Research Article

DULOXETINE FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER: SAFETY AND TOLERABILITY ASSOCIATED WITH DOSE ESCALATION†

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Duloxetine has demonstrated efficacy for the treatment of major depressive disorder (MDD) at a dose of 60 mg/day (given once daily). Whereas the target dose for the majority of patients is 60 mg/day, higher duloxetine doses (up to 120 mg/day) have been studied using a twice-daily dosing schedule. To further investigate the pharmacological profile of duloxetine within a once-daily dosing regimen at doses above 60 mg, we examined the safety and tolerability of duloxetine during a dose escalation from 60 mg/day to 120 mg/day. This single-arm, non-placebo-controlled study incorporated a 7-week dose escalation phase, in which patients and investigators were blinded as to timing of dose increases, followed by an open-label extension phase of up to 2 years duration. Patients (age ≥ 18 years) meeting DSM-IV criteria for MDD (n = 128) received placebo for 1 week, followed by duloxetine (60 mg/day) titrated after 1 week to 90 mg/day, and after a further week to 120 mg/day. The dose of 120 mg/day was then maintained for 4 weeks. The extension phase comprised an initial 6-week dose stabilization period, during which duloxetine was tapered to the lowest effective dose, followed by continuation therapy at the stabilized dose. We assessed safety using spontaneously reported treatment-emergent adverse events (TEAEs), changes in vital signs, electrocardiograms (ECGs), laboratory analytes, and visual analogue scales (VAS) for gastrointestinal (GI) disturbance. Efficacy measures included the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score, the Clinical Global Impression of Severity (CGI-S) and Patient Global Impression of Improvement (PGI-I) scales, and VAS assessments of pain severity and interference. The rate of discontinuation due to adverse events during the acute phase of the study was 15.6%. The most frequently reported TEAEs were nausea, headache, dry mouth, dizziness, and decreased appetite. The majority of TEAEs were associated with initial duloxetine dosing; further escalations in dose produced few additional adverse events. VAS measures of GI disturbance worsened significantly compared with baseline values after 1 week of duloxetine treatment. Subsequent assessments of GI disturbance, following dose escalation to 90 mg/day and 120 mg/day, showed either no significant difference or a significant improvement from baseline.

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Significant improvements (P<.001) were observed in all assessed depression efficacy measures, and in five of six VAS pain outcomes, during acute phase treatment. During 2 years of extension phase therapy, the rate of discontinuation due to adverse events was 11.9%, and the only TEAEs reported by > 10% of patients were upper respiratory tract infection (13.1%), headache (10.7%), and insomnia (10.7%). Mean changes from baseline to the end of the extension phase in supine systolic and diastolic blood pressure were 3.8 and 0.5 mm Hg, respectively, and there were no reports of sustained hypertension. Mean increase in heart rate was 5.9 bpm, while patients exhibited a mean weight increase of 3.1 kg over 2 years of treatment. Results from this study suggest that rapid dose escalation of duloxetine (60 mg/day → 90 mg/day → 120 mg/day) is safe and tolerable. Despite weekly escalation, the majority of adverse events were mild and transient and occurred in the first week of duloxetine dosing (at 60 mg once daily). Long-term treatment at a stabilized duloxetine dose was associated with a relatively low incidence of TEAEs and treatment discontinuation due to adverse events. Time course profiles of body weight and heart rate showed modest increases during 2 years of treatment [ClinicalTrials.gov number, NC T000 42575]. Depression and Anxiety 24:41–52, 2007.

Key words: *depression; safety; tolerability; antidepressant; dose; duloxetine*

INTRODUCTION

It is increasingly recognized that the primary goal of treatment for major depressive disorder (MDD) is the achievement of complete remission of depressive symptoms and a return to normal functioning [Keller, 2003; Lam and Kennedy, 2004]. Patients who fail to achieve full remission have been shown to be at greater risk of subsequent relapse, recurrence, and chronicity [Judd et al., 2000; Paykel et al., 1995], and have impaired long-term social functioning [Kennedy and Paykel, 2004]. However, a substantial proportion of patients exhibit a suboptimal response to an initial course of antidepressant therapy [Hirschfeld et al., 2002]. Although switching or combination/augmentation strategies may eventually be considered for these patients, a first approach to managing patients with an inadequate treatment response is to increase the dose of the current medication [Hirschfeld et al., 2002]. The safety and tolerability profile associated with such a dose escalation is therefore of considerable interest for clinicians.

The antidepressant duloxetine is a dual reuptake inhibitor of serotonin (5-HT) and norepinephrine (NE), with relatively balanced affinity for binding to NE and 5-HT transport sites [Bymaster et al., 2001]. The efficacy and safety of duloxetine in the acute treatment of MDD have been established in a number of double-blind, placebo-controlled studies [Nemeroff et al., 2002]. Whereas some of these studies incorporated an initial dose escalation phase (from 40 mg/day to 80 mg/day [Detke et al., 2004] or 120 mg/day [Detke et al., 2004; Goldstein et al., 2002]), the doses were administered under a twice-daily dosing regimen. Although duloxetine has been studied extensively at the dose of 120 mg/day (given as a twice-daily divided dose of 60 mg), our study is the first to assess the safety and tolerability of duloxetine at 120 once daily. To investigate further the pharmacological profile of duloxetine within a once-daily dosing regimen at doses of 60 mg and above, our study examined two key issues associated with the once-daily dosing regimen and helped to bridge the safety profile from twice-daily to once-daily dosing. We designed this study to assess the safety and tolerability of duloxetine during a weekly dose escalation from 60 mg/day to 120 mg/day, and to assess any changes in electrocardiogram (ECG) parameters after dose escalation and maintenance at peak dose for approximately 1 month.

MDD is a recurrent, sometimes chronic, lifetime illness requiring long-term treatment [American Psychiatric Association, 2000]. Continuation therapy for 16–20 weeks following remission is recommended for all patients with depression [American Psychiatric Association, 2000], and maintenance therapy should be considered for many patients. The risk of relapse and recurrence of depression can be significantly reduced if adequate continuation and maintenance therapy durations are achieved [Hirschfeld, 2001]. The safety and tolerability of duloxetine during long-term treatment (up to 52 weeks) have been investigated at doses of 80 and 120 mg/day [administered 40 mg twice daily and 60 mg twice daily, respectively; Raskin et al., 2003]. To assess the long-term safety profile of once-daily dosing, our study incorporated an open-label extension phase during which patients received a stabilized duloxetine dose (within a range of 60–120 mg/day) for up to 2 years.

METHODS

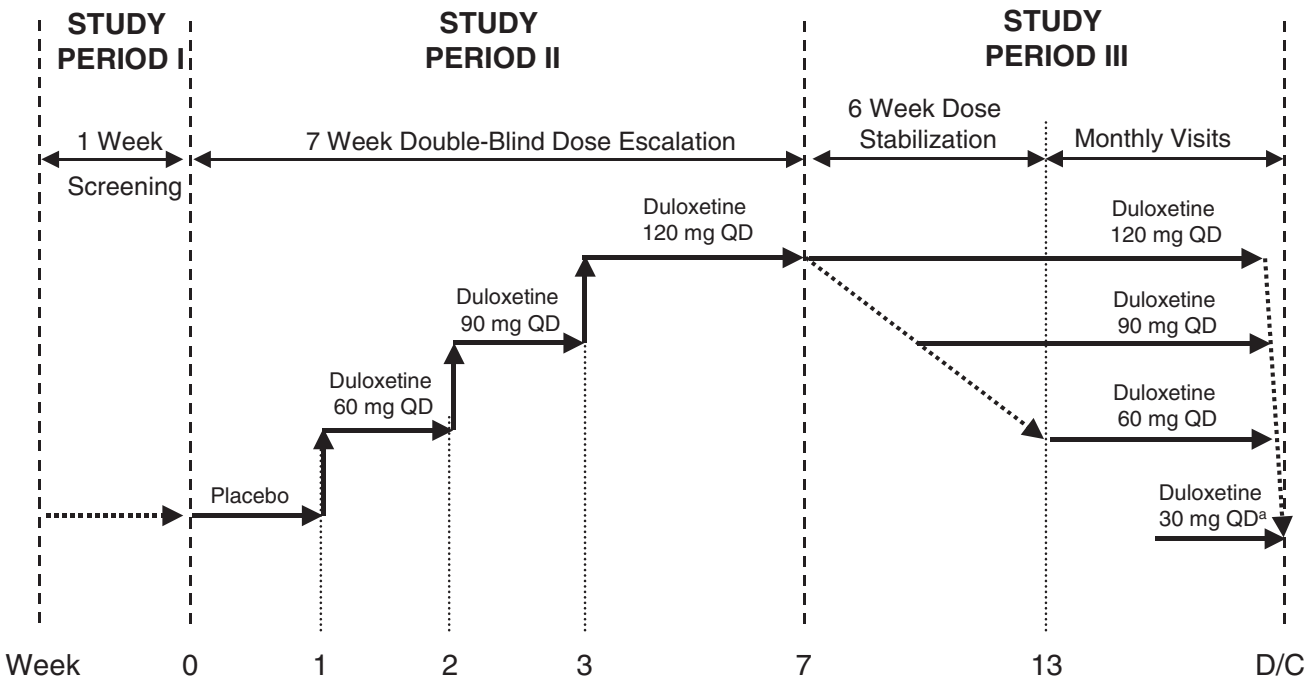
STUDY DESIGN

The protocol for this study (F1J-US-HMBY) was filed with the U.S. Food and Drug Administration prior to study initiation. It included all of the methodology presented here, in addition to a complete statistical analysis plan. In accordance with the principles of the Declaration of Helsinki, all patients provided written informed consent prior to administration of any study drug or study procedures.

The study design (Fig. 1) incorporated a 7-week, double-blind, dose escalation phase followed by an open-label extension phase. The study was conducted at 13 sites in the United States. The primary objective of the study was to evaluate the safety of duloxetine once-daily dosing up to 120 mg in patients diagnosed with MDD.

Patients meeting study criteria after the screening phase (Study Period I) entered the dose escalation phase (Study Period II). All patients received placebo for 1 week, followed by duloxetine 60 mg once daily for 1 week. The duloxetine dose was then increased to 90 mg once daily for 1 week, and finally to 120 mg once daily for the remainder of the acute phase (4 weeks). Both patients and investigators were blinded to the initiation of active study drug and to the timing of dose increases. Patients unable to tolerate any of the duloxetine doses were discontinued. Patients completing acute phase therapy could choose to continue into the extension phase (Study Period III). During the first 6 weeks of the extension phase, each patient's duloxetine dose could be adjusted to the optimal maintenance dose (60, 90, or 120 mg once daily, based upon investigator and patient judgment). The stabilized maintenance dose could neither be lower than 60 mg nor exceed 120 mg. If the dose could not be stabilized within this 6-week period, the patient was discontinued. After the duloxetine dose was stabilized, patients were allowed to continue in the open-label extension period with monthly visits until duloxetine (Cymbalta®) became commercially available (Fall 2004). At the end of the study, duloxetine therapy was tapered and stopped based upon the investigator's judgment, with a suggested dose tapering of 30 mg every 4 days.

In general, concomitant medications with primarily central nervous system activity were not allowed. During the acute dose escalation phase, patients were allowed episodic use of a benzodiazepine or hypnotic provided that usage did not exceed 3 consecutive days and 28 total days, and were allowed chloral hydrate (maximum daily dose 1,000 mg) or zolpidem (maximum daily dose 10 mg) for insomnia, provided that usage did not exceed 12 total days (chloral hydrate) or 6 total days (zolpidem). There were no restrictions on



a. During the study, the duloxetine dose was stabilized at a minimum of 60 mg QD and a maximum of 120 mg QD. The 30 mg QD dose was only used to taper patients at discontinuation.

Figure 1. Summary of study design (QD, once daily).

benzodiazepine or hypnotic use during the extension phase.

Chronic use of certain prescription medications such as angiotensin-converting enzyme (ACE) inhibitors, β-blockers, antiarrhythmics, anticoagulants, and calcium channel blockers was permitted provided the patient had been on a stable dose for a minimum of 3 months prior to study enrollment and remained on the medication for the duration of the study. Use of non-narcotic prescription and over-the-counter pain medications was allowed. Narcotic use was allowed on an episodic basis only.

SELECTION OF PATIENTS

Study participants were adult outpatients at least 18 years of age. All patients met diagnostic criteria for MDD defined in DSM-IV [American Psychiatric Association, 1994], with a current episode duration $\geq$2 weeks. The diagnosis of MDD was confirmed by the Mini-International Neuropsychiatric Interview [MINI; Sheehan et al., 1998]. Patients were required to have a 17-item Hamilton Rating Scale for Depression [HAM-D-17; Hamilton, 1960] total score $\geq$15 at the screening and baseline study visits.

Patients were excluded for the following reasons: any diagnosis of bipolar disorder, schizophrenia or other psychotic disorder; any anxiety disorder as a primary diagnosis within the past 6 months (including panic disorder, obsessive–compulsive disorder, post-traumatic stress disorder, generalized anxiety disorder, and social phobia); serious suicidal risk; serious medical illness or clinically significant laboratory abnormality that would, in the judgment of the investigator, affect the safety of the patient or impair the patient's ability to complete the study; lack of response of the current depressive episode to two or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks or, in the judgment of the investigator, meeting criteria for treatment-resistant depression; the presence of an Axis II disorder that could interfere with compliance with the study protocol; DSM-IV–defined history of substance dependence within the past 6 months, excluding nicotine and caffeine; a positive urine drug screen for any substances of abuse or dependence; electroconvulsive therapy within the past year; abnormal thyroid-stimulating hormone concentrations; treatment with a monoamine oxidase inhibitor within 14 days prior to Visit 1; treatment with fluoxetine within 30 days prior to Visit 1; or taking benzodiazepines on a daily basis for 2 or more weeks prior to enrollment. Women who were pregnant or breast-feeding were also excluded. Patients with uncontrolled hypertension were excluded from the study; however, patients with a diagnosis of hypertension controlled with medications stabilized for at least 3 months were allowed to enroll in this study.

EFFICACY MEASURES

Efficacy measures were secondary and included the HAM-D-17, the Clinical Global Impression of Severity [CGI-S; Guy, 1976] and the Patient Global Impression of Improvement [PGI-I; Guy, 1976] scales, and visual analogue scales (VAS) for pain severity and interference [DeLoach et al., 1998]—overall pain, headache, back pain, shoulder pain, pain interference with daily activities, and proportion of the day with pain.

Response was defined as a 50% decrease from baseline in the HAM-D-17 total score. Remission was defined as a HAM-D-17 total score $\leq$7.

SAFETY ASSESSMENTS

Safety measures recorded at every visit included spontaneously reported treatment-emergent adverse events (TEAEs), supine blood pressure (BP), and heart rate. Elevated BP was defined as supine systolic BP $\geq$140 mm Hg and at least 10 mm Hg greater than baseline, or supine diastolic BP $\geq$90 mm Hg and at least 10 mm Hg greater than baseline. Sustained hypertension was defined as meeting the criterion for either elevated supine systolic BP or elevated diastolic BP at three consecutive visits. Treatment-emergent elevated pulse was defined as $\geq$100 bpm (beats per minute) and at least 10 bpm greater than baseline. Blood for chemistry and hematology laboratories, and ECGs were collected at baseline, at Week 7, and at the last study visit. VAS assessments of gastrointestinal (GI) disturbance (upset stomach, and abdominal pain/cramping) were collected at each visit during the acute phase.

STATISTICAL METHODS

Analyses were conducted on an intent-to-treat basis. All patients who received study drug were included in safety analysis, whereas patients with at least one postbaseline observation were included in the efficacy analyses.

"Baseline" was defined as screening and the placebo lead-in. The extension phase refers to Study Period III. In all analyses, baseline was the latest nonmissing observation across all visits in the screening phase and the placebo lead-in period, before active treatment began. End points for Study Periods II and III were defined as the last nonmissing observation during the relevant phases.

Efficacy data were analyzed using a likelihood-based, mixed-effects model repeated measures (MMRM) approach. The model included the fixed categorical effects of investigator and visit, as well as the continuous fixed covariate of baseline score and baseline × visit interaction. An unstructured covariance matrix was used to model the within-patient errors. Analyses were implemented using the program SAS PROC MIXED.

We summarized the incidence of serious adverse events, discontinuations due to adverse events, and TEAEs, which are reported events that first occurred or worsened during the active treatment period. VAS assessments of upset stomach and abdominal pain/cramping were analyzed using the MMRM approach described earlier. Supine BP, including diastolic and systolic, and heart rate collected at baseline and every postbaseline visit in the active treatment phase were analyzed by a repeated measures analysis described earlier. Change from baseline to end point in each of the vital signs was also analyzed by the analysis of variance (ANOVA) model described earlier.

ECG intervals [Fridericia's corrected QT (QTcF), PR, QRS] and laboratory analytes were not measured with sufficient frequency to permit meaningful time course assessments. For these outcomes, mean changes from baseline to last observation were assessed using within-group *t*-tests. The percentage of patients having an increase in QTcF interval ≥ 30 ms, and the incidence of treatment-emergent abnormal, high, and low laboratory values were also summarized. Lilly reference ranges were used to determine limits for abnormal laboratory values [Thompson et al., 1987, 1990].

RESULTS

ACUTE PHASE (DOUBLE-BLIND DOSE ESCALATION)

Of the 158 patients who entered the screening phase (Study Period I), 128 met entry criteria and entered the acute treatment phase (Study Period II). Baseline patient demographics and psychiatric profile are summarized in Table 1. Of the 123 patients who received duloxetine in the study, 103 patients (84%) reached the highest dose of 120 mg once daily. Patients remained on a dose of duloxetine 120 mg once daily for a total of 4 weeks. Of the 103 patients who reached the highest dose, 83 patients (81%) completed 4 weeks of treatment with duloxetine at 120 mg once daily.

Because of adverse events during acute phase treatment, 20/128 patients (15.6%) discontinued treatment. Other reasons for study discontinuation included loss to follow-up (8.6%), lack of efficacy (3.9%), patient decision (3.9%), and protocol violation (3.1%).

One serious adverse event (SAE) was reported during the acute phase of the study—a suicide attempt. The patient, a Caucasian female with preexisting symptoms consistent with premenstrual dysphoric disorder, had a history of dysmenorrhea and reported that her depression worsened with the onset of her menstrual cycle. The patient complained of increasing insomnia at the Week 1 study visit (following 1 week of treatment with duloxetine 60 mg once daily), and was prescribed diazepam by the study physician. Approximately 1 week later (coincident with the onset of her menstrual cycle) the patient attempted suicide by overdose of diazepam and alcohol. In the opinion of the investigator, the suicide attempt was unrelated to the study drug.

TEAEs events leading to discontinuation in more than one patient were nausea (3 patients, 2.3%), vomiting (3 patients, 2.3%), and sedation (2 patients, 1.6%). For each patient, only one adverse event could be listed as the primary reason for discontinuation. Of the six discontinuations due to nausea or vomiting, four occurred during the first week of duloxetine therapy, one at Week 2, and one at Week 4 (Fig. 2). Events leading to discontinuation in individual patients included diarrhea, dizziness, and fatigue. Two patients discontinued due to the sexual side effects

TABLE 1. Baseline demographics and psychiatric profile for patients entering the dose escalation phase

	Duloxetine ($N = 128$)
Gender	
Female, *n* (%)	76.0 (59.4)
Age, years	
M (*SD*)	42.6 (13.3)
Weight, kg	
M (*SD*)	84.4 (22.0)
Origin	
Caucasian, *n* (%)	103.0 (80.5)
African descent, *n* (%)	9.0 (7.0)
Hispanic, *n* (%)	8.0 (6.3)
Other, *n* (%)	8.0 (6.3)
HAM-D-17 total score	
M (*SD*)	18.9 (5.5)
CGI-S	
M (*SD*)	4.16 (0.69)
VAS overall pain	
M (*SD*)	27.2 (25.9)

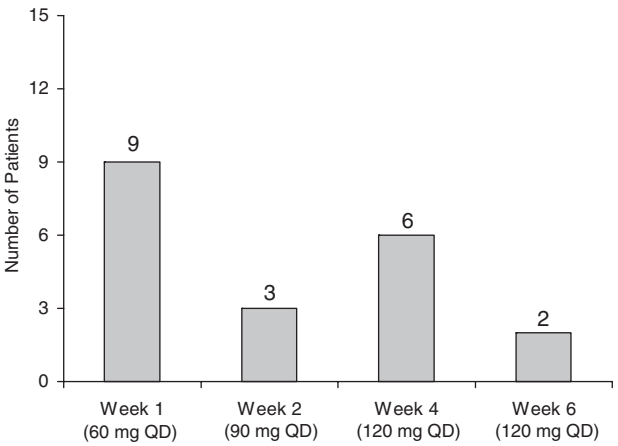


Figure 2. Number of patients discontinuing due to adverse events, by visit. Reasons for discontinuation—Week 1: vomiting (3 patients), sedation (2 patients), nausea, somnolence, diarrhea, headache; Week 2: nausea, feeling jittery, suicide attempt; Week 4: anorgasmia, nausea, delayed ejaculation, fatigue, lower abdominal pain, dizziness; Week 6: urticaria, palpitations.

of anorgasmia (one patient) and delayed ejaculation (one patient).

TEAEs reported by ≥5% of patients during acute phase treatment are shown in Figure 3. Adverse events reported most frequently were nausea, headache, dry mouth, dizziness, and decreased appetite. Most events were reported to be mild or moderate in severity.

The time course plot of mean changes in VAS abdominal pain/cramping (Fig. 4a) showed a significant worsening from baseline to Week 1, corresponding to the first week of duloxetine 60 mg once daily dosing. However, at Week 2 (following the dose escalation to 90 mg once daily) and at Week 4 (at which point most patients had been escalated to 120 mg once daily), mean scores had returned to baseline values. At the end point of the acute phase, there was a significant improvement from baseline in the VAS assessment of abdominal pain/cramping. A similar pattern was observed in the VAS assessment of upset stomach (Fig. 4b).

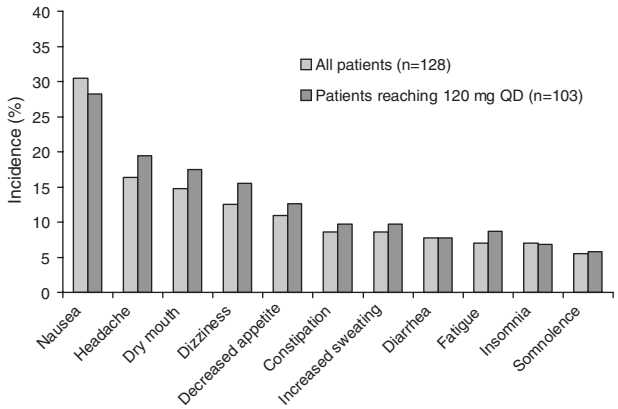


Figure 3. Incidence of TEAEs reported by >5% of patients during acute phase therapy.

Within the whole patient cohort ($N = 128$), mean increases from baseline to end point in supine systolic and diastolic BP were 1.2 mm Hg ($P = .283$) and 0.6 mm Hg ($P = .456$), respectively. There was a statistically significant baseline to end point increase in heart rate (1.7 bpm, $P = .045$) and a statistically significant decrease in weight (1.2 kg, $P < .001$) during acute phase treatment.

Similar results were obtained within the subset of patients reaching a duloxetine dose of 120 mg once daily ($N = 103$). Mean changes from baseline to end point in supine systolic and diastolic BP were 1.7 mm Hg ($P = .154$) and 0.6 mm Hg ($P = .508$), respectively, while there was an increase in heart rate of 1.6 bpm ($P = .075$) and a decrease in weight from baseline of 1.2 kg ($P < .001$).

Within the overall patient cohort, the incidence of abnormal (elevated) systolic and diastolic BP values during acute phase treatment were 13.7% and 8.5%, respectively. No patients developed sustained hypertension. Of 119 patients, three (2.5%) experienced an abnormal (elevated) heart rate measurement during acute phase therapy. The incidence of elevated vital sign values at end point was supine systolic BP: 9.8%; supine diastolic BP: 2.8%; heart rate: 0.8%.

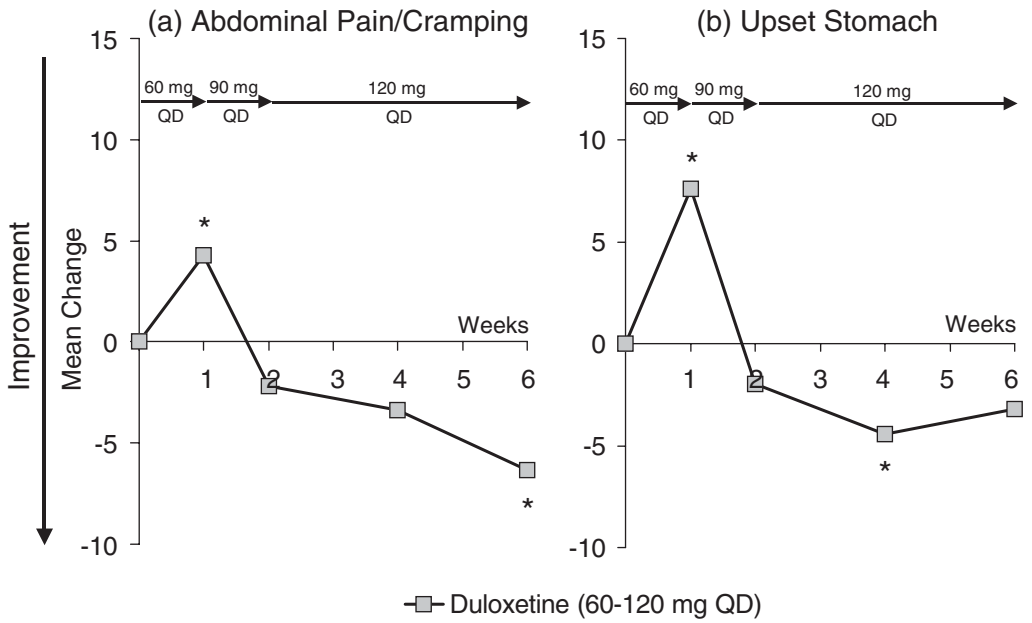


Figure 4. (a) Mean change in VAS assessment of abdominal pain/cramping; and (b) mean change in VAS assessment of upset stomach during acute phase treatment with duloxetine (60–120 mg once daily). Week 0 is the point at which patients transitioned from placebo to duloxetine 60 mg once daily. *$P < .05$ for within-group mean change from baseline.

TABLE 2. Summary of efficacy outcome measures (acute phase)

	Baseline *M*	End point *M* (*SE*)	*P* value
HAM-D-17 total score	18.9	11.05 (0.61)	<.001
HAM-D-17 subscales			
Core	8.21	3.93 (0.30)	<.001
Maier	10.28	5.06 (0.34)	<.001
Anxiety	5.63	3.62 (0.23)	<.001
Retardation	7.00	3.70 (0.24)	<.001
Sleep	3.11	1.95 (0.20)	<.001
HAM-D-17 items			
Item 1 (depressed mood)	2.63	1.07 (0.11)	<.001
Item 3 (suicide)	0.61	0.22 (0.07)	<.001
CGI-S	4.16	2.68 (0.10)	<.001
PGI-I	3.83	2.60 (0.12)	<.001
VAS pain severity/interference			
Overall pain	27.2	16.7 (2.2)	<.001
Back pain	21.9	11.6 (2.0)	<.001
Shoulder pain	13.0	9.6 (1.5)	.027
Headache	20.1	11.7 (2.3)	<.001
Time in pain while awake	31.5	23.4 (3.0)	.008
Interference with daily activities	21.1	17.7 (2.5)	.184

Mean changes from baseline to endpoint in ECG intervals were: PR (−4.2 ms; $P = .002$), QRS (−0.9 ms; $P = .080$), QT (−19.0 ms; $P < .001$), and QTcF (−5.4 ms; $P < .001$). One patient experienced an abnormal increase (≥30 ms) in QTcF interval.

Mean baseline to end point changes for some laboratory values were statistically significant when compared with the baseline value, but the changes were small relative to the standard deviation. The incidence of treatment-emergent abnormal (high or low) values was <5% for all laboratory analytes. One patient, who had normal ALT and AST values at baseline, reached three times the upper limit of the normal reference range for hepatic enzymes.

Baseline to end point improvements in HAM-D-17 total score and other measures of depressive symptom severity (Table 2) were statistically significant ($P < .001$) when compared with the baseline value. At the end of acute phase therapy (6 weeks of duloxetine treatment), the rate of treatment response was 48% (58/120 patients), whereas the rate of remission was 41% (49/120 patients). Statistically significant baseline to endpoint improvements were observed in five of the six assessed VAS measures of pain severity and interference (Table 2).

EXTENSION PHASE (OPEN-LABEL DOSE STABILIZATION AND CONTINUATION TREATMENT)

After completing the acute treatment phase, patients were allowed to continue in the open-label extension phase but were not required to do so. Eighty-four patients completed the acute phase of the study, and 81 patients contributed data to the extension phase. Sixty-six patients completed the stabilization period: 4 patients (6%) stabilized at a duloxetine dose of 60 mg once daily, 16 patients (24%) at 90 mg once daily, and 45 patients (68%) at 120 mg once daily. One patient had a dose of 30 mg once daily due to tapering of the duloxetine dose prior to discontinuing the study.

Taken across both acute and extension phases, the mean exposure to duloxetine was 288 days (median = 135 days). Among the 123 patients who received duloxetine, 68 patients (55.3%) completed at least 3 months of treatment, whereas the number of patients who completed 6, 12, and 18 months of therapy were 54 (43.9%), 40 (32.5%), and 32 (26.0%), respectively. Twenty-nine patients (23.6%) completed at least 2 years of treatment.

The rate of discontinuation due to adverse events during the extension phase was 11.9% (10/84 patients), whereas 21.4% of patients (18/84) discontinued due to lack of efficacy. Other reasons for study discontinuation included loss to follow-up (15.5%), patient decision (11.9%), and protocol violation (3.6%).

There were no deaths reported in the study. Three patients who continued in long-term phase of the study had SAEs: the events were syncope (two patients), and postoperative infection. No single adverse event was reported as the reason for discontinuation by more than one patient during long-term treatment with duloxetine. No patients discontinued due to sexual side effects during long-term treatment. Events leading to discontinuation in individual patients included nausea, diarrhea, insomnia, and hyperhidrosis.

TEAEs reported by >5% of patients during long-term treatment with duloxetine were upper respiratory tract infection (13.1%), headache (10.7%), insomnia (10.7%), anxiety (9.5%), increased weight (9.5%), nasopharyngitis (8.3%), constipation (7.1%), hyperhidrosis (7.1%), abnormal dreams (6.0%), arthralgia (6.0%), postprocedural pain (6.0%), and sinusitis (6.0%). The following sexual side effects were reported during long-term treatment: erectile dysfunction (2.4%), delayed ejaculation (1.2%), decreased libido (1.2%), and loss of libido (1.2%).

In analysis of vital signs, mean baseline to last observation changes in BP of 1.4 mm Hg and 1.1 mm Hg for supine systolic and diastolic BP, respectively, were not statistically significant when compared with baseline values (baseline defined as the first day of duloxetine treatment). There was a statistically significant baseline to last observation increase in heart rate (3.1 bpm, $P < .001$), while the mean change in body weight was 0.9 kg ($P = .065$).

The repeated measures analyses for postbaseline mean changes in vital signs and weight are shown in Figure 5. No patients met criteria for sustained hypertension.

There were statistically significant mean changes for some laboratory values between baseline and end point, but they were small relative to the baseline value

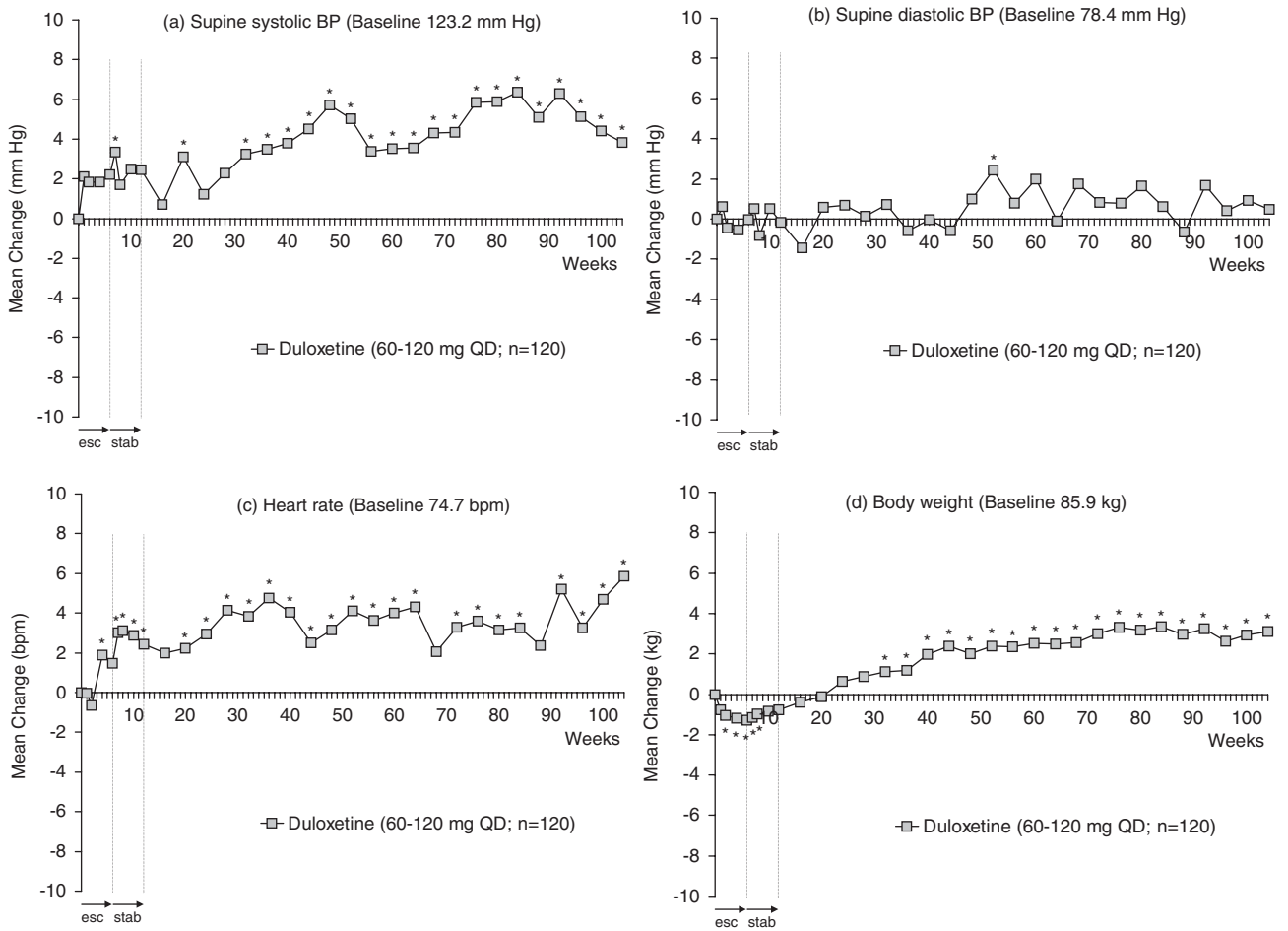


Figure 5. Mean changes in vital signs and weight during acute and extension phase treatment with duloxetine (60–120 mg once daily; *n* = 120): (a) supine systolic BP; (b) supine diastolic BP; (c) heart rate; (d) body weight. Week 0 is the point at which patients transitioned from placebo to duloxetine 60 mg once daily. Abbreviations: esc, dose escalation phase; stab, dose stabilization phase. **P*<.05 for within-group mean change from baseline.

and to the standard deviation. Three patients had treatment-emergent elevated laboratory results that were greater than three times the upper limit normal (ULN) reference range for hepatic enzymes.

The mean HAM-D-17 total score at beginning of the extension phase (following 6 weeks of acute duloxetine treatment) was 10.3. After 1 year of duloxetine treatment, the mean HAM-D-17 total score was 8.7, whereas after 2 years the mean total score was 7.8 (Fig. 6). Mean CGI-S scores after 1 and 2 years of treatment were 2.07 and 1.86, respectively.

DISCUSSION

This study assessed the safety and tolerability associated with a rapid dose escalation of duloxetine from 60 mg to 120 mg once daily and in extended exposure to doses of duloxetine at or above the labeled dose range. The study results suggest that the overall side effect burden during dose escalation was not substantially greater than that associated with fixed dosing at 60 mg once daily. The rate of treatment discontinuation due to adverse events during the 7-week dose escalation phase (15.6%) was comparable to discontinuation rates observed in previous studies of duloxetine at a fixed 60 mg once daily dose, including a 12-week open-label study [11.3%; Detke et al., 2003] and placebo-controlled studies of 7 weeks [duloxetine 14.2% vs. placebo 2.1%; Brannan et al., 2005].

The most frequently reported TEAEs during acute phase treatment were consistent with those observed in previous placebo-controlled studies of duloxetine, and included nausea, headache, dry mouth, dizziness, and constipation. The majority of adverse events were mild and transient, and occurred in the first week of duloxetine dosing (at 60 mg once daily). VAS assessments of GI disturbance were utilized in an effort to provide a more reliable estimate of the severity and duration of treatment-emergent nausea than that provided by spontaneous reports of adverse events.

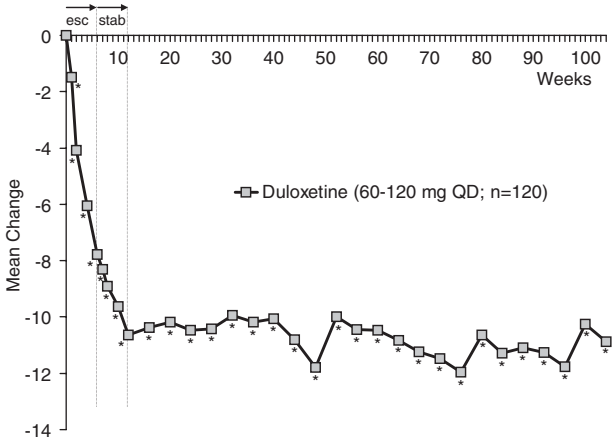


Figure 6. Mean change in HAM-D-17 total score during acute and extension phase treatment with duloxetine (60–120 mg once daily; $n = 120$). Week 0 is the point at which patients transitioned from placebo to duloxetine 60 mg once daily. Abbreviations: esc, dose escalation phase; stab, dose stabilization phase. *$P < .05$ for within-group mean change from baseline. The placebo lead-in is not shown. There was an approximately 3 point decrease in the HAM-D-17 total score during the placebo lead-in. Baseline was defined as screening and the placebo-lead-in.

After 1 week of treatment with duloxetine 60 mg once daily, repeated measures analysis of both measures of GI disturbance (abdominal pain/cramping, and upset stomach) showed a significant increase (worsening) from the baseline value. However, at Week 2, both assessments of GI disturbance had returned to baseline values despite the fact that patients had received a dose increase to 90 mg once daily. Similarly, the VAS assessments at Week 4 did not show any worsening in GI symptoms following the dose increase to 120 mg once daily. Furthermore, four of the six discontinuations due to nausea or vomiting occurred in the first week of duloxetine therapy. These results suggest that treatment-emergent GI disturbance is associated with the initial days of duloxetine dosing, and not with subsequent dose escalation. The data are consistent with those obtained from placebo-controlled studies of duloxetine, in which the median time to onset of treatment-emergent nausea was found to be 1 day, with a median duration of 7 days, and relatively few new cases of nausea occurred after the first week of treatment [Greist et al., 2004].

Mean changes in vital signs during acute phase duloxetine therapy were consistent with those observed during previous placebo-controlled studies of 8–9 weeks duration [Hudson et al., 2004; Nemeroff et al., 2002]. Mean changes in BP at the end of the dose escalation phase were ≤ 2 mm Hg, and there was a small mean increase in heart rate of approximately 2 bpm. In comparison, pooled data from acute placebo-controlled studies of duloxetine showed mean changes of < 1 mm Hg in both systolic and diastolic BP, and a mean increase in heart rate of 1.4 bpm compared with a mean decrease of 0.6 bpm for placebo [Hudson et al., 2004].

During extension phase treatment with duloxetine (60–120 mg once daily), repeated measures analyses showed somewhat larger changes in BP, with mean increases of up to 6 mm Hg in supine systolic blood BP. Because this study was the first to investigate duloxetine treatment for periods greater than 1 year, comparative data are somewhat limited. However, in a 52-week, open-label study of duloxetine at 80 or 120 mg/day [twice-daily dosing, $N = 1{,}279$; Raskin et al., 2003], the largest mean changes in supine systolic and diastolic BP at any visit were 1.6 mm Hg and 0.8 mm Hg, respectively. Furthermore, in pooled data from the extension phases of two placebo-controlled studies [Detke et al., 2002, 2004], mean changes in systolic and diastolic BP following 26 weeks of treatment with duloxetine at doses of 80 mg/day or 120 mg/day (twice-daily dosing) were < 1.5 mm Hg. Taking into account these results, and given the absence of a placebo group in the present study, it is difficult to establish whether the observed trend toward increased systolic BP is associated with long-term duloxetine treatment or once-daily versus twice-daily dosing. The clinical relevance of changes of this magnitude would be dependent upon the cardiovascular profile, and the presence of other risk factors, within individual patients. Furthermore, these findings must also be interpreted in light of the fact that the majority of patients were dosed at 120 mg/day, whereas the highest labeled dose for the treatment of MDD is 60 mg/day, and the fact that no patients discontinued due to hypertension. However, it is recommended that patients receiving antidepressant therapy should have their BP measured prior to initiating treatment and periodically throughout treatment.

Mean increases in heart rate were observed during extension phase treatment with duloxetine: Mean changes were 4.1 bpm and 5.9 bpm after 1 and 2 years of treatment, respectively. In a previous open-label study of duloxetine at 80 or 120 mg/day (twice-daily dosing) [Raskin et al., 2003], repeated measures analysis showed a mean increase in heart rate of 2.7 bpm after 1 year of treatment. The increases in heart rate may be a result of duloxetine's potentiation of noradrenergic activity. As with blood pressure, periodic monitoring of heart rate is warranted during long-term treatment.

The decrease in body weight of approximately 1 kg during acute phase duloxetine treatment is consistent with results observed in placebo-controlled studies [Hudson et al., 2004; Nemeroff et al., 2002]. Furthermore, treatment-emergent decreased appetite was reported as an adverse event by 10.9% of patients during the acute phase. After approximately 20 weeks of treatment, however, mean body weight had returned to baseline values, and at subsequent visits a trend of increasing body weight was observed, reaching 2.4 kg at 1 year and 3.1 kg after 2 years of duloxetine

treatment. The degree of weight gain at 1 year in this study is similar to the increase of 2.1 kg observed in a 52-week, open-label study of duloxetine at doses of 80 or 120 mg/day [Raskin et al., 2003]. The absence of placebo groups in these studies limits our ability to determine causality. Weight gain may be the result of recovery from depression, as well as a potential side effect of antidepressant treatment [Masand and Gupta, 2002; Shioiri et al., 1993]. Epidemiological studies have shown that weight gain of 1 kg/year may occur in a general population of healthy subjects [Lewis et al., 2000], whereas a weight gain of 3.0–3.2 kg has been reported among depressed patients receiving either fluoxetine or placebo for a period of 50 weeks [Michelson et al., 1999]. In pooled data from two placebo-controlled studies of duloxetine (twice-daily dosing), mean increases in body weight during 36 weeks of treatment were 0.76 kg for duloxetine 80 mg/day, 1.00 kg for duloxetine 120 mg/day, and 0.1 kg for placebo [Mallinckrodt et al., 2003]. Thus, the progressive weight gain observed during long-term therapy may be due to a combination of factors: an improvement in appetite as other depressive symptoms resolve, a gradual increase in weight similar to that noted in the general population, and duloxetine-induced weight gain. The relative contribution of each of these factors to the overall weight increase is at present unclear.

Another area of concern during long-term antidepressant therapy is treatment-emergent sexual dysfunction. Data related to sexual side effects were not prospectively collected in this study; however, spontaneously reported adverse events and reasons for discontinuation were collected. Two patients discontinued the study due to sexual side effects (both in the acute therapy phase). There were no discontinuations due to sexual side effects during long-term treatment. We also note as a limitation the underreporting of sexual dysfunction and refer the reader to a better discussion of sexual dysfunction in duloxetine-treated patients [Delgado et al., 2005].

We considered efficacy outcomes in this study to be secondary and discuss them briefly. Improvements in pain severity during acute phase treatment corresponded to reductions of 15–45% from the baseline values. Previous studies of patients with acute and chronic pain have shown that a 30% reduction in pain severity from baseline may be considered to be a clinically important improvement [Farrar et al., 2001]. The mean HAM-D-17 total score at the beginning of the extension phase was 10.3, and the mean score continued to decrease following 1 and 2 years of treatment. Although this study was not designed to assess long-term maintenance of efficacy, results from a prospectively designed relapse prevention study of duloxetine presented elsewhere [Perahia et al., 2006] showed that patients treated with duloxetine had statistically significantly better HAM-D-17 total scores at 9 months and a statistically longer time to relapse compared with patients treated with placebo.

The results of this study should be considered in light of its limitations and strengths. First, although the timing of dose initiation and escalation was blinded, this study did not include either placebo or active comparator; thus, the ability to assess causality of the changes in outcome measures is limited. Second, the primary goal of our study was to evaluate the safety and tolerability of a dose escalation. The timing of dosage increases was specified a priori, and not based upon degree of response to treatment. Thus, the study was not designed to assess whether a weekly dose escalation may be efficacious in patients exhibiting suboptimal response to an initial 60 mg once-daily dose of duloxetine. However, given the blinding of the timing of dose initiation and escalation, this study does provide useful information regarding adverse events associated with weekly dose escalation. Third, this relatively small study may not be adequately powered to assess accurately long-term mean changes in outcome measures. However, the results observed here are generally consistent with those of previous acute phase, placebo-controlled studies, and appropriately powered long-term studies. Fourth, in most previous studies of duloxetine, those patients with tolerability issues were allowed to reduce the number of capsules (and hence the dosage) for a short period during initial treatment. Our study did not allow a capsule/dose reduction, and patients who were unable to tolerate the duloxetine dose during acute phase treatment were discontinued. Thus, those patients who may have been most likely to exhibit tolerability issues during treatment were discontinued early in the study. Finally, because patients with unstable or uncontrolled medical comorbid conditions were excluded from this study, caution may be needed in extrapolating these safety data to more naturalistic settings.

This was the first duloxetine study to incorporate a treatment period of greater than 1 year, and it has been useful in furthering our understanding of long-term exposure to duloxetine.

CONCLUSIONS

In this study, we demonstrated that duloxetine doses may be rapidly escalated from 60 to 90 to 120 mg once daily without undue consequences. The results provide evidence for the safety and tolerability of duloxetine at once-daily doses above 60 mg, and suggest that dose escalation may be achieved without incurring a substantial burden of additional adverse events. Adverse event data and the time course profiles of vital signs during up to 2 years of treatment further our understanding of long-term treatment with duloxetine. During acute phase therapy, significant reductions were observed in measures of depressive symptoms, including anxiety, and these improvements were

maintained during 2 years of extension phase treatment with duloxetine.

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