Notice of Correction: In the print article, a single asterisk was omitted for the duloxetine group at week 52 in Figure 4 on page 711. The online version of Figure 4 has been corrected.

Duloxetine in the Prevention of Depressive Recurrences: A Randomized, Double-Blind, Placebo-Controlled Trial

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Objective: To assess the efficacy of duloxetine 60–120 mg once daily in the prevention of depressive recurrence in outpatients with recurrent major depressive disorder (MDD).

Method: Eligible patients with at least 3 episodes of MDD (DSM-IV diagnosis) in the past 5 years received open-label duloxetine 60–120 mg/day for up to 34 weeks. Patients meeting response criteria were then randomly assigned to either duloxetine or placebo for up to 52 weeks of double-blind maintenance treatment. The primary outcome measure was time to recurrence of a major depressive episode. Safety and tolerability were assessed via analysis of treatment-emergent adverse events (TEAEs), vital signs, weight, and laboratory measures. Patients were recruited from 43 study centers in 5 European countries (France, Germany, Italy, Russia, and Sweden) and the United States. The study was conducted from March 2005 to January 2008.

Results: A total of 288 patients were randomly assigned to duloxetine or placebo. Time to a depressive recurrence was significantly longer in duloxetine-treated patients compared with placebo-treated patients ($p < .001$). During the double-blind maintenance phase, 33.1% of placebo-treated patients experienced a depressive recurrence compared with 14.4% of duloxetine-treated patients ($p < .001$). There were no significant differences between treatment groups in TEAEs, discontinuations due to adverse events, vital signs, or weight.

Conclusions: Treatment with duloxetine was associated with a longer time to depressive recurrence and a significantly lower recurrence rate compared with placebo.

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Major depressive disorder (MDD) has a lifetime prevalence ranging from 10% to 25% in females and 5% to 12% in males.[1] MDD is a highly recurrent disorder, with prospective studies indicating that up to 85% of patients who experience a depressive episode go on to suffer from subsequent episode(s).[2] The risk of depressive recurrence increases with both the number of episodes[3,4] and the duration of episodes,[5] and the most consistent predictor of depressive recurrence is the presence of residual symptoms (i.e., incomplete remission) after a depressive episode.[6–8] It is increasingly recognized that long-term antidepressant treatment may be necessary for those patients with MDD who have a higher risk of experiencing a depressive recurrence.[9–11]

Kupfer[12] conceptualized the course of depressive illness by way of a number of different phases through which a patient moves after progressing from a disease-free state into an episode of MDD. Treatment is initiated during the acute phase of the illness, and assuming a satisfactory treatment response, treatment gains are consolidated during a continuation phase of typically around 6 months' duration, during which the aim is to prevent a depressive relapse. Subsequent to the continuation phase is the maintenance phase, during which continued treatment, sometimes of an indefinite duration, is generally felt to be necessary in patients who are at a high risk of further episodes of depression (i.e., recurrences).

Several tricyclic antidepressants[13,14] and selective serotonin reuptake inhibitors[15–18] have been shown to be effective in preventing depressive recurrences, and venlafaxine,

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a serotonin-norepinephrine reuptake inhibitor (SNRI), has also been shown to be significantly more efficacious than placebo in the prevention of depressive recurrence during 1 year[19] and 2 years[20] of maintenance treatment. The SNRI duloxetine has been shown to be effective in the acute treatment of depression[21,22] and in the prevention of depressive relapse following a depressive episode,[23] but up until now, there have been no studies examining whether duloxetine is also effective in preventing the onset of new depressive episodes. This was the purpose of our study.

METHOD

Study Design

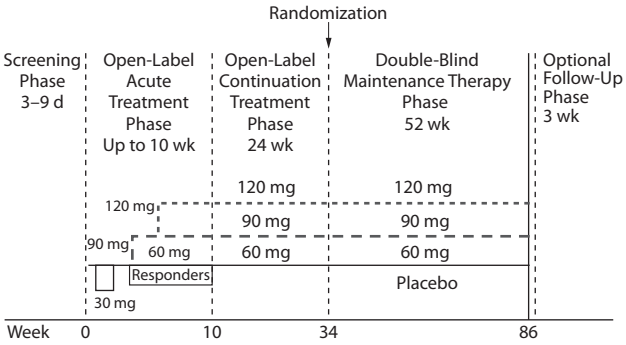
This was a multicenter, randomized, double-blind, placebo-controlled study of patients aged 18 years and over with recurrent MDD. The study consisted of 5 phases (Figure 1). The first phase began with a 3- to 9-day screening period during which patients were assessed for study eligibility. This phase was followed by a 4- to 10-week acute treatment period during which all patients received open-label duloxetine, initially at a dose of 60 mg/day. In the event of nonresponse (see below for definition) after 4 weeks of treatment, the duloxetine dose was increased to 90 mg/day, and if response criteria had still not been met after 6 weeks of treatment, a further dose increase to 120 mg/day occurred.

Patients meeting response criteria were eligible to enter the continuation phase of the study; those patients who failed to meet response criteria after 10 weeks of open-label treatment despite dose increases were discontinued from the study and were eligible to enter the optional follow-up phase. Patients were judged to have responded to treatment if they met all of the following criteria: had a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[24] total score ≤ 9, had a Clinical Global Impressions-Severity of Illness (CGI-S) scale[25] score ≤ 2, and did not meet the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition *(*DSM-IV*)* criteria for a major depressive episode as assessed by the Mini-International Neuropsychiatric Interview (MINI) for the DSM.[26]

During the 24-week open-label continuation phase, patients were continued on the same dose of duloxetine to which they had responded during the acute phase. Patients who continued to meet response criteria after 24 weeks of continuation treatment were eligible for entry into the double-blind maintenance phase. In order to minimize bias, both patients and investigators were blinded as to the exact visit at which randomization occurred. This information was, however, provided to ethics review boards.

The maintenance phase was a 52-week, double-blind, placebo-controlled, therapy phase. Eligible patients were randomly assigned to receive either duloxetine at the same dose to which they had previously responded or placebo for 52 weeks or until they experienced a depressive recurrence. Patients randomly assigned to placebo had their duloxetine treatment gradually down-titrated over a 4-week period in order to minimize any antidepressant discontinuation syndrome that might have accompanied the transition from duloxetine to placebo.

Figure 1. Study Design[a,b]



[a]Response criteria (all must be met): HAM-D-17 score ≤ 9, CGI-S score ≤ 2, and does not meet DSM-IV criteria for major depressive disorder as assessed by the Mini-International Neuropsychiatric Interview for DSM. Recurrence criteria (meet any of the criteria): CGI-S score ≥ 4 and meet DSM-IV criteria for major depressive disorder for at least 2 weeks, 3 consecutive visits that meet re-emergence criteria or 10 total re-emergence visits, or discontinued the study due to lack of efficacy.
[b]Study drug was given once daily.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression.

The follow-up phase was an optional 3-week phase following study discontinuation or completion to assess discontinuation-emergent adverse events (DEAEs) and other safety measures. Subsequent to study discontinuation or completion, down-titration occurred over a 2- to 3-week period depending on the dose the patient had been taking previously.

The study was implemented in accordance with the principles of Good Medical Practice and the Declaration of Helsinki. Each investigative site approved the protocols independently through external review boards, and all patients provided informed written consent. The first patient was enrolled in the study in March 2005 and the last patient completed in January 2008.

Patients

Patients were male and female outpatients of at least 18 years of age who met criteria for recurrent MDD as defined by the DSM-IV and confirmed via the MINI. Patients were recruited from 43 study centers in 5 European countries (France, Germany, Italy, Russia, and Sweden) and the United States. In order to be eligible for the study, patients had to have a HAM-D-17 score ≥ 18 and a CGI-S score ≥ 4 at the screening visit and the beginning of the acute phase and must have had at least 3 episodes of depression (including the presenting episode) within the

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past 5 years. Patients also had to have been in remission between these 3 episodes of depression (in order for DSM-IV criteria for recurrent depression to be met) and had to have been stable and off antidepressant medication for at least 2 months prior to the onset of the presenting episode.

Patients were not eligible to participate in the study if they met any of the following criteria: a current and primary Axis I disorder other than MDD, including but not limited to dysthymia; a previous diagnosis of bipolar disorder, schizophrenia, or other psychotic disorders; any anxiety disorder as a primary diagnosis within the past year; an Axis II disorder that in the judgment of the investigator would interfere with compliance with the study protocol; a DSM-IV–defined history of substance abuse or dependence within the past year, excluding nicotine and caffeine; a positive urine drug screen for any substances of abuse, including benzodiazepines; taking any excluded medications (which included most centrally acting medications such as antidepressants and antipsychotics) within 7 days prior to visit 2; treatment with a monoamine oxidase inhibitor within 14 days prior to study onset; and treatment with fluoxetine within 30 days prior to study onset. Patients who had a prior treatment history with duloxetine, who were judged to be at serious suicide risk, or who had had a serious medical illness likely to require hospitalization and/or the use of prohibited medications were also excluded, as were women who were breastfeeding or pregnant. Women of childbearing potential were required to use reliable methods of birth control.

Efficacy Measures

The primary efficacy measure was the time to depressive recurrence as assessed during 52 weeks of maintenance treatment in patients who had responded to up to 34 weeks of open-label duloxetine. *Time to recurrence* was defined as the time from random assignment to the first visit during the maintenance phase at which the patient met the recurrence criteria. Patients were considered to have a depressive recurrence if they met any of the following criteria: (1) they had a CGI-S score ≥ 4 and met DSM-IV criteria for MDD (as assessed by the MINI depression module) for at least 2 weeks; (2) they had 3 consecutive visits that met re-emergence criteria (see below) or 10 total re-emergence visits; or (3) they discontinued the study with a reason of "lack of efficacy."

Significant *re-emergence* of depressive symptoms was defined as having a CGI-S score ≥ 4, but not meeting the DSM-IV criteria for MDD as assessed by the MINI depression module. If re-emergence criteria were met, patients had weekly re-emergence visits until re-emergence criteria were no longer met or the patient met criteria for a recurrence. If a patient had 3 consecutive weekly re-emergence visits or a total of 10 re-emergence visits (of a total of up to 16 visits) throughout the maintenance phase, the patient was considered to have had a depressive recurrence and was discontinued from the study and was eligible to enter the follow-up phase.

Secondary efficacy measures included the following: HAM-D-17 total score and subscales (core, Maier, anxiety/somatization, retardation/somatization, and sleep),[27] CGI-S and Patient Global Impressions of Improvement (PGI-I) scales,[25] Symptom Questionnaire-Somatic Subscale (SQ-SS),[28] and Visual Analog Scales (VAS) for pain.[29] Health outcome and quality-of-life measures included the 36-item Short-Form Health Survey (SF-36),[30] the Sheehan Disability Scale (SDS),[31] and the Resource Utilization and Hospitalization Modules.[32,33] *Time to worsening*, which was defined as the time from random assignment to the first visit during the maintenance phase at which the patient met the worsening criteria (> 50% increase from maintenance phase baseline on the HAM-D-17 and a CGI-S score ≥ 3), was assessed as was loss of response (HAM-D-17 total score > 9 and a CGI-S score > 2 at any time during the double-blind maintenance phase).

Safety and Tolerability Assessments

Spontaneously reported adverse events, vital signs, and weight were recorded at each visit. An adverse event was considered treatment emergent if it was new or a worsening of a pre-existing symptom compared with the event reported at baseline. Sexual function was prospectively assessed by the Arizona Sexual Experiences Scale (ASEX).[34] Blood chemistry and hematology tests were conducted at screening and at various times during the open-label and maintenance phases, and urinalysis was undertaken at the time of screening.

Statistical Analyses

For the purposes of powering the study, it was assumed that recurrence rates over 52 weeks for placebo- and duloxetine-treated patients would be 40% and 20%, respectively, on the basis of previously published recurrence data on other antidepressants. It was also assumed that the time to recurrence and dropout would both follow exponential distributions and that 25% of the patients in each treatment group would drop out by 52 weeks. Under these assumptions, a total of 257 patients were planned to be randomly assigned in order to achieve 90% power to detect 40% versus 20% recurrence rates over 52 weeks, using a log-rank test at a 2-sided significance level of .05. It was anticipated that 70% of the patients enrolled in the acute phase of the study would respond and enter the continuation phase and that 75% of the patients who entered the continuation phase would meet the randomization criteria and be randomly assigned. Therefore, to randomly assign 257 patients to the study, we planned to enroll 490 patients in the acute phase.

All analyses were conducted on an intent-to-treat (ITT) basis. An ITT analysis is an analysis of data by the groups to which patients are randomly assigned, even if the

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Table 1. Baseline Characteristics Among Patients With Major Depressive Disorder

	Acute Phase	Continuation Phase	Maintenance Phase[a]	
Variable	Duloxetine 60–120 mg (N = 514)	Duloxetine 60–120 mg (N = 413)	Placebo (N = 142)	Duloxetine 60–120 mg (N = 146)
Age, mean (SD), y	47.6 (13.3)	47.4 (13.0)	48.0 (12.3)	47.1 (12.8)
Race, n (%)				
White	504 (98.1)	404 (97.8)	139 (97.9)	143 (97.9)
Black	3 (0.6)	3 (0.7)	1 (0.7)	1 (0.7)
Hispanic	5 (1.0)	4 (1.0)	2 (1.4)	1 (0.7)
East Asian	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.7)
South Asian	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)
Women, n (%)	359 (69.8)	291 (70.5)	106 (74.6)	100 (68.5)
Age at first episode, mean (SD), y	33.2 (13.4)	32.9 (13.1)	33.5 (13.9)	32.4 (12.3)
Duration of current episode, mean (SD), mo	4.0 (4.7)	3.9 (4.9)	3.5 (3.4)	3.9 (3.4)
No. of previous episodes, mean (SD)	4.2 (3.5)	4.3 (3.8)	4.0 (1.5)	4.4 (2.3)
Duration of last episode, mean (SD), mo	6.1 (5.3)	6.1 (5.3)	5.8 (3.6)	6.9 (7.4)
Time interval between episodes, mean (SD), mo	8.4 (6.8)	8.5 (6.9)	8.1 (6.6)	8.1 (6.9)
HAM-D-17 total score, mean (SD)	23.07 (3.57)	6.65 (2.06)	4.49 (2.51)	4.12 (2.52)
CGI-S score, mean (SD)	4.49 (0.60)	1.83 (0.39)	1.46 (0.50)	1.49 (0.52)
VAS overall pain score, mean (SD)	34.39 (26.55)	17.36 (20.17)	16.08 (21.18)	13.80 (18.08)

[a]There were no statistically significant differences for any baseline measure in the maintenance phase.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, VAS = Visual Analog Scales.

patient might not have taken the assigned treatment, received the correct treatment, or followed the protocol. In each phase, all patients taking duloxetine formed 1 duloxetine treatment group, regardless of their doses of duloxetine. Treatment comparisons during the maintenance phase compared the duloxetine treatment group with the placebo treatment group; however, no statistical comparisons were made between dose groups.

Treatment effects were evaluated based on a 2-sided significance level of .05 and interaction effects at a significance level of .10 unless otherwise stated. No adjustments were made for multiple comparisons. Unless otherwise specified, when a total score was calculated from individual items, it was considered missing if any of the individual items were missing. When a mean score was computed from individual items, it was calculated from nonmissing values.

Unless otherwise specified, when an analysis of variance (ANOVA) model was used to analyze a continuous variable, the model contained the terms of treatment and investigator. The treatment-by-investigator interaction was tested using a full model. When the interaction was statistically significant, the nature of the interaction was investigated and the interaction term was included in the model. Similar logic was applied to an analysis of covariance (ANCOVA), which refers to the model that consists of the terms used in the ANOVA with baseline score added as a covariate. Type II sum of squares for the least-squares (LS) mean was used for the statistical comparison using ANOVA or ANCOVA. Response and remission rates comparing duloxetine and placebo were analyzed using Cochran-Mantel-Haenszel controlling for investigator; all other categorical analyses used Fisher exact test. A paired t test was used to compare endpoint with baseline within each group for the acute, continuation, and follow-up phases.

The baseline that was used for numerical variables during each study phase was the last nonmissing value of all visits at or before the start of the given phase. The baseline to be used for determination of a treatment-emergent adverse event (TEAE), a treatment abnormal laboratory value, or a DEAE was the maximum severity of that event or highest value of that laboratory test in all visits at or before the start of the given phase. The baseline used for determination of sustained elevation of blood pressure was the maximum nonmissing value at or before the start of the given phase. The endpoint measurement for a phase was the last nonmissing postbaseline measurement obtained during that phase.

RESULTS

Patient Characteristics

Baseline demographic and illness characteristics are shown for the acute, continuation, and maintenance phases (Table 1). There were no significant differences between treatment groups on any measure of baseline demographics at the start of the double-blind, randomized maintenance phase, nor was there evidence of selective attrition of patients on the basis of age or other characteristics during the open-label phases (Table 1). Study participants were primarily white (97.9%) and female (71.5%), with a mean age of 47.5 years at the start of the maintenance phase.

Patient Disposition

Of the 579 patients who entered screening, 514 patients entered the open-label acute phase and received

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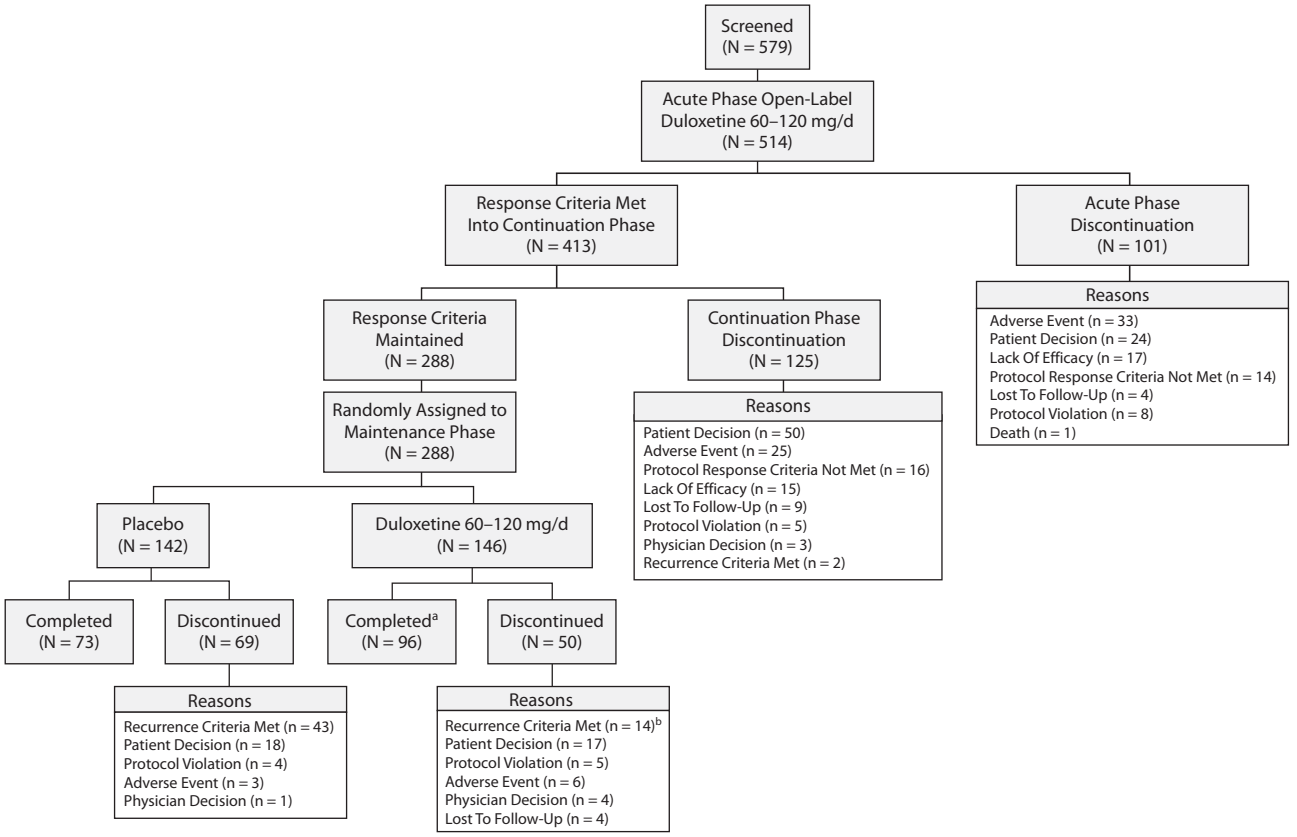
Figure 2. Patient Disposition Flowchart



[a]p ≤ .05 vs. placebo.
[b]p ≤ .001 vs. placebo.

duloxetine (Figure 2). A total of 413 (80.4%) of these patients subsequently met response criteria for entry into the continuation phase, and 288 patients maintained their response during the continuation phase, of whom 142 were randomly assigned to placebo and 146 were randomly assigned to duloxetine in the maintenance phase. As previously stated, patients had their dose of duloxetine increased during the acute phase in the event of nonresponse; doses were then fixed during the continuation and maintenance phases. The doses being taken by the 288 randomized patients during the maintenance phase were as follows: 60 mg once daily (44%), 90 mg once daily (31%), and 120 mg once daily (25%). The only reason for discontinuation that was significantly different ($p < .001$) between treatment groups during the double-blind maintenance phase was "recurrence criteria met," which was significantly higher in the placebo group.

Open-Label Treatment Phases

There was a significant decrease ($p < .05$) in symptom severity scores during open-label treatment on all efficacy measures including the HAM-D-17 total score. There was a small but statistically significant increase in the number of mean (SD) patient visits to a psychiatrist from baseline (0.03 [0.03]) to endpoint (0.06 [0.04], $p < .001$) during the acute phase, followed by a subsequent decrease from baseline (0.07 [0.04]) to endpoint (0.04 [0.03], $p < .001$) during the continuation phase.

There were a total of 10 serious adverse events (suicide attempt, completed suicide, depression, head injury, hypotension, acute pancreatitis, sensation of foreign body, somatization disorder, throat tightness, and vomiting) affecting 7 patients reported during the open-label acute phase. The event "throat tightness" was felt by the investigator to be related to the study drug. Twenty-five serious adverse events occurred among 17 patients during the open-label continuation phase. Events included 2 cases of appendicitis and 1 case each of affective disorder, suicide attempt (not considered by the investigator to be related to study drug), breast cancer, cholelithiasis, circulatory collapse, depression, diarrhea, diverticulitis, drug exposure during pregnancy, dysfunctional uterine bleeding, ectopic pregnancy, knee operation, lower abdominal pain, mania, peritonitis, pneumonia, pregnancy, pulmonary embolism,

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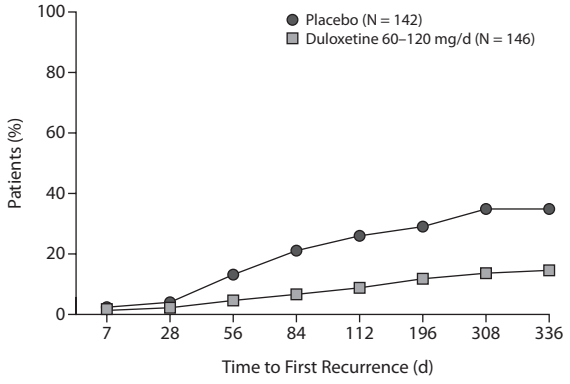
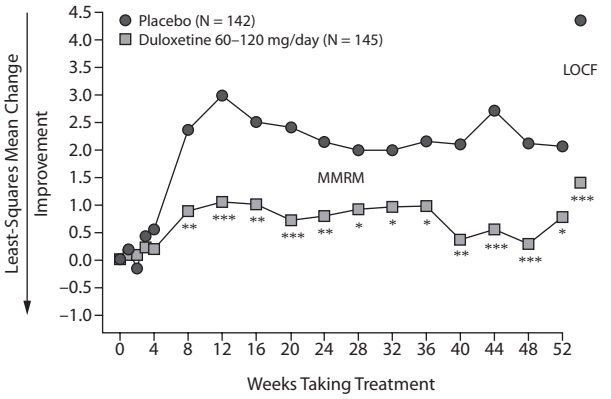
Figure 3. Time to First Depressive Recurrence[a]



[a]P value from log-rank test controlling for country < .001.

Figure 4. Change From Baseline in HAM-D-17 Total Score During Maintenance Phase



*p ≤ .05 vs. placebo.
**p ≤ .01 vs. placebo.
***p ≤ .001 vs. placebo.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, MMRM = mixed-effects model repeated measures.

QT prolongation, septic shock, unintended pregnancy, uterine leiomyoma, and vomiting.

The proportion of patients who discontinued the study during the acute and continuation phases due to adverse events was 6.4% and 6.1%, respectively. The percentage of patients experiencing a TEAE in the acute phase was 67.9%. The most common TEAEs were nausea (29.2%), headache (15.4%), dry mouth (14.8%), and hyperhidrosis (14.8%). The percentage of patients experiencing a TEAE in the continuation phase was 59.1%. The most common TEAEs were headache (9.4%), nasopharyngitis (6.3%), and hyperhidrosis (6.1%).

In the acute phase, women (–1.31, $p < .001$), but not men (0.13, $p = .785$), showed significant within-group mean change improvement in overall score (sum of the 5 items) on the ASEX. Women demonstrated additional significant improvement (–0.99, $p = .002$) in the continuation phase. Men showed numerical but not statistically significant improvement (–0.67, $p = .100$).

There were small and nonsignificant mean increases in diastolic and systolic blood pressure during the acute and continuation phases. Heart rate increased by a statistically significant amount (1.42 bpm, SD = 9.18, $p < .001$) during the acute phase, and pulse increased significantly (1.75 bpm, SD = 10.39, $p < .001$) during the continuation phase. Body weight decreased by a small but statistically significant amount during acute treatment (–0.69 kg, SD = 2.12, $p < .001$), followed by a modest but statistically significant increase during the continuation phase (0.88 kg, SD = 3.29, $p < .001$).

Primary Outcome and Other Efficacy Outcomes: Double-Blind Maintenance Phase

Patients treated with duloxetine had a significantly longer time to depressive recurrence compared with placebo-treated patients ($p < .001$, Figure 3), which was the primary outcome of the study. Furthermore, the recurrence rate at any time was significantly greater in the placebo group (33.1%) compared with the duloxetine group (14.4%, $p < .001$). Time to worsening of depressive symptoms was significantly longer in duloxetine-treated patients compared with placebo-treated patients ($p = .006$). The rate of loss of response at any time was significantly greater in the placebo group (46.5%) compared with the duloxetine group (30.1%, $p = .003$). The proportion of patients in remission at endpoint for placebo and duloxetine was 56.3% and 68.3%, respectively ($p = .025$). In addition, placebo-treated patients experienced a significantly greater baseline to endpoint worsening in their HAM-D-17 total scores compared with duloxetine-treated patients (Figure 4).

A similar finding of greater worsening in placebo-treated patients compared with duloxetine-treated patients was also seen for most other efficacy measures, including all HAM-D-17 subscales, CGI-S, and PGI-I, although not for VAS for pain or SQ-SS (Table 2). A significant difference ($p = .029$) between treatment groups was found in SDS global score, with the placebo group worsening, while the duloxetine group showed a slight improvement. There were no significant differences between treatment groups in resource utilization measures except for a difference in mean change in the number of missed paid work hours per week (duloxetine, 0.27; placebo, –0.75; $p = .037$), although data from patients experiencing a depressive recurrence were not captured for this assessment.

Safety and Tolerability: Double-Blind Maintenance Phase

No deaths or suicide attempts occurred during the maintenance phase. A total of 5 serious adverse events

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Table 2. Summary of Secondary Outcome Measures During the Maintenance Phase

Measure	Placebo (N = 142)[a,b]	Duloxetine 60–120 mg (N = 145)[a,b]	p
HAM-D-17 total score	4.36 (0.57)	1.40 (0.53)	≤ .001
HAM-D-17 subscale score			
Anxiety/somatization	1.54 (0.22)	0.46 (0.20)	≤ .001
Core factor	1.74 (0.24)	0.75 (0.22)	.002
Maier	2.25 (0.31)	0.91 (0.29)	.002
Retardation	1.49 (0.22)	0.59 (0.20)	.003
Sleep	0.71 (0.13)	0.13 (0.12)	.001
Depressed mood item 1	0.67 (0.10)	0.27 (0.09)	.003
CGI-S score	0.84 (0.10)	0.24 (0.10)	≤ .001
PGI-I score (at endpoint)[c]	2.34 (0.11)	1.72 (0.11)	≤ .001
VAS score			
Overall pain	4.57 (1.86)	3.92 (1.78)	.792
Headache	2.80 (1.80)	4.77 (1.72)	.407
Back pain	3.40 (1.72)	1.77 (1.65)	.475
Shoulder pain	3.02 (1.62)	0.51 (1.55)	.241
Interference with daily activities	2.81 (1.82)	3.16 (1.74)	.885
Pain while awake	4.69 (2.19)	3.64 (2.10)	.717
SQ-SS total score	0.81 (0.40)	0.79 (0.39)	.979
SDS global functioning score	2.06 (0.77)	–0.05 (0.71)	.029
SF-36 mental component summary score	–5.74 (1.20)	–1.11 (1.11)	.002
SF-36 physical component summary score	0.33 (0.76)	–0.45 (0.70)	.415

[a]Least-squares mean (SE) change.
[b]For all measures, except for the SF-36, an increase in the score signifies worsening.
[c]The PGI-I outcome is the endpoint score, not a mean change score.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, PGI-I = Patient Global Impressions of Improvement, SDS = Sheehan Disability Scale, SF-36 = 36-item Short Form Health Survey, SQ-SS = Symptom Questionnaire-Somatic Subscale, VAS = Visual Analog Scales.

Table 3. Treatment-Emergent Adverse Events During the Maintenance Phase

Adverse Event, n (%)[a,b]	Placebo (N = 142)	Duloxetine 60–120 mg/d (N = 146)	p
≥ 1 Event	89 (62.7)	89 (61.0)	.809
Headache	11 (7.7)	13 (8.9)	.832
Back pain	7 (4.9)	13 (8.9)	.247
Nasopharyngitis	11 (7.7)	9 (6.2)	.648
Influenza	11 (7.7)	5 (3.4)	.128
Insomnia	9 (6.3)	7 (4.8)	.615
Dizziness	9 (6.3)	5 (3.4)	.284
Fatigue	4 (2.8)	8 (5.5)	.378

[a]Adverse events occurring at a rate ≥ 5% in any treatment group.
[b]No statistically significant differences occurred between treatment groups for any treatment-emergent adverse event.

were experienced by placebo-treated patients (uterine leiomyoma, diabetes mellitus, intervertebral disc protrusion, major depression, and respiratory failure) and 13 by 12 duloxetine-treated patients (abscess, bacterial skin infection, chlamydial pneumonia, depression, diverticular perforation [n = 2], intervertebral disc protrusion, migraine, myocardial ischemia, pyelonephritis, staphylococcal endocarditis, transient ischemic attack, and uterine leiomyoma) during the maintenance phase (p = .132).

The proportion of patients who discontinued the maintenance phase due to adverse events was 2.1% in the placebo group versus 4.1% in the duloxetine group (p = .501). No adverse event leading to discontinuation occurred in more than 1 patient within any treatment group.

Treatment-emergent adverse events experienced by at least 5% of patients in any treatment group during the maintenance phase are presented in Table 3. Overall, marginally more patients experienced a TEAE in the placebo group (62.7%) than in the duloxetine group (61.0%, p = .809). The most common TEAEs were headache, back pain, and nasopharyngitis; however, no significant differences were seen between treatment groups for any individual TEAE, and there were no significant differences between treatment groups in maximum severity of any TEAE.

Men and women in both the placebo and duloxetine groups showed overall improvement on the ASEX (Table 4). The improvements were not significantly different between treatment groups.

Results of pulse, blood pressure, and electrocardiogram assessments in the maintenance phase are summarized in Table 5. Mean changes in pulse and supine systolic and diastolic blood pressure did not differ significantly between the duloxetine and placebo groups, and there were no significant differences between the groups in the number of treatment-emergent potentially clinically significant values at endpoint for any vital sign or for weight. A total of 5 patients met criteria for sustained elevation in blood pressure, including 2 taking placebo and 3 taking duloxetine. The incidence of hypertension, reported as a spontaneous adverse event, occurred in 3 placebo-treated patients and in 1 duloxetine-treated patient.

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Table 4. Mean Change From Baseline to Endpoint on the ASEX[a,b] During the Maintenance Phase

	n	Placebo, LS Mean (SE)	n	Duloxetine, LS Mean (SE)	p
Men	29	–0.77 (0.58)	35	–0.97 (0.47)	.773
Women	66	–0.35 (0.56)	63	–0.33 (0.55)	.979

[a]Sum of items 1–5. Item 1: How strong is your sex drive? Item 2: How easily are you sexually aroused? Item 3: Men: Can you easily get and keep an erection? Women: How easily does your vagina get moist? Item 4: How easily can you reach orgasm? Item 5: Are your orgasms satisfying?
[b]The higher the score, the more sexual dysfunction. This scale is scored 1 (extremely strong/satisfying/easily) to 6 (absent/never).
Abbreviations: ASEX = Arizona Sexual Experiences Scale, LS = least squares.

Table 5. Vital Signs and Weight During the Maintenance Phase[a]

Measure	Placebo (N = 142)	Duloxetine 60–120 mg/d (N = 145)	p
Pulse, bpm	–1.72 (0.78)	–1.86 (0.76)	.891
Systolic blood pressure, mm Hg[b]	–0.59 (1.04)	1.48 (1.00)	.134
Diastolic blood pressure, mm Hg[c]	0.07 (0.74)	–0.16 (0.71)	.816
Sustained elevation in blood pressure, n (%)[d]	2 (1.41)	3 (2.05)	1.00[e]
Weight, kg	0.39 (0.37)	0.88 (0.36)	.314
Underwent electrocardiogram	n = 103	n = 113	
Heart rate, bpm	–4.75 (1.02)	0.21 (0.95)	≤ .001
QT interval, ms	10.02 (2.59)	0.89 (2.42)	.004
Bazett's QTc, ms	1.38 (1.73)	1.34 (1.61)	.985

[a]Values shown as least-squares mean (SE) change unless otherwise noted.
[b] Sustained elevation = diastolic blood pressure ≥ 90 and increase from baseline ≥ 10 for at least 3 consecutive visits.
[c]Sustained elevation = systolic blood pressure ≥ 140 and increase from baseline ≥ 10 for at least 3 consecutive visits.
[d]Sustained elevation = patient experienced sustained elevated systolic blood pressure or sustained elevated diastolic blood pressure.
[e]Frequencies were analyzed using Fisher exact test.

There was a significant increase in the QT interval (uncorrected) for the placebo group compared with the duloxetine group (10.02 vs. 0.89 ms, respectively, p = .004), but the corrected QT (QTc) interval using Bazett's method was not different between treatment groups (Table 5). There were also no significant differences between treatment groups for potentially clinically significant QTc interval increases at any time. Change in heart rate was significantly different between the placebo group (–4.75 bpm) compared with the duloxetine group (0.21 bpm, p ≤ .001). A small increase in weight (kg) occurred in both the placebo (0.39) and duloxetine groups (0.88, p = .314), and a post hoc analysis found that the percentage of patients with a weight gain ≥ 7% was not statistically significantly different between the placebo (7.0%) and duloxetine (10.3%) groups (Fisher exact test, p = .404).

Statistically significant differences were observed in mean change from baseline to endpoint between placebo and duloxetine for some clinical laboratory values, but differences were small and not considered to be clinically relevant. Alanine aminotransferase was the only liver function test observed to have a significantly different mean (SD) change between treatment groups (placebo, –0.38 [12.53]; duloxetine, 2.52 [15.40]; p = .035). No significant differences in the percentage of patients exhibiting treatment-emergent abnormal laboratory analytes at any time were observed, with the exception of abnormally high levels of total bilirubin in the placebo group (3.9%) compared with the duloxetine group (0.0%, p = .025). Mean changes in high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, hemoglobin A1c, fasting glucose, and triglyceride levels did not significantly differ between the placebo and duloxetine groups.

The number of patients entering the optional follow-up (taper) phase following the double-blind, maintenance therapy phase was 48 and 61 in the placebo and duloxetine groups, respectively. The number of patients with at least 1 DEAE was 4 (8.3%) following placebo treatment and 14 (23.0%) following duloxetine treatment (p = .067). No individual DEAE was reported significantly more frequently with duloxetine compared with placebo. One placebo-treated patient experienced a serious adverse event (uterine leiomyoma), whereas 1 duloxetine-treated patient experienced 3 serious adverse events (convulsion, hypertension, and hypertensive crisis). Mean changes in pulse and supine systolic and diastolic blood pressure in the duloxetine treatment group did not differ significantly from those in the placebo group.

DISCUSSION

Duloxetine reduced the risk of depressive recurrence in this study, and long-term duloxetine treatment was well

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tolerated compared with placebo, although it should be noted that some patients with significant tolerability issues would have dropped out of the study prior to the placebo-controlled phase. Duloxetine-treated patients had a significantly longer time to a depressive recurrence, and fewer duloxetine patients experienced a depressive recurrence during maintenance treatment compared with patients receiving placebo. Furthermore, the time to worsening of depressive symptoms was significantly longer in duloxetine-treated patients, and treatment with placebo was associated with significant worsening of the HAM-D-17 total score, HAM-D-17 subscales, CGI-S, and other measures. These findings are consistent with the outcomes of studies of other antidepressants in the prevention of depressive recurrences,[15,19,35] once again underscoring the importance of long-term antidepressant treatment in patients with recurrent MDD. Some commentators have suggested that a depressive recurrence ratio of 2:3 between placebo and drug treatment might be useful for comparing treatments.[36] The ratio in our study was 2.3 (33.1%:14.4%), which is very similar to the ratios observed in studies of fluoxetine (2.0 and 2.2),[15,37] escitalopram (2.4),[35] and venlafaxine (1.8 and 2.5).[19,36]

There are some specific aspects of the design of this study that merit further discussion. First, some previous long-term MDD studies characterized by randomization to drug or placebo following an open-label treatment period have reported significant transient worsening of depressive symptoms immediately after randomization in both the antidepressant and placebo groups, followed by a period of improvement.[23] This phenomenon may be due to anxiety in patients who, having been treated with an open-label antidepressant up until randomization, are aware that they will subsequently have a 50% chance of receiving placebo.[23] Investigators are also aware of this fact, which has the potential of introducing a subtle bias into their ratings. In order to try to address this issue, blinded randomization was employed in our study so that neither investigators nor their patients were aware of the exact visit at which randomization would occur. On the basis of Figure 4, it would appear that this strategy was successful, with no significant transient worsening of mean HAM-D-17 scores immediately after randomization being evident.

Second, concerns have been raised previously that patients randomly assigned to placebo in studies of this type may experience antidepressant discontinuation symptoms that mimic depressive symptoms and thus inflate symptom ratings and recurrence rates in the placebo group. In order to address this concern, we employed a 4-week taper period for patients randomly assigned to placebo treatment in the maintenance phase, despite the fact that the duloxetine prescribing information supports discontinuing treatment over a significantly shorter period of time. Once again, this strategy appears to have been a success on the basis of the data presented in Figure 4, in which statistical separation between duloxetine and placebo on mean change in the HAM-D-17 total score did not appear until 8 weeks after randomization.

The lack of difference between duloxetine and placebo with respect to change in pain scores during the maintenance phase was unexpected. A substantial reduction in pain severity was seen during open-label treatment, resulting in low baseline VAS scores at randomization ranging from 9 to 17 mm on a 100-mm scale depending on pain type. Following randomization, there was little worsening in pain scores for either duloxetine or placebo-treated patients, which was in marked contrast to the significantly greater worsening in placebo-treated patients compared with duloxetine-treated patients with respect to other symptom measures including HAM-D-17 and subscales, CGI-S, and PGI-I. It is unclear why pain appears not to have worsened in line with other depressive symptoms during maintenance treatment.

This study is the longest controlled trial of duloxetine to date in any therapeutic indication, and it therefore provides unique insights into duloxetine's long-term safety and tolerability. It is reassuring that during the maintenance phase, no adverse event was reported with a greater frequency in duloxetine-treated patients compared with placebo-treated patients, and the overall adverse event burden was almost identical in the 2 treatment groups. This finding is consistent with previous published work, which suggests that adverse events experienced by patients taking duloxetine tend to occur early in treatment, with little in the way of new adverse events occurring later in treatment.[38,39]

One might have predicted that, because of duloxetine's mechanism of action, and more specifically its effects on norepinephrine, an impact on blood pressure might have been expected. In fact, however, open-label acute and continuation treatment with duloxetine was associated with minimal change in diastolic or systolic blood pressure, and no significant differences were seen between the placebo and duloxetine groups with respect to mean change in systolic or diastolic blood pressure during the 1-year maintenance phase. Of note, the rates of sustained elevation of blood pressure during maintenance treatment were low, with no significant difference found between treatment groups. These findings are consistent with what was observed in relapse prevention studies of duloxetine for patients with MDD[23] and generalized anxiety disorder.[40]

Weight and sexual functioning are topics of particular concern to patients taking antidepressants.[41,42] In our study, patient weight was almost unchanged during open-label acute and continuation phase treatment with duloxetine, with a mean weight change of +0.19 kg being reported. During the maintenance phase, there was no significant difference between treatment groups with

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respect to mean change in weight, suggesting that duloxetine is not associated with significant weight gain during long-term treatment of MDD. This finding is consistent with a previously published analysis of more than 15,000 patients taking duloxetine in clinical trials lasting from 3 months to more than 1 year that found an overall mean weight gain of 0.1 kg.[38]

Sexual functioning was assessed via the ASEX, a solicited scale. The ASEX was used because spontaneous reporting of sexual dysfunction in antidepressant studies is notoriously unreliable and is generally accepted to greatly underestimate the problem.[43] As measured by the ASEX, sexual functioning improved significantly in women during open-label duloxetine treatment. There was a trend for improvement in men that did not reach statistical significance. During maintenance treatment, there was further improvement in sexual functioning in both duloxetine and placebo treatment groups, with no difference seen between treatment groups for either sex. Moreover, there were no spontaneous reports of erectile or ejaculatory dysfunction in men and 1 report of a sexually related TEAE in a woman (vulvovaginal dryness). Given the well-documented association between the use of antidepressants and sexual dysfunction,[44] these results are encouraging.

There are several possible limitations of this study. Due to the extensive study inclusion and exclusion criteria, the results should be extrapolated to normal clinical practice with caution. Furthermore, 97% of the study population was white, so the results may not necessarily generalize to other racial groups. One common limitation of recurrence prevention studies is that patients lost to follow-up may have left the study because of depressive recurrence but would not, of course, be assessed as such in the analyses.[19] However, in our study, only 4 patients in the duloxetine group and none in the placebo group were lost to follow-up, and even if these 4 patients had been classified as having experienced a depressive recurrence, the overall findings of the study would not have been affected. Finally, other studies have suggested that ASEX analyses other than the a priori-specified mean change analyses may be more sensitive to specific changes in sexual functioning and more consistent with clinician assessment of sexual dysfunction.[34,45] Such post hoc ASEX analyses are planned for a subsequent article.

In conclusion, duloxetine at a dose of 60 to 120 mg/day was effective and well tolerated compared with placebo in the prevention of depressive recurrences during 1 year of maintenance treatment.

Drug names: duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), venlafaxine (Effexor and others).

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