.9)	15 (2.3)	
Missing	0	0	0	0	1 (0.3)	1 (0.2)	
Weight, mean ± SD, kg	106.75 ± 17.837	110.88 ± 23.899	108.68 ± 20.884	90.41 ± 19.138	92.05 ± 19.031	91.24 ± 19.087	< .001
BMI, mean ± SD, kg/m^2	33.34 ± 5.018	34.55 ± 6.199	39.91 ± 5.605	33.18 ± 6.484	33.64 ± 6.248	33.41 ± 6.365	.414
BMI range, n (%)							.224
< 18.5 kg/m^2	0	0	0	1 (0.3)	0	1 (0.2)	
≥ 18.5 to < 25 kg/m^2	3 (5.4)	3 (6.1)	6 (5.7)	39 (12.3)	24 (7.4)	63 (9.8)	
≥ 25 to < 30 kg/m^2	11 (19.6)	9 (18.4)	20 (19.0)	64 (20.3)	83 (25.6)	147 (23.0)	
≥ 30 to < 35 kg/m^2	23 (41.1)	15 (30.6)	38 (36.2)	80 (25.3)	81 (25.0)	161 (25.2)	
≥ 35 to < 40 kg/m^2	12 (21.4)	12 (24.5)	24 (22.9)	74 (23.4)	72 (22.2)	146 (22.8)	
≥ 40 kg/m^2	7 (12.5)	10 (20.4)	17 (16.2)	58 (18.4)	64 (19.8)	122 (19.1)	
Met criterion for obesity							.094
Yes (BMI ≥ 30 kg/m^2)	42 (75.0)	37 (75.5)	79 (75.2)	212 (67.1)	217 (67.0)	429 (67.0)	
No (BMI < 30 kg/m^2)	14 (25.0)	12 (24.5)	26 (24.8)	104 (32.9)	107 (33.0)	211 (33.0)	
	Age < 40 y			Age ≥ 40 y			
n	192	206	398	180	167	347	
Age, mean ± SD, y	29.73 ± 5.604	29.90 ± 5.506	29.82 ± 5.547	47.12 ± 4.632	47.60 ± 4.739	47.35 ± 4.683	NA
Gender, n (%)							.282
Male	22 (11.5)	29 (14.1)	51 (12.8)	34 (18.9)	20 (12.0)	54 (15.6)	
Female	170 (88.5)	177 (85.9)	347 (87.2)	146 (81.1)	147 (88.0)	293 (84.4)	
Identified race, n (%)							.149
White	147 (76.6)	156 (75.7)	303 (76.1)	134 (74.4)	124 (74.3)	258 (74.4)	
Black/African American	26 (13.5)	43 (20.9)	69 (17.3)	35 (19.4)	33 (19.8)	68 (19.6)	
Native Hawaiian/Other Pacific Islander	1 (0.5)	1 (0.5)	2 (0.5)	0	3 (1.8)	3 (0.9)	
Asian	5 (2.6)	3 (1.5)	8 (2.0)	4 (2.2)	3 (1.8)	7 (2.0)	
American Indian/Alaska Native	2 (1.0)	0	2 (0.5)	4 (2.2)	2 (1.2)	6 (1.7)	
Multiple	11 (5.7)	3 (1.5)	14 (3.5)	3 (1.7)	1 (0.6)	4 (1.2)	
Missing	0	0	0	0	1 (0.6)	1 (0.3)	
Weight, mean ± SD, kg	91.85 ± 20.075	95.44 ± 21.685	93.70 ± 20.974	93.97 ± 19.516	93.39 ± 19.437	93.69 ± 19.452	.992
BMI, mean ± SD, kg/m^2	32.84 ± 6.693	34.03 ± 6.475	33.45 ± 6.600	33.59 ± 5.799	33.44 ± 5.942	33.52 ± 5.860	.887
BMI range, n (%)							.005
< 18.5 kg/m^2	1 (0.5)	0	1 (0.3)	0	0	0	
≥ 18.5 to < 25 kg/m^2	26 (13.5)	16 (7.8)	42 (10.6)	16 (18.9)	11 (6.6)	27 (7.8)	
≥ 25 to < 30 kg/m^2	44 (22.9)	52 (25.2)	96 (24.1)	31 (17.2)	40 (24.0)	71 (20.5)	
≥ 30 to < 35 kg/m^2	52 (27.1)	47 (22.8)	99 (24.9)	51 (28.3)	49 (29.3)	100 (28.8)	
≥ 35 to < 40 kg/m^2	30 (15.6)	43 (20.9)	73 (18.3)	56 (31.1)	41 (24.6)	97 (28.0)	
≥ 40 kg/m^2	39 (20.3)	48 (23.3)	87 (21.9)	26 (14.4)	26 (15.6)	52 (15.0)	
Met criterion for obesity							.051
Yes (BMI ≥ 30 kg/m^2)	121 (63.0)	138 (67.0)	259 (65.1)	133 (73.9)	116 (69.5)	249 (71.8)	
No (BMI < 30 kg/m^2)	71 (37.0)	68 (33.0)	139 (34.9)	47 (26.1)	51 (30.5)	98 (28.2)	

[a]Based comparisons of the overall treatment populations for each subgroup using *t* tests for continuous measures and χ^2/Fisher exact test for categorical measures.
Abbreviations: BMI = body mass index, LDX = lisdexamfetamine dimesylate, NA = not applicable, SD = standard deviation.

Data Presentation and Statistical Analyses

Across endpoints, data are reported by gender (men vs women) and age (< 40 vs ≥ 40 years) in each treatment arm; the overall treatment population (placebo and LDX treatment arms combined) is also reported for baseline demographic and clinical characteristics. For all inferential analyses, reported *P* values are nominal (descriptive and not adjusted for multiplicity).

Baseline demographic and clinical characteristics are reported for the pooled safety analysis set (randomized participants taking ≥ 1 study drug dose and having ≥ 1 postbaseline safety assessment). The data are reported descriptively, with group differences based on comparisons of the overall treatment population for each subgroup using *t* tests for continuous measures and χ^2 or Fisher exact test for categorical measures.

Efficacy was assessed in the pooled full analysis set (FAS; randomized participants taking ≥ 1 study drug dose and having ≥ 1 postbaseline primary efficacy assessment). Data are reported using descriptive and inferential statistics. Least squares (LS) mean treatment differences (LDX – placebo) with 95% CIs for the change from baseline in BE days/wk at weeks 11–12 and for Y-BOCS-BE total score at week 12 were calculated using mixed-effects models for repeated measures over all postbaseline visits during the double-blind treatment phase, with change from baseline as the outcome variable; treatment group, visit, and subgroup and their interactions as factors; and baseline value as a covariate, with its interactions with visit and subgroup also in the model. For the dichotomized CGI-I, the percentage of improved participants (scores of 1 [very much improved] or 2 [much improved]) at week 12/ET and the risk difference (LDX – placebo) with 95% CIs based on the binomial proportion for participants categorized as improved are reported. For the dichotomized CGI-I, χ^2 tests were used for within-subgroup comparisons, and Breslow-Day tests were used for the test of interaction.

Safety and tolerability are reported using descriptive statistics in the pooled safety analysis set. The frequencies of overall treatment-emergent AEs (TEAEs), specific TEAEs, and TEAEs considered by study investigators to be serious, severe, or related to LDX or to have led to discontinuation are reported. Vital sign data include changes from baseline at weeks 11/12/ET and observations of potentially clinically important (PCI) changes in SBP (≥ 140 mm Hg and an increase > 10 mm Hg at any postbaseline visit), DBP (≥ 90 mm Hg and an increase > 10 mm Hg at any postbaseline visit), and pulse (≥ 110 bpm and an increase > 15 bpm at any postbaseline visit).

RESULTS

Disposition and Demographics

The pooled safety analysis set and FAS included 745 and 724 participants, respectively (men, n = 105 and n = 97; women, n = 640 and n = 627; < 40 years old, n = 398 and n = 386; ≥ 40 years old, n = 347 and n = 338). Most participants in the pooled safety analysis set identified themselves as being White, with the second highest percentage of participants identifying themselves as being Black/African American (Table 1). In regard to ethnicity, the majority of participants identified themselves as not being Hispanic or Latino (84.0%–91.0% across subgroups). Most participants had a BMI ≥ 30 kg/m^2, and an additional 17.2%–25.6% of participants across subgroups met criteria for being overweight (BMI ≥ 25 kg/m^2 to < 30 kg/m^2) (Table 1). Between genders, mean weight was nominally greater in men than in women (P < .001; Table 1). The only nominally significant demographic difference between ages was observed for BMI range (P = .005), with greater percentages of individuals < 40 years of age having BMIs < 30 kg/m^2 and ≥ 40 kg/m^2 (Table 1).

Adherence rates measured based on the total number of capsules taken ([(capsules dispensed – capsules returned) × 100]/total days of dosing) were high, with 738 of 743 (99.3%) participants having adherence rates between 80% and 120%. Only 5 participants across both studies had adherence rates < 80%.

Efficacy

Gender. The mean ± SD number of BE days/wk and of Y-BOCS-BE total scores were comparable between men and women at baseline and at end of study (Figure 1A and 1C). LS mean (95% CI) treatment differences for the change from baseline in BE days/wk at weeks 11 to 12 and for Y-BOCS-BE total score at week 12 nominally favored LDX in men and women (both P < .001), with no significant gender-by-treatment interactions (Table 2). Higher percentages of participants were improved on the CGI-I at week 12/ET with LDX compared with placebo in men and women (Figure 1E), with risk differences nominally favoring LDX (both P < .001). There was not a significant gender-by-treatment interaction (Table 2).

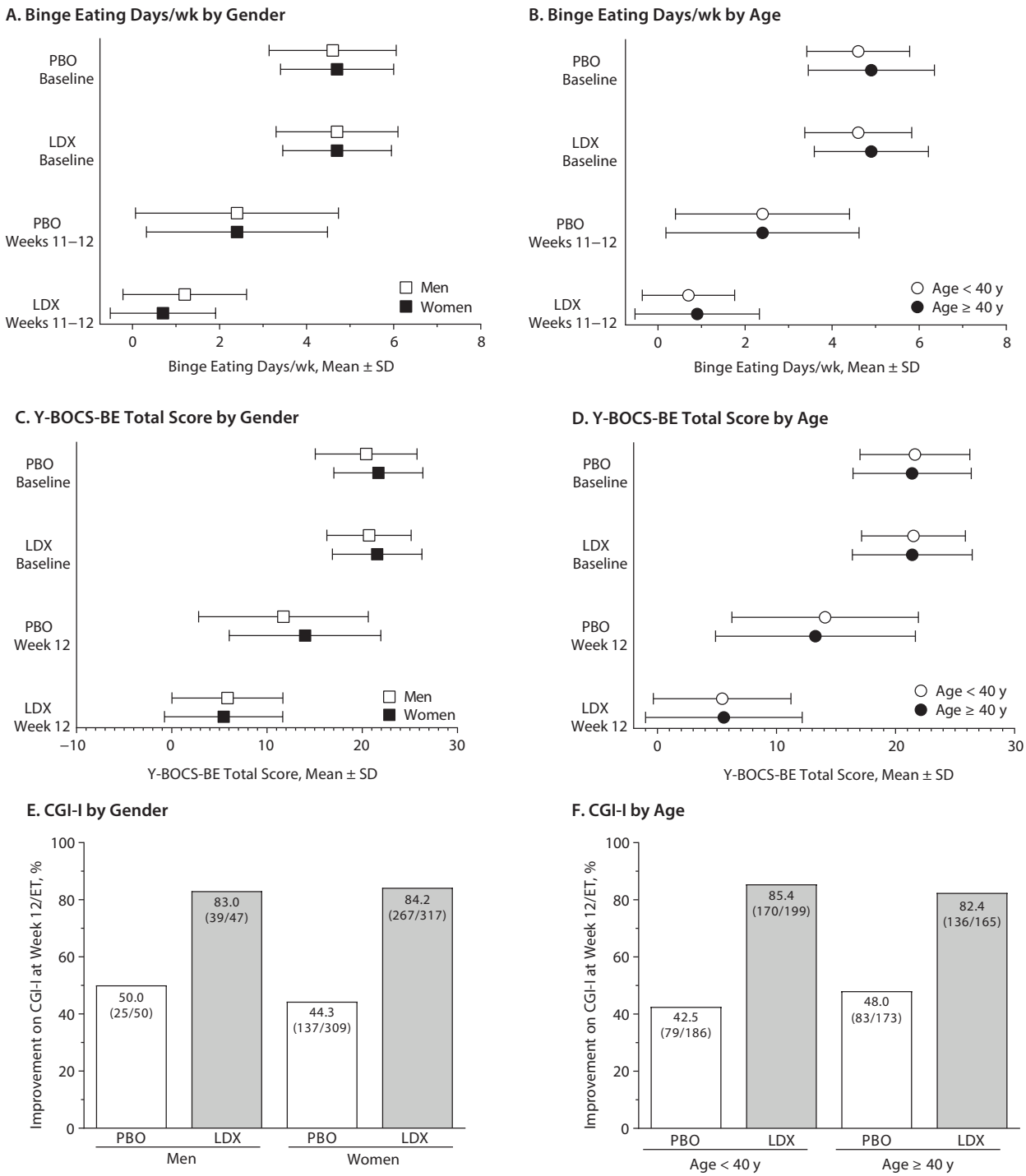
Age. The mean ± SD number of BE days/wk and of Y-BOCS-BE total scores were comparable across age subgroups at baseline and at end of study (Figure 1B and 1D). LS mean (95% CI) treatment differences for changes from baseline in BE days/wk at weeks 11–12 and for Y-BOCS-BE total score at week 12 nominally favored LDX in both age subgroups (both P < .001), with no significant age-by-treatment interactions (Table 2). Higher percentages of participants were improved on the CGI-I at week 12/ET with LDX compared with placebo in both age subgroups (Figure 1F), with risk differences nominally favoring LDX (both P < .001). There was no significant age-by-treatment interaction (Table 2).

Safety and Tolerability

Gender. TEAE frequency was numerically greater with LDX compared with placebo in men (any, related to study drug, severe) and women (any, related to study drug, leading to discontinuation, severe) (Table 3). Frequencies of TEAEs with LDX were numerically greater in women compared with men, with the exception that serious and severe TEAEs occurred more frequently in men. The most frequently reported TEAEs with LDX occurring in ≥ 5% of participants and at ≥ 2 times the placebo rate were dry mouth, decreased appetite, decreased weight, and diarrhea in men and dry mouth, insomnia, decreased appetite, constipation, increased heart rate, feeling jittery, and anxiety in women (Table 3). TEAEs occurring more frequently (≥ 5% of participants with ≥ 2-fold differences between subgroups) with LDX were decreased weight and diarrhea in men and headache, nausea, fatigue, constipation, increased heart rate, feeling jittery, and anxiety in women.

Blood pressure decreased with placebo and increased with LDX in both men and women (Table 4), with LDX-associated increases being numerically greater in women compared with men. Increases in pulse from baseline with LDX were numerically greater compared with placebo and were comparable in men and women (Table 4). Percentages

Figure 1. Binge Eating Days per Week (A and B),[a] Y-BOCS-BE Total Score (C and D),[b] and Dichotomized Improvement on the CGI-I (E and F)[c] by Gender, Age, and Treatment Group, Pooled FAS



[a]Sample size by gender (men at baseline [PBO, n = 50; LDX, n = 47] and weeks 11–12 [PBO, n = 40; LDX, n = 38]; women at baseline [PBO, n = 310; LDX, n = 317] and weeks 11–12 [PBO, n = 262; LDX, n = 266]) and age (< 40 years at baseline [PBO, n = 187; LDX, n = 199] and weeks 11–12 [PBO, n = 156; LDX, n = 164]; ≥ 40 years at baseline [PBO, n = 173; LDX, n = 165] and weeks 11–12 [PBO, n = 146; LDX, n = 140]).

[b]Sample size by gender (men at baseline [PBO, n = 50; LDX, n = 47] and week 12 [PBO, n = 40; LDX, n = 39]; women at baseline [PBO, n = 309; LDX, n = 315] and week 12 [PBO, n = 266; LDX, n = 274]) and age (< 40 years at baseline [PBO, n = 187; LDX, n = 198] and week 12 [PBO, n = 158; LDX, n = 169]; ≥ 40 years at baseline [PBO, n = 172; LDX, n = 164] and week 12 [PBO, n = 148; LDX, n = 144].

[c]Sample size by gender (men at week 12/ET [PBO, n = 50; LDX, n = 47]; women at week 12/ET [PBO, n = 309; LDX, n = 317]) and age (< 40 years at week 12/ET [PBO, n = 186; LDX, n = 199]; ≥ 40 years at week 12/ET [PBO, n = 173; LDX, n = 165]). Improvement defined as CGI-I scores of 1 (very much improved) or 2 (much improved).

Abbreviations: CGI-I = Clinical Global Impressions–Improvement, ET = early termination, FAS = full analysis set, LDX = lisdexamfetamine dimesylate, PBO = placebo, SD = standard deviation, Y-BOCS-BE = Yale-Brown Obsessive Compulsive Scale modified for Binge Eating.

Table 2. Summary of Treatment Effects on Efficacy-Related Endpoints, Pooled FAS

	Men		Women		Age < 40 y		Age ≥ 40 y	
	Placebo	LDX	Placebo	LDX	Placebo	LDX	Placebo	LDX
Binge eating days/wk								
n	40	38	262	266	156	164	146	140
Mean ± SD change from baseline	−2.2 ± 2.16	−3.6 ± 1.43	−2.4 ± 2.13	−4.0 ± 1.57	−2.2 ± 2.01	−3.9 ± 1.44	−2.5 ± 2.25	−4.0 ± 1.68
LS mean (95% CI) treatment difference for change from baseline at weeks 11–12[a]	−1.32 (−2.03, −0.62)		−1.56 (−1.83, −1.28)		−1.52 (−1.87, −1.17)		−1.52 (−1.90, −1.15)	
Nominal *P* value	< .001		< .001		< .001		< .001	
Interaction	0.386				0.721			
Y-BOCS-BE total score								
n	40	39	266	272	158	168	148	143
Mean ± SD change from baseline at week 12	−8.60 ± 7.056	−15.26 ± 6.912	−7.64 ± 8.722	−16.08 ± 7.072	−7.38 ± 8.346	−16.27 ± 6.778	−8.17 ± 8.710	−15.64 ± 7.359
LS mean (95% CI) treatment difference for change from baseline[a]	−6.00 (−9.01, −3.00)		−7.99 (−9.16, −6.83)		−7.92 (−9.42, −6.41)		−7.42 (−9.02, −5.82)	
Nominal *P* value	< .001		< .001		< .001		< .001	
Interaction	0.226				0.657			
CGI-I								
Risk difference (95% CI) for improved at week 12/ET[b]	33.0 (15.4, 50.5)		39.9 (33.1, 46.7)		43.0 (34.3, 51.6)		34.4 (25.0, 43.9)	
Nominal *P* value	< .001		< .001		< .001		< .001	
Interaction	0.537				0.211			

[a]From a mixed-effects model for repeated measures over all postbaseline visits during the double-blind treatment phase, with change from baseline as the outcome variable; treatment group, visit, and subgroup (men vs women; age < 40 years vs ≥ 40 years) and their interactions as factors; baseline value as a covariate and its interactions with visit and subgroup also in the model.

[b]Difference calculated as LDX − placebo, with the 95% CIs based on binomial proportion (improved defined as scores of 1 [very much improved] or 2 [much improved]); χ^2 tests were used for comparisons within subgroups; Breslow-Day tests were used for the test of interaction.

Abbreviations: CGI-I = Clinical Global Impressions–Improvement, ET = early termination, FAS = full analysis set, LDX = lisdexamfetamine dimesylate, LS = least squares, SD = standard deviation, Y-BOCS-BE = Yale-Brown Obsessive Compulsive Scale modified for Binge Eating.

Table 3. Summary of TEAEs, Pooled Safety Analysis Set

	Men		Women		Age < 40 y		Age ≥ 40 y	
TEAE, n (%)	Placebo (n = 56)	LDX (n = 49)	Placebo (n = 316)	LDX (n = 324)	Placebo (n = 192)	LDX (n = 206)	Placebo (n = 180)	LDX (n = 167)
Any TEAE	29 (51.8)	34 (69.4)	175 (55.4)	264 (81.5)	109 (56.8)	166 (80.6)	95 (52.8)	132 (79.0)
Serious TEAEs	1 (1.8)	1 (2.0)	3 (0.9)	3 (0.9)	1 (0.5)	2 (1.0)	3 (1.7)	2 (1.2)
TEAEs related to study drug	18 (32.1)	26 (53.1)	109 (34.5)	227 (70.1)	74 (38.5)	139 (67.5)	53 (29.4)	114 (68.3)
TEAEs leading to discontinuation	3 (5.4)	2 (4.1)	6 (1.9)	17 (5.2)	2 (1.0)	11 (5.3)	7 (3.9)	8 (4.8)
Severe TEAEs	1 (1.8)	6 (12.2)	11 (3.5)	18 (5.6)	6 (3.1)	13 (6.3)	6 (3.3)	11 (6.6)
TEAEs occurring in ≥ 5% of any group								
Dry mouth	2 (3.6)	10 (20.4)	25 (7.9)	126 (38.9)	17 (8.9)	73 (35.4)	10 (5.6)	63 (37.7)
Headache	3 (5.4)	4 (8.2)	30 (9.5)	54 (16.7)	19 (9.9)	32 (15.5)	14 (7.8)	26 (15.6)
Insomnia	5 (8.9)	7 (14.3)	15 (4.7)	46 (14.2)	11 (5.7)	28 (13.6)	9 (5.0)	25 (15.0)
Decreased appetite	2 (3.6)	6 (12.2)	7 (2.2)	22 (6.8)	4 (2.1)	13 (6.3)	5 (2.8)	15 (9.0)
Decreased weight	0	4 (8.2)	0	10 (3.1)	0	7 (3.4)	0	7 (4.2)
Nausea	1 (1.8)	2 (4.1)	21 (6.6)	30 (9.3)	15 (7.8)	23 (11.2)	7 (3.9)	9 (5.4)
Irritability	2 (3.6)	3 (6.1)	17 (5.4)	22 (6.8)	11 (5.7)	20 (9.7)	8 (4.4)	5 (3.0)
Diarrhea	2 (3.6)	4 (8.2)	5 (1.6)	12 (3.7)	4 (2.1)	9 (4.4)	3 (1.7)	7 (4.2)
Fatigue	2 (3.6)	0	17 (5.4)	24 (7.4)	11 (5.7)	13 (6.3)	8 (4.4)	11 (6.6)
Increased blood pressure	4 (7.1)	2 (4.1)	3 (0.9)	11 (3.4)	4 (2.1)	6 (2.9)	3 (1.7)	7 (4.2)
Constipation	0	1 (2.0)	5 (1.6)	20 (6.2)	2 (1.0)	14 (6.8)	3 (1.7)	7 (4.2)
Increased heart rate	1 (1.8)	0	4 (1.3)	19 (5.9)	3 (1.6)	13 (6.3)	2 (1.1)	6 (3.6)
Feeling jittery	0	1 (2.0)	2 (0.6)	20 (6.2)	1 (0.5)	12 (5.8)	1 (0.6)	9 (5.4)
Initial insomnia	0	2 (4.1)	5 (1.6)	15 (4.6)	4 (2.1)	11 (5.3)	1 (0.6)	6 (3.6)
Anxiety	1 (1.8)	1 (2.0)	2 (0.6)	19 (5.9)	1 (0.5)	10 (4.9)	2 (1.1)	10 (6.0)

Abbreviations: LDX = lisdexamfetamine dimesylate, TEAE = treatment-emergent adverse event.

Table 4. Summary of Vital Signs, Pooled Safety Analysis Set

	Men		Women		Age < 40 y		Age ≥ 40 y	
	Placebo	LDX	Placebo	LDX	Placebo	LDX	Placebo	LDX
SBP								
Mean ± SD baseline value, mm Hg[a]	125.3 ± 7.83	121.7 ± 9.44	114.6 ± 9.96	114.1 ± 10.50	114.3 ± 9.74	112.8 ± 9.83	118.3 ± 10.68	118.0 ± 11.01
Mean ± SD change from baseline at week 11/12/ET, mm Hg[b]	−2.0 ± 8.13	0.1 ± 10.94	−2.6 ± 8.88	0.9 ± 10.46	−2.0 ± 8.08	0.7 ± 10.25	−3.1 ± 9.41	0.9 ± 10.86
SBP ≥ 140 mm Hg and increase > 10 mm Hg from baseline at any postbaseline visit, n/N (%)	5/56 (8.9)	4/48 (8.3)	10/314 (3.2)	15/322 (4.7)	2/190 (1.1)	6/204 (2.9)	13/180 (7.2)	13/166 (7.8)
DBP								
Mean ± SD baseline value, mm Hg[a]	78.1 ± 6.68	76.6 ± 8.31	75.7 ± 8.08	75.7 ± 7.82	74.8 ± 8.29	74.5 ± 7.93	77.4 ± 7.29	77.5 ± 7.51
Mean ± SD change from baseline at week 11/12/ET, mm Hg[b]	−1.2 ± 8.70	1.0 ± 8.57	−1.5 ± 6.88	1.5 ± 7.84	−1.0 ± 7.21	1.4 ± 8.19	−1.9 ± 7.12	1.5 ± 7.62
DBP ≥ 90 mm Hg and increase > 10 mm Hg from baseline at any postbaseline visit, n/N (%)	9/56 (16.1)	5/48 (10.4)	13/314 (4.1)	38/322 (11.8)	8/190 (4.2)	14/204 (6.9)	14/180 (7.8)	29/166 (17.5)
Pulse								
Mean ± SD baseline value, bpm[a]	70.0 ± 11.12	71.6 ± 12.12	71.7 ± 9.10	73.4 ± 9.86	72.1 ± 9.12	74.4 ± 10.57	70.8 ± 9.74	71.8 ± 9.52
Mean ± SD change from baseline at week 11/12/ET, bpm[b]	1.7 ± 10.76	5.3 ± 10.85	1.8 ± 8.48	5.4 ± 10.44	1.8 ± 8.82	5.1 ± 11.15	1.8 ± 8.90	5.8 ± 9.61
Pulse ≥ 110 bpm and increase > 15 bpm from baseline at any postbaseline visit, n/N (%)	1/56 (1.8)	1/48 (2.1)	1/314 (0.3)	10/322 (3.1)	1/190 (0.5)	9/204 (4.4)	1/180 (0.6)	2/166 (1.2)

[a]Sample size at baseline: men (PBO, n = 56; LDX, n = 49); women (PBO, n = 316; LDX, n = 324); age < 40 years (PBO, n = 192; LDX, n = 206); age ≥ 40 years (PBO, n = 180; LDX, n = 167).
[b]Sample size at week 11/12/ET: men (PBO, n = 56; LDX, n = 48); women (PBO, n = 314; LDX, n = 321); age < 40 years (PBO, n = 190; LDX, n = 203); age ≥ 40 years (PBO, n = 180; LDX, n = 166).
Abbreviations: DBP = diastolic blood pressure, ET = early termination, LDX = lisdexamfetamine dimesylate, SBP = systolic blood pressure, SD = standard deviation.

of participants exhibiting PCI changes in SBP or DBP were numerically higher with LDX compared with placebo in women, but not in men. Percentages of participants exhibiting PCI changes in pulse were numerically greater with LDX compared with placebo in men and women, with the differences between LDX and placebo being numerically greater in women than in men.

Age. TEAE frequency (overall, related to study drug, leading to discontinuation, and severe) was numerically greater with LDX compared with placebo in both age subgroups (Table 3), with TEAE frequencies with LDX being comparable between subgroups. The most frequently reported TEAEs with LDX occurring in ≥ 5% of participants and ≥ 2 times the placebo rate (Table 3) were dry mouth, insomnia, decreased appetite, constipation, increased heart rate, feeling jittery, and initial insomnia in participants < 40 years old and dry mouth, headache, insomnia, decreased appetite, feeling jittery, and anxiety in participants ≥ 40 years old. The TEAEs of nausea and irritability occurred more frequently with LDX (≥ 5% of participants with ≥ 2-fold differences between subgroups) in younger than older participants.

Blood pressure decreased with placebo and increased with LDX comparably in both age subgroups (Table 4). Pulse increased with LDX and placebo in both age subgroups, with LDX-associated increases being numerically greater than with placebo and comparable between ages (Table 4). The percentages of participants exhibiting PCI changes in SBP or DBP were numerically greater with LDX than placebo and in older compared with younger participants. The percentages of participants exhibiting PCI changes in pulse were numerically greater with LDX compared with placebo in both age subgroups and in younger compared with older participants treated with LDX.

DISCUSSION

This study is the first to examine differences in clinical characteristics and treatment response to LDX by gender and age in adults with BED. These post hoc analyses demonstrate 3 key findings. First, the clinical characteristics (age, racial distribution, mean BMI, and BMI distribution) of participants from these LDX studies did not differ as a function of gender or age (< 40 vs ≥ 40 years), with the exception of men weighing more than women. Second, LDX was nominally superior to placebo across gender and age subgroups as measured by reductions in BE days/wk and Y-BOCS-BE total score and by the percentage of participants categorized as improved on the CGI-I. There was no evidence of statistical interactions by gender or age. Third, the overall frequency of TEAEs and of vital sign changes was numerically greater with LDX

compared with placebo across gender and age, with some numerical differences observed between genders and ages.

The characteristics of participants (predominantly female with obesity [BMI ≥ 30 kg/m^2]) in these studies were consistent with reports that BED is more commonly observed in women than men[6–8,22,23] and that obesity is more common in individuals with BED than in individuals without an eating disorder.[6,8,24–27] These data do not provide evidence for differences in BE frequency or Y-BOCS-BE total scores across gender or age. This finding is consistent with studies that report that men and women diagnosed with *DSM-IV*–defined BED do not exhibit differences in BE frequency[9,28] and with reports indicating that the ratio of women to men does not significantly differ across *DSM-5*–defined BED severity levels, which is based on the number of BE episodes/wk.[22,23] Despite the fact that these data generally support the published literature, it should be noted that the lack of a difference in BE days/wk and Y-BOCS-BE total score at baseline in the current study could be related to the entry criteria, which stipulated that individuals have ≥ 3 BE days/wk during the 14 days before baseline and CGI-S scores ≥ 4 at screening and baseline. These criteria excluded individuals with milder BE symptoms. It is not known if the proportion of excluded individuals would have differed by gender or age.

Dose-optimized LDX produced nominally superior reductions in BE days/wk and Y-BOCS-BE total scores and was associated with nominally greater percentages of participants being improved on the dichotomized CGI-I than placebo in both gender and age subgroups, without evidence of statistically significant interactions by gender or age subgroup. To the best of our knowledge, there are limited published data describing the influence of gender or age on response to pharmacotherapy in adults with BED. In one study of adults diagnosed with BED being treated with cognitive behavioral therapy (CBT), fluoxetine, or CBT + fluoxetine, younger age and female gender were reported to be moderators of treatment response to pharmacotherapy.[10] The current findings are partially consistent with an analysis of 11 randomized controlled psychosocial treatment studies for BED, which did not find a main effect of gender for treatment outcome.[29] However, the aforementioned analysis did report a significant interaction of gender, treatment length, and shape/weight concerns on objective BE episode remission.[29] In this interaction, participants achieved higher rates of objective BE remission with longer treatment, and men with lower shape/weight concerns achieved sustained remission independent of treatment length compared with men having higher shape/weight concerns and with women having either any level of shape/weight concerns. In an exploratory study of predictors of response to psychosocial treatment in adults diagnosed with eating disorders, a significant relationship between baseline age (< 24 vs ≥ 24 years old) and treatment outcome was not observed.[30]

Regarding safety and tolerability, the only TEAEs reported across all subgroups with LDX in ≥ 5% of participants and ≥ 2 times the placebo rate were dry mouth and decreased appetite. Assessment of TEAEs by gender indicated that women treated with LDX reported TEAEs more frequently. Headache, fatigue, constipation, nausea, increased heart rate, feeling jittery, and anxiety were reported more frequently by women than by men treated with LDX; decreased weight and diarrhea were reported more frequently in men than women with LDX treatment. The overall TEAE frequency did not differ by age, but nausea and irritability were reported more frequently in individuals < 40 years old. LDX treatment produced small mean increases in blood pressure and pulse across gender and age subgroups, with the magnitude of changes being slightly greater in women compared with men and in older compared with younger participants.

These findings should be interpreted in light of several limitations. First, all analyses were conducted post hoc. Therefore, the data are descriptive, and reported *P* values are nominal (descriptive and unadjusted for multiple comparisons). Second, the small sample size for men limits the ability to interpret comparisons of within-subgroup treatment effects and between-gender interactions. Third, study entry criteria related to BED severity could have contributed to a floor effect that limited the ability to discern differences in BE frequency at baseline. Fourth, study participants did not have current psychiatric comorbidities, so it is not known how these findings generalize to a more diverse, real-world population of individuals diagnosed with BED. Lastly, this article focused on the influence of gender and age, but the influence of other factors, including the duration of BED diagnosis or of race or ethnicity on BED characteristics and treatment response, are also of interest. Therefore, it is important to further examine these factors in future studies.

CONCLUSIONS

These post hoc analyses from 2 phase 3 studies in adults with BED suggest that clinical characteristics of study participants diagnosed with BED and the effects of dose-optimized LDX treatment were generally comparable regardless of gender or age.

Submitted: May 24, 2018; accepted September 17, 2018.

Published online: February 26, 2019.

Potential conflicts of interest: **Dr Kornstein** has received research support from Pfizer, Allergan, Takeda, Palatin, and Marinus; has served as consultant to Shire, Pfizer, Lilly, Takeda, Allergan, Palatin, Sunovion, and Alkermes; and has received royalties from Guilford Press. **Drs Bliss** and **Madhoo** are employees of Shire, a member of the Takeda group of companies, and hold Takeda stock. **Dr Kando** is a former employee of Shire, a member of the Takeda group of companies, and holds Takeda stock and Johnson & Johnson stock. She is a current employee of Tris Pharma, Monmouth Junction, New Jersey.

Funding/support: This clinical research was funded by Shire Development LLC, Lexington, Massachusetts, a member of the Takeda group of companies.

Role of the sponsor: The sponsor of the studies included in these analyses was involved in the design of the studies, analysis of the data, and interpretation of the data. The manuscript was reviewed by staff of the sponsor, but the content of the manuscript and final approval for the decision to submit the manuscript were the decisions of the authors.

Previous presentation: These data were presented at the American Society for Clinical Psychopharmacology Annual Meeting (Miami Beach, Florida; May 29–June 2, 2017).

Acknowledgments: Under the direction of the authors, Craig Slawecki, PhD, an employee of Complete Healthcare Communications, LLC (CHC; North Wales, Pennsylvania), a CHC Group company, provided writing assistance for this manuscript. Shire Development (Lexington, Massachusetts), LLC, a member of the Takeda group of companies, provided funding to CHC for support in writing and editing this manuscript.

REFERENCES

1. Vyvanse [package insert]. Lexington, MA: Shire US Inc; 2017.
2. Gasior M, Hudson J, Quintero J, et al. A phase 3, multicenter, open-label, 12-month extension safety and tolerability trial of lisdexamfetamine dimesylate in adults with binge eating disorder. *J Clin Psychopharmacol*. 2017;37(3):315–322.
3. McElroy SL, Hudson J, Ferreira-Cornwell MC, et al. Lisdexamfetamine dimesylate for adults with moderate to severe binge eating disorder: results of two pivotal phase 3 randomized controlled trials. *Neuropsychopharmacology*. 2016;41(5):1251–1260.
4. McElroy SL, Hudson JI, Mitchell JE, et al. Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry*. 2015;72(3):235–246.
5. Hudson JI, McElroy SL, Ferreira-Cornwell MC, et al. Efficacy of lisdexamfetamine in adults with moderate to severe binge-eating disorder: a randomized clinical trial. *JAMA Psychiatry*. 2017;74(9):903–910.
6. Hudson JI, Hiripi E, Pope HG Jr, et al. The prevalence and correlates of eating disorders in the National Comorbidity Survey Replication. *Biol Psychiatry*. 2007;61(3):348–358.
7. Cossrow N, Pawaskar M, Witt EA, et al. Estimating the prevalence of binge eating disorder in a community sample from the United States: comparing *DSM-IV-TR* and *DSM-5* criteria. *J Clin Psychiatry*. 2016;77(8):e968–e974.
8. Kessler RC, Berglund PA, Chiu WT, et al. The prevalence and correlates of binge eating disorder in the World Health Organization World Mental Health Surveys. *Biol Psychiatry*. 2013;73(9):904–914.
9. Barry DT, Grilo CM, Masheb RM. Gender differences in patients with binge eating disorder. *Int J Eat Disord*. 2002;31(1):63–70.
10. Grilo CM, Masheb RM, Crosby RD. Predictors and moderators of response to cognitive behavioral therapy and medication for the treatment of binge eating disorder. *J Consult Clin Psychol*. 2012;80(5):897–906.
11. Suzuki Y, Tajiri M, Sugimoto A, et al. Sex differences in the effect of atomoxetine on the QT interval in adult patients with attention-deficit hyperactivity disorder. *J Clin Psychopharmacol*. 2017;37(1):27–31.
12. Sušilová L, Češková E, Hampel D, et al. Changes in BMI in hospitalized patients during treatment with antipsychotics, depending on gender and other factors. *Int J Psychiatry Clin Pract*. 2017;21(2):112–117.
13. Smith PH, Zhang J, Weinberger AH, et al. Gender differences in the real-world effectiveness of smoking cessation medications: findings from the 2010–2011 Tobacco Use Supplement to the Current Population Survey. *Drug Alcohol Depend*. 2017;178:485–491.
14. Scott J, Brichant-Petitjean C, Etain B, et al. A re-examination of antidepressant treatment-emergent mania in bipolar disorders: evidence of gender differences. *Acta Psychiatr Scand*. 2017;135(5):479–488.
15. Yang SJ, Kim SY, Stewart R, et al. Gender differences in 12-week antidepressant treatment outcomes for a naturalistic secondary care cohort: the CRESCEND study. *Psychiatry Res*. 2011;189(1):82–90.
16. Kornstein SG, Schatzberg AF, Thase ME, et al. Gender differences in treatment response to sertraline versus imipramine in chronic depression. *Am J Psychiatry*. 2000;157(9):1445–1452.
17. Wang GJ, Volkow ND, Telang F, et al. Evidence of gender differences in the ability to inhibit brain activation elicited by food stimulation. *Proc Natl Acad Sci U S A*. 2009;106(4):1249–1254.
18. Peacock K, Ketvertis KM. Menopause. *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2018.
19. First M, Spitzer R, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), Clinician Version*. Arlington, VA: American Psychiatric Publishing; 1997.
20. Guy W. Clinical Global Impressions. *ECDEU Assessment Manual for Psychopharmacology*. DHEW Publication No. 76-338. Rockville, MD: National Institute of Mental Health; 1976.
21. Deal LS, Wirth RJ, Gasior M, et al. Validation of the Yale-Brown Obsessive Compulsive Scale modified for Binge Eating. *Int J Eat Disord*. 2015;48(7):994–1004.
22. Grilo CM, Ivezaj V, White MA. Evaluation of the *DSM-5* severity indicator for binge eating disorder in a community sample. *Behav Res Ther*. 2015;66:72–76.
23. Grilo CM, Ivezaj V, White MA. Evaluation of the *DSM-5* severity indicator for binge eating disorder in a clinical sample. *Behav Res Ther*. 2015;71:110–114.
24. Sandberg RM, Dahl JK, Vedul-Kjelsås E, et al. Health-related quality of life in obese presurgery patients with and without binge eating disorder, and subdiagnostic binge eating disorders. *J Obes*. 2013;2013:878310.
25. Fandiño J, Moreira RO, Preissler C, et al. Impact of binge eating disorder in the psychopathological profile of obese women. *Compr Psychiatry*. 2010;51(2):110–114.
26. Kolotkin RL, Westman EC, Østbye T, et al. Does binge eating disorder impact weight-related quality of life? *Obes Res*. 2004;12(6):999–1005.
27. Barnes RD, Ivezaj V, Grilo CM. An examination of weight bias among treatment-seeking obese patients with and without binge eating disorder. *Gen Hosp Psychiatry*. 2014;36(2):177–180.
28. Tanofsky MB, Wilfley DE, Spurrell EB, et al. Comparison of men and women with binge eating disorder. *Int J Eat Disord*. 1997;21(1):49–54.
29. Shingleton RM, Thompson-Brenner H, Thompson DR, et al. Gender differences in clinical trials of binge eating disorder: an analysis of aggregated data. *J Consult Clin Psychol*. 2015;83(2):382–386.
30. Cooper Z, Allen E, Bailey-Straebler S, et al. Predictors and moderators of response to enhanced cognitive behaviour therapy and interpersonal psychotherapy for the treatment of eating disorders. *Behav Res Ther*. 2016;84:9–13.