A Post Hoc Analysis of the Effect of Weight on Efficacy in Depressed Patients Treated With Desvenlafaxine 50 mg/d and 100 mg/d

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ABSTRACT

Objective: To assess the effect of baseline body mass index (BMI) on efficacy and weight change in adults with major depressive disorder (MDD) treated with desvenlafaxine or placebo in a pooled, post hoc analysis.

Method: Adults with MDD were randomly assigned to placebo or desvenlafaxine (50 mg or 100 mg) in 8 short-term, double-blind studies and 1 longer-term randomized withdrawal study (the studies were published between 2007 and 2013). Change from baseline in 17-item Hamilton Depression Rating Scale (HDRS-17) total score at week 8 was analyzed in normal (BMI ≤ 25 kg/m^2), overweight (25 kg/m^2 < BMI ≤ 30 kg/m^2), and obese (BMI > 30 kg/m^2) subgroups using analysis of covariance (ANCOVA). Weight change was analyzed in BMI subgroups using ANCOVA and a mixed-effects model for repeated measures.

Results: Desvenlafaxine 50 mg/d or 100 mg/d improved HDRS-17 scores significantly from baseline to week 8 (last observation carried forward) versus placebo in all BMI subgroups (normal: n = 1,122; overweight: n = 960; obese: n = 1,302; all $P \leq .0027$); improvement was greatest in normal BMI patients. There was a statistically significant decrease in weight (< 1 kg) with short-term desvenlafaxine 50 mg/d and 100 mg/d versus placebo in all BMI subgroups (all $P < .0001$). In the randomized withdrawal study (n = 548), no statistically significant difference in weight was observed for desvenlafaxine versus placebo in any BMI subgroup. Baseline BMI predicted weight change in short-term and longer-term desvenlafaxine treatment.

Conclusions: Desvenlafaxine significantly improved symptoms of depression versus placebo regardless of baseline BMI. In all BMI subgroups, desvenlafaxine was associated with statistically significant weight loss (< 1 kg) versus placebo over 8 weeks, but no significant differences longer term.

Trial Registration: ClinicalTrials.gov identifiers: NCT00072774, NCT00277823, NCT00300378, NCT00384033, NCT00798707, NCT00863798, NCT01121484, NCT00824291, NCT00887224

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The incidence of obesity is reported to be higher among depressed individuals than in the general population,[1] but the nature of the relationship between body weight and depression is complex.[2] Meta-analyses of prospective cohort[3] and community-based studies[4] suggest that obesity is associated with the development of depressive symptoms and, conversely, that depression predicts overweight and obesity. The foregoing observations were confirmed in an analysis specifically designed to assess the bidirectional relationship between body weight and depression using data collected over a 10-year period in the Nurses' Health Study (N = 65,955 women)[5]: depression at baseline increased the odds of becoming overweight (adjusted odds ratio [95% CI]: 1.19 [1.13–1.24]) or obese (1.82 [1.73–1.92]), and baseline overweight (1.16 [1.11–1.21]) and obesity (1.63 [1.56–1.71]) were associated with an increased risk of depression over the 10-year period. The interaction between weight and depressive symptoms is further complicated by the effect of antidepressant treatment on body weight during acute and long-term treatment.[6]

While achievement of remission from depression is a primary consideration in treatment decisions for patients with major depressive disorder (MDD), the selection of an antidepressant without significant effect on weight, among medications with similar efficacy, is recommended—particularly in the treatment of patients who are overweight or obese.[2,7] Weight change is a common concern during antidepressant treatment for MDD and can negatively affect adherence during long-term treatment.[8] Moreover, patient weight or body mass index (BMI) at baseline may affect weight change during antidepressant treatment[9,10] and also may influence the effectiveness of antidepressant drugs.[11–14]

Desvenlafaxine (administered as desvenlafaxine succinate) is a serotonin-norepinephrine reuptake inhibitor (SNRI) approved for the treatment of adults with MDD.[15,16] Weight change during treatment with desvenlafaxine has been assessed at doses up to 400 mg/d; however, the relationship between baseline BMI and weight change during desvenlafaxine treatment has not been determined.[17] The effect of baseline BMI on efficacy and weight during treatment with desvenlafaxine 50 mg/d and 100 mg/d, the doses approved for treatment of MDD, was therefore examined in this post hoc analysis of data from 8 short-term and 1 longer-term double-blind, placebo-controlled studies of patients with MDD.[18–26] The primary objectives of the analysis were to assess the effect of baseline BMI on efficacy outcomes and weight change in adults with MDD treated with desvenlafaxine 50 mg/d or 100 mg/d versus placebo.

Clinical Points

- Desvenlafaxine 50 mg/d and 100 mg/d effectively reduced the symptoms of depression regardless of body mass index (BMI) at baseline.
- In all BMI subgroups, desvenlafaxine was associated with a statistically significant mean weight loss (< 1 kg) during acute treatment for MDD and no significant weight change compared with placebo after longer-term treatment.
- Baseline BMI predicted both response to treatment and weight change: slightly greater improvement in depressive symptoms was observed in patients with normal BMI, and short-term weight loss was greatest for patients who were obese at baseline.

METHOD

Data Set

The post hoc analysis was conducted based on a preplanned statistical analysis plan. Patient-level data were pooled from 8 short-term, multicenter, randomized, double-blind, placebo-controlled fixed-dose studies of desvenlafaxine in MDD (published between 2007 and 2013; ClinicalTrials.gov identifiers: NCT00072774, NCT00277823, NCT00300378, NCT00384033, NCT00798707, NCT00863798, NCT01121484, NCT00824291).[18–25] At the time these analyses were conducted, this study set comprised all available short-term, placebo-controlled studies in MDD conducted by the sponsor company (Pfizer) that included fixed-dose desvenlafaxine 50-mg or 100-mg treatment arms.

The pooled short-term studies were of similar design. Patients were randomly assigned to receive placebo or a fixed dose of desvenlafaxine (or duloxetine 60 mg/d in 1 trial[21]); data from placebo and desvenlafaxine 50-mg/d and 100-mg/d treatment arms only were included in this analysis. Six studies were 8 weeks in duration,[18–23] 1 study[24] was 10 weeks in duration with a week 8 primary endpoint, and 1 study[25] continued for 12 weeks. The primary efficacy outcome for each study was change from baseline in the 17-item Hamilton Depression Rating Scale[27] (HDRS-17) total score at endpoint.

A 12-month, randomized withdrawal study (published in 2013; ClinicalTrials.gov identifier: NCT00887224)[26] was analyzed separately for weight change only. The study consisted of a 20-week, open-label treatment period (8-week response phase + 12-week stability phase) and a 6-month, double-blind, placebo-controlled, randomized withdrawal period. All enrolled patients received 8-week, open-label treatment with desvenlafaxine 50 mg/d (response phase), and 8-week responders received open-label desvenlafaxine 50 mg/d for an additional 12 weeks (stability phase). Patients with continued stable response at open-label week 20 were randomly assigned to receive 6-month, double-blind treatment with placebo or desvenlafaxine 50 mg/d (1:1) after completion of the open-label period.

Patients

Enrollment criteria for patients in the studies in this analysis have been described previously.[18–26] Briefly, all studies enrolled adult outpatients with a diagnosis of MDD consistent with criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[28] or the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision,[29] with depressive symptoms for at least 30 days. Patients also met depression scale score criteria at screening and baseline (HDRS-17 total score ≥ 20 or Montgomery-Asberg Depression Rating Scale[30] [MADRS] total score ≥ 25). Eight of the 9 studies enrolled male or female patients at least 18 years of age (or ≥ 20 years in Japan), with an upper age limit of 75 years in 1 study. One of the short-term studies[24] enrolled perimenopausal and postmenopausal women only (aged 40 to 70 years). Exclusion criteria for each study were designed to select a sample of medically stable patients with a principal diagnosis of MDD (excluding bipolar and psychotic depression).

Assessments

The primary endpoint for the post hoc efficacy analysis was change from baseline in HDRS-17 total score. Other efficacy endpoints included change from baseline in MADRS total score and Clinical Global Impressions–Severity (CGI-S)[31] and Sheehan Disability Scale[32] (SDS) scores and change from baseline in the World Health Organization 5-item Well-Being Index[33] (WHO-5; collected in 6 short-term studies). Rates of HDRS-17 response (defined as ≥ 50% reduction from baseline in HDRS-17 total score),[34] HDRS-17 remission (HDRS-17 total score ≤ 7),[35] MADRS response (≥ 50% reduction in MADRS total score),[34] and MADRS remission (MADRS total score ≤ 10)[36] were also determined.

Height was measured at the screening visit in all studies. In the short-term studies, weight was collected at baseline and weeks 1 (7 studies only), 2, 3 (6 studies), 4 (7 studies), 6, and 8. In the randomized withdrawal study, weight was collected at baseline and weeks 1, 2, 3, 4, 6, 8, 12, 16, and 20 (open-label phase) and weeks 21, 22, 23, 24, 26, 30, 34, 38, 42, and 46 (double-blind phase). Baseline BMI was calculated based on height at screening and weight at baseline visit.

Statistical Analysis

The post hoc efficacy analysis was based on the desvenlafaxine 50-mg/d and 100-mg/d and placebo arms in the pooled short-term studies only. The intent-to-treat (ITT) population was defined for the pooled studies as all patients who took at least 1 dose of study drug and had a baseline and at least 1 primary efficacy evaluation after the first dose of double-blind study drug.

Treatment effects on continuous efficacy outcomes were analyzed using an analysis of covariance (ANCOVA) model with treatment, study, and baseline in the model. Categorical outcomes were analyzed using logistic regression with study in the model. Three subgroups were defined on the basis of baseline BMI: normal (BMI ≤ 25 kg/m^2), overweight (25 kg/m^2 < BMI ≤ 30 kg/m^2), and obese (BMI > 30 kg/m^2). An

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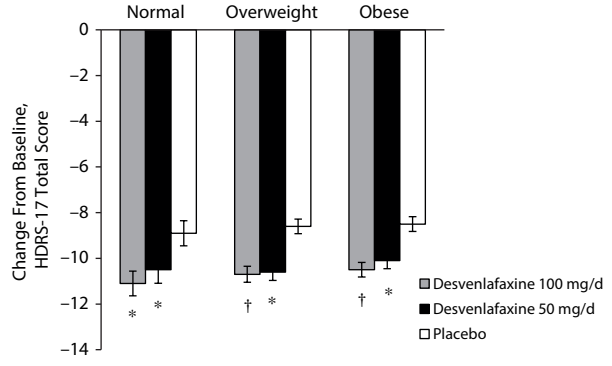
Table 1. Safety Population Baseline Demographics and Clinical Characteristics

Characteristic	Pooled Short-Term Studies: Desvenlafaxine 50 mg (n = 1,425)	Pooled Short-Term Studies: Desvenlafaxine 100 mg (n = 574)	Pooled Short-Term Studies: Placebo (n = 1,400)	Long-Term Study (n = 874)[a,b]
Age, y				
Mean	43.7	42.2	43.3	45.0
Range	18–86	18–78	18–85	18–87
Sex, n (%)				
Female	981 (68.8)	366 (63.8)	953 (68.1)	608 (69.6)
Race, n (%)				
White	1,033 (72.5)	457 (79.6)	1,001 (71.5)	729 (83.4)
Black	217 (15.2)	70 (12.2)	192 (13.7)	55 (6.3)
Asian	132 (9.3)	12 (2.1)	139 (9.9)	9 (1.0)
Other	43 (3.0)	35 (6.1)	68 (4.9)	81 (9.3)
Weight, kg				
Mean (SD)	83.3 (23.3)	81.7 (21.0)	81.6 (22.5)	77.2 (19.5)
BMI category, n (%)[c]				
Underweight	37 (2.6)	13 (2.3)	36 (2.6)	24 (2.8)
Normal	409 (28.7)	190 (33.1)	446 (31.8)	321 (36.7)
Overweight	399 (28.0)	166 (28.9)	399 (28.5)	271 (31.0)
Obese	580 (40.7)	205 (35.7)	519 (37.1)	258 (29.5)
Baseline HDRS-17 total score				
Mean (SD)	23.0 (3.1)	23.7 (2.6)	23.1 (3.1)	24.2 (2.8)

[a]Twenty weeks of open-label desvenlafaxine 50 mg/d, followed by 6 months of double-blind desvenlafaxine 50 mg/d or placebo.
[b]From open-label baseline.
[c]BMI categories: normal = BMI ≤ 25 kg/m^2, overweight = 25 kg/m^2 < BMI ≤ 30 kg/m^2, obese = BMI > 30 kg/m^2.
Abbreviations: BMI = body mass index, HDRS-17 = 17-item Hamilton Depression Rating Scale.

Figure 1. HDRS-17 Total Score Mean (SE) Change From Baseline at Week 8 (last observation carried forward) by Baseline BMI[a]



[a]Normal: BMI ≤ 25 kg/m^2, overweight: 25 kg/m^2 < BMI ≤ 30 kg/m^2, obese: BMI > 30 kg/m^2.
*P < .001 vs placebo.
†P < .01 vs placebo.
Abbreviations: BMI = body mass index, HDRS-17 = 17-item Hamilton Depression Rating Scale.

underweight subgroup (BMI < 18.5 kg/m^2) was collapsed into the normal group due to the low group sample sizes. Efficacy analyses were conducted for the overall pooled population and separately for the 3 baseline BMI subgroups. For all efficacy endpoints, the analysis was performed for each week using observed cases and at week 8 using the last observation carried forward (LOCF) approach for handling missing data, with the exception of the MADRS in the 12-week study. For that study, week 12 (LOCF) data were used because MADRS data were not collected at week 8. Baseline BMI (as a continuous variable) was also examined as a predictor of change from baseline in HDRS-17 total score using regression analysis, response and remission using logistic regression, and time to response (first week with ≥ 50% decrease in HDRS-17 total score) using Cox regression, assessed overall and for each treatment.

The effect of treatment on weight was analyzed using ANCOVA, with treatment, study, and baseline in the model, in the overall population and in the 3 baseline BMI subgroups. Weight change was assessed in the pooled short-term studies using observed cases data at weeks 1–4, 6, and 8 and at week 8 LOCF, and in the randomized withdrawal study double-blind phase at weeks 1–4, 6, 10, 14, 18, 22, and 26. The mean weight change over time was also assessed using a mixed-effects model for repeated measures. In the pooled studies, weight change at endpoint was summarized for HDRS-17 responders and remitters and for nonresponders and nonremitters.

Baseline BMI (as a continuous variable) was examined as a predictor of change in weight and BMI at week 8 (LOCF), overall and for each treatment, using regression analysis. The proportions of patients with clinically meaningful increases or decreases in body weight (≥ 7% change from baseline) were analyzed using Fisher exact test by BMI subgroup.

RESULTS

Patients

A total of 3,399 patients took at least 1 dose of study drug in the pooled, short-term studies and were included in the safety population for the pooled post hoc analysis. Of those, two-thirds were either overweight or obese at baseline: 1,131 (33.3%) had a BMI in the normal (or underweight) range; 964 (28.4%) were overweight; and 1,304 (38.4%) were obese. A total of 3,384 patients in the pooled studies (1,122 normal; 960 overweight; and 1,302 obese) had at least 1 postbaseline primary efficacy assessment and were included in the ITT population. The randomized withdrawal study enrolled 874 patients in the 20-week open-label phase (normal BMI: n = 345 [39.5%], overweight: n = 271 [31.0%], obese: n = 258 [29.5%]); 548 patients were randomized in the subsequent 6-month, double-blind phase, and 542 had at least 1 on-therapy weight assessment in the double-blind phase and were included in the weight change analysis. Baseline demographic and clinical characteristics were generally similar between treatment groups in the pooled short-term studies and the randomized withdrawal study (Table 1).

Efficacy

The HDRS-17 total scores improved significantly from baseline to week 8 (LOCF) for desvenlafaxine 50 mg/d and 100 mg/d compared with placebo for all BMI subgroups (all P ≤ .0027, Figure 1). The

Table 2. Secondary Efficacy Outcome Measures, Week 8 (last observation carried forward), Intent-to-Treat Population[a]

	MADRS		CGI-S		SDS		WHO-5	
	Adjusted Mean Difference (95% CI)	*P* Value	Adjusted Mean Difference (95% CI)	*P* Value	Adjusted Mean Difference (95% CI)	*P* Value	Adjusted Mean Difference (95% CI)	*P* Value
Desvenlafaxine 50 mg/d								
Normal	−2.19 (−3.48 to −0.90)	.0009	−0.27 (−0.42 to −0.11)	.0007	−1.64 (−2.55 to −0.74)	.0004	1.16 (0.37 to 1.95)	.0040
Overweight	−2.77 (−4.19 to −1.36)	.0001	−0.31 (−0.49 to −0.14)	.0004	−1.53 (−2.59 to −0.47)	.0047	0.89 (−0.04 to 1.83)	.0614
Obese	−1.98 (−3.17 to −0.79)	.0012	−0.20 (−0.34 to −0.06)	.0046	−1.67 (−2.57 to −0.77)	.0003	1.40 (0.55 to 2.25)	.0012
Desvenlafaxine 100 mg/d								
Normal	−3.21 (−4.96 to −1.45)	.0004	−0.44 (−0.65 to −0.23)	< .0001	−1.80 (−3.02 to −0.58)	.0038	0.95 (−0.02 to 1.92)	.0548
Overweight	−2.98 (−4.90 to −1.05)	.0025	−0.27 (−0.51 to −0.04)	.0220	−1.19 (−2.61 to 0.22)	.0989	1.66 (0.54 to 2.77)	.0037
Obese	−2.69 (−4.50 to −0.87)	.0037	−0.39 (−0.61 to −0.18)	.0004	−2.37 (−3.72 to −1.02)	.0006	2.08 (1.03 to 3.12)	.0001

(cont. below)

	HDRS-17 Response[b]		HDRS-17 Remission[c]	
	n/N (%)	*P* Value	n/N (%)	*P* Value
Desvenlafaxine 50 mg/d				
Normal	228/443 (51.5)	.001	124/443 (28.0)	.009
Overweight	188/398 (47.2)	.025	117/398 (29.4)	.230
Obese	274/580 (47.2)	.003	160/580 (27.6)	.008
Desvenlafaxine 100 mg/d				
Normal	113/200 (56.5)	.014	75/200 (37.5)	< .001
Overweight	85/166 (51.2)	.025	53/166 (31.9)	.200
Obese	105/203 (51.7)	.018	58/203 (28.6)	.039
Placebo				
Normal	191/479 (39.9)		91/479 (19.0)	
Overweight	146/396 (36.9)		94/396 (23.7)	
Obese	192/519 (37.0)		99/519 (19.1)	

[a]BMI categories: normal = BMI ≤ 25 kg/m^2, overweight = 25 kg/m^2 < BMI ≤ 30 kg/m^2, obese = BMI > 30 kg/m^2.
[b] ≥ 50% reduction from baseline in HDRS-17 total score.
[c]HDRS-17 total score ≤ 7.
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions Scale–Severity, HDRS-17 = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, WHO-5 = World Health Organization 5-item Well-Being Index.

adjusted mean difference (95% CI) from placebo at week 8 (LOCF) ranged from –1.99 (–3.29 to –0.69, *P* = .0027) for the obese group to –2.24 (–3.46 to –1.01, *P* = .0003) for the normal group at the desvenlafaxine 100-mg/d dose, and from –1.54 (–2.39 to –0.69, *P* = .0004) for the obese group to –2.02 (–3.02 to –1.03, *P* < .0001) for the overweight group at the desvenlafaxine 50-mg/d dose.

Desvenlafaxine treatment (50 mg/d and 100 mg/d) was associated with significant improvement from baseline compared with placebo on the MADRS and CGI-S scales for all BMI groups (Table 2). Significant improvement with desvenlafaxine versus placebo was also observed on the SDS and WHO-5 scales overall and for all subgroups except for overweight patients in the 100-mg/d group on the SDS and normal BMI patients in the 100-mg/d group and overweight patients in the 50-mg/d group on the WHO-5. Response rates based on HDRS-17 scores were significantly higher at week 8 (LOCF) for both desvenlafaxine doses compared with placebo for each BMI subgroup (Table 2). For normal BMI and obese patients, but not overweight patients, HDRS-17 remission rates at week 8 (LOCF) were significantly higher for desvenlafaxine compared with placebo (Table 2). Results for MADRS response and remission were similar, except the remission rate in obese patients treated with desvenlafaxine 100 mg/d did not reach significance (desvenlafaxine 100 mg/d: 39%, placebo: 32%, *P* = .059).

Baseline BMI was a significant predictor of change in HDRS-17 total score for the overall pooled population (*P* = .0022). Baseline BMI predicted change in HDRS-17 total score (higher baseline BMI, smaller change) for the desvenlafaxine 50-mg/d (*P* = .048) and 100-mg/d (*P* = .031) groups, but not for placebo (*P* = .097). Baseline BMI was also a significant predictor of HDRS-17 response overall (*P* = .0194) and for the desvenlafaxine 50-mg/d group (*P* = .0397): patients with higher BMI were less likely to be responders compared with patients with lower BMI. Baseline BMI was not a significant predictor of remission or time to response.

Mean Weight Change

In each of the BMI subgroups, small but significant adjusted mean decreases in weight from baseline were observed with desvenlafaxine 50-mg/d and 100-mg/d treatment compared with placebo at week 8 (observed cases) and at final on-therapy evaluation (week 8, LOCF) in the pooled short-term studies (all *P* ≤ .0195, Figure 2). These small reductions in weight were not clinically meaningful. In the mixed-effects model for repeated measures analysis, placebo-treated patients in the normal and overweight subgroups had small but statistically significant mean weight gain over time (adjusted mean ± SE: +0.18 ± 0.07 kg and + 0.21 ± 0.09 kg, respectively, both *P* ≤ .0159), and no statistically significant weight change was observed in placebo-treated obese patients (–0.08 ± 0.09 kg). The adjusted mean ± SE change in mean weight over time associated with desvenlafaxine treatment was smallest for the normal BMI group (desvenlafaxine 50 mg/d: –0.19 ± 0.06 kg, 100 mg/d: –0.36 ± 0.09 kg, both *P* < .0001), and largest for the obese group (desvenlafaxine 50 mg/d: –0.51 ± 0.07 kg, 100 mg/d: –0.73 ± 0.12 kg, both *P* < .0001). For overweight

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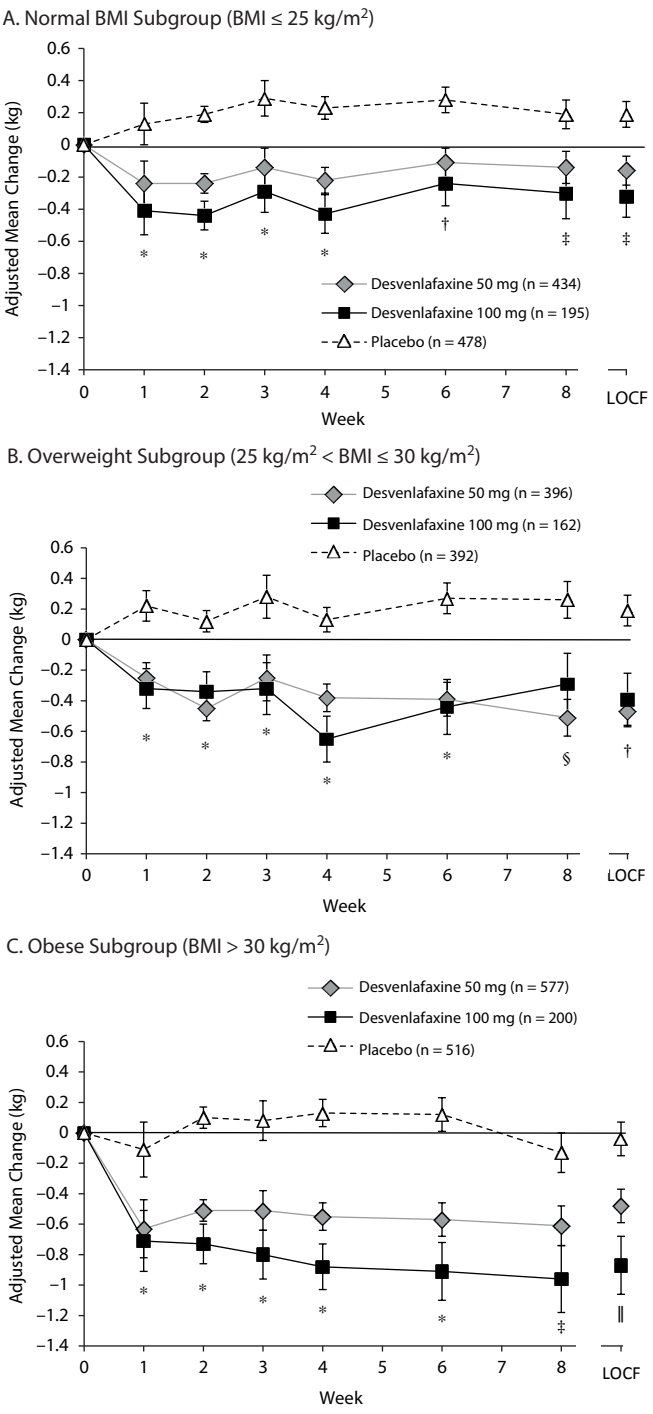
Figure 2. Adjusted Mean (SE) Change From Baseline in Body Weight (observed), Pooled Population



*$P \leq .001$, desvenlafaxine 50 mg/d and 100 mg/d vs placebo.
†$P < .001$, desvenlafaxine 50 mg/d vs placebo; $P < .01$, desvenlafaxine 100 mg/d vs placebo.
‡$P < .01$, desvenlafaxine 50 mg/d and 100 mg/d vs placebo.
§$P < .001$, desvenlafaxine 50 mg/d vs placebo; $P < .05$, desvenlafaxine 100 mg/d vs placebo.
‖$P < .01$, desvenlafaxine 50 mg/d vs placebo; $P < .001$, desvenlafaxine 100 mg/d vs placebo.
Abbreviations: BMI = body mass index, LOCF = last observation carried forward.

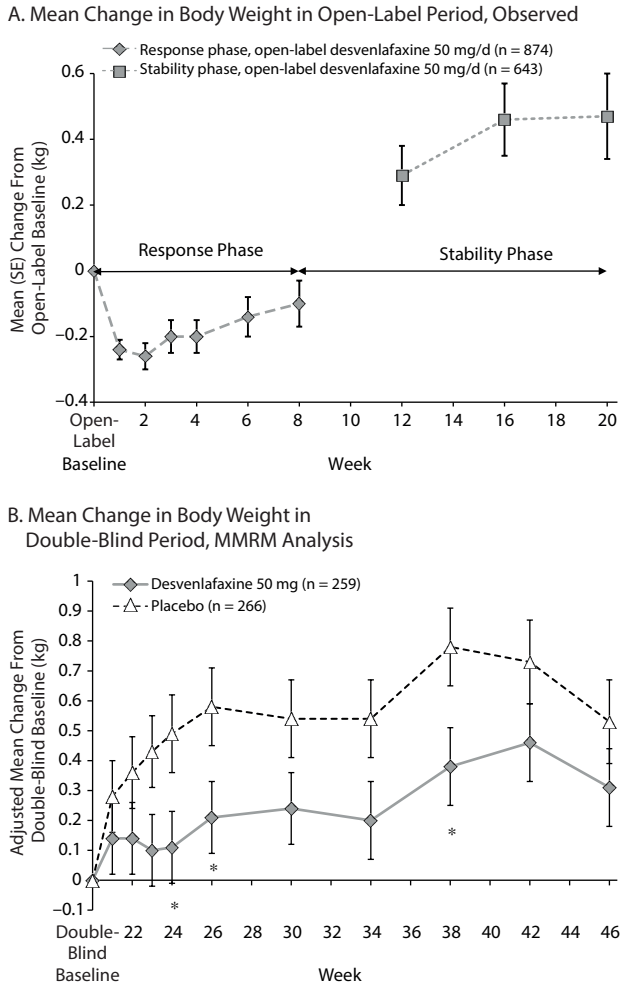
patients, the adjusted mean change in mean weight over time was –0.41 ± 0.07 kg and –0.41 ± 0.11 kg for the desvenlafaxine 50-mg/d and 100-mg/d groups, respectively (both $P < .0001$). Baseline BMI was a significant predictor of change in weight and BMI for the overall population (both $P \leq .0035$) and for the desvenlafaxine 100-mg/d group (both $P \leq .0354$). Higher baseline BMI was associated with greater short-term (8-week) weight loss, particularly in the desvenlafaxine 100-mg/d group. Statistically significant weight loss was observed at week 8 (LOCF) for both desvenlafaxine doses compared with placebo in responders, nonresponders, and nonremitters (all $P \leq .0018$). In remitters, statistically significant weight change versus placebo was observed in patients treated with desvenlafaxine 100 mg/d ($P = .0005$)—but not 50 mg/d.

In the randomized withdrawal study, open-label desvenlafaxine 50 mg/d was associated with a transient mean decrease in weight followed by an increase of 0.47 kg from baseline in the open-label period (Figure 3A). During double-blind treatment (after 20-week open-label desvenlafaxine 50 mg/d), treatment with desvenlafaxine 50 mg/d resulted in significantly less mean weight gain over time versus placebo overall (0.24 kg vs + 0.52 kg, respectively, $P = .004$, Figure 3B). No statistically significant change from baseline was observed in the normal and overweight subgroups after 8-week open-label treatment with desvenlafaxine 50 mg/d, but a mean change of –0.38 ± 0.15 kg was observed in obese patients ($P = .012$ vs baseline, Figure 4A). Weight increased significantly with desvenlafaxine treatment versus baseline at open-label week 20 in the normal and overweight subgroups (0.67 ± 0.18 kg and 0.58 ± 0.19 kg, respectively, both $P \leq .003$), but not in the obese subgroup (Figure 4A). After 26 weeks of double-blind treatment with desvenlafaxine 50 mg/d (study week 46), desvenlafaxine-treated patients in the normal BMI subgroup, but not the overweight or obese subgroups, had a statistically significant increase in weight from double-blind baseline (0.97 ± 0.26 kg, $P < .001$). However, no statistically significant differences between desvenlafaxine-treated patients and placebo-treated patients who had previously received open-label desvenlafaxine treatment were observed in any BMI subgroup (Figure 4B). Baseline BMI was a significant predictor of change in weight and BMI for the overall population (both $P \leq .009$) and for the desvenlafaxine 50-mg/d group (both $P \leq .0112$) in the randomized withdrawal study. Patients with higher baseline BMI, and the obese group in particular, had smaller weight gain longer-term.

Clinically Meaningful Weight Change

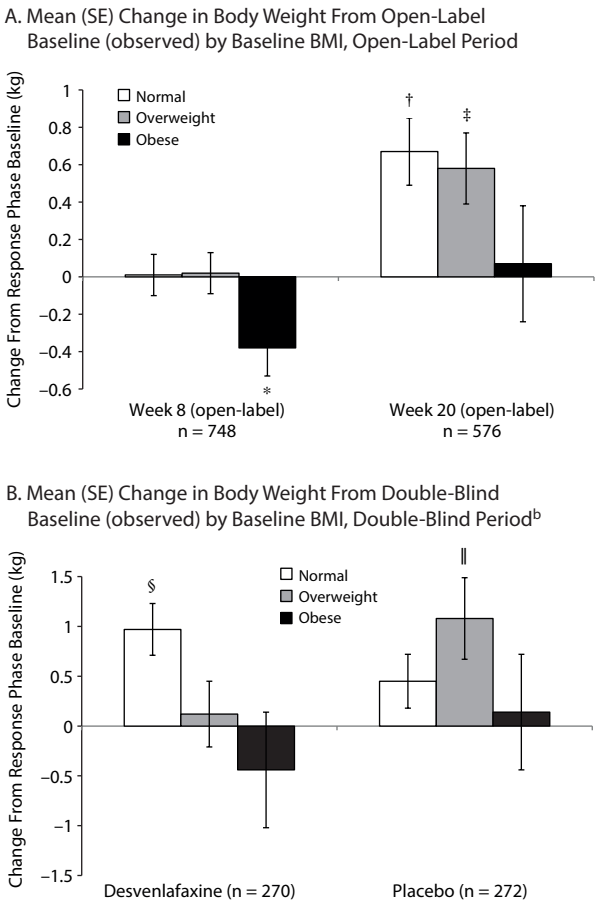
Obese patients generally had the highest rates of clinically meaningful decreases in weight (≥ 7% decrease from baseline) and lowest rates of clinically

Figure 3. Mean Change From Baseline in Body Weight, Randomized Withdrawal Study



*$P < .05$ for desvenlafaxine 50 mg/d vs placebo.
Abbreviation: MMRM = mixed-effects model for repeated measures.

Figure 4. Mean (SE) Change in Body Weight (observed) by Baseline BMI, Randomized Withdrawal Study[a]



[a]Normal: BMI ≤ 25 kg/m^2, overweight: 25 kg/m^2 < BMI ≤ 30 kg/m^2, obese: BMI > 30 kg/m^2.
[b]Desvenlafaxine vs placebo, all $P > .05$.
*$P \leq .05$ vs baseline.
†$P < .001$ vs baseline.
‡$P < .01$ vs baseline.
§$P \leq .001$ vs double-blind baseline.
||$P < .01$ vs double-blind baseline.
Abbreviation: BMI = body mass index.

meaningful increases (≥ 7% increase from baseline) both short-term and longer-term. In the pooled short-term studies, rates of clinically meaningful decreases in weight were 1.6%, 1.5%, and 1.2% for desvenlafaxine 50-mg/d–treated patients and 1.0%, 1.9%, and 3.0% for desvenlafaxine 100-mg/d–treated patients in the normal, overweight, and obese subgroups, respectively (placebo: 0.4%, 0.5%, and 0.8%, respectively). In these same subgroups, clinically meaningful increases in weight were reported in 0.9%, 1.3%, and 0.4% of desvenlafaxine 50-mg/d–treated patients and 1.0%, 0.6%, and 0% of desvenlafaxine 100-mg/d–treated patients, respectively (placebo: 1.0%, 0.3%, and 0%, respectively). In the randomized withdrawal study, rates of clinically meaningful increases in weight in the normal, overweight, and obese subgroups were 3.9%, 3.0%, and 7.4%, respectively, among desvenlafaxine 50-mg/d–treated patients, and 1.9%, 2.4%, and 6.1%, respectively, among placebo-treated patients. In these same subgroups, clinically meaningful increases in weight were reported in 15.7%, 10.0%, and 5.9% of desvenlafaxine 50-mg/d–treated patients and 7.6%, 10.7%, and 6.1% of placebo-treated patients. One patient in the pooled short-term population discontinued treatment due to increased weight (obese, placebo group). One patient each discontinued from the open-label response and stability phases of the randomized withdrawal study due to increased weight, both obese at baseline; no patients in the double-blind phase discontinued due to increased weight. No patients in the pooled short-term population or the randomized withdrawal study discontinued due to weight loss.

DISCUSSION

The notably high percentage of overweight (28.4%) and obese (38.4%) patients in this pooled study population (an aggregate of 66.7%) highlights the importance of possibly considering BMI in antidepressant treatment selection. In this analysis, there was statistically significant improvement from baseline in the primary efficacy endpoint for both

desvenlafaxine doses compared with placebo for all BMI subgroups. Nonetheless, baseline BMI was a significant predictor of change in HDRS-17 total score overall and for the 2 desvenlafaxine dose groups; the smallest effect size at both desvenlafaxine doses was observed in the obese subgroup. Results for secondary outcomes were generally statistically significant for each BMI subgroup, although there were a few results that were not, particularly for the overweight group. The current results are in line with the findings of several published studies. Obese patients tended to have a poorer response to treatment compared with normal and overweight patients in a study of outpatients treated with selective serotonin reuptake inhibitors (SSRIs),[11] and in a study of inpatients treated with 1 or more antidepressant drugs, including SSRIs, mirtazapine, or tricyclic antidepressants.[12] A significantly greater response to antidepressant treatment was also reported for normal weight patients compared with overweight and obese patients in a meta-analysis of 3 active-controlled trials of SSRIs and SNRIs.[37] Greater baseline body weight predicted less improvement in depression scale scores among nortriptyline-treated patients (but not among escitalopram-treated patients).[14] Greater baseline body weight also predicted nonresponse in depressed patients treated with fluoxetine in an 8-week open-label trial,[13] and higher baseline body weight and BMI were associated with poorer improvement in depressive and functional symptoms and lower rates of remission (but not response) in a post hoc analysis of a second, 6-week open-label fluoxetine trial.[38] In contrast—and consistent with results of the current analysis—BMI at admission did not predict remission in inpatients treated for depression in the naturalistic Munich Antidepressant Response Signature project.[39]

The changes in body weight observed in the pooled short-term studies and in the randomized withdrawal study are generally consistent with those reported for desvenlafaxine doses up to 400 mg/d,[17] for the SNRIs duloxetine and venlafaxine, and for some of the SSRIs.[6] In a meta-analysis[6] of 116 studies assessing tricyclic antidepressant drugs, SSRIs, SNRIs, and atypical antidepressants, small but significant weight loss compared with placebo was reported during acute treatment (4–12 weeks) with duloxetine (–0.55 kg), venlafaxine (–0.50 kg), and some SSRIs (–0.94 kg [fluoxetine] to –0.28 kg [paroxetine]); weight change was not statistically significant for fluvoxamine. In longer-term studies[6,10] (≥ 4 months), early weight loss was generally followed by a return to baseline weight in patients treated with duloxetine or SSRIs. The increase in weight later in treatment was significant compared with placebo for duloxetine- and paroxetine-treated patients after 32 to 34 weeks of treatment.[10] The relationship between baseline BMI and weight change observed in this analysis (patients with higher baseline BMI had greater weight loss early in treatment and smaller weight gain longer-term) has also been reported with other antidepressant drugs.[9,10]

A limitation of this pooled, post hoc analysis is that study designs varied across the pooled studies, and the study population was not uniform; in particular, 1 study population comprised perimenopausal and postmenopausal women only. None of the studies were designed to assess weight as a primary outcome. Results cannot be generalized to patients excluded from the pooled studies, including patients with any unstable hepatic, renal, pulmonary, cardiovascular (including uncontrolled hypertension), or other medical condition.

CONCLUSIONS

The approved desvenlafaxine doses of 50 mg/d and 100 mg/d effectively reduced the symptoms of depression regardless of BMI at baseline. Baseline BMI was, however, a significant predictor of response in desvenlafaxine-treated patients: slightly greater improvement in depressive symptoms was observed in the normal BMI subgroup. Desvenlafaxine treatment for MDD was associated with a significant, but not clinically relevant, mean weight loss (< 1 kg) compared with placebo regardless of BMI category in the pooled, short-term studies. Weight loss was significantly predicted by baseline BMI and largest in obese patients. Longer-term weight changes during treatment with desvenlafaxine 50 mg/d were also predicted by baseline BMI. Lower baseline weight and BMI were associated with a greater increase in weight during longer-term treatment; no statistically significant change from baseline weight was observed in overweight or obese patients.

Drug names: desvenlafaxine (Pristiq), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), venlafaxine (Effexor and others).

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