Duloxetine: A New Treatment for the Emotional and Physical Symptoms of Depression

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Background: Depression is underdiagnosed in the primary care setting. Physical symptoms such as aches, pains, and gastrointestinal disturbance are frequently associated with major depressive disorder (MDD) and are often the presenting symptoms. Duloxetine, a dual-reuptake inhibitor of serotonin and norepinephrine, may have a positive effect on physical symptoms in addition to efficacy in treating emotional symptoms of depression.

Method: Efficacy was evaluated in 6 double-blind, placebo- and/or active comparator–controlled trials of duloxetine for patients with MDD (DSM-IV criteria). Efficacy in depression was determined primarily using the 17-item Hamilton Rating Scale for Depression (HAM-D-17). Secondary efficacy measures included subscales of the HAM-D-17 and assessment of physical symptoms. Safety evaluations included adverse events, vital signs, laboratory analyses, and electrocardiograms. Safety was evaluated by pooling the data from the MDD trials and a study of duloxetine in nondepressed patients.

Results: Duloxetine demonstrated significant differences from placebo on core mood symptoms, physical symptoms (e.g., back pain), and global functioning as early as week 1 of treatment. The estimated probabilities of remission in the studies that demonstrated efficacy ranged from 43% to 57%. The most frequently observed adverse events for duloxetine-treated patients included nausea, dizziness, insomnia, fatigue, and somnolence. Duloxetine did not prolong corrected QT intervals, and the rate of sustained elevations of blood pressure did not differ significantly from placebo.

Conclusion: In these studies, duloxetine was safe and effective in the treatment of both emotional and physical symptoms of MDD. Based on dose assessments, 60 mg q.d. appears to be the optimum starting and therapeutic dose.

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Depression is estimated to affect nearly 340 million people worldwide and 18 million people in the United States at any given time.[1] A number of studies have documented the enormous impact of this debilitating condition on both patients and the health care system.[2–5] In the primary care setting, diagnosis of a depressive disorder is complicated by the fact that depressed patients frequently present with a combination of emotional and physical symptoms.[6–10] The importance of physical symptoms was highlighted by a recent international study which found that almost 70% of depressed patients reported physical symptoms as the only reason for visiting their physician.[11] Physical symptoms often associated with depression include headaches, back pain, gastrointestinal disturbance (e.g., irritable bowel syndrome), and generalized aches and pains.[12]

Even with proper diagnosis, the front-line therapeutic approach currently used to treat major depressive disorder (MDD), namely, treatment with selective serotonin (5-HT) reuptake inhibitors (SSRIs), may be inferior in clinical effect to antidepressant medications that act upon more than one neurotransmitter system.[13,14] Thus, in an open-label study, the combination of a norepinephrine (NE) reuptake inhibitor (desipramine) and an SSRI (fluoxetine) provided greater antidepressant efficacy than that of either medication alone,[15] while remission rates obtained with certain dual-action medications have been reported to be higher than those of SSRIs.[16,17] There are, however, some major drawbacks in the clinical utility of

currently available agents that possess dual-reuptake inhibition. Tricyclic antidepressants (TCAs) exhibit a range of secondary pharmacologic actions that produce undesirable adverse effects, including the potential for cardiotoxicity due to quinidine-like effects.[18] Even among the more recently developed antidepressant agents possessing dual-reuptake inhibition, i.e., serotonin-norepinephrine reuptake inhibitors, significant tolerability issues (e.g., nausea, hypertension) may limit their usefulness and hinder long-term treatment compliance. An antidepressant that demonstrates the potentially superior efficacy of a dual-reuptake inhibitor without compromising safety and tolerability would represent a valuable additional treatment option for clinicians.

Not only do 5-HT and NE play an important role in the regulation of mood, but they are increasingly recognized as key modulatory neurotransmitters in the descending pain pathways that inhibit afferent pain fibers ascending through the spinal cord.[19] This may be an important regulatory system for endogenous pain control. The combined activity of 5-HT and NE appears to result in the maintenance of a pain threshold and a reduction of pain sensitivity. Notably, there are an increasing number of literature reports which suggest that dual-reuptake inhibitor antidepressants may possess significant analgesic properties.[20,21] Therefore, the dual-reuptake inhibition of duloxetine may be of clinical utility in the alleviation of painful physical symptoms associated with depression. It was hypothesized that an antidepressant treatment that is able to address both the emotional and physical symptoms of depression could provide more comprehensive relief from the burden of depression and thereby achieve higher rates of complete symptom resolution (remission).

Duloxetine is a potent and balanced inhibitor of both 5-HT and NE reuptake, possessing comparable affinities in binding to NE and 5-HT transport sites, in contrast to most other dual-reuptake inhibitors.[22] In addition, duloxetine has a low affinity for muscarinic, histamine-1, and β_1-adrenergic receptors, which may result in a side effect profile similar to that observed for SSRI medications. Furthermore, on the basis of its neurochemical profile, duloxetine may demonstrate the superior efficacy (i.e., higher remission rates) associated with dual-reuptake inhibitors.

Duloxetine is well absorbed after oral administration of capsules containing enteric-coated pellets, with a median time to maximum concentration (T_{max}) of 6 hours. Protein binding of duloxetine exceeds 90%, and it exhibits a mean plasma elimination half-life of 12.1 hours. Food does not affect the maximum concentration of duloxetine but marginally decreases the extent of absorption and delays T_{max} by about 4 hours. However, the food effect is not considered to be clinically important, such that duloxetine can be taken without regard to meals.[23]

Duloxetine is eliminated primarily in the urine after being extensively metabolized in the liver by oxidative enzymes, principally cytochrome P450 (CYP) isoenzyme 2D6 and, to a lesser extent, CYP1A2. Duloxetine is considered to be a moderate inhibitor of CYP2D6. More specifically, area-under-the-curve analyses indicate that the degree of CYP2D6 inhibition exhibited by duloxetine is greater than that of sertraline but less than that of fluoxetine or paroxetine. Since at least 2 pathways are involved in metabolism, it is less likely that duloxetine pharmacokinetics will be significantly affected by CYP2D6 inhibitors. Once formed, the circulating metabolites of duloxetine are pharmacologically inactive.[23]

These characteristics led to the study of duloxetine in clinical trials of major depressive disorder. This report summarizes the findings of clinical trials evaluating the efficacy and safety of duloxetine in the treatment of MDD. Evaluating efficacy results and pooling safety data across studies provides a more thorough assessment of efficacy and safety than that obtained by examining results from individual trials. Summaries of the results from 4 of the studies discussed here have been published recently.[24–27] The remaining studies are unpublished studies, Eli Lilly and company.

METHOD

All trials were multisite, randomized, double-blind, placebo- and/or active comparator–controlled studies (fluoxetine in studies 3 and 4, paroxetine in studies 5 and 6). Depression studies (studies 1–6) incorporated double-blind, variable-duration placebo lead-in and lead-out periods to mask the start and end of active therapy from both patients and investigators. Study protocols were approved by the ethics committee at each site in accordance with the principles of the Declaration of Helsinki, and all patients had completed signed informed consent documents prior to the administration of any study procedures or study drug. Further details of the clinical studies are presented in Table 1.

All patients in the depression studies were at least 18 years of age and met the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (DSM-IV), criteria for MDD. The diagnosis of MDD was confirmed by the Mini-International Neuropsychiatric Interview,[28] a standardized diagnostic interview based on DSM-IV criteria. Depressed patients had both a Clinical Global Impressions-Severity of Illness scale (CGI-S) rating ≥ 4 (moderate) and a clinician-rated 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score ≥ 15 at visits 1 and 2.

Patients were excluded for the following reasons: current and primary Axis I disorder (other than MDD); anxiety disorder as a primary diagnosis within a year of study entry; an Axis II disorder that could interfere with compliance with the study protocol; lack of response of the current depression episode to 2 or more adequate courses of

Table 1. Study Design for 7 Controlled Studies of Duloxetine Treatment[a]

Study	Disease State	Patients, N	Drug	Drug Dose[b]	Treatment Duration	Analyses
1	MDD	122	Placebo	…	9 wk	Efficacy/safety
		123	Duloxetine	60 mg qd		
2	MDD	139	Placebo	…	9 wk	Efficacy/safety
		128	Duloxetine	60 mg qd		
3	MDD	70	Placebo	…	8 wk	Efficacy/safety
		70	Duloxetine	Up to 120 mg/d		
		33	Fluoxetine	20 mg qd		
4	MDD	75	Placebo	…	8 wk	Efficacy/safety
		82	Duloxetine	Up to 120 mg/d		
		37	Fluoxetine	20 mg qd		
5	MDD	90	Placebo	…	8 wk	Efficacy/safety
		91	Duloxetine	40 mg/d		
		84	Duloxetine	80 mg/d		
		89	Paroxetine	20 mg qd		
6	MDD	89	Placebo	…	8 wk	Efficacy/safety
		86	Duloxetine	40 mg/d		
		91	Duloxetine	80 mg/d		
		87	Paroxetine	20 mg qd		
7[c]	SUI	138	Placebo	…	12 wk	Safety only
		137	Duloxetine	40 mg/d		
		140	Duloxetine	80 mg/d		

[a]Study 1 reported in Detke et al.[25]; study 2 reported in Detke et al.[26]; study 3 reported in Goldstein et al.[24]; study 7 reported in Norton et al.[27]; studies 4–6 are unpublished studies, Eli Lilly and Company.
[b]Doses of 40 mg/day, 80 mg/day, and 120 mg/day were administered 20 mg b.i.d., 40 mg b.i.d., and 60 mg b.i.d., respectively.
[c]Study 7 patient findings used only for safety data analysis.
Abbreviations: MDD = major depressive disorder, SUI = stress urinary incontinence.

antidepressant therapy, or treatment-resistant depression; serious medical illness; a history of substance abuse or dependence within a year of study entry; or a positive urine drug screen. Concomitant medications with primarily central nervous system activity were not allowed, with the exception of chloral hydrate or zolpidem for insomnia, on no more than 6 nights during the study. Chronic use of prescription analgesic medications (except narcotics) was allowed only in studies 3 and 4, while episodic use was permitted in studies 1 through 4. Narcotics were permitted in studies 1, 2, 5, and 6 only upon approval of the Lilly physician. Antihypertensive medications were not allowed unless the patient had been on a stable dose for at least 3 months.

All patients in study 7 were otherwise healthy women aged 18 to 65 years who had been diagnosed with stress urinary incontinence (SUI); patients with SUI suffer leakage of small amounts of urine during physical movement such as coughing, sneezing, or exercising. Patients were excluded for the following reasons: history of significant cardiac arrhythmia; history of angina or any cardiac ischemic condition; major surgery within 3 months of study entry; pregnancy within 12 months prior to study entry; current use of monoamine oxidase inhibitors, clonidine, α-methyl-dopa, β-blockers, or α-receptor antagonists/agonists; or a history of substance abuse or dependence within 5 years of study entry. Concomitant medication regimens including estrogens, anti-estrogens, or diuretics were not allowed unless the dose had been stable for 12 weeks prior to the trial.

The primary efficacy measure for all studies of MDD was the HAM-D-17 total score,[29] for which a decrease in HAM-D-17 total score indicated an improvement in symptoms of depression. Remission was defined as a HAM-D-17 total score ≤ 7. Secondary measures included the following subfactors of the HAM-D-17: anxiety (items 10, 11, 12, 13, 15, and 17), core factor (items 1, 2, 3, 7, and 8), Maier (items 1, 2, 7, 8, 9, and 10),[30] retardation (items 1, 7, 8, and 14),[31] and sleep (items 4, 5, and 6).[32] In addition, the following secondary measures were also employed (the specific combination of secondary measures varied by protocol): Hamilton Rating Scale for Anxiety,[33] Montgomery-Asberg Depression Rating Scale,[34] Quality of Life in Depression Scale,[35] Somatic Symptom Inventory,[36] Visual Analog Scales (VAS) for pain,[37] Short Form-36 Health Survey,[38] CGI-S,[39] and Patient Global Impression of Improvement (PGI-I).[39] Improvement in physical symptoms associated with depression was assessed in studies 1, 2, 5, and 6 by means of VAS scores of pain severity on 6 separate measures—overall pain, headaches, back pain, shoulder pain, interference with daily activities, and time in pain while awake.

Evaluated safety measures included adverse events, vital signs, laboratory analyses, electrocardiograms (ECGs), and the Arizona Sexual Experience Scale (ASEX).[40] Mean changes in the ASEX were evaluated in studies 3 through 6. Negative changes in the ASEX indicated improvement in sexual function, while positive changes indicated worsening of sexual function as determined by patient answers to the 5-question survey. The ASEX was administered

prior to randomization and either once or twice postbaseline, depending on the study. ECG findings were evaluated in studies 5 and 6. Treatment-emergent prolongation in corrected QT (QTc) intervals was defined as a change from baseline ≥ 30 msec.

A patient was considered hypertensive if supine systolic blood pressure was ≥ 140 mm Hg and an increase from baseline of at least 10 mm Hg occurred, or if supine diastolic blood pressure was ≥ 90 mm Hg and an increase from baseline of at least 10 mm Hg occurred. These definitions were based on diagnostic criteria from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.[41] Sustained hypertension was defined as meeting the above hypertensive criteria for 3 consecutive visits. The analysis of sustained elevations in blood pressure did not include patients from study 7, because the patients in this study were seen only 3 times (at 4-week intervals) during study participation.

All efficacy analyses involved only studies 1 through 6. Efficacy data were analyzed separately for each of the MDD studies. In order to maximize the number of duloxetine-treated patients in the safety analyses, data were pooled from the 6 double-blind, placebo-controlled depression studies and from the duloxetine (40 mg/day and 80 mg/day) and placebo arms of study 7. All analyses were conducted on an intent-to-treat basis. All randomized patients were included in the safety analysis, and all randomized patients with at least 1 postbaseline assessment were included in the efficacy analysis.

In the case of studies 1, 2, 5, and 6, the protocols specified a likelihood-based mixed-effects model repeated-measures (MMRM) approach as the primary analysis for continuous efficacy measures. For studies 3 and 4, analysis of covariance (ANCOVA) was employed as the primary analysis. Further details of the statistical methods and the rationale for their use are detailed in the literature.[24–27] All hypotheses were tested using a 2-sided $\alpha = 0.05$.

In safety data, mean changes in vital signs and laboratory analytes were evaluated using analysis of variance (ANOVA), while ANCOVA was used to evaluate the ASEX scores. Categorical data (adverse events, abnormal laboratory results or vital signs, and QTc values) were assessed using the Fisher exact test. Abnormal laboratory values were determined on the basis of established reference limits (data on file, Eli Lilly and Company).

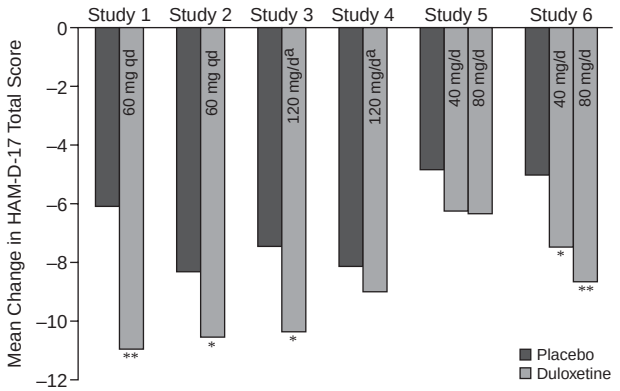
Efficacy results presented throughout this article are from the MMRM analyses unless otherwise noted. The term *significant* indicates statistical significance ($p \leq .05$).

RESULTS

Patient Characteristics and Disposition

In the 7 trials under study, a total of 1755 patients were randomly allocated to placebo (N = 723), duloxetine 40 mg/day (N = 314), duloxetine 60 mg q.d. (N = 251), duloxetine 80 mg/day (N = 315), or duloxetine 120 mg/day (N = 152) (see Table 1 for details). Ages of patients within the overall group (N = 1755) ranged from 18.0 to 82.9 years, with a mean of 43.6 years. A total of 85.6% of patients were of white origin, while 73.7% were female. No significant differences existed within treatment groups on any measure of baseline demographics.

Figure 1. Mean Change in HAM-D-17 Total Score From Baseline to Endpoint in the 6 Trials of Duloxetine for Major Depressive Disorder (MMRM analysis)[a]

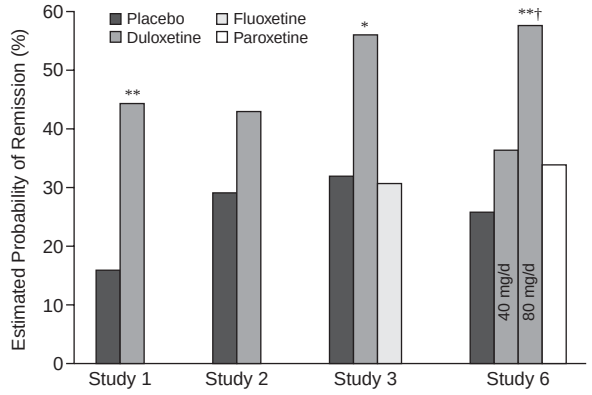


[a]Study 1 reported in Detke et al.[25]; study 2 reported in Detke et al.[26]; study 3 reported in Goldstein et al.[24]; studies 4–6 are unpublished studies, Eli Lilly and Company. The 120-mg/day dose in studies 3 and 4 was administered as a forced titration from 20 mg b.i.d. to 60 mg b.i.d.
*$p \leq .05$ vs. placebo.
**$p \leq .005$ vs. placebo.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MMRM = mixed-effects model repeated-measures.

Efficacy

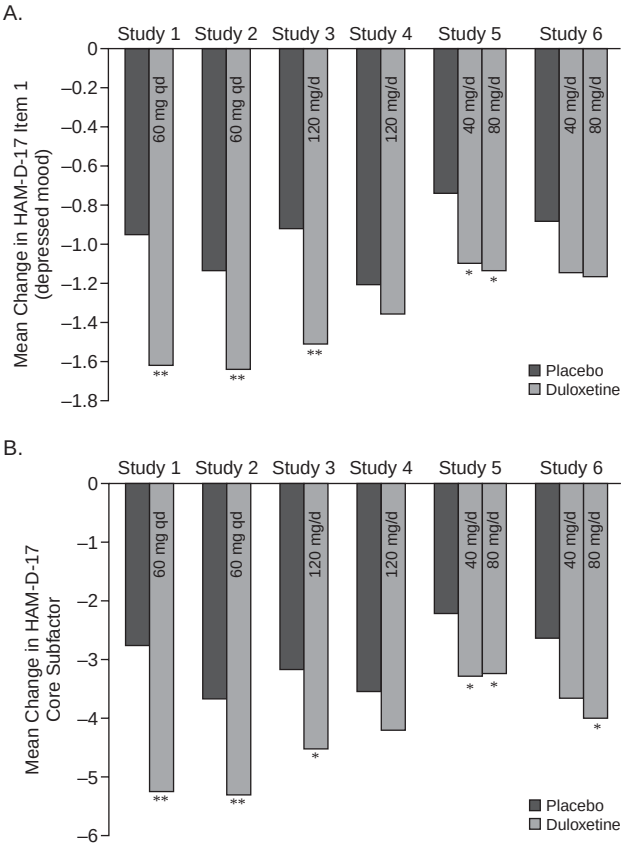
The results from a mean change analysis of the HAM-D-17 total scores for all 6 MDD studies are summarized in Figure 1; larger decreases in HAM-D-17 total score correspond to greater improvement in depressive symptoms. In both studies that included 60-mg q.d. dosing (studies 1 and 2), duloxetine exhibited significantly greater mean changes from baseline to endpoint compared with placebo on the primary outcome measure of the HAM-D-17 total score ($p < .001$ for study 1 and $p = .024$ for study 2). Duloxetine also demonstrated superiority over placebo on the HAM-D-17 total score in studies 3 and 6 at doses ranging from 40 to 120 mg/day. The magnitude of the effects seen at 40 mg/day were somewhat smaller than those observed at 60 mg q.d., while the effects at 80 mg/day and 120 mg/day were comparable to those seen with the 60-mg q.d. dose. The estimated probabilities of remission (i.e., complete symptom resolution) at endpoint for duloxetine 60 mg q.d. in studies 1 and 2 were 44% and 43%, respectively, while remission probabilities were 57% for duloxetine 80 mg/day in study 6 and 56% for duloxetine 120 mg/day in study 3 (Figure 2).

Figure 2. Estimated Probabilities of Remission (MMRM analysis) for All Randomized Patients in Those Studies Showing Superiority of Duloxetine Over Placebo on the Primary Efficacy Measure[a]



[a]Study 1 reported in Detke et al.[25]; study 2 reported in Detke et al.[26]; study 3 reported in Goldstein et al.[24]; study 6 is an unpublished study, Eli Lilly and Company. Duloxetine doses of 40 mg/day, 80 mg/day, and 120 mg/day were administered 20 mg b.i.d., 40 mg b.i.d., and 60 mg b.i.d., respectively. LOCF remission rates: study 1: placebo 15%, duloxetine 31%*; study 2: placebo 24%, duloxetine 32%; study 3: placebo 27%, duloxetine 43%, fluoxetine 30%; study 6: placebo 30%, duloxetine (40 mg/day) 35%, duloxetine (80 mg/day) 50%*, paroxetine 37%.
*p ≤ .05 vs. placebo.
**p ≤ .005 vs. placebo.
†p < .05 vs. paroxetine.
Abbreviations: LOCF = last observation carried forward, MMRM = mixed-effects model repeated-measures.

Figure 3. Mean Change in (A) HAM-D-17 Item 1 (depressed mood) and (B) HAM-D-17 Core Subfactor From Baseline to Last Visit for Duloxetine vs. Placebo (MMRM analysis)[a]



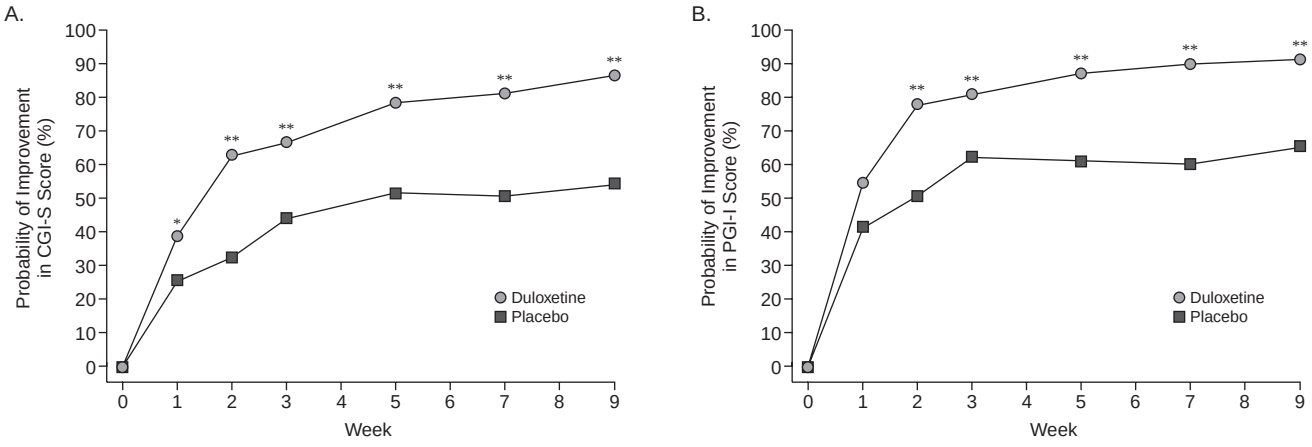
[a]Study 1 reported in Detke et al.[25]; study 2 reported in Detke et al.[26]; study 3 reported in Goldstein et al.[24]; studies 4–6 are unpublished studies, Eli Lilly and Company. The 120-mg/day dose in studies 3 and 4 was administered as a forced titration from 20 mg b.i.d. to 60 mg b.i.d.
*p ≤ .05 vs. placebo.
**p ≤ .005 vs. placebo.
Abbreviations: HAM-D-17 = 17-item Hamilton Rating Scale for Depression, MMRM = mixed-effects model repeated-measures.

Of the 5 assessed subfactors of the HAM-D-17 (anxiety, core, retardation, Maier, and sleep), duloxetine (60 mg q.d.) exhibited significantly greater improvement than placebo in all 5 subfactors in study 1 and in 3 of the subfactors in study 2. Comparison of the 6 studies using measures of core emotional symptoms of depression, i.e., HAM-D-17 item 1 (depressed mood) and the HAM-D-17 core factor (comprising items 1, 2, 3, 7, and 8; Figure 3), provided further evidence for the efficacy of duloxetine at 60 mg q.d. Significantly greater improvement for duloxetine-treated patients over placebo was also demonstrated on the CGI-S scale in study 1 and on the PGI-I scale in studies 1 and 2. As was seen with the HAM-D-17 total score, duloxetine doses of 80 mg/day and 120 mg/day also exhibited significant differences from placebo on these scales. Duloxetine also demonstrated significantly greater improvement than placebo on the HAM-D-17 anxiety/somatization subscale in studies 1 (60 mg q.d.), 3 (120 mg/day), 5 (80 mg/day), and 6 (80 mg/day).

In many of the assessed efficacy measures, duloxetine (60 mg q.d.) demonstrated significant differences from placebo as early as week 1 of treatment. For example, in study 1 the estimated probabilities of improvement for duloxetine-treated patients at weeks 1, 2, and 9 on the CGI-S scale were 38.8%, 62.8%, and 86.4%, respectively ($p < .05$ in all cases; Figure 4). The corresponding percentages based on the PGI-I scale were 54.8%, 78.1%, and 91.1% at weeks 1, 2, and 9, respectively ($p = .063$ at week 1; $p \leq .005$ for weeks 2 and 9; Figure 4).

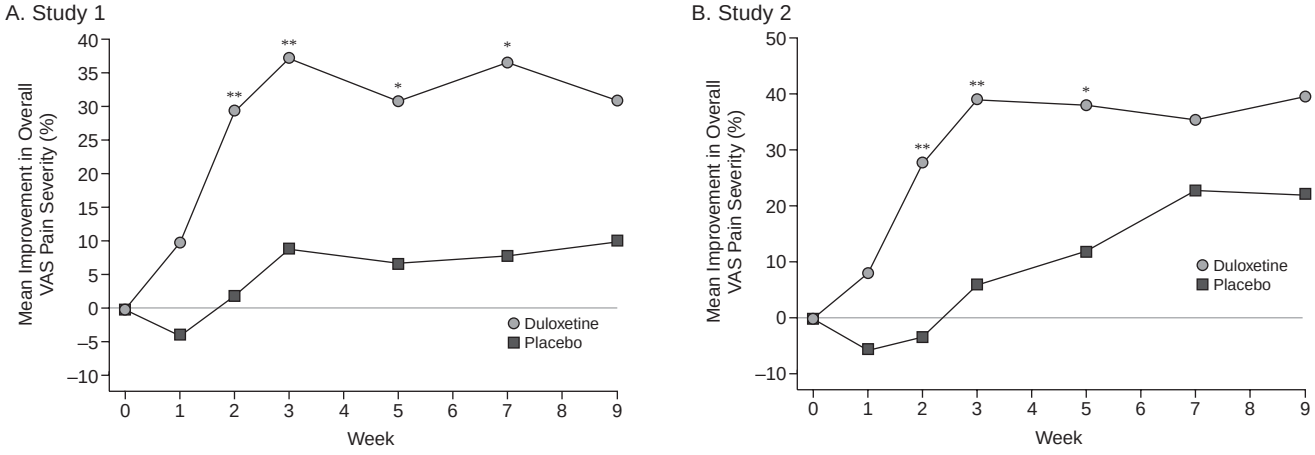
In study 1 (duloxetine 60 mg q.d.), statistically significant differences between duloxetine- and placebo-treated patients were observed in the following painful physical symptoms, as measured by VAS: overall pain, back pain, shoulder pain, pain while awake, and interference with daily activities. In the other study that included 60-mg q.d. dosing (study 2), similar results were observed for overall pain and back pain. Once again, significant improvements over placebo in some of these measures (e.g., back pain) were observed as early as week 1 of treatment (overall pain data from studies 1 and 2 are presented in Figure 5). Mean changes in pain outcomes typically cor-

Figure 4. Estimated Probability of Patients' Demonstrating at Least a 1-Point Improvement in (A) CGI-S Score and (B) PGI-I Score in Study 1[a]



[a]Data from Detke et al.[25]
*p ≤ .05 vs. placebo.
**p ≤ .005 vs. placebo.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PGI-I = Patient Global Impression of Improvement.

Figure 5. Mean Percentage Improvement in Overall Visual Analogue Scale (VAS) Pain Severity Score in (A) Study 1 and (B) Study 2[a]



[a]Study 1 reported in Detke et al.[25]; study 2 reported in Detke et al.[26]
*p ≤ .05 vs. placebo.
**p ≤ .005 vs. placebo.

responded to reductions in patient-rated pain severity of 25% to 50%, relative to baseline severity. In contrast, placebo-treated patients reported improvements in pain severity that were generally less than 20%. Notably, path analyses of data from studies 1 and 2 revealed that for most VAS pain measures, between 30% and 70% of the observed improvement in pain severity occurred independent of improvement in the emotional symptoms of depression.

As was observed for the depression outcomes, doses other than 60 mg q.d. also demonstrated significant advantages over placebo on many physical symptom measures. But again, doses greater than 60 mg q.d. did not appear to offer substantial advantages over the 60-mg q.d. dose, while the responses in pain outcomes at 40 mg/day were of smaller magnitude than at 60 mg q.d.

Results from subgroup analyses of studies 1 and 2 of HAM-D-17 total score showed that the efficacy of duloxetine did not differ significantly by age group, gender, or racial origin (white or non-white).

Safety

For all safety analyses, data were pooled from the 6 double-blind, placebo-controlled depression studies

Table 2. Treatment-Emergent Adverse Events From All Placebo-Controlled Studies of Duloxetine Treatment[a]

	Placebo (N = 723)		Duloxetine[c] (N = 1032)	
Adverse Event[b]	N	%	N	%
Nausea	50	6.9	225	21.8
Dry mouth	47	6.5	166	16.1
Fatigue	33	4.6	114	11.0
Insomnia	41	5.7	113	10.9
Dizziness	38	5.3	110	10.7
Constipation	27	3.7	109	10.6
Diarrhea	45	6.2	92	8.9
Somnolence	21	2.9	80	7.8
Decreased appetite	15	2.1	67	6.5
Increased sweating	11	1.5	56	5.4

[a]Includes data from studies 1–7. Study 1 reported in Detke et al.[25]; study 2 reported in Detke et al.[26]; study 3 reported in Goldstein et al.[24]; study 7 reported in Norton et al.[27]; studies 4–6 are unpublished studies, Eli Lilly and Company.
[b]Adverse events reported by 5.0% or more of duloxetine-treated patients. Duloxetine dose range, 40 mg/day to 120 mg/day.
[c]All p values for duloxetine < .001 compared with placebo, except for diarrhea (p = .046).

(studies 1–6) and from the duloxetine 40 mg/day, 80 mg/day, and placebo arms of study 7 (an SUI study).

The incidence of discontinuation due to adverse events was significantly greater for duloxetine compared with placebo (14.6% vs. 5.0%, respectively; p < .001). Adverse events for which the discontinuation rate in duloxetine-treated patients was significantly greater than the rate seen for placebo were nausea (2.4% vs. 0.3%, respectively; p < .001) and dizziness (1.1% vs. 0.1%; p = .019). The incidence of serious adverse events (e.g., those involving hospitalization or life-threatening experience) did not differ significantly between duloxetine and placebo (duloxetine 0.8% vs. placebo 1.0%, p = .793), and no event was reported with a frequency greater than 0.1%. In active comparator–controlled studies, the rates of discontinuation due to adverse events did not differ significantly between duloxetine and fluoxetine (9.9% vs. 5.7%, p = .440) or between duloxetine and paroxetine (13.6% vs. 10.2%, p = .329).

Treatment-emergent adverse events reported by at least 5% of duloxetine-treated patients are presented in Table 2. Nausea was the most frequently reported adverse event (21.8% vs. 6.9% for placebo). Approximately 70% of these cases were first reported within 2 days of initiating duloxetine dosing, and 92% were rated as mild or moderate in severity. The median duration of nausea for duloxetine-treated patients was 5 days, and after the first week of treatment the incidence of new cases of nausea was essentially equal for the duloxetine and placebo groups. In studies that compared duloxetine with fluoxetine (studies 3 and 4), the incidence of nausea was nearly identical (duloxetine 17.1% vs. fluoxetine 15.7%, p = .849). In studies that had paroxetine as the active comparator (studies 5 and 6), the incidence of nausea was again not significantly different across treatment groups (duloxetine 21.0% vs. paroxetine 15.3%, p = .128). This comparison was noteworthy in that fluoxetine- and paroxetine-treated patients were administered 20 mg q.d., which is at the lower end of their respective labeled dose ranges, whereas duloxetine-treated patients were administered doses that spanned the anticipated labeled dose range (40- to 120-mg total daily dose). Adverse events most frequently reported upon abrupt cessation of duloxetine therapy were dizziness (9.9%), nausea (4.7%), and headache (4.3%).

The mean baseline-to-endpoint change in supine blood pressure for duloxetine-treated patients was approximately 1.5 mm Hg and did not increase markedly with dose. The incidence of treatment-emergent elevated systolic and diastolic blood pressure at endpoint for duloxetine-treated patients compared with placebo-treated patients was 6.9% vs. 3.3% (p = .003) for systolic pressure and 4.4% vs. 2.3% (p = .027) for diastolic pressure, respectively. Differences between duloxetine and placebo treatment groups in the incidence of sustained blood pressure elevations (at least 3 consecutive visits) were not significant (sustained systolic blood pressure: duloxetine 0.5% vs. placebo 0.2%, p = .395; sustained diastolic pressure: duloxetine 0.3% vs. placebo 0.2%, p = 1.00; either systolic or diastolic pressure: duloxetine 0.7% vs. placebo 0.4%, p = .706). Duloxetine did not prolong QTc or other cardiac intervals; the incidences of abnormal increases in QTc were 4.2% and 5.3% for duloxetine- and placebo-treated patients, respectively.

Placebo-treated patients exhibited a mean increase in weight of 0.6 lb (0.3 kg) during the acute therapy phases (8–12 weeks), while those patients receiving duloxetine showed a mean decrease in weight of 1.2 lb (0.5 kg).

No significant differences between duloxetine and placebo groups were observed for mean change from baseline to endpoint on the solicited ASEX total scores. The only significant difference on mean change from baseline to endpoint in ASEX individual items was noted for the response to a question concerning ease of orgasm, for which the mean change from baseline to endpoint was greater (i.e., worsening) for duloxetine-treated patients (0.33 for duloxetine vs. –0.02 for placebo, p = .001). Analysis by gender indicated that the significant difference was due to a difference in the responses of male patients; data from female patients showed no significant differences between treatment groups for any questions.

The incidences of suicidal or self-injurious ideation were 0.2% and 0.1% for duloxetine-treated patients compared with 0.3% and 0.0% for placebo-treated patients (p = 1.00 for both events). Mean improvements on HAM-D-17 item 3 (suicide) were significantly greater for duloxetine-treated patients than for those receiving placebo in 4 of the 6 trials. In addition, both groups of duloxetine-treated patients (40 mg/day and 80 mg/day) demonstrated significantly greater mean improvement on HAM-D-17 item 3 than paroxetine-treated patients in study 6.

No significant differences between duloxetine and placebo were noted in the incidence of treatment-emergent abnormal laboratory values at endpoint. Although significant mean changes from baseline were seen for some analytes, these changes were small and were not considered to be clinically relevant due to the small number of cases outside normal limits.

DISCUSSION

Substantial improvement in the core symptoms of MDD is an important foundation for the demonstration of efficacy in the treatment of this condition. Duloxetine 60 mg q.d., together with other studied doses from 40 mg/day to 120 mg/day, demonstrated efficacy in treating the core symptoms of depression, as shown by a significant reduction in HAM-D-17 total score and HAM-D-17 subfactors. Duloxetine 60 mg q.d. also produced significant change in clinician- and patient-rated assessments of global improvement, again as early as week 1 of treatment. These results establish the rapid and sustained efficacy of duloxetine in treating the core emotional symptoms of depression.

However, MDD is a condition characterized not only by emotional symptoms but also by a range of physical symptoms, which often include aches and pains as an associated element. Together, this range of symptoms can lead to impairment of daily activities and a reduction in many patients' perceptions of overall quality of life.[42] Clinical presentation of depression with physical symptoms is frequent, especially in nonpsychiatric health care settings, the environment in which most diagnosis and care of patients with MDD occurs. Among unexplained symptoms, those characterized as painful bodily distress (including diffuse musculoskeletal pain, back pain, headache, and chest pain) are usually the most common.[8] Given its pharmacologic profile as a dual-reuptake inhibitor of both 5-HT and NE, it was hypothesized that duloxetine may produce a beneficial impact on both the core emotional symptoms of depression and also the associated painful physical symptoms.

Patients in the MDD studies described here were not screened specifically for a predefined severity threshold of painful symptoms, and the studies were not specifically powered to assess pain outcomes. It is reasonable to postulate that improvement in core emotional symptoms of depression would lead to some improvement in the associated physical symptoms. Indeed, duloxetine (60 mg q.d.) yielded improvement in both the emotional and physical symptoms associated with depression after 1 week of therapy. In addition, path analyses demonstrated that a substantial proportion (30%–70%) of the improvement in pain measures was independent of the improvement in depression. Given that the proposed mechanism for improvement in painful physical symptoms requires dual-reuptake inhibition for significant effect, the improvement of painful symptoms independent of improvement in emotional symptoms supports the hypothesis that the dual-reuptake inhibition of duloxetine is present at the recommended starting dose. The ability to address both emotional and physical symptom domains may in turn be responsible for the relatively high probabilities of remission (complete symptom resolution) observed in the 4 positive MDD studies, ranging from 43% in study 2 to 57% in study 6 (duloxetine 80 mg/day).

Since antidepressant medications are often taken chronically, the nature and severity of treatment-emergent adverse events play an important role in determining a patient's compliance with dosing instructions and his or her decision to discontinue treatment. In the 7 studies described here, the overall discontinuation rate due to adverse events in duloxetine-treated patients was 14.6%. This rate is comparable to those reported for SSRIs (14.9%) and TCAs (19.0%) in a meta-analysis of discontinuation rates in depression trials.[43] In addition, discontinuation rates observed for duloxetine-treated patients were not significantly different from those of the active comparators fluoxetine (studies 3 and 4) and paroxetine (studies 5 and 6) in head-to-head studies.

Treatment-emergent adverse events reported most frequently by duloxetine-treated patients were similar to those observed for SSRI antidepressants and include nausea, dry mouth, fatigue, and insomnia. The rate of treatment-emergent nausea (21.8%) is comparable to the rates reported for sertraline (21%–30%), paroxetine (15%–36%), and venlafaxine (31%–58%).[44]

In these studies, duloxetine had no significant effect on the incidence of hypertension and produced no clinically significant differences on other cardiovascular measures (e.g., no prolongation of QTc interval). Duloxetine did, however, produce a statistically significant, but clinically unremarkable, increase in heart rate of about 2 b.p.m. relative to placebo. This small change in heart rate may actually be a sensitive peripheral sign of NE enhancement as a result of duloxetine treatment.

Mania and suicide are additional areas of concern in the treatment of MDD in the outpatient setting. Patients with bipolar disorder were excluded from all studies of duloxetine. The number of duloxetine-treated patients who reported treatment-emergent mania in these placebo-controlled studies was zero. No patients from these placebo-controlled studies attempted suicide; the occurrence rates of suicidal or self-injurious ideation were 0.2% and 0.1% for duloxetine-treated patients and 0.3% and 0% for placebo-treated patients, respectively.

Duloxetine studies included once- and twice-daily dosing regimens in order to fully explore the range of potential therapeutic doses for major depressive disorder. In order to establish a dose recommendation, the relative tolerability and efficacy of duloxetine doses from 40 mg/day

to 120 mg/day were assessed. With respect to efficacy, it has been noted that 2 identical and independent studies (studies 1 and 2) each established the superiority of a 60-mg q.d. duloxetine dose over placebo using the primary efficacy measure. Analyses of mean change in both HAM-D-17 item 1 (depressed mood) and the HAM-D-17 core subfactor also revealed in each case that duloxetine 60 mg q.d. appeared to be the most efficacious dosing regimen. Given that different duloxetine doses were studied in 3 separate protocols, direct statistical evaluation of dose-response across the different protocols was not considered appropriate. Discontinuation rates due to adverse events were, however, somewhat higher at 80 mg/day than at a once-daily dose of 60 mg, suggesting that duloxetine 60 mg q.d. provides an optimal combination of efficacy and tolerability.

In addition, duloxetine doses of 60 mg q.d. and 80 mg/day (administered 40 mg b.i.d.) demonstrated superiority over placebo on most other secondary measures (HAM-D-17 subfactors, PGI-I, CGI-S), while at 40 mg/day (20 mg b.i.d.) duloxetine showed statistically significant separation from placebo on fewer secondary efficacy measures. Effect size calculations for HAM-D-17 total score and remission rate also suggested that duloxetine 60 mg q.d. was somewhat more efficacious than duloxetine 40 mg/day, while the efficacy of duloxetine 60 mg q.d. and 80 mg/day doses was comparable. Based on the consideration that once-daily dosing is advantageous, especially with regard to ease of use and associated patient compliance, duloxetine 60 mg q.d. was the lowest dose providing consistent efficacy while also being safe and well tolerated.

CONCLUSION

Duloxetine has been examined in clinical studies of patients with MDD in doses up to 120 mg/day. These studies have shown duloxetine to be effective in the treatment of both the emotional and physical symptoms of depression, demonstrating rapid and sustained efficacy within both of these symptom domains. In addition, duloxetine has been shown to possess a safety profile similar to that of available SSRI medications.

The ability of duloxetine to address this spectrum of depressive symptoms may in turn be responsible for the relatively high probabilities of remission (i.e., complete symptom resolution) observed in these trials. However, additional studies will be required to further define the extent of the efficacy of duloxetine within each of these symptom domains, and to investigate how improvements in each area may, individually or in combination, influence remission rates and other treatment outcomes.

The results suggest that the lowest dose associated with substantial and consistent efficacy, while also being safe and well tolerated, is 60 mg once daily. If clinically indicated, dose adjustments to a maximum of 120 mg/day (in divided doses) appear to be safe on the basis of assessment of the results of these controlled trials.

Drug names: clonidine (Catapres and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor), zolpidem (Ambien).

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