Duloxetine in the Treatment of Major Depressive Disorder: A Double-Blind Clinical Trial

David J. Goldstein, M.D., Ph.D.; Craig Mallinckrodt, Ph.D.; Yili Lu, Ph.D.; and Mark A. Demitrack, M.D.

Background: Duloxetine hydrochloride, a dual reuptake inhibitor of serotonin and norepinephrine, was evaluated for therapeutic efficacy and safety/tolerability in the treatment of major depression.

Method: In an 8-week multicenter, double-blind, placebo-controlled study, 173 patients (aged 18–65 years) with DSM-IV major depressive disorder were randomly allocated to receive placebo (N = 70), duloxetine (N = 70), or fluoxetine, 20 mg q.d. (N = 33). Duloxetine dose was titrated in the first 3 weeks in a forced-titration regimen from 40 mg (20 mg b.i.d.) to 120 mg/day (60 mg b.i.d.). Patients were required to have a Clinical Global Impressions (CGI)-Severity of Illness scale score of at least moderate severity (≥ 4) and a 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score of at least 15. Patients could not have had any current primary DSM-IV Axis I diagnosis other than major depressive disorder, or any anxiety disorder as a primary diagnosis within the past year, excluding specific phobias. The primary efficacy measurement was the HAM-D-17 total score, and secondary measures included the Montgomery-Asberg Depression Rating Scale, CGI-Severity of Illness and CGI-Improvement, and Patient Global Impression of Improvement. Safety was evaluated by recording the occurrence of discontinuation rates and treatment-emergent adverse events and by measurement of vital signs and laboratory analytes.

Results: Duloxetine was superior to placebo in change on the HAM-D-17 ($p = .009$). Estimated probabilities of response and remission were 64% and 56%, respectively, for duloxetine, compared with 52% and 30% for fluoxetine and 48% and 32% for placebo. Duloxetine was numerically superior to fluoxetine on the primary and most of the secondary outcome measures. In general, duloxetine was well tolerated; 76% of patients achieved the maximum dose, and insomnia and asthenia were the only adverse events reported statistically significantly ($p < .05$) more frequently by duloxetine-treated patients compared with placebo-treated patients.

Conclusion: These data indicate that duloxetine is efficacious for the treatment of major depressive disorder and is well tolerated and safe.

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Received June 13, 2001; accepted Dec. 20, 2001. From the Duloxetine Antidepressant Team, Eli Lilly and Company, Eli Lilly Corporate Center (all authors); and the Departments of Pharmacology and Toxicology (Dr. Goldstein) and Psychiatry (Dr. Demitrack), Indiana University Medical School, Indianapolis.

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Corresponding author and reprints: David J. Goldstein, M.D., Ph.D., Lilly Corporate Center, Indianapolis, IN 46285 (e-mail: GOLDSTEIN_DAVID_J@LILLY.COM).

Major depressive disorder is the third most costly and disabling illness in the United States.[1] It has been estimated that this illness will be the second most important cause of disability worldwide by the year 2020.[2]

Introduction of the current first-line treatments for major depression, namely the selective serotonin reuptake inhibitors (SSRIs), represented a notable advance in safety, tolerability, and convenience. However, SSRIs do not offer a corresponding improvement in overall therapeutic efficacy or reduced time to onset of clinical effect compared with previous standard treatments. At present, fewer than 70% of patients are expected to have meaningful symptomatic response to the first treatment recommended by their physician, while only approximately 30% of patients may be expected to achieve nearly full symptom relief or remission of illness.[3] Furthermore, of those who receive drug treatment for depression, nearly one fourth experience a relapse or recurrence of depression during the 9 months following the initial diagnosis of depression.[4]

Whether improvements in monoamine-based approaches can be obtained has been actively discussed.[5,6] Because multiple neurotransmitter systems have been implicated in the pathophysiology of depression,[7] it has been hypothesized that the enhancement of multiple monoamine neurotransmitters may provide a more robust clinical effect. Consistent with this hypothesis, the Danish

University Antidepressant Group has provided evidence to suggest that the tricyclic antidepressant clomipramine has greater clinical efficacy than the SSRI citalopram.[8] Furthermore, it has been noted that the noradrenergic reuptake inhibitor desipramine is effective at enhancing the efficacy of the SSRI fluoxetine.[9] The results of these studies strongly support the use of mixed monoamine reuptake inhibitors to improve the outcome of initial treatment of patients with major depression and therefore shorten the time to meaningful symptomatic clinical change.

Duloxetine hydrochloride (LY248686, [+]-N-methyl-g-[1-naphthalenyloxy]-2-thiophenepropanamine hydrochloride) inhibits both serotonin and norepinephrine reuptake transport sites in vitro and in vivo.[10,11] Relative to currently marketed antidepressants, duloxetine has greater similarity of, or balance between, affinities for the serotonin (5-HT) and norepinephrine transporters.[12] Moreover, duloxetine lacks significant affinity for muscarinic, histamine-1, β_1-adrenergic, dopamine-2, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, and opioid receptors.[13] Thus, duloxetine offers the potential to test the hypothesis that a potent and balanced dual-reuptake inhibitor will have a greater antidepressant effect than an SSRI without significant limiting adverse events.

Preliminary data on duloxetine suggest that it might have hypothetical advantages over a reuptake inhibitor of a single monoamine. In an open-label pilot study of 79 patients with unipolar major depression, duloxetine (20 mg q.d.) administered over 6 weeks produced a significant reduction in depression scores (17-item Hamilton Rating Scale for Depression [HAM-D-17]), with 78.2% of patients exhibiting clinical response (i.e., 50% reduction in HAM-D-17 scores) and 60.3% achieving symptom remission (i.e., endpoint HAM-D-17 score of ≤ 6).[14]

The present study reports the results of a phase 2 double-blind, placebo-controlled, randomized clinical trial conducted to assess the therapeutic efficacy and safety/tolerability of duloxetine in patients with major depressive disorder. In this study, duloxetine was administered in a forced titration from 40 mg/day (20 mg b.i.d.) to 120 mg/day (60 mg b.i.d.) during the first 3 weeks of an 8-week treatment period. Fluoxetine (20 mg q.d.) was used as an internal control.

METHOD

Study Design

This was an 8-site, double-blind, placebo-controlled, randomized clinical trial, designed to assess the effectiveness of duloxetine during 8 weeks of treatment. The primary efficacy measure was HAM-D-17 total score. This study utilized a double-blind placebo lead-in such that investigators and patients did not know when randomization occurred and when active study drug was first administered. A double-blind placebo lead-out period was used in conjunction with a 1-week follow-up period while patients were off all treatments to assess potential discontinuation-emergent events following treatment cessation. This study protocol was approved by the ethics committee of each site in accordance with the principles of the Declaration of Helsinki, and patients provided informed consent prior to any study procedures.

Patients were randomly allocated to placebo, duloxetine, or fluoxetine treatment groups in a 2:2:1 ratio. Participants were male and female outpatients, aged 18 to 65 years, who met criteria for nonpsychotic major depressive disorder as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[15] The diagnosis of major depressive disorder was confirmed by the Mini-International Neuropsychiatric Interview.[16] In addition, patients were required to have a Clinical Global Impressions-Severity of Illness (CGI-S)[17] rating of at least 4 (moderate) at visit 1 and a clinician-rated HAM-D-17 total score of at least 15 at visits 1 and 2. Patients were excluded if they had any primary DSM-IV Axis I diagnosis other than major depressive disorder or any anxiety disorder as a primary diagnosis within the past year, with the exception of specific phobias. Patients were also excluded if they had a history of substance abuse or dependence within the past year or had a positive urine drug screen at study entry. Patients could not have failed 2 or more adequate courses of antidepressant therapy during the current episode.

Treatments

Duloxetine, placebo, or fluoxetine were given for 8 weeks. Initial dosing of duloxetine was 40 mg/day administered b.i.d., with forced titration decisions occurring at weekly intervals such that the earliest time of maximum dosing to 120 mg/day (administered 60 mg b.i.d.) was 3 weeks after the first dose. Forced-titration decisions were allowed in a blinded manner by the investigators through a telephone voice-response drug allocation system. The clinician was permitted the option of refusing a dose escalation for a patient, based solely on the safety and tolerability of the current dose. Fluoxetine (20 mg q.d.) was used as an internal control. The number of capsules administered daily (4 capsules every morning, 3 capsules every evening) was consistent among groups.

Efficacy Measures

Response to treatment was assessed using the HAM-D-17 as the primary efficacy measure.[18] Secondary measures included the Montgomery-Asberg Depression Rating Scale (MADRS),[19] the CGI,[17] the Patient Global Impression of Improvement (PGI),[17] and the Hamilton Rating Scale for Anxiety (HAM-A).[20]

During the study initiation meeting, the 18 investigators and site personnel who were administering the HAM-D-17 were evaluated for their ability to rate a

videotaped interview and their interviewing skills. For their assessment of the videotape, mean ± SD percentage agreement (percentage of items that agreed with the modal answer of all other raters) was 73.8% ± 12.8%, and the mean intraclass correlation coefficient (relative variability of the scores of 1 rater compared with the variability of the scores of all other raters; values can range from 1.00 [perfect agreement] to –1.00 [inverse relationship]) was 0.87 ± 0.07. Raters who were judged to have inadequate interviewing skills were precluded from administering the HAM-D-17, HAM-A, or MADRS.

Blood Pressure Measurement

If a patient met any 1 of the following conditions maintained over 3 consecutive visits, the patient was considered to have hypertension: supine systolic blood pressure ≥ 140 mm Hg and at least 10 mm Hg greater than baseline, supine diastolic pressure ≥ 90 mm Hg and at least 10 mm Hg greater than baseline, standing systolic blood pressure ≥ 140 mm Hg and at least 10 mm Hg greater than baseline, or standing diastolic pressure ≥ 90 mm Hg and at least 10 mm Hg greater than baseline. Within these criteria, baseline was defined as the highest value of the measurements prior to randomization.

Statistical Analysis

It was estimated that a sample size of 70 patients in the duloxetine and placebo groups would yield 65% power to detect a difference between these groups in mean change from baseline to endpoint of 3.25 units on the HAM-D-17, assuming a common standard deviation in change scores of 7.0. Fluoxetine was an underpowered qualitative comparison treatment.

Efficacy outcomes, both continuous and categorical, were analyzed using a mixed-effects likelihood-based repeated-measures (MMRM) analysis. Although depression data are commonly analyzed via last-observation-carried-forward (LOCF) analysis of variance (ANOVA), LOCF requires assumptions regarding the missing data that were not met in this trial[21,22] and therefore LOCF is likely to yield biased results such as those demonstrated by Siddiqui and Ali.[23] These 2 critical assumptions are that first, data are missing completely at random, i.e., not influenced by efficacy or adverse events; and second, the condition of the dropouts would not have changed from the last observation to the endpoint if the patients had remained in the trial. Because these assumptions are often violated, in most cases the MMRM technique provides more accurate estimates of treatment effects and provides superior control of type I error compared with LOCF.[24]

In this analysis, change from baseline to each visit was the dependent variable. The model included the fixed, categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous, fixed covariates of baseline score and baseline score-by-visit interaction. An unstructured (co)variance matrix was used to model the within-patient errors. The primary treatment comparison was between the duloxetine and placebo treatment groups at the last visit at which patients received active study drug.

Response (≥ 50% reduction in HAM-D-17 total score) and remission (HAM-D-17 total score ≤ 7) probabilities after 8 weeks of treatment were estimated using a mixed-effects repeated measures approach, as discussed by Leon.[22] The model structure for this categorical analysis was similar to the one used for the continuous variables with the addition of a probit link function and a binomial error distribution. In addition, response and remission rates at endpoint were calculated using the LOCF method and were analyzed using the Fisher exact test.

Gender, ethnicity, incidence of adverse events reported as a reason for discontinuation, treatment-emergent adverse events, treatment-emergent abnormal vital signs, discontinuation-emergent adverse events, and treatment-emergent abnormal laboratory tests were summarized by treatment group, with the significance of differences assessed by the Fisher exact test. Limits for determining abnormal laboratory values were based on previously established Lilly Research Laboratories reference limits (W. L. Thompson, M.D.; L. Brunelle, M.A.; G. G. Enas, Ph.D., data on file, Eli Lilly and Company, Indianapolis, Ind., 1990). Limits for determining abnormal vital signs were based on Joint National Committee-VI criteria.[25]

For laboratory analytes, vital signs, and the Arizona Sexual Experience Scale (ASEX),[26] mean change from baseline to endpoint was assessed using ANOVA. The significance of differences between groups was based on tests using ranked data for laboratory analytes and raw data for vital signs and ASEX total score.

RESULTS

Patient Summary

A total of 173 patients were randomly allocated to either placebo (N = 70), duloxetine (N = 70), or fluoxetine (N = 33). Of these, 167 patients had postbaseline efficacy data (duloxetine, N = 66; placebo, N = 68; fluoxetine, N = 33). There were no clinically meaningful differences among treatment groups on any measure of baseline demographics (Table 1). The majority (75.7%, N = 53) of the duloxetine-treated patients were titrated to the maximum allowable dose of 120 mg/day. However, 6 duloxetine-treated and 2 placebo-treated patients discontinued after randomization but prior to completing 1 week of therapy.

Efficacy

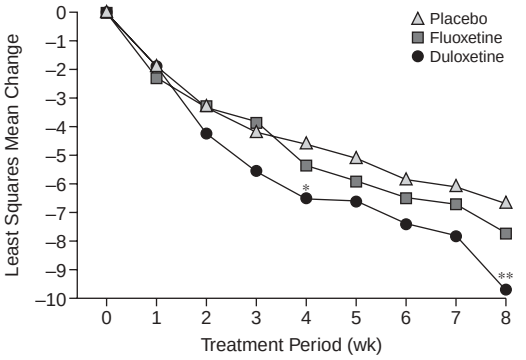
Principal efficacy results are displayed in Figures 1 and 2 and in Table 2. On the primary efficacy measure, HAM-D-17 score, duloxetine showed a statistically significantly greater mean change from baseline to week 8 than

Table 1. Baseline Patient Demographics[a]

Characteristic	Placebo (N = 70)	Duloxetine (N = 70)	Fluoxetine (N = 33)
Sex, N (%)			
Male	22 (31.4)	26 (37.1)	14 (42.4)
Female	48 (68.6)	44 (62.9)	19 (57.6)
Age, mean (SD), y	41.4 (13.3)	42.3 (10.8)	39.7 (10.5)
Racial origin, N (%)			
White	57 (81.4)	62 (88.6)	24 (72.7)
African American	7 (10.0)	3 (4.3)	4 (12.1)
Other	6 (8.6)	5 (7.1)	5 (15.1)
Psychiatric profile, mean (SD)			
HAM-D-17 total	19.2 (5.0)	18.4 (4.0)	17.9 (4.3)
MADRS total	24.9 (6.7)	22.9 (6.1)	22.6 (6.9)
CGI-S	4.3 (0.6)	4.2 (0.6)	4.1 (0.6)
HAM-A	15.4 (4.8)	14.2 (4.2)	15.5 (5.8)
HAM-D-17 subscales			
Anxiety	6.2 (1.7)	5.4 (2.0)	5.5 (2.2)
Core factor	7.8 (2.4)	7.5 (2.6)	7.5 (2.3)
Retardation	7.3 (2.1)	7.2 (2.0)	6.8 (1.9)
Maier	10.0 (2.9)	9.1 (3.0)	9.3 (2.5)
Sleep	3.3 (1.8)	3.5 (1.7)	2.6 (1.7)
ASEX total score, mean (SD)			
Male	16.1 (4.4)	16.7 (5.2)	16.1 (4.3)
Female	17.7 (5.1)	19.3 (3.6)	19.7 (3.2)
Weight, mean (SD), kg	75.9 (16.2)	83.6 (20.0)	78.5 (17.8)
Standing heart rate, mean (SD), bpm	76.9 (10.2)	78.8 (10.4)	79.7 (10.6)
Standing systolic BP, mean (SD), mm Hg	118.2 (12.7)	121.8 (13.2)	118.8 (11.8)
Standing diastolic BP, mean (SD), mm Hg	76.6 (9.2)	79.5 (8.7)	78.1 (8.8)

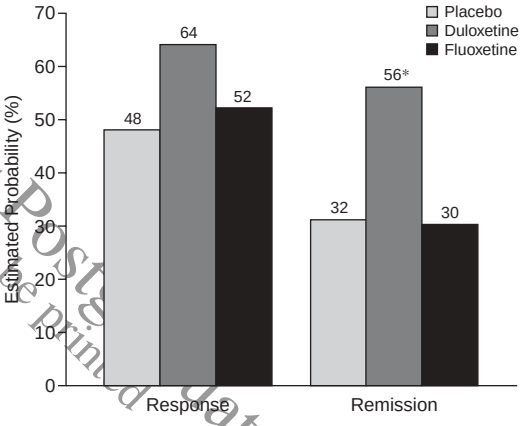
[a]Abbreviations: ASEX = Arizona Sexual Experience Scale, BP = blood pressure, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 1. Effect of Placebo (N = 68), Duloxetine (N = 66), and Fluoxetine (N = 33) on HAM-D-17 Total Scores (least squares mean change from baseline) During the 8-Week Treatment[a]



[a]Duloxetine differed significantly from placebo at week 4 (*p = .049) and week 8 (**p = .009) (see text for statistical methods).

Figure 2. Estimated Probability of Response and Remission of Placebo (N = 68), Duloxetine (N = 66), and Fluoxetine (N = 33) Treatment Groups After 8 Weeks of Treatment[a]



[a]The advantage of duloxetine over placebo in remission was statistically significant (*p = .02) (see text for statistical methods).

placebo (duloxetine change = –9.73, placebo change = –6.61, p = .009; see Figure 1). Excluding the 8 patients who discontinued prior to completing 1 week of double-blind therapy, the mean change (LOCF) analysis results were –8.58 for duloxetine and –6.20 for placebo (p = .012), which closely resembled the MMRM results. Treatment-by-investigator interaction was not significant.

An analysis of HAM-D-17 total score comparing patients with a score of less than 19 and those with a score of 19 and above at baseline demonstrated a nonsignificant but greater decrease in baseline-to-endpoint change in HAM-D-17 for all treatments in the more severely ill group. For baseline HAM-D-17 score less than 19, the changes were as follows: placebo, –5.15; duloxetine, –6.16; fluoxetine, –5.00. For baseline HAM-D-17 score equal to or greater than 19, the changes were as follows: placebo, –6.72; duloxetine, –9.30; fluoxetine, –7.77.

Results from the categorical response and remission analyses are displayed in Figure 2. The estimated probability of remission after 8 weeks of treatment for duloxetine-treated patients (56%) was statistically significantly greater (p = .022) than that observed for placebo-treated patients (32%, see Figure 2). By mean change (LOCF) analysis, the response rates were 36%, 49% (p = .167), and 45% (p = .393) and the remission rates were 27%, 43% (p = .072), and 30% (p = .815) for placebo, duloxetine, and fluoxetine, respectively.

Duloxetine-treated patients showed a statistically significantly greater mean improvement than placebo-treated patients for nearly all secondary efficacy outcomes (Table 2). On the HAM-D-17 subscales, the duloxetine patient group had a statistically significantly greater reduction than the placebo group on the anxiety (items 10, 11, 12, 13, 15, and 17), core factor (items 1, 2, 3, 7, and 8), retardation (items 1, 7, 8, and 14),[27] and Maier (items 1, 2, 7, 8, 9, and 10)[28] subscales (see Table 2).

Duloxetine-treated patients had a statistically significantly greater improvement on the HAM-D-17 anxiety

Table 2. Summary of Primary and Secondary Efficacy Outcomes[a]

Scale	Least Squares Mean Change From Baseline to Last Visit: Placebo (N = 68)	Duloxetine (N = 66)	Fluoxetine (N = 33)	p Value[b]
HAM-D-17	–6.61	–9.73	–7.75	.009
HAM-A total	–5.05	–6.87	–6.97	.077
MADRS	–9.53	–12.91	–11.76	.047
CGI-S	–1.07	–1.67	–1.31	.007
CGI-I	2.69	2.10	2.40	.005
PGI	2.92	2.27	2.60	.006
HAM-D-17 subscales				
Anxiety	–1.95	–2.92	–1.82	.027
Core factor	–3.19	–4.52	–3.76	.023
Retardation	–2.67	–4.11	–3.30	.004
Maier	–3.65	–5.61	–3.85	.005
Sleep	–0.82	–1.28	–1.75	.157

[a]Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, PGI = Patient Global Impression of Improvement.
[b]Duloxetine vs. placebo (repeated-measures analysis).

Table 3. Patient Disposition[a]

Reason for Discontinuation	Placebo (N = 70)	Duloxetine (N = 70)	Fluoxetine (N = 33)	p Value[b]
Adverse event	3 (4.3)	7 (10.0)	1 (3.0)	.417
Lack of efficacy (patient and physician)	10 (14.3)	2 (2.9)	3 (9.1)	.047
Lost to follow-up	6 (8.6)	1 (1.4)	2 (6.1)	.147
Personal conflict or other patient decision	3 (4.3)	9 (12.9)	5 (15.2)	.099
Protocol violation	2 (2.9)	5 (7.1)	1 (3.0)	.572
Patients completing acute phase	46 (65.7)	46 (65.7)	21 (63.6)	.956

[a]Values shown as N (%).
[b]Duloxetine vs. placebo (Fisher exact text).

Table 4. Common Treatment-Emergent Adverse Events (%)[a]

Adverse Event	Placebo (N = 70)	Duloxetine (N = 70)	Fluoxetine (N = 33)	p Value[b]
Dry mouth	17.1	30.0	21.2	.110
Headache	31.4	20.0	33.3	.175
Insomnia	7.1	20.0	9.1	.046
Somnolence	10.0	18.6	21.2	.227
Sweating	8.6	18.6	9.1	.137
Asthenia	4.3	17.1	15.2	.026
Dizziness	7.1	15.7	6.1	.183
Rhinitis	17.1	15.7	15.2	1.00
Diarrhea	10.0	14.3	30.3	.606
Nausea	12.9	12.9	18.2	1.00
Constipation	5.7	11.4	15.2	.366
Anorexia	4.3	10.0	6.1	.326

[a]Selected adverse events that had an incidence > 10% for duloxetine.
[b]Duloxetine vs. placebo (Fisher exact test).

subscale compared with fluoxetine-treated patients (p = .041). Duloxetine was also numerically superior to fluoxetine for all primary and most secondary efficacy outcome measures.

Adverse Events

No patients died or experienced a serious adverse event (initial or prolonged inpatient hospitalization, a life-threatening experience, severe or permanent disability, or a congenital anomaly). The proportions of patients who discontinued during the active treatment phase were 34.3% (N = 24) for those taking placebo, 34.3% (N = 24) for those taking duloxetine, and 36.4% (N = 12) for those taking fluoxetine. During the active treatment phase, 10.0% (N = 7) of the duloxetine-treated patients discontinued due to adverse events compared with 4.3% of placebo-treated patients (N = 3) (Table 3), a difference that was not statistically significant. A second major reason for discontinuation was lack of efficacy. Statistically significantly more patients in the placebo treatment group discontinued for perceived lack of efficacy compared with the duloxetine treatment group (p = .047).

The overall incidence of patients having at least 1 treatment-emergent adverse event did not significantly differ between the duloxetine and placebo groups (p = .469). These events are summarized in Table 4. The only adverse events with an incidence significantly greater (p < .05) for duloxetine-treated patients compared with placebo-treated patients were asthenia (17.1% vs. 4.3%) and insomnia (20.0% vs. 7.1%). Most of these events were reported to be of mild severity. Spontaneous report of sexual dysfunction as an adverse event may underestimate the magnitude of this outcome; therefore, we specifically included the ASEX as a solicited measure of sexual function. The ASEX total score for either sex showed no statistically significant difference between duloxetine- and placebo-treated patients in change from baseline to endpoint (Table 5).

Hypertension was reported as an adverse event by 4.3% of duloxetine-treated patients compared with 5.7% of placebo-treated patients. The incidence of any cardiovascular adverse event (as defined by COSTART) was similar for duloxetine-treated patients compared with placebo-treated patients (20.0% vs. 22.9%).

Only 1 discontinuation-emergent adverse event, abnormal dreams, was notable for patients previously taking duloxetine, although the incidence did not differ significantly from patients previously taking placebo (p = .056).

Vital Signs and Body Weight

Mean changes from baseline to endpoint for all vital signs and body weight are displayed in Table 5. Overall, the differences were not clinically meaningful, although there were 3 that were statistically significant. The mean increase for supine heart rate in duloxetine-treated patients was 3.49 beats per minute greater than for placebo-treated patients (p = .042). The mean increase in standing diastolic blood pressure for duloxetine-treated patients

Table 5. Mean Change From Baseline to Endpoint of Vital Signs, Body Weight, and ASEX[a]

Measurement	Placebo (N = 70)	Duloxetine (N = 70)	Fluoxetine (N = 33)	p Value[b]
Standing heart rate, bpm	–0.09	3.09	–2.55	.071
Standing systolic BP, mm Hg	–1.14	1.29	–1.06	.215
Standing diastolic BP, mm Hg	–0.92	1.88	–1.79	.041
Supine heart rate, bpm	0.11	3.60	–1.55	.042
Supine systolic BP, mm Hg	0.15	1.76	0.82	.398
Supine diastolic BP, mm Hg	0.59	2.03	–1.91	.269
Weight change, kg	0.68	–0.59	–0.58	.005[c]
ASEX total score				
Male	–2.22	1.00	–1.43	.305
Female	–0.78	0.81	0.86	.631

[a]Abbreviations: ANCOVA = analysis of covariance, ANOVA = analysis of variance, ASEX = Arizona Sexual Experience Scale, BP = blood pressure.
[b]Duloxetine vs. placebo (ANOVA model) unless otherwise specified.
[c]Duloxetine vs. placebo (ANCOVA model).

was 2.80 mm Hg greater than for placebo-treated patients (p = .041). Duloxetine-treated patients exhibited a small but statistically significant reduction in body weight relative to placebo-treated patients (p = .005).

The rates of hypertension (standing) were 2.9% (N = 2) and 0% (N = 0) for duloxetine- and placebo-treated patients, respectively, which were not statistically significantly different (p = .496).

Laboratory Values

Changes in laboratory tests were transient and of no clinical relevance. Mean changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were significantly greater (p < .05) for duloxetine-treated patients compared with placebo-treated patients (ALT: placebo mean change = –0.63, duloxetine mean change = 3.91; AST: placebo mean change = –1.30, duloxetine mean change = 5.77). Transaminase elevations were all < 3 times the upper limit of normal and resolved upon either continued treatment or discontinuation. None of the patients treated with duloxetine who had treatment-emergent abnormalities in transaminases at any time during the trial had concurrent treatment-emergent abnormal bilirubin levels.

DISCUSSION

Although there are a number of therapeutic choices available for the treatment of major depression, it is generally acknowledged that current first-line therapies provide less than satisfactory outcomes in many instances. This is because nearly two thirds of all patients are either partially or completely nonresponsive, only one third experience full remission, and many have tolerability concerns that limit long-term treatment.[29] Thus, the development of new agents that can meaningfully expand the expected therapeutic effect and tolerability of antidepressant therapy options is an important medical need.

In the present study, duloxetine, a potent and balanced dual reuptake inhibitor of serotonin and norepinephrine, demonstrated a statistically significant superiority to placebo in improvement in the total score on the HAM-D-17 and on nearly all secondary efficacy measures, including remission, MADRS, CGI, PGI, and all HAM-D-17 subscales except sleep. The subset analysis by HAM-D-17 total score indicated that the antidepressant effect was more robust for patients with greater symptom severity. Although the remission rate for duloxetine-treated patients was high, the response and remission rates were very similar. This finding is unlikely to be due to the study design, because fluoxetine did not show a similar result. This will need to be investigated further in future trials. In addition, the significant improvement in the HAM-D anxiety subscale scores and marginally significant improvement in HAM-A scores for duloxetine versus placebo despite the exclusion of patients with primary anxiety disorders indicate that duloxetine has a demonstrable anxiolytic effect.

The study was not designed to be a comparison of duloxetine and fluoxetine. The fluoxetine treatment group was an underpowered qualitative control arm. If duloxetine treatment had failed to separate from placebo, the fluoxetine treatment group would have been evaluated to assess the sensitivity of the study for detection of efficacy. In retrospect, the fluoxetine group was unsatisfactory for this purpose, in part because it was underpowered and perhaps because it lacked sufficient efficacy in this particular study, given the relatively high placebo response rate. Titration of the fluoxetine arm might have increased its efficacy.[30]

Discontinuations due to adverse events were similar across treatment arms in this study. Duloxetine-treated patients experienced insomnia and asthenia at statistically significantly higher rates than placebo-treated patients. Duloxetine is also being studied in stress urinary incontinence; however, there were no cases of urinary retention reported by duloxetine-treated patients in this study.

It is notable that the rate of spontaneously reported sexual dysfunction, although numerically higher in the duloxetine-treated subjects, was not statistically significantly different from placebo (data not shown). Furthermore, the ASEX total score, which was used as a solicited measure of sexual function, was also not statistically significantly different from placebo. The increase in sexual dysfunction common to SSRIs[31] was not observed in this study. This might have been due to the small sample size, an inadequate study duration, or insensitivity of the ASEX to detect subtle effects in this trial. Although the sexual adverse event profile found in this study was encouraging, a more complete description of the sexual adverse event profile of duloxetine awaits further clinical study.

Consistent with norepinephrine reuptake inhibition, there was a small but statistically significant mean increase from baseline to endpoint in supine heart rate and standing diastolic blood pressure. However, there was no clinical significance to these small changes. The favorable cardiovascular profile of duloxetine is underscored by observations that the rate of hypertension and the rates of cardiovascular adverse events were not statistically significantly different from placebo-treated subjects.

This study confirms earlier open-label data suggesting that duloxetine may represent a potentially important advance in the treatment of patients with major depression.[13] In this randomized, double-blind, placebo-controlled trial, duloxetine was statistically superior to placebo in reducing the symptoms of major depressive disorder. Moreover, the safety and tolerability profile, especially with regard to the cardiovascular system, was favorable. A more complete profile of duloxetine should be provided by the results of phase 3 clinical studies.

Drug names: citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac and others).

REFERENCES

1. Thompson D, Buesching D, Gregor KJ, et al. Patterns of antidepressant use and their relation to costs of care. Am J Manag Care 1996;2: 1239–1246
2. Davidson JRT, Meltzer-Brody SE. The underrecognition and undertreatment of depression: what is the breadth and depth of the problem? J Clin Psychiatry 1999;60(suppl 7):4–9
3. Richelson E. Treatment of acute depression. Psychiatr Clin North Am 1993;16:461–478
4. Melfi CA, Chawla AJ, Croghan TW, et al. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. Arch Gen Psychiatry 1998;55:1128–1132
5. Nelson JC. Augmentation strategies in depression 2000. J Clin Psychiatry 2000;61(suppl 2):13–19
6. Demitrack MA. Is there room to improve monoamine-based therapies? Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
7. Briley M. Specific serotonin and noradrenaline reuptake inhibitors (SNRIs): a review of their pharmacology, clinical efficacy and tolerability. Hum Psychopharmacol 1998;13:99–111
8. Andersen J, Bech P, Benjaminsen S, et al. Citalopram: clinical effect profile in comparison with clomipramine. A controlled multicenter study. Danish University Antidepressant Group. Psychopharmacology (Berl) 1986;90:131–138
9. Nelson JC, Mazure CM, Bowers MB, et al. A preliminary study of the combination of fluoxetine and desipramine for rapid treatment of depression. Arch Gen Psychiatry 1991;48:303–307
10. Pitsikas N. Duloxetine. Curr Opin Investig Drugs 2000;1:116–121
11. Wong DT. Duloxetine (LY248686): an inhibitor of serotonin and noradrenaline uptake and an antidepressant drug candidate. Exp Opin Invest Drugs 1998;7:1–9
12. Bymaster FP, Dreschfield-Ahmad LJ, Threlkeld PG, et al. Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. Neuropsychopharmacology 2001;25:871–880
13. Wong DT, Bymaster FP, Mayle DA, et al. LY248686, a new inhibitor of serotonin and noradrenaline uptake. Neuropsychopharmacology 1993;8: 23–33
14. Berk M, du Plessis AD, Birkett M, et al. An open-label study of duloxetine hydrochloride, a mixed serotonin and noradrenaline reuptake inhibitor, in subjects with DSM-III-R major depressive disorder. Lilly Duloxetine Depression Study Group. Int Clin Psychopharmacol 1997;12:137–140
15. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington DC: American Psychiatric Association; 1994
16. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33
17. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
18. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
19. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
20. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959;32:50–55
21. Verbeke G, Molenberghs G. Linear Mixed Models for Longitudinal Data. New York, NY: Springer; 2000
22. Leon AC. Measuring onset of antidepressant action in clinical trials: an overview of definitions and methodology. J Clin Psychiatry 2001:62 (suppl 4):12–16
23. Siddiqui O, Ali MW. A comparison of the random-effects pattern mixture model with last-observation-carried-forward (LOCF) analysis in longitudinal clinical trials with dropouts. J Biopharm Stat 1998;8:545–563
24. Mallinckrodt CH, Clark WS, David SR. Type 1 error rates from mixed-effects model repeated measures compared with fixed-effects ANOVA with missing values imputed via LOCF. Drug Information J 2001;35: 1215–1225
25. JNC-VI Criteria: the Sixth Report of the Joint National Committee on Prevention, Direction, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997;157:2413–2446
26. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona Sexual Experience Scale (ASEX): reliability and validity. J Sex Marital Ther 2000;26:25–40
27. Cleary MA, Guy W. Factor analysis of the Hamilton Depression Scale. Drugs Exp Clin Res 1975;1:115–120
28. Maier W, Philipp M. Improving the assessment of severity of depressive states: a reduction of the Hamilton Depression Scale. Pharmacopsychiatry 1985;18:114–115
29. Mulrow CD, Williams JW, Chiquette E, et al. Efficacy of newer medications for treating depression in primary care patients. Am J Med 2000; 108:54–64
30. Fava M, Rosenbaum JF, Cohen L, et al. High-dose fluoxetine in the treatment of depressed patients not responsive to a standard dose of fluoxetine. J Affect Disord 1992;25:229–234
31. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol 1999;19:67–85