Effects of the Antidepressant Duloxetine on Body Weight: Analyses of 10 Clinical Studies

Thomas N. Wise, M.D.; David G. S. Perahia, M.D.; Beth A. Pangallo, R.N.; William G. Losin, Pharm.D.; and Curtis G. Wiltse, Ph.D.

Objective: To assess the effect of duloxetine, an inhibitor of serotonin and norepinephrine reuptake, on body weight of patients with major depressive disorder (MDD).

Method: Body weight data were obtained from all 10 phase II and III registration studies of duloxetine in the treatment of MDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), performed by Eli Lilly and Company between February 1999 and July 2003. Both acute (8–9 weeks) and long-term (26, 34, and 52 weeks) studies were analyzed.

Results: In the acute placebo-controlled studies, duloxetine-treated patients had a mean change of –0.5 kg compared with a change of 0.2 kg for placebo-treated patients ($p < .001$); no consistent relationship between duloxetine dose and weight change was observed. In placebo-controlled studies including an active comparator arm, similar acute mean weight changes were seen in duloxetine-treated and fluoxetine-treated patients (–0.7 kg vs. –0.6 kg) and in duloxetine-treated and paroxetine-treated patients (–0.3 kg vs. –0.2 kg). During longer-term treatment (34 weeks), mean weight change in patients treated with duloxetine 40 mg b.i.d. was not significantly different from that seen in placebo-treated patients (0.7 kg vs. 0.1 kg), while patients treated with the higher duloxetine dose of 60 mg b.i.d. or with paroxetine gained significantly ($p \leq .05$) more weight than placebo-treated patients (0.9 kg, 1.0 kg, and 0.1 kg, respectively). In a 52-week open-label study, duloxetine-treated patients had a mean weight gain of 1.1 kg at endpoint ($p < .001$).

Conclusion: Duloxetine-treated patients experienced weight loss after short-term treatment, followed by modest weight gain on longer-term treatment. The size of the weight changes observed suggests that the antidepressant duloxetine has minimal effects on weight for the majority of patients.

(Prim Care Companion J Clin Psychiatry 2006;8:269–278)

Received Dec. 16, 2005; accepted Jan. 31, 2006. From Inova Fairfax Hospital, Falls Church, Va. (Dr. Wise); Eli Lilly and Co., Lilly Research Centre, Windlesham, Surrey, U.K. and The Gordon Hospital, London, U.K. (Dr. Perahia); and Eli Lilly and Co., Lilly Research Laboratories, Indianapolis, Ind. (Ms. Pangallo and Drs. Losin and Wiltse).

This work was sponsored and funded by Eli Lilly and Co., Indianapolis, Ind.

Dr. Wise has consulted for Eli Lilly, Pfizer, and GlaxoSmithKline; has received grant/research support from Eli Lilly; has received honoraria from Eli Lilly, Pfizer, GlaxoSmithKline, and Bristol-Myers Squibb; and has served on the speakers or advisory boards of Eli Lilly, Pfizer, GlaxoSmithKline, AstraZeneca, and Bristol-Myers Squibb. Drs. Perahia, Losin, and Wiltse and Ms. Pangallo are employees and stock shareholders of Eli Lilly.

The authors thank the Duloxetine Team, the clinical investigators and staff, and the many patients for their participation in the clinical studies that provided the data for this publication. We also thank David J. Goldstein, M.D., Ph.D., and Thomas C. Lee, M.A., for their contributions to early drafts of the manuscript; Sharie Sipowicz, B.S., for editorial assistance; and Barry Brolley, M.S., and Wenqi You, M.S., for programming assistance.

Corresponding author and reprints: David G. S. Perahia, M.D., Lilly Research Centre, EMC Building, Erl Wood Manor, Sunninghill Rd., Windlesham, Surrey, GU20 6PH, U.K. (e-mail: d.perahia@lilly.com).

Many antidepressants affect body weight. Weight gain, in particular, may lead to patient dissatisfaction, noncompliance, and eventual discontinuation of therapy.[1] The tricyclic antidepressants are commonly associated with weight gain that can be disturbing to patients and may interfere with patients' willingness to continue long-term maintenance treatment.[2] Conversely, the selective serotonin reuptake inhibitors (SSRIs) fluoxetine[3,4] and sertraline[5] and the dopamine reuptake inhibitor bupropion[5] are associated with short-term weight loss. In the long term, patients treated with fluoxetine tend to regain their weight after experiencing an initial short-term weight loss.[6] Another SSRI, paroxetine, is associated with long-term weight gain,[7] whereas bupropion may induce long-term weight loss.[8] Sibutramine, a monoamine reuptake inhibitor of norepinephrine (NE) and serotonin (5-HT)[9] that was initially studied as an antidepressant, is used as an anti-obesity agent to induce weight loss.[10,11]

Duloxetine hydrochloride (hereafter referred to as duloxetine), a dual-reuptake inhibitor of both 5-HT and NE, lacks significant affinity for muscarinic, histamine$_1$, α_1-adrenergic, dopamine$_2$, 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, 5-HT$_{2A}$, 5-HT$_{2C}$, and opioid receptors.[12] Duloxetine blocks 5-HT and NE reuptake by the inhibition of binding to 5-HT and NE transporters, which has been demonstrated both in vitro and in vivo.[12,13]

Table 1. Description of the Major Depressive Disorder Studies Used in the Integrated Analyses

Study	Participating Countries	Phase	Treatment Groups	Dose	N	Duration	Randomization Ratio
1[21] and 2[22] (F1J-MC-HMAQa[21] and HMAQb[22])	USA	Acute	Duloxetine Fluoxetine Placebo	20–60 mg bid[a] 20 mg qd …	152 70 145	8 weeks	2:1:2
3[22] and 4[14] (F1J-MC-HMATa[22] and HMATb[14])	USA	Acute	Duloxetine Duloxetine Paroxetine Placebo	20 mg bid 40 mg bid 20 mg qd …	177 175 176 179	8 weeks	1:1:1:1
5[15] and 6[16] (F1J-MC-HMAYa[15] and HMAYb[16])	Bulgaria, Croatia, Hungary, Poland, Romania, Russia, Slovakia	Acute + Long-term continuation[b]	Duloxetine Duloxetine Paroxetine Placebo	40 mg bid 60 mg bid 20 mg qd …	188 196 183 192	8 weeks + 26 weeks (34 weeks total)	1:1:1:1
7[17] and 8[18] (F1J-MC-HMBHa[17] and HMBHb[18])	USA	Acute	Duloxetine Placebo	60 mg qd …	251 261	9 weeks	1:1
9[19] (F1J-MC-HMBC[19]) (Relapse Prevention Study)	USA, France, Italy, Spain	Acute	Duloxetine	60 mg qd	533	12 weeks uncontrolled	NA
		Long-term continuation	Duloxetine Placebo	60 mg qd …	136 142	26 weeks double-blind	1:1
10[23] (F1J-MC-HMAU[23])	Argentina, Brazil, Canada, Colombia, USA, Mexico, Venezuela	Long-term	Duloxetine	40–60 mg bid	1279[c]	52 weeks uncontrolled	NA

[a]Optional titration to 120 mg/day.
[b]Patient numbers (N) are for the acute treatment phase. Patient numbers for the continuation phase were: 40 mg b.i.d., N = 141; 60 mg b.i.d., N = 156; 20 mg paroxetine q.d., N = 140; placebo, N = 129.
[c]For 1 patient, it appeared that the weight at the last visit was recorded in pounds rather than kilograms; therefore, the weight at the preceding visit was used as the endpoint observation.
Abbreviation: NA = not applicable. Abbreviations in Study column represent Lilly study codes.

Duloxetine has demonstrated efficacy in the treatment of major depressive disorder (MDD) in double-blind placebo-controlled studies[14–19] and is licensed in the United States, Europe, and elsewhere for the treatment of MDD. The weight data for patients with MDD treated with duloxetine have not previously been comprehensively analyzed. Data from acute and long-term treatment clinical studies were therefore analyzed to evaluate whether duloxetine has an effect on weight in patients with MDD.

METHOD

Overview of Studies

Body weight data were obtained from all 10 phase II and III registration studies of duloxetine in the treatment of MDD, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV),[20] performed by Eli Lilly and Company between February 1999 and July 2003. In addition to the actual weight data, treatment-emergent weight-related adverse events (appetite decreased, appetite increased, and anorexia) were collected in all the studies. Treatment assignments and relevant details of each study (studies 1–10) are summarized in Table 1; pairs of studies were conducted under a common protocol. Except for study 10 and the acute phase of study 9 (a relapse-prevention study), all studies were randomized, double-blind, and controlled (with placebo, fluoxetine, and/or paroxetine used as comparators). Both once-daily (q.d.) and twice-daily (b.i.d.) dosing were used in these studies. The primary outcomes of all the studies (except study 6, which is currently in press) have been previously published (see Table 1 for citations). The appropriate ethical review committees approved all the studies, and the study participants provided signed informed consent before study participation.

The primary focus of these analyses was on the duloxetine versus placebo comparisons. Comparisons of duloxetine with fluoxetine and paroxetine were used to help put the comparisons with placebo into a clinically relevant context. Because paroxetine and fluoxetine arms did not coexist in any study, the effects of these treatments on body weight were not directly compared. Duloxetine doses spanned the therapeutically relevant dose range, whereas fluoxetine and paroxetine doses were at the lower end of their respective recommended dose ranges. Thus, comparisons between duloxetine and the active comparators should be interpreted in light of the doses used.

Statistical Analyses

Analyses were performed using the intent-to-treat principle, in which all patients were included in the groups to which they were randomly allocated, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. All treatment hypotheses were tested using a 2-sided

$\alpha = .05$. Analyses were performed using SAS statistical software (SAS Institute, Cary, N.C.).

For some analyses of acute data, all duloxetine dose groups in the therapeutically relevant range (40–120 mg/day) were combined into 1 group. This approach created the largest possible number of patients per group and avoided the confounding of dose with protocol that would have otherwise existed.

Datasets. The following data-pooling strategies were used to match the corresponding hypotheses to be tested:

1. Acute placebo-controlled dataset. Acute (8–9 weeks) data from the duloxetine and placebo arms of studies 1–8 were pooled and compared.
2. Acute fluoxetine-controlled dataset. Data from the duloxetine and fluoxetine arms of studies 1 and 2 were pooled and compared.
3. Acute paroxetine-controlled dataset. Acute (8 weeks) data from the duloxetine and paroxetine arms of studies 3–6 were pooled and compared.
4. Long-term placebo- and paroxetine-controlled dataset. Long-term (34 weeks) data from the 4 individual treatment arms of the acute and continuation phases combined of studies 5 and 6 were pooled and compared.

In addition, the following datasets did not involve pooling across duloxetine doses or studies:

5. Acute uncontrolled dataset. Acute (12 weeks) duloxetine data from study 9.
6. Long-term placebo-controlled dataset. Long-term (26 weeks) data from the duloxetine and placebo arms of study 9.
7. Long-term uncontrolled dataset. Long-term (52 weeks) duloxetine data from study 10.

Mean change analyses. The change in weight from baseline to endpoint (each patient's last observation during the treatment period) was compared among treatment groups using a fixed-effects analysis of variance (ANOVA) model. When analyses were performed across protocols, such as the acute placebo- and acute paroxetine-controlled datasets, an ANOVA model with terms for treatment, study, and treatment-by-study interaction was used. Treatment effects were assessed using Type III sums of squares, which weighted each study equally. When 1 study (long-term placebo-controlled dataset) or 2 studies conducted under a common protocol (acute fluoxetine-controlled and long-term placebo- and paroxetine-controlled datasets) were analyzed, the ANOVA model included the categorical effects of treatment and investigator. The analysis of the long-term placebo- and paroxetine-controlled dataset, in which only efficacy responders continued beyond 8 weeks, also included the baseline weight. There was a significant ($p \leq .10$) investigator-by-treatment interaction for the long-term placebo-controlled dataset, so the interaction was retained in the model, using Type II sums of squares for comparing treatments.

Demographic analyses. Continuous demographic data were analyzed using an ANOVA model that contained terms for investigator (the term study was used for the acute placebo-controlled and acute paroxetine-controlled datasets) and treatment. Categorical demographic data were analyzed using Fisher exact test (acute fluoxetine-controlled dataset) or the χ^2 test (other controlled datasets).

Subgroup analyses. Subgroup analyses of change in weight for the acute placebo-controlled dataset were performed, with subgroups based on body mass index (BMI) (< 25 vs. 25 to < 30 vs. ≥ 30 kg/m^2), age (< 55 vs. ≥ 55 years), gender, and ethnic origin (Caucasian vs. other). An analysis of covariance (ANCOVA) model with terms for treatment, study, baseline, subgroup, and treatment-by-subgroup effects was used to obtain the interaction p value, which was tested at the .10 significance level. An ANCOVA model with terms for treatment, study, and baseline effects was used for within-subgroup treatment comparisons. In a similar analysis of the long-term placebo-controlled and paroxetine-controlled dataset by BMI subgroup, the term for investigator, rather than study, was used. For the long-term uncontrolled dataset, the change from baseline to endpoint was summarized by each of the 4 subgroup variables.

Repeated measures analyses. A likelihood-based, mixed-effects repeated measures model was also used to analyze change in weight for studies 3 and 4 (pooled), and 7 and 8 (pooled). Dose titration was not used in these studies, thus preventing the confounding of dose with visit that is present in studies 1 and 2, for which investigator-initiated dose titration within the range of 20–60 mg b.i.d. could occur at any time during the acute phase. A similar analysis was performed for the long-term placebo- and paroxetine-controlled dataset, for which automatic short-term dose titration (3 and 6 days for patients randomly assigned to duloxetine 40 and 60 mg b.i.d., respectively) was used. The repeated measures model contained fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the fixed continuous covariates of baseline and baseline-by-visit interaction. An unstructured covariance matrix was used to model the within-patient errors. For the long-term uncontrolled dataset, the repeated measures model used fixed categorical effects of investigator and visit, as well as the fixed continuous covariate of the baseline weight. A compound symmetric matrix was used to model the within-patient errors.

Potentially clinically significant changes in weight and weight-related adverse events. The frequencies of potentially clinically significant (PCS) measured changes in weight (loss or gain of $\geq 7\%$) from baseline to endpoint or any time, as well as the frequencies of treatment-emergent weight-related adverse events (weight decreased/increased

Table 2. Baseline Patient Characteristics in Acute Studies

Characteristic	Placebo- and Active Comparator–Controlled Studies[a]				Acute Uncontrolled[b]
	Placebo (N = 777)	Duloxetine (N = 1139)	Fluoxetine 20 mg qd (N = 70)	Paroxetine 20 mg qd (N = 359)	Duloxetine 60 mg qd (N = 533)
Gender, N (%)					
Female	530 (68.2)	761 (66.8)	42 (60.0)	229 (63.8)	383 (71.9)
Male	247 (31.8)	378 (33.2)	28 (40.0)	130 (36.2)	150 (28.1)
Age, mean (SD), y	42.2 (12.9)	42.7 (12.2)	39.7 (11.6)	43.2 (12.0)	43.4 (12.7)
Ethnicity, N (%)					
Caucasian	674 (86.7)	1016 (89.2)	58 (82.9)	320 (89.1)	479 (89.9)
African descent	48 (6.2)	55 (4.8)	7 (10.0)	17 (4.7)	34 (6.4)
Hispanic	47 (6.0)	49 (4.3)	3 (4.3)	18 (5.0)	14 (2.6)
East/Southeast Asian	5 (0.6)	5 (0.4)	0 (0.0)	1 (0.3)	2 (0.4)
Western Asian	2 (0.3)	5 (0.4)	0 (0.0)	2 (0.6)	1 (0.2)
Other	1 (0.1)	9 (0.8)	2 (2.9)	1 (0.3)	3 (0.6)
Weight, mean (SD), kg[c]	78.3 (20.0)	79.7 (20.7)**	82.3 (20.8)	77.8 (22.4)	82.1 (22.3)

[a]Placebo and duloxetine: studies 1–8; fluoxetine: studies 1–2; paroxetine: studies 3–6.
[b]Study 9 (acute phase).
[c]Numbers of patients with baseline weight data were as follows: placebo, N = 774; duloxetine (controlled studies), N = 1136; fluoxetine, N = 70; paroxetine, N = 357; duloxetine (uncontrolled study), N = 532.
**p ≤ .01 vs. placebo.

Table 3. Baseline Patient Characteristics in Long-Term Studies

Characteristic	Studies 5 and 6 (34 weeks, long-term placebo- and paroxetine-controlled, all randomly assigned patients)				Study 9 (26 weeks, long-term placebo-controlled)		Study 10 (52 weeks, long-term uncontrolled),
	Placebo (N = 192)	Duloxetine 40 mg bid (N = 188)	Duloxetine 60 mg bid (N = 196)	Paroxetine 20 mg qd (N = 183)	Placebo (N = 142)	Duloxetine 60 mg qd (N = 136)	Duloxetine 40–60 mg bid (N = 1279)
Gender, N (%)							
Female	134 (69.8)	132 (70.2)	147 (75.0)	127 (69.4)	110 (77.5)	92 (67.6)	928 (72.6)
Male	58 (30.2)	56 (29.8)	49 (25.0)	56 (30.6)	32 (22.5)	44 (32.4)	351 (27.4)
Age, mean (SD), y	44.2 (11.1)	44.8 (12.0)	44.3 (10.7)	44.0 (10.8)	44.8 (11.9)	45.7 (12.7)	44.4 (13.2)
Ethnicity, N (%)							
Caucasian	192 (100.0)	188 (100.0)	195 (99.5)	183 (100.0)	132 (93.0)	128 (94.1)	542 (42.4)
African descent	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	8 (5.6)	5 (3.7)	35 (2.7)
Hispanic	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.5)	584 (45.7)
East/Southeast Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (0.2)
Western Asian	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.3)
Other	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.7)	0 (0.0)	112 (8.8)
Weight, mean (SD), kg[a]	69.3 (14.4)	70.9 (14.4)	72.4 (17.4)	69.7 (14.1)	80.9 (22.2)	83.3 (22.1)	70.3 (17.4)

[a]For study 10, number of patients with baseline weight data = 1274.

and anorexia), were compared between treatment groups using Fisher exact test, or across protocols, by the Cochran-Mantel-Haenszel test stratified by study.

Association of weight change with HAM-D scores. The association between the change from baseline to endpoint in the Hamilton Rating Scale for Depression–17 items (HAM-D-17) total score and weight in the long-term uncontrolled dataset was evaluated using Spearman's Rho correlation coefficient.

RESULTS

Patient Characteristics

Baseline patient characteristics, including gender, age, ethnicity, and weight, are presented in Table 2 for the acute treatment studies and Table 3 for the long-term treatment studies. Treatment groups did not differ significantly for any of these characteristics except that patients in the duloxetine treatment group of the acute placebo-controlled dataset weighed significantly more than patients in the placebo treatment group (p ≤ .01).

Acute Placebo-Controlled Dataset

Weight change and treatment-emergent weight-related adverse events during 8 to 9 weeks of acute treatment are summarized in Table 4. Duloxetine-treated patients (pooled doses) lost significantly more weight from baseline to endpoint than did placebo-treated patients, who gained slightly (–0.5 kg vs. 0.2 kg, p < .001). Repeated measures analysis revealed no consistent relationship between duloxetine dose and weight change (Table 5; Figures 1A, 1B, and 2A [first 8 weeks]). In studies 3 and 4

Table 4. Body Weight Change and Treatment-Emergent Weight-Related Adverse Events in Acute Placebo-Controlled Studies (studies 1–8)

Analyses	Placebo (N = 757)	Duloxetine (N = 1115)	p Value
Weight change from baseline to endpoint, mean (SD), kg	0.2 (2.2)	–0.5 (2.2)	< .001
Baseline BMI strata,[a] least squares mean			
BMI < 25 kg/m^2	0.3	–0.2	< .001
BMI 25 to < 30 kg/m^2	0.1	–0.5	< .001
BMI ≥ 30 kg/m^2	0.4	–0.9	< .001
PCS weight change at endpoint, n (%)			
≥ 7% weight loss	3 (0.4)	14 (1.3)	.035
≥ 7% weight gain	9 (1.2)	7 (0.6)	.103
PCS weight change at any time, n (%)			
≥ 7% weight loss	3 (0.4)	17 (1.5)	.010
≥ 7% weight gain	10 (1.3)	10 (0.9)	.281
Treatment-emergent weight-related adverse events, n (%)[b]			
Appetite decreased	15 (1.9)	67 (5.9)	< .001
Appetite increased	11 (1.4)	12 (1.1)	.637
Anorexia	1 (0.1)	19 (1.7)	.001

[a]Therapy-by-subgroup interaction p value = .001.
[b]Numbers of patients for analyses of treatment-emergent weight-related adverse events were as follows: placebo, N = 777; duloxetine, N = 1139.
Abbreviations: BMI = body mass index, PCS = potentially clinically significant.

Table 5. Effect of Duloxetine on Change in Body Weight From Baseline to Last Study Visit of Acute Phase (placebo-controlled, acute studies): Repeated Measures Analysis by Dose[a]

		Duloxetine			
Analyses	Placebo	20 mg bid	60 mg qd	40 mg bid	60 mg bid
Studies 3 and 4					
N	176	174	…	167	…
Least squares mean (SE) change, kg	0.4 (0.2)	–0.2 (0.2)*	…	–0.6 (0.2)***	…
Studies 5 and 6					
N	192	…	…	186	195
Least squares mean (SE) change, kg	0.1 (0.1)	…	…	–0.1 (0.2)	–0.2 (0.1)
Studies 7 and 8					
N	251	…	244	…	…
Least squares mean (SE) change, kg	0.0 (0.2)	…	–0.8 (0.2)***	…	…

[a]N represents the number of patients with baseline and post-baseline values.
*p ≤ .05 vs. placebo.
***p ≤ .001 vs. placebo.
Symbol: … = not applicable.

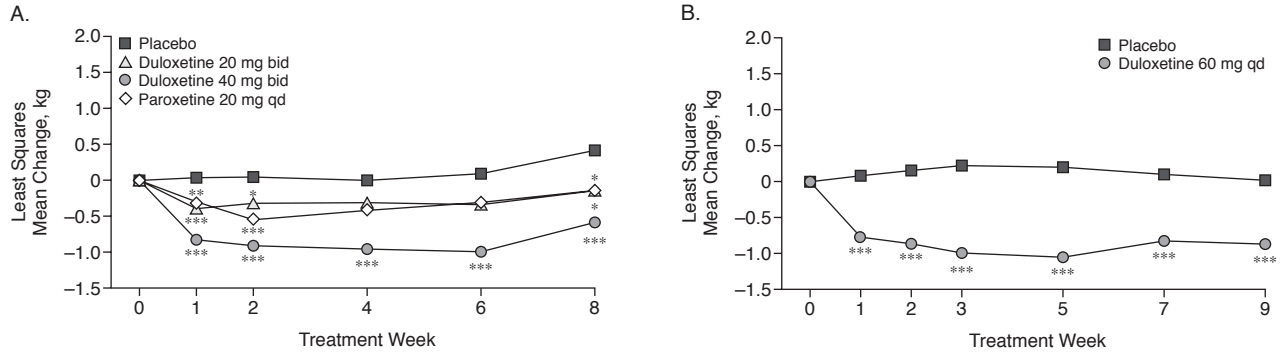
and studies 7 and 8, patients who received duloxetine 40 mg/day, 60 mg/day, or 80 mg/day lost significantly more weight than did placebo-treated patients (see Table 5 for p values), but the differences in studies 5 and 6 were not significant. The subgroup analysis of change in weight by baseline BMI strata showed that there was a significant treatment-by-BMI interaction (p = .001), with the amount of weight loss in duloxetine-treated patients compared with placebo-treated patients increasing with higher BMI (Table 4). In each BMI stratum, duloxetine-treated patients lost significantly more weight compared with placebo-treated patients, who gained slightly (p < .001). The incidences of PCS weight loss (≥ 7%) from baseline to endpoint or any time were significantly greater for duloxetine-treated than for placebo-treated patients (p = .035 and p = .010, respectively). The incidences of PCS weight gain (≥ 7%) from baseline to endpoint or at any time were not significantly different for duloxetine-treated compared with placebo-treated patients.

Duloxetine-treated patients reported the treatment-emergent weight-related adverse events of appetite decreased (p < .001) and anorexia (p = .001) significantly more often than did placebo-treated patients (Table 4). A lower percentage of duloxetine-treated patients (1.1%) compared with placebo-treated patients (1.4%) reported appetite increased; however, this difference was not significant. The incidences of weight-related events were similar across duloxetine doses. Anorexia was the only weight-related event reported as a reason for treatment discontinuation (duloxetine, 0.1%; placebo, 0.0%). Subgroup analyses of weight change by age (< 55 vs. ≥ 55 years), origin (Caucasian vs. other), and gender found no significant treatment-by-subgroup interactions.

Acute Fluoxetine-Controlled and Paroxetine-Controlled Datasets

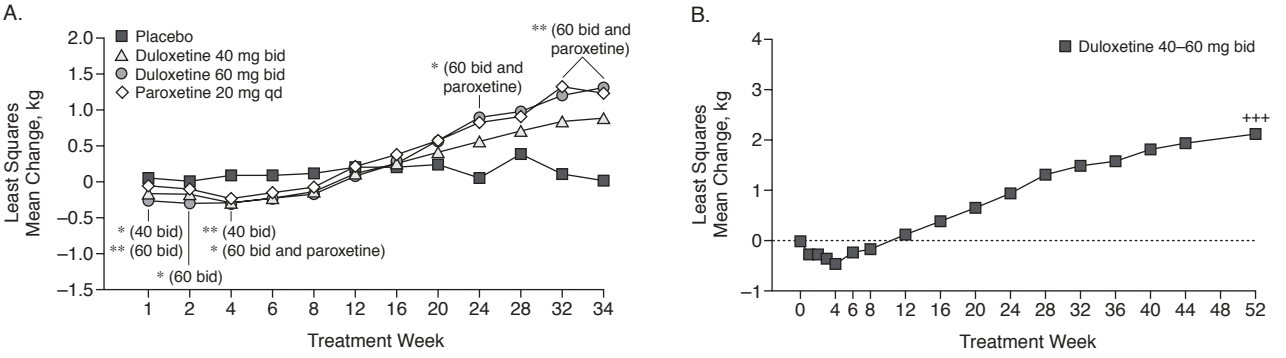
In studies comparing duloxetine with fluoxetine (studies 1 and 2) during 8 weeks of acute treatment, the mean

Figure 1. Change in Body Weight During (A) 8 Weeks of Acute Treatment With Duloxetine 40 mg/day (20 mg b.i.d.), Duloxetine 80 mg/day (40 mg b.i.d.), Paroxetine 20 mg/day (20 mg q.d.), or Placebo (studies 3 and 4; repeated measures analysis) and (B) 9 Weeks of Acute Treatment With Duloxetine 60 mg/day (60 mg q.d.) or Placebo (studies 7 and 8; repeated measures analysis)



*p ≤ .05 vs. placebo, **p ≤ .01 vs. placebo, ***p ≤ .001 vs. placebo.

Figure 2. Change in Body Weight During (A) 34 Weeks of Long-Term Treatment With Duloxetine 80 mg/day (40 mg b.i.d.), Duloxetine 120 mg/day (60 mg b.i.d.), Paroxetine 20 mg/day (20 mg q.d.), or Placebo (studies 5 and 6; repeated measures analysis) and (B) 52 Weeks of Long-Term Treatment With Duloxetine 80 to 120 mg/day (40–60 mg b.i.d.) (study 10; repeated measures analysis)



*p ≤ .05 vs. placebo, **p ≤ .01 vs. placebo, +++p < .001 for change from baseline to week 52; p values at previous weeks not shown.

change in weight from baseline to endpoint was not significantly different for duloxetine-treated compared with fluoxetine-treated patients (–0.7 kg vs. –0.6 kg; Table 6). No significant differences were observed between duloxetine-treated patients and fluoxetine-treated patients with regard to PCS weight gain or loss, or incidence of treatment-emergent weight-related adverse events. The treatment-emergent weight-related adverse events of appetite decreased, appetite increased, and anorexia were not reported as a reason for discontinuation in these studies.

In studies that compared duloxetine with paroxetine (studies 3–6) during 8 weeks of acute treatment, the mean change in weight from baseline to endpoint was not significantly different for duloxetine-treated compared with paroxetine-treated patients (–0.3 kg vs. –0.2 kg; Table 6). No significant differences were observed between duloxetine-treated patients and paroxetine-treated patients with regard to the incidence of PCS weight gain or PCS weight loss. Significantly more duloxetine-treated patients reported appetite decreased than did paroxetine-treated patients (4.2% vs. 1.4%; p = .011). Appetite decreased, appetite increased, and anorexia were not reported as a reason for discontinuation in these studies.

Long-Term Treatment Datasets

In studies 5 and 6, patients whose HAM-D-17 total score was reduced at least by 30% from baseline to the end (week 8) of the acute phase were eligible to enter a 26-week continuation phase. These patients continued on the same treatment, still under double-blind conditions. Weight data for these studies were analyzed across the acute and continuation phases combined (34 weeks; Table 7). Pooling the corresponding arms of studies 5 and 6, of the patients initially randomly assigned, 129 of the 192 placebo-treated patients, 141 of the 188 duloxetine 40 mg b.i.d.-treated patients, 156 of the 196 duloxetine 60 mg

Table 6. Body Weight Change and Treatment-Emergent Weight-Related Adverse Events in Acute Active Comparator–Controlled Studies

	Studies 1 and 2 (acute fluoxetine-controlled)			Studies 3–6 (acute paroxetine-controlled)		
Analyses	Duloxetine 20–60 mg bid (N = 149)	Fluoxetine 20 mg qd (N = 70)	p Value	Duloxetine 20–60 mg bid (N = 722)	Paroxetine 20 mg qd (N = 352)	p Value
Weight change from baseline to endpoint, mean (SD), kg	–0.7 (2.2)	–0.6 (2.3)	.640	–0.3 (2.1)	–0.2 (2.2)	.416
PCS weight change at endpoint, n (%)						
≥ 7% weight loss	1 (0.7)	2 (2.9)	.240	7 (1.0)	2 (0.6)	.498
≥ 7% weight gain	0 (0.0)	0 (0.0)	…	7 (1.0)	6 (1.7)	.266
PCS weight change at any time, n (%)						
≥ 7% weight loss	1 (0.7)	2 (2.9)	.240	8 (1.1)	2 (0.6)	.385
≥ 7% weight gain	2 (1.3)	0 (0.0)	1.00	8 (1.1)	6 (1.7)	.380
Treatment-emergent weight-related adverse events, n (%)[a]						
Appetite decreased	0 (0.0)	0 (0.0)	…	31 (4.2)	5 (1.4)	.011
Appetite increased	5 (3.3)	1 (1.4)	.668	5 (0.7)	1 (0.3)	.385
Anorexia	10 (6.6)	3 (4.3)	.759	13 (1.8)	4 (1.1)	.400

[a]Numbers of patients for analyses of treatment-emergent weight-related adverse events were as follows: Studies 1 and 2: duloxetine, N = 152; fluoxetine, N = 70; studies 3–6: duloxetine, N = 736; paroxetine, N = 359.
Abbreviation: PCS = potentially clinically significant.

b.i.d.-treated patients, and 140 of the 183 paroxetine 20 mg q.d.-treated patients entered the continuation phase. The mean changes in weight from baseline to the end of the acute phase ranged across the 4 treatment groups from –0.17 to 0.18 kg for all randomly assigned patients and from –0.06 to 0.19 kg for the patients who entered the continuation phase. These results do not suggest a selection bias with respect to weight for the patients who entered the continuation phase. For this reason, the long-term placebo- and paroxetine-controlled dataset included all available data for the entire 34 weeks of treatment for all randomized patients.

The least squares mean weight change from baseline to endpoint for patients treated with duloxetine at a dose of 40 mg b.i.d. was not significantly different from that seen in placebo-treated patients (0.7 kg vs. 0.1 kg; Table 7). Weight changes in duloxetine 60 mg b.i.d.-treated patients (0.9 kg) and paroxetine 20 mg q.d.-treated patients (1.0 kg) were, however, significantly greater than those seen in placebo-treated patients (0.1 kg, $p \leq .05$ for each). The least squares mean weight changes by repeated measures at 34 weeks show similar results; changes during the 34 weeks for each treatment group are shown in Figure 2A. No significant treatment-by-BMI subgroup interaction was observed. The treatment groups did not differ significantly in the rates of PCS weight loss at endpoint or any time, whereas the rates of PCS weight gain at endpoint were significantly higher in all active treatment arms compared with placebo (see Table 7 for p values). However, the rates of PCS weight gain at any time did not differ significantly between patients receiving duloxetine 40 mg b.i.d. and patients receiving placebo, whereas significantly more patients receiving duloxetine 60 mg b.i.d. and patients receiving paroxetine experienced PCS weight gain at any time compared with placebo ($p \leq .05$ and $p \leq .001$, respectively). No significant differences between treatment groups were seen in the incidence of treatment-emergent weight-related adverse events. In addition, no patients discontinued from the studies due to appetite decreased, appetite increased, or anorexia. The comparisons of both duloxetine treatment groups (40 mg b.i.d. and 60 mg b.i.d.) with paroxetine 20 mg q.d. did not reveal any significant differences in weight change from baseline to endpoint or to week 34, PCS weight change at endpoint or any time, or in treatment-emergent weight-related adverse events.

The acute uncontrolled dataset and the long-term placebo-controlled dataset are based on the acute and continuation phases, respectively, of study 9. In the acute uncontrolled dataset, the mean weight change from baseline to endpoint for duloxetine-treated patients was not significant (–0.1 kg). The corresponding mean change for patients who were subsequently randomly assigned in the 26-week continuation phase was 0.1 kg. In this long-term placebo-controlled dataset, mean changes in weight from baseline to endpoint did not differ significantly between the groups (duloxetine 60 mg q.d., 1.0 kg; placebo, 0.9 kg).

In the long-term uncontrolled dataset (study 10), there was a significant within-group mean weight change from baseline to endpoint for duloxetine-treated patients of 1.1 kg ($p < .001$; Table 7). After 52 weeks of duloxetine treatment, there was a significant within-group least squares mean weight increase of 2.1 kg ($p < .001$) by repeated measures analysis. The rate of weight gain decreased as the duration of exposure became greater (Figure 2B). Anorexia (0.1%) was the only treatment-emergent weight-related adverse event reported as a reason for treatment discontinuation. Mean weight gain decreased with increasing BMI (Table 7), but mean weight changes

Table 7. Body Weight Change and Treatment-Emergent Weight-Related Adverse Events in Long-Term Studies

Analyses	Studies 5 and 6 (34 weeks, long-term placebo- and paroxetine-controlled; all randomly assigned patients)[a] Placebo (N = 192)	Duloxetine 40 mg bid (N = 186)	Duloxetine 60 mg bid (N = 195)	Paroxetine 20 mg qd (N = 181)	Study 10 (52 weeks, long-term uncontrolled), Duloxetine 40–60 mg bid (N = 1222)
Weight change from baseline to endpoint,[b] least squares mean (SE),[c] kg	0.1 (0.2)	0.7 (0.2)	0.9 (0.2)*	1.0 (0.3)*	1.1 (4.0)+++
Weight change from baseline to last study visit (repeated measures), least squares mean (SE), kg	0.0 (0.3)	0.9 (0.3)	1.3 (0.3)**	1.2 (0.3)**	2.1 (0.1)+++
Baseline BMI strata,[d] least squares mean					
BMI < 25 kg/m^2	0.8	0.9	1.8**	1.3	1.6
BMI 25 to < 30 kg/m^2	–0.5	0.5	0.0	0.3	1.1
BMI ≥ 30 kg/m^2	–0.2	0.1	–0.8	0.5	0.1
PCS weight change at endpoint, n (%)					
≥ 7% weight loss	8 (4.2)	8 (4.3)	5 (2.6)	4 (2.2)	45 (3.7)
≥ 7% weight gain	6 (3.1)	16 (8.6)*	25 (12.8)***	25 (13.8)***	183 (15.0)
PCS weight change at any time, n (%)					
≥ 7% weight loss	10 (5.2)	11 (5.9)	8 (4.1)	6 (3.3)	97 (7.9)
≥ 7% weight gain	11 (5.7)	20 (10.8)	26 (13.3)*	29 (16.0)***	251 (20.5)
Treatment-emergent weight-related adverse events, n (%)[e]					
Appetite decreased	0 (0.0)	3 (1.6)	3 (1.5)	0 (0.0)	104 (8.1)
Appetite increased	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.5)	50 (3.9)
Anorexia	2 (1.0)	3 (1.6)	1 (0.5)	2 (1.1)	104 (8.1)

[a]There were no significant differences between duloxetine 40 mg b.i.d. or 60 mg b.i.d. vs. paroxetine 20 mg q.d.
[b]Except for repeated measures.
[c]For study 10, results are given as mean (SD).
[d]Therapy-by-subgroup interaction for studies 5 and 6, p value = .450.
[e]Numbers of patients for analyses of treatment-emergent weight-related adverse events were as follows: placebo, N = 192; duloxetine 40 mg b.i.d. (controlled studies), N = 188; duloxetine 60 mg b.i.d. (controlled studies), N = 196; paroxetine, N = 183; duloxetine 40–60 mg b.i.d. (uncontrolled study), N = 1279.
*p ≤ .05 vs. placebo, **p ≤ .01 vs. placebo, ***p ≤ .001 vs. placebo, +++p < .001 for change from baseline to endpoint.
Abbreviations: BMI = body mass index, PCS = potentially clinically significant.

from baseline to endpoint in subgroups based on age (< 55 vs. ≥ 55 years), gender, and ethnic origin (Caucasian vs. other) were similar. The incidences of PCS weight gain were numerically greater than those for PCS weight loss. To better understand the group that experienced the PCS weight gain at endpoint, the data were stratified into 2 groups (PCS weight gain vs. no PCS weight gain), but no statistical inferences were made between these groups because they were based on post-baseline data. The groups were relatively equally matched with regard to age and ethnic origin. However, the PCS weight gain group had a somewhat higher percentage of female patients compared with the no PCS weight gain group (79.2% vs. 71.1%). The mean baseline BMI scores were slightly lower in the PCS weight gain group compared with the no PCS weight gain group (24.9 vs. 26.8 kg/m^2), similarly for baseline weight (65.0 vs. 71.1 kg). The mean baseline HAM-D-17 total score was slightly higher for the PCS weight gain group compared with the no PCS weight gain group (23.3 vs. 22.2).

The Spearman's Rho correlation between the change in the HAM-D-17 total score and change in weight from baseline to endpoint was –0.20 (p < .001). These 2 variables were further explored in patient subgroups defined by overall compliance in taking the study medication. The patient was considered compliant if at each visit the patient, in the investigator's opinion, was compliant in taking the study medication. There were 984 compliant and 257 noncompliant patients. The mean weight gain and improvement in HAM-D-17 total score were greater among the compliant patients than among the noncompliant patients (1.3 vs. 0.1 kg and –15.5 vs. –8.7, respectively).

DISCUSSION

During 8 to 9 weeks of acute therapy, duloxetine-treated patients lost weight when compared with placebo-treated patients. Self-reports of treatment-emergent weight-related adverse events were consistent with the observed weight loss, in that patients in the duloxetine treatment group reported appetite decreased and anorexia significantly more often than patients in the placebo treatment group, whereas reports of appetite increased were similar. No duloxetine-treated patients reported appetite decreased or appetite increased as a reason for discontinuation, whereas 0.1% of duloxetine-treated patients discontinued due to anorexia. Patients treated with duloxetine 40 to 120 mg/day experienced weight loss similar to that seen in patients treated with fluoxetine

20 mg/day or paroxetine 20 mg/day during 8 weeks of therapy. No consistent relationship was observed between duloxetine dose and weight change.

After longer-term treatment with duloxetine, paroxetine, or placebo, a different picture emerged, namely, modest weight gain rather than weight loss with duloxetine. Weight gain in patients treated with duloxetine 40 mg b.i.d. did not differ significantly from that seen in placebo-treated patients. Patients treated with the highest dose of duloxetine, 60 mg b.i.d., and at the lowest recommended dose of paroxetine, 20 mg q.d., did, however, gain significantly more weight than did placebo-treated patients. Consistent with this finding, PCS weight gain was also seen more often in patients in these treatment arms. These data suggest a possible relationship between duloxetine dose and weight gain during longer-term treatment, but further study would be needed to confirm this.

In the relapse prevention study (study 9), patients treated with duloxetine 60 mg q.d. during the 12-week, open-label, acute phase gained on average 0.1 kg. Responders were then randomly assigned to duloxetine 60 mg q.d. or placebo for an additional 26 weeks, during which time both duloxetine-treated and placebo-treated patients gained approximately 1 kg on average. This weight gain with placebo following successful acute treatment with duloxetine is particularly interesting, the most likely explanation perhaps being "normal" weight gain over time in successfully treated patients. The fact that patients who continued on duloxetine during continuation treatment gained no more weight than placebo-treated patients during this time suggests that at its recommended dose of 60 mg q.d., duloxetine may not be associated with significant weight change during longer-term treatment, although this needs further investigation. During the 52-week open-label study (study 10), duloxetine-treated patients gained a mean of 1.1 kg of weight.

Overall, these data suggest a pattern of acute weight loss with duloxetine, followed by weight gain after longer-term treatment that appears modest and possibly dose-related. This pattern of long-term weight gain after acute weight loss has also been observed in studies of fluoxetine and sertraline.[6,7] Of the studies presented here, the 52-week uncontrolled study best approximates the experience of patients treated in real clinical practice, and weight changes accompanying long-term treatment with duloxetine are therefore most likely to follow the patterns seen in this study. However, it is unclear to what extent the mean 1.1-kg weight gain seen in duloxetine-treated patients in this study is attributable to the effect of duloxetine treatment itself rather than other factors, such as normal weight gain over time. For example, in a review of private-practice patients with depression, the 72% of patients who remitted from depression gained an average of 6.4 kg.[24] Patients who gained weight did not differ from patients who did not gain weight in terms of age, gender, diagnosis, duration of remission, or use of tricyclic antidepressants, tricyclic-SSRI combination, benzodiazepines, neuroleptics, and mood stabilizers. Benazzi[24] suggests that weight gain in remitted patients with depression is, at least in part, an effect of recovery from depression rather than a pharmacologic effect of antidepressants. In the 52-week uncontrolled study, the patients who exhibited PCS weight gain, on average, weighed less and had lower BMI scores at baseline than those who did not experience PCS weight gain. Patients with a baseline BMI of ≤ 25 kg/m^2 experienced the greatest weight gain.

The negative correlation between change in HAM-D-17 total scores and change in weight indicates that patients tended to gain weight as their depression improved. Although this correlation was highly significant, it was very small. Thus, the change in the HAM-D-17 total score may play only a small role in explaining the change in weight. The fact that the mean weight gain and improvement in the HAM-D-17 total score were greater among the compliant patients than among the non-compliant patients suggests that the changes in weight and depression symptoms are both, at least to some extent, related to duloxetine.

The analyses presented in this article have a number of limitations that merit consideration. First, the results must be considered in light of the dosing used for the active comparators. Although the 20-mg/day dose of paroxetine used in these studies is approved, commonly prescribed, and effective,[25] it is at the low end of the approved dose range. The same can be said for the 20-mg/day dose of fluoxetine that was used in these studies. In contrast, the doses of duloxetine spanned its entire dose range. In retrospect, it would have been more informative to practitioners if the studies had permitted the full dose range of the comparators. Second, because paroxetine and fluoxetine arms did not coexist in any study, the effects of these treatments on body weight could not be directly compared. Third, our ability to examine whether there is a relationship between duloxetine dose and weight change is limited by the fact that the full dose range was not investigated within any individual study. Fourth, despite the large number of subjects overall, comparisons involving relatively rare events undoubtedly lacked adequate statistical power. By contrast, some analyses of actual weight change had so much power that small differences were determined to be statistically significant. Hence, emphasis should be placed on the number of subjects with particular events. Finally, although analyses of weight change, treatment-emergent adverse events, and adverse events reported as the reason for discontinuation were specified in each protocol, and between-study variability was controlled for in the analyses, the decision to pool these data was not planned at the outset of this research program.

Many factors may be taken into consideration when choosing the most appropriate antidepressant for a particular patient, including the effect of the drug on body weight.

For the patient who is overweight, an antidepressant that induces significant weight gain may be less appropriate. Furthermore, patient satisfaction, and hence adherence to the treatment regimen, may be negatively impacted by a drug that is associated with significant weight gain in the short and long term.[1] In fact, patients are reluctant to be treated with a medication that has weight-related side effects.[7]

Duloxetine appears to have minimal short-term and long-term effects on weight for the majority of patients and thus may prove to be an acceptable therapy when effects on weight are a consideration in the selection of an antidepressant medication.

Drug names: bupropion (Wellbutrin and others), duloxetine (Cymbalta), fluoxetine (Prozac and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), sibutramine (Meridia).

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