Duloxetine in the Long-Term Treatment of Major Depressive Disorder

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Background: Depression is a chronic recurring disorder and guidelines recommend long-term therapy. This clinical trial evaluated the long-term (1 year) safety and efficacy of duloxetine, a dual reuptake inhibitor of serotonin and norepinephrine, in patients with DSM-IV major depressive disorder.

Method: This was an open-label, 52-week, multinational clinical trial in outpatients (age ≥ 18 years) who received duloxetine at 80 mg/day (administered 40 mg twice daily) to 120 mg/day (administered 60 mg twice daily) for up to 1 year.

Results: A total of 1279 patients had postbaseline data. Of these, 520 were exposed to duloxetine for at least 360 days, yielding approximately 808 patient-years of total exposure. Mean changes in Clinical Global Impressions-Severity of Illness scale (CGI-S) score, 17-item Hamilton Rating Scale for Depression total score and subfactor scores, Beck Depression Inventory-II score, and Sheehan Disability Scale score and mean Patient Global Impression-Improvement scale (PGI-I) scores all showed highly significant ($p < .001$) improvements at all assessment times. The estimated probabilities of improvement in CGI-S and PGI-I scores at week 1 were 40.4% and 59.2%, respectively, and at week 2 were 70.0% and 78.3%. The estimated probabilities of remission at weeks 6, 28, and 52 were 50.8%, 75.6%, and 81.8%, respectively. Adverse events led to discontinuation in 218 patients (17.0%). The most frequent specific events leading to discontinuation were nausea (1.5%), somnolence (1.4%), vomiting (0.9%), hypomania (0.8%), pregnancy (0.8%), dizziness (0.6%), insomnia (0.6%), and hypertension (0.5%). Treatment-emergent adverse events that were reported by > 10% of patients included nausea, insomnia, headache, somnolence, dry mouth, dizziness, constipation, sweating increase, anxiety, diarrhea, and fatigue. Most events occurred early in the study. Of those events that first occurred or worsened after discontinuation, only dizziness (8.3%) occurred in more than 5% of patients. Mean changes from baseline to last observation for standing and supine pulse were less than 2 b.p.m. Mean changes in blood pressure (< 1.0 mm Hg), corrected QT interval (< 1 msec), and body weight (2.4 kg [5.3 lb]) were not clinically significant. Laboratory analyses varied across visits, and mean changes after 52 weeks were generally close to zero. The incidence of laboratory values above or below normal limits at any time during treatment was low.

Conclusion: Duloxetine was effective, safe, and well tolerated in the long-term treatment of major depression at a dose of 80 to 120 mg/day in this study.

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At the time of this study, all of the authors were employed by Eli Lilly & Co. and accept full responsibility for the conduct of this trial. The authors had full access to all data from the trial and participated in the decision to publish the data.

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Major depressive disorder (MDD) is the third most costly and disabling illness in the United States.[1,2] MDD is estimated to affect 18 million people in the United States and 340 million people worldwide[3] and is projected to be the second leading cause of disability in the world by the year 2020.[4] Depression follows a chronic course without remission in about 20% of cases,[5] especially when adequate treatment is not available. The recurrence rate for those who recover from the first episode is about 60% at 12 years, and the recurrence rate is higher in those who are older than 45 years of age.[5] Patients with major depression also have a higher mortality risk, attributed in part to an increased probability of committing suicide.[6,7] In addition, depressed patients have health care costs approximately 2 times higher than those of nondepressed patients.[8] Thus, improving the available treatment modalities of depression, including treatments with favorable long-term tolerability profiles, could have potentially profound global epidemiologic impact.

Despite advances in antidepressant treatment, limitations still exist in both efficacy and safety. Selective serotonin reuptake inhibitors (SSRIs) attained clinical acceptance over tricyclic antidepressants (TCAs) in part due to their improved tolerability profile through lower rates of anticholinergic events, orthostatic hypotension, sedation, and toxicity in overdose. Some evidence also suggests that remission rates (i.e., 17-item Hamilton Rating Scale

for Depression [HAM-D-17] scores of 7 or less) obtained with SSRIs are lower than those for tricyclics.[9–13] Only 30% to 40% of patients achieve remission,[14,15] and a similar percentage demonstrate a lack of response (i.e., less than a 50% reduction in total HAM-D-17 score) in placebo-controlled trials.[15] Furthermore, newer antidepressants provide little or no improvement in time to onset of action. Combined serotonin (5-HT) and norepinephrine (NE) therapeutic action has been proposed to provide a more robust clinical effect compared with the enhancement of a single neurochemical system.[16,17] The Danish University Antidepressant Group demonstrated that the TCA clomipramine, an agent with substantial effect on both 5-HT and NE, has greater clinical efficacy than the SSRIs citalopram and paroxetine.[18,19] Desipramine, an NE reuptake inhibitor, has been reported to enhance the efficacy of the SSRI fluoxetine.[20] Finally, the antidepressant venlafaxine, at higher doses that have dual 5-HT and NE uptake inhibition, has greater remission rates than SSRIs.[16] These data support the hypothesis that a monoamine reuptake strategy that combines action at more than one neurotransmitter system may be a useful approach to improving the outcome of initial treatment of patients with major depression.

Duloxetine is a potent and relatively balanced inhibitor of 5-HT and NE reuptake.[21] In this context, balance is defined from preclinical pharmacologic data that demonstrated little difference in the relative affinity for duloxetine in binding to the NE and 5-HT transport sites. Duloxetine lacks significant affinity for muscarinic, histaminergic, α-adrenergic, dopaminergic, serotonergic, and opioid receptors,[21,22] suggesting that duloxetine might have a superior antidepressant effect without significant limiting adverse events.

The effectiveness of duloxetine in the acute treatment of the emotional and painful physical symptoms of depression has been established in randomized, double-blind, placebo-controlled studies.[23–26] Safety and tolerability of duloxetine have also been demonstrated in acute treatment studies.[23–26] In placebo-controlled trials (data on file, Eli Lilly & Co., Indianapolis, Ind.), the most frequently reported adverse events for duloxetine-treated patients, pooled across doses of 40 to 120 mg/day, were nausea, headache, dry mouth, fatigue, and insomnia. The only adverse events leading to discontinuation in greater than 1.0% of patients were nausea, dizziness, and somnolence. The safety and efficacy of duloxetine did not vary significantly across demographic subgroups defined by age, gender, and origin. Nevertheless, since depression is a recurring chronic condition, antidepressant use is now recommended for at least 9 months.[27] As a consequence, evaluation of longer-term use is important for both efficacy and safety. The U.S. Food and Drug Administration (FDA) requires 300 patients exposed to drug for 6 months and 100 patients exposed for 1 year for assessment of long-term safety.[28] The present open-label study with flexible dosing at the high end of the dose range is a complement to the double-blind, placebo-controlled trials. It was anticipated that this design would provide clinicians with data from a more typical patient experience, while the use of a higher dose regimen was expected to provide a better assessment of the safety of duloxetine. The efficacy and safety of duloxetine were evaluated in this 1-year, open-label trial in patients with MDD.

METHOD

Study Objectives

The primary objective of the study was to evaluate the safety of duloxetine, 40 mg twice daily to 60 mg twice daily, in patients diagnosed with major depressive disorder. Secondary objectives were to evaluate the efficacy of long-term duloxetine treatment and to evaluate patient quality of life, using the rating measures described below.

Study Design

This was a 52-center, 52-week, open-label, single-arm study of outpatients meeting criteria for MDD. This study included 8 investigative sites in Argentina (N = 168), 10 sites in Brazil (N = 365), 11 sites in Canada (N = 142), 4 sites in Columbia (N = 195), 6 sites in Mexico (N = 248), 10 sites in the United States (N = 91), and 3 sites in Venezuela (N = 70). Given FDA requirements for 100 exposures for 1 year, and a projected 10% completion rate, at least 1000 patients were to be enrolled.

Patients

Patients, recruited from clinical practice and advertisements, were at least 18 years of age with a major depressive episode as defined by DSM-IV criteria who had a Clinical Global Impressions-Severity of Illness scale (CGI-S) score ≥ 3 at visits 1 and 2. Patients did not have any previous or current diagnosis of schizophrenia or bipolar disorder, an Axis II disorder that would interfere with protocol compliance, or history of substance abuse within the last year and were not judged to be at risk for suicide. Although not strictly outlined as an exclusion criterion in the protocol, investigators were advised that if psychotherapy was initiated 6 weeks or less prior to study enrollment or initiated at any point during the study, those patients should be excluded from study participation. Patients in ongoing psychotherapy at the time of study enrollment were permitted to continue therapy if the therapy was initiated more than 6 weeks prior to study enrollment and if, in the clinician's judgment, the therapy was not in its active phase. Treatment compliance was assessed by the physician on the basis of capsule counts and/or patient interview. All patients provided written informed consent. The protocol was reviewed and approved by the ethical review board at each center. The study was conducted in

accordance with the ethical principles stated in the most recent version of the Declaration of Helsinki or the applicable guidelines on Good Clinical Practices, whichever provided greater protection of the individual.

Treatments

Patients were administered duloxetine as 2 equal doses of 40 to 60 mg per day (total dose = 80 to 120 mg/day), in 20-mg capsules for up to 52 weeks. In order to optimize antidepressant therapy, the patients' doses were adjusted up to 60 mg twice daily or down to 40 mg twice daily based on the physician's clinical evaluation of tolerability and efficacy. Patients unable to tolerate 40 mg twice daily were discontinued from the study.

Concomitant Medications

Most medications, including antihypertensives, antiarrhythmics, antibiotics, and multivitamins, were allowed in the study in order to permit generalizations to clinical practice. Only medications with primary central nervous system effects, which may have confounded the results of the study, were excluded. Patients were not permitted to receive other antidepressant or antimanic agents during the study. Patients were not allowed to take antipsychotic medications within 7 days prior to visit 1, or at any time during the study. Episodic use (≤ 3 consecutive days, and no more than 100 total days) of benzodiazepines was permitted. Diphenhydramine, chloral hydrate, cough and cold medications, and narcotics were allowed on an episodic basis only.

Efficacy Measures

Efficacy was assessed using the CGI-S[29] (a priori specified as the primary outcome variable), the HAM-D-17,[30] the Beck Depression Inventory-II (BDI-II),[31] and the Patient Global Impressions-Improvement scale (PGI-I).[29] Patient-rated quality of life was evaluated using the Sheehan Disability Scale.[32] All outcomes were assessed at weeks 6, 28, and 52, or upon early discontinuation, except for the PGI-I and the CGI-S, which were administered at all visits. Patients were defined as responders if they had a decrease from baseline of at least 50% in HAM-D-17 total score. Patients were defined as remitters if they had a HAM-D-17 total score ≤ 7. Onset of action was assessed by estimating the probabilities of improvement at early visits, with improvement defined as at least a 1-point improvement on the CGI-S and/or a PGI-I score of 3 or less.

Safety Measures

Safety measures included spontaneously reported adverse events, serious adverse events (hospitalization, cancer, permanent disability, life-threatening conditions, or other), vital signs, electrocardiograms (ECGs), and laboratory analyses. Data on adverse events and vital signs were collected at every visit. A treatment-emergent adverse event was an adverse event that first occurred or worsened after baseline. Chemistry analyses were collected at baseline and at weeks 1, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 52, or at the time of early discontinuation. Hematology was collected at baseline and at weeks 1, 3, 4, 28, and 52, or at the time of early discontinuation.

Treatment-emergent sustained hypertension was defined as any one of the following, occurring any time between starting and stopping duloxetine (with the baseline defined as the highest blood pressure measurements taken before duloxetine initiation):

- Supine systolic blood pressure of ≥ 140 mm Hg and an increase from baseline of ≥ 10 mm Hg at 3 consecutive visits, or
- Supine diastolic blood pressure of ≥ 90 mm Hg and an increase from baseline of ≥ 10 mm Hg at 3 consecutive visits.

An additional analysis of blood pressure was conducted to compare mean changes in patients who were hypertensive at baseline with changes in those who were not hypertensive. Patients were considered hypertensive at baseline if they had a historical diagnosis, secondary condition, or adverse event at the start of treatment consistent with a clinical diagnosis of hypertension or high blood pressure. The Medical Dictionary for Regulatory Activities (MedDRA) terms reported by patients at baseline that were consistent with a clinical diagnosis of hypertension were *high arterial pressure*, *increased diastolic pressure*, *high blood pressure*, *diastolic hypertension*, *hypertension*, *arterial hypertension*, and *hypertensive heart disease*.

Electrocardiograms were collected at baseline; at weeks 1, 6, 28, and 52; and upon early discontinuation. Patients at 2 sites in Mexico and 1 site in Columbia who also had pharmacokinetics samples obtained had ECGs read by a cardiologist at a central location. For these ECGs, QT intervals were corrected (QTc) using Fridericia's (QTcF) and Bazett's (QTcB) correction. All other patients had ECGs read at the site for classification as either normal or abnormal. Limits for the potentially clinically significant QTc values were an increase in QTcF of ≥ 30 msec, and any postbaseline value ≥ 450 msec for men or ≥ 470 msec for women.[33]

Statistical Analyses

Mean changes from baseline to last observation in laboratory analyses, vital signs, and ECG intervals were assessed using analysis of variance with models that included investigator. Longitudinal mean changes and categorical changes (temporal patterns) were assessed via likelihood-based mixed-models repeated measure. Models for mean changes included investigator, visit, baseline value, and baseline-by-visit interaction. Unless otherwise specified, results are repeated measures.

Table 1. Summary of Patient Demographics (N = 1279)

Variable	Value
Gender, N (%)	
Female	928 (72.6)
Male	351 (27.4)
Age, y	
Mean (SD)	44.4 (13.2)
Range	18–87
Weight, mean (SD)	
kg	70.27 (17.41)
lb	156.16 (38.69)
Ethnicity, N (%)	
African descent	35 (2.7)
Western Asian	4 (0.3)
White	542 (42.4)
East/southeast Asian	2 (0.2)
Hispanic	584 (45.7)
Other	112 (8.8)

RESULTS

Patient Disposition

Patient characteristics at baseline are summarized in Table 1. This report is based on data from 1279 patients, of whom 553 completed the 52-week open-label therapy phase of the study. Of these, 540 patients completed all regularly scheduled visits and 520 were exposed to duloxetine for at least 360 days. This study represented approximately 808 patient-years of exposure to duloxetine, with a median duration of exposure of 267 days. The majority of patients were female (72.6%), while the predominant ethnic origins of the patients were Hispanic (45.7%) and white (42.4%). The mean (SD) age was 44.4 (13.2) years, with 101 patients aged 65 years or older (age range, 18–87 years).

After approximately 2 weeks of therapy, patients who were unable to tolerate a dose of at least 80 mg/day (administered 40 mg b.i.d.) were discontinued from the study. Approximately half (49.3%) of the patients had the maximal dose, as encouraged per the protocol, of 120 mg/day (administered 60 mg b.i.d.) as their last dose and 50.6% of the patients had a modal dose of 120 mg/day. Treatment compliance, assessed at each visit, ranged from 93.0% (at week 1) to 100% (week 44).

In total, 72.9% of patients reported at least 1 concomitant medication. Concomitant medications used by at least 5% of patients during the duloxetine therapy phase were paracetamol (15.6%), ibuprofen (12.3%), acetylsalicylic acid (8.5%), and metamizole sodium (5.6%). Thus, the most frequently reported concomitant medications were non-narcotic analgesics.

Treatment Discontinuation

Approximately 42.2% of patients completed the 52-week study. The reasons for study discontinuation included adverse event (17%), personal conflict/other reasons (10.2%), lost to follow-up (9.3%), noncompliance (6.6%), lack of efficacy (5.9%), sponsor decision (3.2%), protocol violation (3.1%), physician decision (0.9%), other (0.4%), and death (0.1%—the cause of death was cardiac arrest following an accidental injury). Thirteen patients (1.0%) discontinued during the 2-week no-study-drug phase between visit 18 (week 52) and visit 19 (week 54). The adverse events most frequently leading to discontinuation included nausea (1.5%), somnolence (1.4%), vomiting (0.9%), hypomania (0.8%), pregnancy (0.8%), dizziness (0.6%), insomnia (0.6%), and hypertension (0.6%). Most events occurred early in the study.

Efficacy

Efficacy outcome mean changes at weeks 6, 28, and 52 are summarized in Table 2. Mean changes for all efficacy outcomes were highly significant ($p < .001$) at all assessment times. For example, mean changes for CGI-S score, the primary efficacy outcome, at weeks 6, 28, and 52, were –2.2, –2.9, and –3.0, respectively, compared with a baseline mean of 4.6. A score of 1 on the CGI-S indicates absence of symptoms. Therefore, the mean score of 1.6 at week 52 suggested that many subjects had complete resolution of symptoms.

The estimated probabilities of response (defined as a 50% improvement in HAM-D-17 total score) at weeks 6, 28, and 52 were 62.9%, 84.3%, and 89.1%, respectively. The corresponding probabilities of remission (defined as HAM-D-17 total score of ≤ 7) were 50.8%, 75.6%, and 81.8%, respectively. Using last-observation-carried-forward (LOCF) analysis, rates of response and remission were 71% and 60%, respectively. The estimated probabilities of improvement at week 1 were 40.4% and 59.2% based on the CGI-S and PGI-I, respectively. The corresponding probabilities at week 2 were 70.0% and 78.3%, and the probabilities at week 6 were 88.0% and 86.9%.

For the HAM-D-17 total score, the baseline mean was approximately 22.5, and mean changes at weeks 6, 28, and 52 were –13.1, –16.6, and –17.4, respectively. A similar pattern of mean changes was observed for all subfactors of the HAM-D-17 (anxiety, sleep, retardation, and core depressive symptoms—Maier and core subfactors), the BDI-II total score, and the 3 components of the Sheehan Disability Scale.

Adverse Events

Treatment-emergent adverse events for which the incidence was ≥ 5% during the open-label therapy phase (weeks 1–52) are summarized in Table 3. The incidence for those same adverse events for weeks 1 through 8 and 9 through 52 are also listed in Table 3. During weeks 1 through 52, adverse events that were reported by more than 10% of patients included nausea, insomnia, headache, somnolence, dry mouth, dizziness, constipation, sweating increase, anxiety, diarrhea, and fatigue. Most

Table 2. Efficacy Outcome Measures[a]

Outcome Measure	Baseline	Week 6	Week 28	Week 52
HAM-D-17				
Total Score	22.46	9.34 (0.24)	5.89 (0.26)	5.04 (0.27)
Anxiety subfactor	7.09	2.98 (0.09)	2.08 (0.10)	1.82 (0.10)
Core subfactor	9.21	3.47 (0.11)	1.97 (0.12)	1.64 (0.13)
Maier subfactor	11.30	4.54 (0.13)	2.74 (0.14)	2.36 (0.15)
Retardation subfactor	7.76	3.34 (0.09)	1.92 (0.10)	1.64 (0.11)
Sleep subfactor	3.36	1.58 (0.06)	1.03 (0.06)	0.87 (0.07)
CGI-Severity	4.57	2.42 (0.03)	1.72 (0.04)	1.56 (0.04)
PGI-Improvement	N/A	2.41 (0.04)	2.02 (0.04)	1.83 (0.04)
BDI-II total score	33.67	15.76 (0.42)	11.13 (0.46)	9.52 (0.49)
Sheehan Disability Scale				
Work item	6.57	3.71 (0.11)	2.56 (0.12)	2.18 (0.13)
Family item	6.71	3.65 (0.10)	2.68 (0.12)	2.13 (0.12)
Social item	7.17	4.14 (0.11)	2.92 (0.12)	2.32 (0.13)

[a]Baseline values are shown as means; values at weeks 6, 28, and 52 are shown as mean (SE). Means are from the repeated-measures analysis. Within-group mean changes from baseline were significant ($p < .001$) for all outcomes at all visits. Change from baseline was not analyzed for the PGI because this scale inherently assesses change and was therefore not administered at baseline.

Abbreviations: BDI-II = Beck Depression Inventory-II, CGI = Clinical Global Impressions scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, PGI = Patient Global Impressions scale.

Table 3. Treatment-Emergent Adverse Events Occurring in ≥ 5% of Patients (total N = 1279)

	Weeks 1–8		Weeks 9–52		Weeks 1–52	
Adverse Event	N	%	N	%	N	%
Nausea	407	31.8	44	3.4	435	34.0
Somnolence	354	27.7	36	2.8	381	29.8
Insomnia	318	24.9	94	7.3	400	31.3
Headache NOS	287	22.4	128	10.0	389	30.4
Dry mouth	283	22.1	35	2.7	300	23.5
Constipation	240	18.8	42	3.3	273	21.3
Dizziness	228	17.8	82	6.4	298	23.3
Sweating increase	147	11.5	55	4.3	192	15.0
Diarrhea NOS	131	10.2	48	3.8	174	13.6
Tremor	108	8.4	17	1.3	120	9.4
Anxiety	106	8.3	93	7.3	186	14.5
Fatigue	95	7.4	44	3.4	134	10.5
Appetite decreased NOS	94	7.3	11	0.9	104	8.1
Anorexia	92	7.2	15	1.2	104	8.1
Vomiting NOS	85	6.6	33	2.6	116	9.1

Abbreviation: NOS = not otherwise specified.

treatment-emergent adverse events were of mild or moderate severity. The incidence of treatment-emergent adverse events was lower during the entire period of weeks 9 through 52 than during the first 8 weeks. All treatment-emergent adverse events with an incidence of at least 5% during weeks 9 through 52 were also present at the same or higher rate during the first 8 weeks. Treatment-emergent adverse events with an incidence of at least 2% that had a higher incidence during the last 44 weeks compared with the first 8 weeks included influenza, back pain, hypertension, increased weight, nasopharyngitis, arthralgia, and influenza-like illness.

Adverse events related to sexual functioning included decreased libido (4.1%), ejaculation failure (2.7%), and erectile dysfunction (2.5%).

Serious Adverse Events

The rate of serious adverse events per patient-year-exposure was low—approximately 1 event per 13 years of exposure. A total of 64 enrolled patients reported serious adverse events. Investigators considered most of these events unrelated to duloxetine exposure. The serious adverse events reported by more than 1 patient included suicidal ideation (N = 7), suicide attempt (N = 7), accident (N = 3), hip fracture (N = 3), angina pectoris (N = 2), anxiety (N = 2), cholelithiasis (N = 2), confusion (N = 2), depression aggravated (N = 2), depression (N = 2), mania (N = 2), and non-accidental overdose (N = 2). There was no clear temporal pattern to the incidence of the serious adverse events as there were so few events of each type. Between 4 and 10 patients reported a serious adverse event during each 40 days (approximately deciles) of duloxetine exposure with no clear increasing or decreasing trend. The 7 events of suicide attempt correspond to 1 attempt per 115 patient-years of exposure to duloxetine.

Cardiovascular Profile

Vital signs (supine and standing blood pressure and pulse) were measured at each visit. Mean changes from baseline to last observation for standing and supine systolic and diastolic blood pressures were all less than 1 mm Hg and not significantly different from zero. Statistically significant mean increases were observed for standing pulse (1.5 b.p.m.) and supine pulse (1.8 b.p.m.).

In an analysis comparing patients who were hypertensive versus non-hypertensive at baseline, mean changes in standing and supine systolic and diastolic blood pressure did not differ significantly between hypertensive and non-hypertensive patients.

Of the 1039 patients who did not have hypertension at baseline, 46 patients (4.4%) met criteria for sustained hypertension. Of these 46 patients, 23 patients returned to his or her baseline blood pressure while continuing on study drug, and 2 additional patients no longer met criteria for sustained hypertension. Therefore, only 21 patients (1.6%) without baseline hypertension met criteria for sustained hypertension during the study and did not return to baseline. None of the 23 patients who met criteria for sustained hypertension and did not return to his or her baseline blood pressure discontinued from the study due to hypertension. Only 2 patients (0.16%) had at least one value during a sustained hypertensive episode that met stage 3 criteria (systolic ≥ 180 mm Hg or diastolic ≥ 110 mm Hg).[34]

There were no significant differences in cardiac intervals detected by ECG. In particular, mean change from baseline to last observation in QTcF was 0.52 msec and not

significantly different from zero. Mean changes in QTcF were –3.43 msec at week 4, 1.84 msec at week 28, and 0.44 msec at week 52. One female patient experienced a treatment-emergent abnormal QTcF value ≥ 470 msec, and 1 male patient experienced a treatment-emergent abnormal QTcF value ≥ 450 msec.

Body Weight

Mean changes in weight at early visits were negative (weight loss), mean changes at intermediate visits were near zero, and mean changes at later visits were positive (weight gain). After 52 weeks of treatment, using repeated-measures analysis, a statistically significant within-group mean weight increase of 2.4 kg (5.3 lb) was observed (mean change was 1.1 kg [2.4 lb] using LOCF analysis).

Laboratory Analyses

Significant mean changes from baseline to last observation were observed for some laboratory analyses. The magnitudes of the mean changes were small compared with the baseline means and standard deviations and were not considered clinically relevant in light of the low incidence of values that were outside of normal ranges. Furthermore, repeated-measures analyses of key laboratory values were conducted to assess the temporal pattern of changes. In general, mean increases at weeks 12 and earlier were similar in magnitude to those from analyses of mean changes to last observation. The magnitude of mean changes after week 12 tended to decline, and by week 52 mean changes were typically close to zero.

Detailed examination of data from patients with abnormal values suggested that abnormal values were typically transient, resolved with continued therapy, lacked a time course relationship, and were not associated with clinical symptoms.

Discontinuation-Emergent Adverse Events

All patients who proceeded past visit 18 (N = 553) received no study drug for 2 weeks until visit 19 via abrupt discontinuation (no taper). The discontinuation-emergent adverse events for the no–study-drug phase (events experienced during the period after visit 18 in which the patient did not receive study drug) for which the incidence was ≥ 2% were dizziness (8.3%), anxiety (4.3%), nausea (4.2%), headache (3.1%), insomnia (2.9%), and irritability (2.6%).

DISCUSSION

The effectiveness of duloxetine in acute treatment of major depressive disorder has been established in randomized, double-blind, placebo-controlled studies.[26] In 4 of these studies, duloxetine had significantly greater mean changes from baseline to endpoint compared with placebo on the primary outcome measure of the HAM-D-17 total score. Estimated probabilities of remission (HAM-D-17 total score ≤ 7) ranged from 43% to 57%. Significant differences from placebo were detected as early as week 1 on measures of the emotional symptoms of depression (core factor and Maier subscales of the HAM-D), painful physical symptoms (visual analogue scales for pain), and global wellness (CGI-S).

Although interpreting results in an open-label study must be approached cautiously, the remission rates in this 52-week study were high, implying duloxetine therapy was effective in relieving depressive illness. Efficacy was demonstrated on all assessed measures, both clinician- and patient-rated. That the study was expected to have a 10% completion rate and actually had a 40.7% completion rate further substantiates the efficacy and tolerability of duloxetine in the treatment of MDD.

Onset of efficacy, while critically important, is problematic to define and assess.[35] These issues may warrant even greater consideration in an open-label trial. However, the high rates of improvement at weeks 1 and 2 are consistent with results from double-blind, placebo-controlled trials in which duloxetine was significantly superior to placebo as early as week 1 on a number of symptom severity measures.[23] About half of the improvement in the HAM-D-17 total score was due to improvement on the core symptoms of depression measured by the Maier and the core subfactors.

Accumulating evidence suggests that remission should be the endpoint of efficacy studies in depression rather than response. Remission indicates more complete resolution of the full spectrum of symptoms of depression than does response. Responders who do not remit may have appreciable residual symptomatology, and patients with residual symptoms are at higher risk for relapse or recurrence.[36] The estimated probability of remission at 6 weeks in this study (50.8%) is comparable to the remission rates reported from 8-week double-blind placebo-controlled trials using similar doses.[23–25]

The balanced reuptake inhibition of both 5-HT and NE may account for the observed efficacy and high remission rate, as previous studies have shown that dual reuptake inhibitors are more effective than agents with single monoamine inhibition.[16,18–20] Remission rates at 52 weeks in this study were only slightly less than the response rates (81.8% and 89.1%, respectively), implying that those subjects who responded had a high probability of achieving complete resolution. Duloxetine has demonstrated efficacy in treating both the emotional and painful physical symptoms of depression,[26] which may explain the high rates of remission and the observation that most duloxetine-treated patients who responded also remitted.

Duloxetine was safely administered and well tolerated in long-term chronic dosing. Most treatment-emergent adverse events were either mild or moderate in severity, occurred early in the study, and were transient. During

the first 8 weeks of treatment, the incidence and pattern of treatment-emergent adverse events were generally similar to the rates and patterns in double-blind, placebo-controlled trials of 8 to 9 weeks' duration. Treatment-emergent adverse events with an incidence of at least 2% during the last 44 weeks that were more frequent than during the first 8 weeks included influenza, back pain, nasopharyngitis, arthralgia, influenza-like illness, and hypertension and 1 event that may be reflective of depression improvement, increased body weight. The incidence of spontaneously reported adverse events related to sexual functioning was low. However, spontaneous reports frequently underrepresent the actual incidence of sexual side effects, and more accurate estimates may be elicited using validated, structured questionnaires.[37] Thus, in a series of 4 double-blind, placebo- and paroxetine-controlled studies of up to 9 months' duration, the Arizona Sexual Experiences scale was utilized to compare the incidence of sexual dysfunction in patients receiving duloxetine with the corresponding rates in paroxetine- and placebo-treated patients; results of an analysis of pooled data from these studies showed that the incidence of sexual dysfunction in patients receiving long-term (≤ 9 months) duloxetine treatment did not differ significantly from the placebo rate.[38]

Patients who tolerated duloxetine during the early period of the trial were likely to tolerate long-term dosing, suggesting minimal or no clinically significant tolerability issues that were attributable to chronic versus acute administration of duloxetine. The proportion of patients completing the protocol (42.2%) compared favorably with that observed in a pooled analysis of 6- to 12-month venlafaxine clinical trials (38%).[39] Given that the tolerability of duloxetine compares favorably with that of existing therapies, that the prevalence of early-onset adverse events decreases over time, the lack of chronic adverse effects, and the high adherence to a b.i.d. dosing regimen, this study provides preliminary evidence of the acceptability of long-term duloxetine treatment consistent with clinical recommendations for depression therapy.

Duloxetine produced small mean changes in blood pressure (less than 1 mm Hg) and heart rate (less than 2 b.p.m.), and lacked significant effects on QT intervals (mean changes in QTc were essentially zero). Half of the hypertensive cases resolved without treatment while patients continued to take duloxetine. Patients with preexisting hypertension fared well, with a mean decrease in blood pressure compared with normotensive patients. The frequency of visits and 1-year duration of this trial account for the higher percentage of hypertension (4.4%, with half of those returning to baseline levels) found in this study compared with the placebo-controlled short-term trials in which duloxetine had a similar rate of sustained hypertension compared with placebo. By way of comparison, the rate of hypertension for extended-release venlafaxine (doses ranging from 75 to 225 mg/day) in placebo-controlled, acute-phase studies is 4% versus 1% for placebo.[40] It is also to be expected that in a trial of 1 year's duration with more than 1200 patients, some patients may naturally develop hypertension, and some could have had preexisting hypertension that was not evident at a single baseline visit. Therefore, this study may overestimate the frequency of hypertension attributable to duloxetine, and it extends results from short-term trials showing placebo-like rates of sustained hypertension. Consistent with NE reuptake inhibition, mean pulse increases were observed. No temporal pattern in cardiovascular parameters was observed, since pulse rate, blood pressure, and QTc did not change with duration of treatment.

It is unclear whether the repeated-measures weight increase at 1 year (2.4 kg) is due to duloxetine treatment, the passage of time, weight recovery following successful treatment of depression, or some combination of these factors. However, we note that a 50-week study of fluoxetine versus placebo showed a 3.2-kg weight gain in placebo-treated patients,[41] and that Benazzi[42] associated weight increase with an improvement in depressive symptoms. Furthermore, a follow-up of National Health Interview Survey participants indicated a slight excess of self-reported weight gain over weight loss by women over a 1-year interval,[43] and a 2-year study monitoring body weights of men and women observed a gradual increase over this period.[44]

In a large study, small, clinically irrelevant mean changes in laboratory values commonly achieve statistical significance. Thus, in this large study, mean changes in many laboratory values were statistically significant, but small in magnitude and of doubtful clinical relevance. However, definitive evidence of noncausality is problematic in the absence of placebo control. Nevertheless, consistent with the conclusion that such effects do not have clinical relevance, controlled studies of duloxetine[23–26] have not demonstrated changes in laboratory values of clinical concern.

As has been seen with other antidepressants,[45] symptoms related to duloxetine discontinuation did occur in some patients. However, despite the duration of the study and the higher doses used, the rates of discontinuation-emergent adverse events were low and, in general, the symptoms were well tolerated.

It is important to consider the safety findings of this study in light of the dosing and design. Duloxetine has demonstrated significant superiority over placebo at 60 mg once daily in 2 trials.[23,24] Therefore, the doses used in this study to assess safety were 2-fold greater than doses yielding robust efficacy in most patients. It might be expected that the tolerability of duloxetine would be even greater with a lower dose regimen without substantial decrement in efficacy.[26] Furthermore, this study included an intense visit schedule, with 4 visits in the first 4 weeks and 19 total visits on therapy. These dosing and design features were

specifically included to maximize the probability of uncovering adverse reactions to duloxetine. This study provides evidence regarding the longer-term safety of duloxetine and builds on the short-term studies that demonstrated efficacy in the treatment of major depressive disorder.

Drug names: citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), diphenhydramine (Benadryl and others), fluoxetine (Prozac and others), ibuprofen (Motrin and others), paroxetine (Paxil), venlafaxine (Effexor).

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