Duloxetine, 60 mg Once Daily, for Major Depressive Disorder: A Randomized Double-Blind Placebo-Controlled Trial

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Background: Despite treatment advances, major depressive disorder (MDD) is still a significant cause of morbidity and mortality. Current therapies frequently fall short of providing full remission. In addition, physical symptoms are commonly seen in MDD patients, increasing overall morbidity and health care utilization. Duloxetine hydrochloride, a dual reuptake inhibitor of serotonin and norepinephrine, was evaluated for efficacy and tolerability/safety in the treatment of MDD and associated physical symptoms.

Method: In this multicenter, double-blind, parallel-group study, adult patients with DSM-IV MDD were randomly assigned to receive placebo (N = 122) or duloxetine (60 mg/day, N = 123) for 9 weeks. The primary efficacy measure was the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score. Painful physical symptoms were assessed using visual analog scales, and global illness and quality of life were evaluated using the Clinical Global Impressions-Severity scale, the Patient Global Impressions-Improvement scale, and the Quality of Life in Depression Scale. Safety and tolerability were determined by monitoring discontinuation rates, adverse events, vital signs, and laboratory results.

Results: Duloxetine was significantly superior to placebo (p < .001) in reducing HAM-D-17 total scores, starting at week 2. The estimated probability of remission for duloxetine-treated patients (44%) was almost 3 times that of placebo patients (16%). Duloxetine significantly reduced painful physical symptoms in comparison with placebo. Discontinuation due to adverse events for duloxetine-treated patients (13.8%) compared favorably with the rates reported for SSRIs in other studies. Nausea, dry mouth, and somnolence were the most common adverse events; no significant incidence of hypertension was seen.

Conclusion: Duloxetine, 60 mg/day, is a well-tolerated and effective treatment for MDD that reduces painful physical symptoms. These findings suggest that duloxetine may be a first-line treatment for patients with MDD and associated painful physical symptoms.

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Major depressive disorder (MDD) continues to be a considerable problem, both for the clinician and at the public health level. It is currently the fourth leading cause of disease or disability worldwide, and it is projected to rise to second by the year 2020.[1] Unfortunately, many current therapies for depression provide remission in only approximately one third of cases in controlled trials.[2] A substantial body of literature and clinical experience support the notion that enhancing both serotonergic and noradrenergic neurotransmission simultaneously may provide greater efficacy in depression treatment. For example, clomipramine, a tricyclic antidepressant (TCA) that is relatively nonselective, produced significantly greater symptom reduction than the selective serotonin reuptake inhibitors (SSRIs) paroxetine and citalopram.[3,4] Likewise, combining an SSRI such as fluoxetine and a selective norepinephrine reuptake inhibitor (NRI) such as desipramine produces greater efficacy than desipramine alone.[5] And finally, venlafaxine, an antidepressant with dual serotonin (5-HT) and norepinephrine (NE) reuptake inhibition, although substantially more of the former than the latter, has been shown to produce greater remission rates than SSRIs.[2]

Duloxetine hydrochloride demonstrates higher affinity for both 5-HT and NE reuptake transporters, and greater balance in its affinity for 5-HT and NE transporters, than does venlafaxine in the 5 different preparations in which both have been studied.[6] Because of this potent and balanced dual reuptake inhibition of both 5-HT and NE,

duloxetine may produce clinically significant inhibition of both 5-HT and NE reuptake in most patients starting at 60 mg/day (reference 7 and data on file, Eli Lilly and Co., Indianapolis, Ind.). Duloxetine may therefore produce dual reuptake inhibition from a starting dose for most patients, unlike venlafaxine (e.g., Harvey et al.[8]). Such immediate dual reuptake means that duloxetine may not require titration for most patients. If the advantages of enhancing multiple monoamines are present from a starting dose for most patients taking duloxetine, there is some potential for more rapid efficacy.

There is reason to believe that balanced enhancement of 5-HT and NE may provide another benefit as well: relief of painful physical symptoms. Neural pathways that have origins in the cerebral cortex and limbic system and descend through the brainstem and spinal cord provide inhibitory modulation of pain signals via release of 5-HT and NE.[9–13] This neuroanatomy is consistent with the large literature (e.g., Collins et al.,[14] Lynch,[15] Magni,[16] Sindrup and Jensen[17]) on the use of TCAs in the treatment of chronic pain. In fact, there is evidence that *dual* 5-HT/NE reuptake inhibition specifically is more effective, as certain TCAs appear to have greater analgesic efficacy than SSRIs.[15,17] This is consistent with the widespread clinical use of the relatively balanced (5-HT vs. NE) reuptake inhibitor amitriptyline in the treatment of chronic pain conditions. However, as Sindrup and Jensen[17(p389)] note, "Tricyclic antidepressants . . . appear to be the most effective treatment for neuropathic pain, but some of the other treatments may be important due to their better tolerability." Duloxetine also holds some promise for greater tolerability, as it does not bind appreciably to muscarinic, cholinergic, and other receptors thought to mediate many TCA side effects.[6] In addition, duloxetine reduces chronic pain in several animal models, in a manner similar to amitriptyline but with greater potency where the 2 have been compared.[18]

Physical symptoms, in fact, may be more prevalent in depression than is widely recognized and may comprise part of a broader cluster of symptoms that constitute depression. Jackson et al.[19] have shown that having 5 or more physical symptoms is an independent predictor of MDD in medical outpatients, with an odds ratio of 4.0. This increasing awareness of the role of physical symptoms in MDD has now been formally recognized in DSM-IV's Text Revision, which describes associated features of major depressive episodes, including " . . . excessive worry over physical health, and complaints of pain (e.g., headaches or joint, abdominal, or other pains)."[20(p352)] In addition to their prevalence, physical symptoms predict greater severity of depression. Painful physical symptoms such as back pain, musculoskeletal complaints, and chest pain have been shown to predict higher scores on depression scales.[21] The widespread prevalence of painful physical symptoms in depression and the increase in severity of

depression such symptoms induce would seem to make a medication that treats all of these aspects of MDD more useful than those that would not.

In previous double-blind, placebo-controlled studies, duloxetine at an 80-mg/day and 120-mg/day total daily dose exhibited efficacy in the treatment of MDD by separating significantly from placebo and displayed suggestions of high efficacy, with estimated probabilities of remission in those studies of 56% and 57% (reference 22 and Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted). In the 80-mg/day study, duloxetine was also assessed for its effect on painful physical symptoms, and it significantly reduced them (Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted). But in both of these trials, duloxetine was administered in divided doses (i.e., 40 mg b.i.d., 60 mg b.i.d.), and we were interested in whether duloxetine might be effective if dosed once daily. Although duloxetine has a mean plasma half-life of approximately 12 hours,[23] medications that penetrate the blood-brain barrier may have much longer half-lives in the CNS than in plasma (see, e.g., Tsuneizumi et al.[24]) and therefore maintain therapeutic CNS levels after plasma levels have decreased.[25] In fact, a recent meta-analysis of clinical data revealed results consistent with this, showing that once-daily dosing of antidepressants was equal in effectiveness to multiple doses per day, even for agents with short half-lives.[26] In addition, it is well-recognized that simpler dosing regimens improve patient compliance,[27] so determining if once-daily dosing is effective for a new medication is important for optimizing patient care. Thus, the present study was designed to compare a fixed once-daily dose (60 mg/day) of duloxetine with placebo in the treatment of MDD and associated painful physical symptoms.

METHOD

Selection of Patients

All patients provided written informed consent prior to any study procedures, in accordance with the Declaration of Helsinki. All patients met diagnostic criteria for MDD defined in the DSM-IV. The diagnosis was confirmed by the Mini International Neuropsychiatric Interview (MINI),[28] a standardized diagnostic interview based on DSM-IV criteria. Baseline disease severity was defined by patients' scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17)[29,30] and the Clinical Global Impressions-Severity (CGI-S) scale.[31] All patients studied scored ≥ 15 on the HAM-D-17 and ≥ 4 on the CGI-S, indicating at least moderate illness, at the screening and second study visits. Study participants were men and women at least 18 years of age. Patients were excluded for the following reasons: current 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 antidepressant therapy or treatment-resistant depression, serious medical illness, initiating or stopping psychotherapy within 6 weeks prior to enrollment or initiating psychotherapy at any time during the study, a history of substance abuse or dependence within a year of study entry or a positive urine drug screen.

Study Design

This was a randomized, double-blind, parallel-group, placebo-controlled study conducted at 18 centers in the United States. The study design incorporated double-blind, variable-duration placebo lead-in and lead-out periods to blind patients and investigators to the start and end of active therapy. Qualified patients were randomly assigned (1:1 ratio) to placebo or duloxetine, 60 mg/day. The double-blind treatment period lasted 9 weeks. Study drug consisted of 3 capsules (either placebo or 20 mg of duloxetine in each capsule) taken once daily in the morning. If necessary, the dose could be reduced to 2 capsules (duloxetine, 40 mg/day, or 2 capsules of placebo), but had to be escalated back to 3 capsules after 3 weeks on study drug and remain at the 3-capsule level for the majority of the study. Concomitant medications with primarily central nervous system activity were not allowed, with the exception of chloral hydrate (up to 1000 mg) or zolpidem (up to 10 mg) for insomnia on no more than 6 nights during the study. Prescription pain medications were not allowed. Antihypertensive medications were not allowed unless the patient had been on a stable dose for at least 3 months.

Efficacy Measures

The primary efficacy assessment was the HAM-D-17 total score, recorded at every study visit. The HAM-D was administered only by site personnel who underwent training on the use of the instrument and met predetermined criteria for interviewing skills and HAM-D scoring, which were evaluated during rater training sessions at the start-up meeting. Secondary measures recorded at every visit included the physician-assessed CGI-S and visual analog scales for pain (VAS).[32] The Patient Global Impressions-Improvement (PGI-I) scale[31] was also a secondary efficacy measure collected at every study visit after the first week. In addition, the Quality of Life in Depression Scale (QLDS)[33] was collected at baseline and after 9 weeks of treatment.

Safety Assessments

Safety measures recorded at every visit included spontaneously reported adverse events, drug dosage, concomitant medications, weight, supine blood pressure, and heart rate. Blood for chemistry and hematology laboratory assay was collected at screening, after 5 and 9 weeks, and at the end of the placebo lead-out period.

Statistical Methods

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 post-baseline assessment were included in the efficacy analysis. The study was designed to have 80% power to detect a difference of 2.73 points on the HAM-D-17 total score, assuming a standard deviation of 7.0 and a 2-sided significance level of .05. This set the sample size at N = 240. The estimated treatment group difference was derived from a linear interpolation between previous studies conducted at lower doses and anticipated treatment group differences for studies that were ongoing at higher doses.

The protocol-specified primary efficacy analysis used a likelihood-based mixed-effects model repeated-measures (MMRM) analysis on all continuous efficacy measures except the QLDS, which was collected only at 2 times. The model included the fixed categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, as well as the continuous fixed covariates of baseline and baseline-by-visit interaction. A more traditional last-observation-carried-forward (LOCF) analysis was also conducted on the change from baseline to endpoint for all continuous efficacy measures. This model included the fixed categorical effects of treatment, investigator, and treatment-by-investigator interaction, as well as the continuous fixed covariate of baseline.

Response ($\geq$ 50% reduction in HAM-D-17 total score from baseline) and remission (HAM-D-17 $\leq$ 7) probabilities at the last week of the acute phase were estimated using a categorical MMRM approach similar to that discussed by Leon.[34] The model structure for this categorical analysis was similar to the one used for the continuous variables, with the addition of a probit link function and a binomial error distribution. Response and remission rates at endpoint were also calculated using the LOCF approach, for comparative purposes.

The MMRM approach has been shown to better account for the bias caused by nonrandom missing data than the LOCF approach.[35,36] Nonrandom missing data occur in clinical trials when patients discontinue prematurely, because of adverse events or lack of efficacy, for example. If a patient discontinues early from a trial, the LOCF approach assumes that the patient's condition would not have changed had they stayed in the trial. In contrast, MMRM uses the data available up to the point of a patient's discontinuation, in combination with the data from other patients in the same treatment group who continued, in order to estimate the magnitudes of improvement. Mallinckrodt et al.[35,36] compared MMRM and LOCF in 40 clinical trial settings, including 20 settings patterned specifically after depression trials. The MMRM method consistently provided better protection against type I *and* type II errors and yielded more accurate estimates of treatment effects than LOCF.

Table 1. Baseline Patient Demographics and Psychiatric History[a]

Characteristic	Placebo (N = 122)	Duloxetine 60 mg qd (N = 123)	Overall p Value
Female, N (%)	83 (68.0)	80 (65.0)	.685
Age, mean (SD), y	42.34 (12.58)	42.44 (13.74)	.936
Weight, mean (SD), kg	83.45 (22.81)	85.67 (23.46)	.444
Ethnicity, N (%)			.145
Caucasian	103 (84.4)	107 (87.0)	
Hispanic	12 (9.8)	9 (7.3)	
African descent	6 (4.9)	3 (2.4)	
Other	1 (0.8)	4 (3.3)	
Psychiatric profile, mean (SD)			
HAM-D-17 total	21.14 (3.72)	21.42 (4.11)	.443
CGI-S	4.31 (0.50)	4.35 (0.51)	.438
VAS for overall pain, mm	28.16 (23.21)	29.02 (25.10)	.815

[a]Abbreviations: CGI-S = Clinical Global Impressions-Severity scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, VAS = visual analog scale.

Figure 1. Effect of Placebo and Duloxetine 60 mg/day on HAM-D-17 Total Score

***p < .001 for duloxetine vs. placebo. Abbreviation: LS = least-squares.

Figure 2. Estimated Probability of Response and Remission of Placebo (N = 115) and Duloxetine (N = 121) Treatment Groups

***p < .001 for duloxetine vs. placebo.

Continuous baseline measures and continuous safety measures were evaluated using a fixed-effects (treatment, investigator) ANOVA. Categorical safety measures were analyzed using Fisher exact test. Abnormal laboratory values were determined based on established reference limits.[37] Rank-transformed laboratory analytes were analyzed using the ANOVA model.

Efficacy results presented throughout this article are from the MMRM analyses unless otherwise noted. LS mean refers to the least-squares mean, which is the mean adjusted slightly (e.g., baseline and investigative site differences). The term *significant* indicates statistical significance (p ≤ .05) and *marginal significance* is defined as .05 < p ≤ .10.
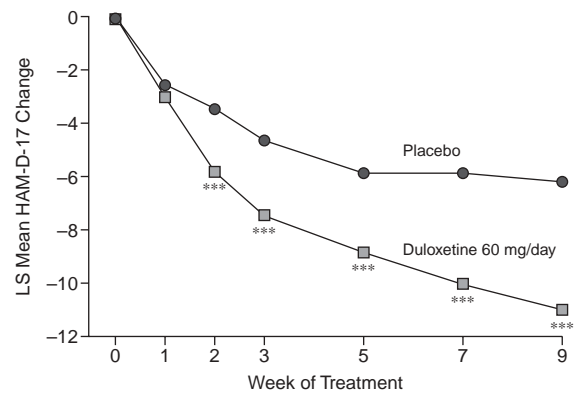
RESULTS

Patient Characteristics

A total of 341 patients entered the screening phase of the study. Of these, 96 failed to meet entry criteria or declined to participate. The remaining 245 patients were randomly assigned to placebo (N = 122) or duloxetine 60 mg/day (N = 123). All 245 of these patients were included in the safety analyses; 236 patients had at least 1 post-randomization visit and were thus included in the efficacy analyses (placebo, N = 115; duloxetine, N = 121). There were no significant differences between treatment groups in baseline demographics or psychiatric history (Table 1).
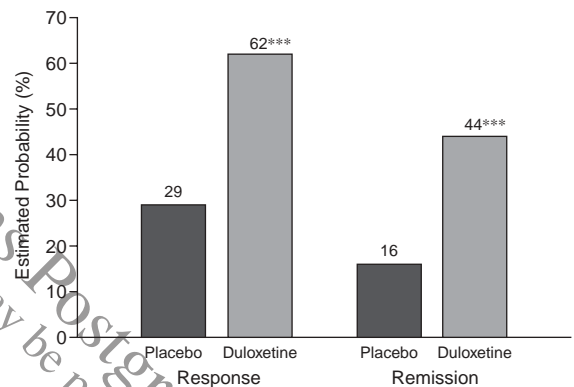
Efficacy

Results from the analysis of the primary efficacy measure, mean HAM-D-17 total score, measuring traditional symptoms of depression, are depicted in Figure 1. Patients treated with duloxetine had significantly (p < .001) greater improvement than placebo-treated patients beginning 2 weeks after randomization and continuing through

the end of treatment. Duloxetine-treated patients also had significantly greater estimated probabilities of response (p < .001) and remission (p < .001) than placebo-treated patients at 9 weeks (Figure 2). The estimated probability of remission for duloxetine patients was 44%, almost 3 times as high as the 16% seen for placebo-treated patients. The rates of response calculated using LOCF were 45% for duloxetine-treated patients and 23% for placebo-treated patients (p < .001). The rates of remission calculated using LOCF were 31% for duloxetine-treated patients and 15% for placebo-treated patients (p = .003).

The results of analyses of secondary efficacy measures are depicted in Table 2. Compared with placebo-treated patients, duloxetine-treated patients had significantly greater improvement on all 5 of the assessed subfactors of the HAM-D-17 (anxiety, core, retardation, Maier, and sleep). The duloxetine group also exhibited a significant (p = .013) reduction compared with placebo on item 13

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

Measure	Placebo (N = 115)	Duloxetine 60 mg qd (N = 121)	Overall p Value
HAM-D-17	−6.05	−10.91	<.001
HAM-D-17 subscales			
Anxiety	−1.99	−3.00	.004
Core factor	−2.76	−5.26	<.001
Retardation	−3.21	−5.96	<.001
Maier	−2.23	−4.22	<.001
Sleep	−1.03	−1.88	.001
HAM-D item 13	−0.49	−0.78	.013
CGI-S	−0.97	−1.87	<.001
PGI-I	3.27	2.48	<.001
QLDS	−4.55	−8.64	.001[b]

[a]Least-squares mean change from baseline to last observation.
Abbreviations: CGI-S = Clinical Global Impressions-Severity scale,
HAM-D-17 = 17-item Hamilton Rating Scale for Depression,
PGI-I = Patient Global Impressions-Improvement, QLDS = Quality of
Life in Depression Scale.
[b]Last-observation-carried-forward (LOCF) analysis; no mixed-effects
model repeated measures (MMRM) analysis was performed on QLDS
because it was collected only 2 times.

of the HAM-D-17 scale, "somatic symptoms (general)." Item 13 asks most specifically about painful physical symptoms, including backaches, headaches, and muscle aches. In addition, duloxetine-treated patients experienced significantly greater global improvement, as rated by both physicians (CGI-S) and patients (PGI-I), and significantly greater improvement in quality of life, as measured by the QLDS, compared with placebo-treated patients. All of the variables reported in Table 2 were also analyzed by LOCF. All were significantly more improved in the duloxetine-treated patients than the placebo-treated patients by this analysis as well, except HAM-D item 13, which was marginally significant (p = .082).

The effects of duloxetine and placebo on painful physical symptoms as measured by visual analog scales are depicted in Figure 3. Duloxetine produced significantly greater improvement than placebo in 5 of the 6 measures (overall pain, back pain, shoulder pain, interference with daily activities, and amount of time in pain while awake) at least once during acute treatment. At week 9, there was significant superiority of duloxetine over placebo for back pain (p < .001) and marginally significant superiority of duloxetine over placebo for overall pain, headaches, shoulder pain, and time in pain while awake (.05 < p values < .10). By LOCF analysis of the change from baseline to endpoint, there was significant superiority of duloxetine over placebo for back pain (p < .001) and overall pain (p = .019) and marginally significant superiority of duloxetine over placebo for shoulder pain and time in pain while awake (.05 < p values < .10).

Safety

Seventeen duloxetine-treated patients (13.8%) and 3 placebo-treated patients (2.5%) discontinued because of adverse events during the acute therapy phase. The most frequently reported reasons for discontinuation for duloxetine-treated patients were abnormal ejaculation (N = 3), rash (N = 2), migraine (N = 2), and somnolence (N = 2). Of the duloxetine-treated patients, 85.4% were able to tolerate the 60-mg/day dose without a temporary dose reduction.

The treatment-emergent adverse events reported by at least 10% of duloxetine-treated patients during the acute therapy phase are presented in Table 3. On a mild-moderate-severe rating scale, most adverse events were rated mild or moderate by clinicians. There were no significant differences in the incidence of severe adverse events when these were analyzed separately.

During the placebo lead-out phase, dizziness was reported by 11.3% of duloxetine patients and 0% of placebo patients (p = .001). This was the only adverse event that was significantly different between treatment groups during this phase.

Because of the incidence of hypertension and other cardiovascular risks associated with NE reuptake inhibitors such as TCAs and venlafaxine, heart rate and blood pressure were monitored very closely. Duloxetine-treated patients had a mean increase of 0.97 beat per minute (bpm) in heart rate, significantly (p = .03) different from placebo-treated patients, who averaged a decrease of 1.36 bpm. Duloxetine-treated patients had a mean decrease of 0.58 mm Hg in systolic blood pressure, which was a significant (p = .013) *relative increase* compared with the mean decrease of 4.31 mm Hg for placebo-treated patients. These differences, while statistically significant, are not clinically meaningful. No significant difference was observed in diastolic blood pressure. New cases of hypertension were defined as supine systolic blood pressure ≥ 140 mm Hg and at least 10 mm Hg greater than baseline, *or* supine diastolic blood pressure ≥ 90 mm Hg and at least 10 mm Hg greater than baseline, maintained for 3 consecutive visits. There was 1 case of hypertension among duloxetine-treated patients (0.8%), and none among placebo-treated patients (0.0%); this difference was not significant (p = 1.0).

Duloxetine-treated patients had a mean decrease of 0.76 kg (1.68 lb) in weight, significantly (p = .005) different from placebo-treated patients, who gained 0.21 kg (0.46 lb) on average. There were significant differences between the treatment groups in some laboratory values (uric acid and platelet count, data not shown), but these differences were small and were not clinically relevant.

DISCUSSION

In this randomized, double-blind, placebo-controlled trial, duloxetine 60 mg/day was highly effective in the treatment of MDD. These results confirm and extend earlier findings with duloxetine given twice a day at doses up to 120 mg/day (reference 22 and Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted). Patients treated

Figure 3. Effect of Placebo and Duloxetine 60 mg/day on Visual Analog Scale Measures of Pain Severity
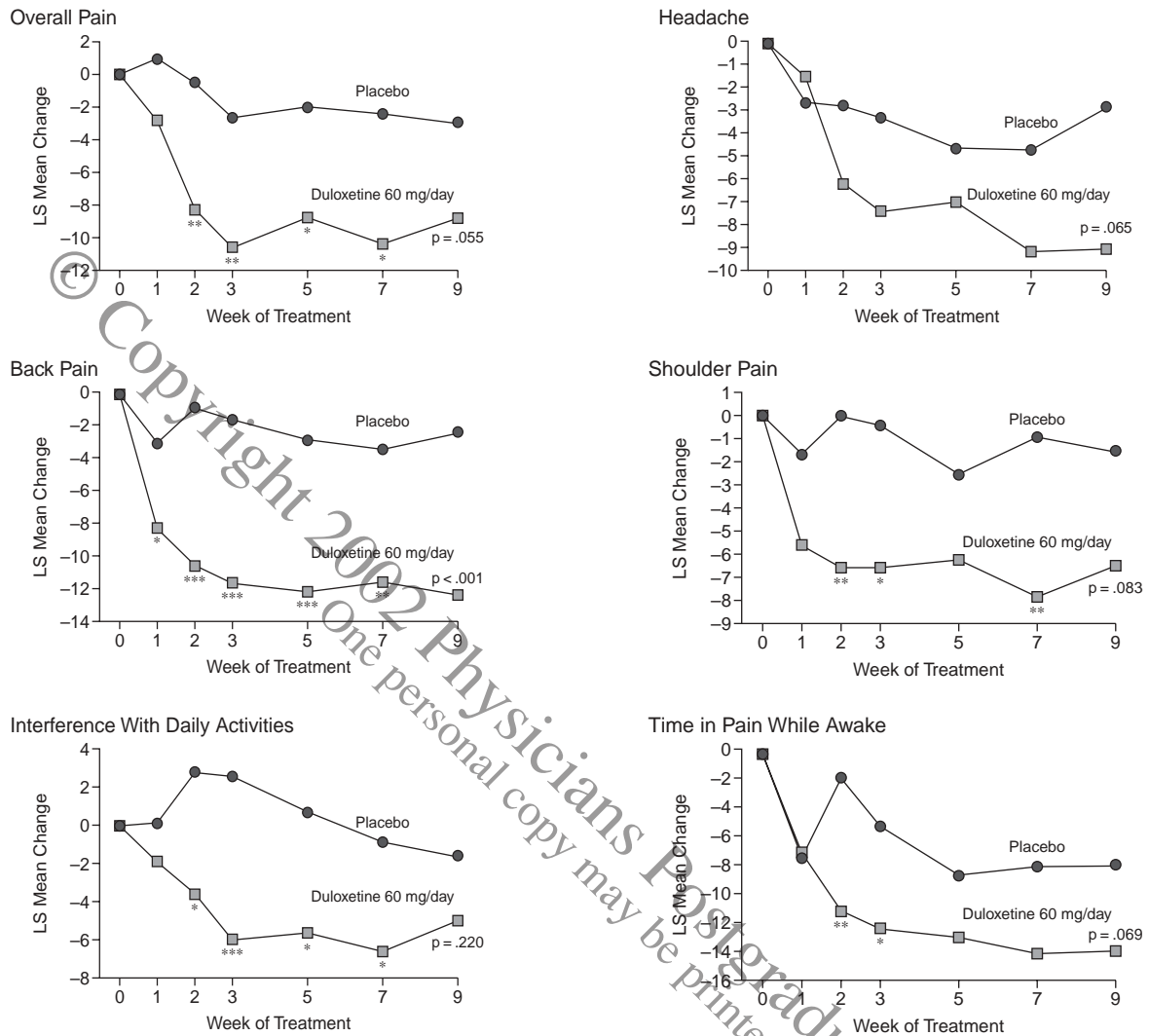
*p < .05, **p < .01, ***p < .001 for duloxetine vs. placebo. Abbreviation: LS = least-squares.

with duloxetine in this study experienced significantly greater improvement on the HAM-D-17 total score and all 5 assessed subfactors of the HAM-D-17, in addition to significantly higher estimated probabilities of response and remission. The breadth, magnitude, and speed of duloxetine's effects on depression were noteworthy: duloxetine produced significantly greater improvement on all of the traditional measures of depression assessed, produced an estimated 44% probability of remission (almost 3-fold higher than placebo), and improved the HAM-D-17 total significantly more than placebo after 2 weeks. These findings are all consistent with the hypothesis that duloxetine, a potent and balanced dual 5-HT and NE reuptake inhibitor, may produce substantial relief from depression. Thus, the present data are also consistent with the larger literature (e.g., Danish University

Antidepressant Group,[3,4] Nelson et al.,[5] Thase et al.[2]) on the benefits of antidepressants with multiple actions.

In addition to the efficacy seen on traditional measures of depressive symptomatology, duloxetine 60 mg/day produced significant improvements on several measures of painful physical symptoms compared with placebo, including those utilizing VAS scales and item 13 of the HAM-D-17. These findings also confirm a previous report (Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted). These results are all the more striking given that the patient population was not selected for pain and the study was not powered to observe differences on these measures. The baseline scores on the VAS overall pain measure were 28–29 on a 100-point scale, indicating relatively little room to see reduction. Collectively, these results on measures of painful physical symptoms are

Table 3. Treatment-Emergent Adverse Events[a]

Event	Placebo (N = 122)		Duloxetine 60 mg/day (N = 123)		
	N	%	N	%	p Value
Nausea	11	9.0	57	46.3	<.001
Dry mouth	8	6.6	34	27.6	<.001
Somnolence	6	4.9	26	21.1	<.001
Dizziness	10	8.2	25	20.3	.010
Diarrhea	8	6.6	23	18.7	.006
Insomnia	7	5.7	19	15.4	.021
Anorexia	2	1.6	16	13.0	.001
Constipation	2	1.6	16	13.0	.001
Vomiting	2	1.6	13	10.6	.006

[a]Events included in the table are those that had an incidence > 10% for duloxetine patients during the acute therapy phase and were significantly more frequently reported for duloxetine-treated than for placebo-treated patients.

consistent with the hypothesis that 5-HT and NE act as inhibitory neurotransmitters in descending pain pathways[9–13] and that therefore a potent, balanced dual reuptake inhibitor of both 5-HT and NE may be effective in reducing painful physical symptoms. They are consistent with the literature on pain reduction by other antidepressants with dual 5-HT/NE mechanisms, such as some TCAs (e.g., Magni[16]).

Duloxetine also significantly improved patients' global assessment of their depression (PGI), as well as the clinicians' global impressions (CGI), and patients' self-assessed quality of life (QLDS). These findings, too, confirm results seen in earlier studies (reference 22 and Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted). While it would be premature to draw firm conclusions from these results, it is interesting to speculate that effective treatment of traditional depressive symptomatology, coupled with effective treatment of associated physical symptoms, might produce broad improvement in well-being and quality of life.

Tolerability is also a critical feature of an antidepressant drug. Because of the need to take antidepressants chronically, and the sometimes subtle nature of the symptomatic benefits, adverse events often weigh heavily in patients' risk-benefit assessment and therefore lead to noncompliance and/or discontinuation. The single most important measure of a drug's tolerability is whether a patient will continue to take the medication. Overall, 13.8% of duloxetine-treated patients discontinued due to adverse events in this trial, a rate that compares well to 14.9% for SSRIs and 19.0% for TCAs in one meta-analysis and rates of 27%–40% for paroxetine and 11%–36% for sertraline in individual studies.[38] However, such comparisons across studies should be interpreted with caution until within-study comparisons become available to confirm or contradict them.

The most frequently reported adverse event in the present study was nausea, as it is for many other antidepressant drugs.[39] In other published studies of duloxetine,

with doses ranging up to 120 mg/day, nausea rates of 13%–25% were observed (reference 22 and Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted), suggesting that the rate seen here is not representative. Approximately 80% of patients with nausea reported it in the first week, and it subsided after a median of 7 days. Nausea was judged to be mild to moderate in virtually all cases, with only 1 (0.8%) rated as severe, and only 1 patient discontinuing treatment for this reason. Data from all placebo-controlled trials of duloxetine at doses of 40–120 mg/day reveal an overall rate of nausea of 21.8% (data on file, Lilly Research Laboratories, Indianapolis, Ind.). This compares to rates of 21%–30% for sertraline, 15%–36% for paroxetine, and 31%–58% for venlafaxine.[40]

Weight gain is another adverse effect of some antidepressants that might reduce a medication's acceptability to patients. Patients treated with duloxetine, 60 mg/day, experienced a small but significant decrease in weight compared with placebo-treated patients. This is consistent with earlier findings with duloxetine and thus appears to be consistent in the acute treatment setting (reference 22 and Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted). Long-term placebo-controlled studies would be valuable to clarify the effects of duloxetine on weight in patients treated chronically, but such studies have not yet been performed.

Perhaps the most important finding regarding safety was that there was no significant effect of duloxetine on the incidence of new cases of hypertension, nor were there any clinically significant differences on other cardiovascular measures. This, too, confirms the findings from previous duloxetine trials (reference 22 and Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted). So-called "sustained" hypertension has been reported with venlafaxine at rates of up to 13% at higher doses.[40(p3495)] This difference exists despite the fact that the definition of hypertension used in this and other duloxetine trials was *more* inclusive than that used for venlafaxine; the latter includes only diastolic hypertension, whereas the former includes both diastolic and systolic. The fact that duloxetine does not seem to induce hypertension should continue to receive further assessment in the future. This lack of clinically significant effect on blood pressure occurred while duloxetine produced a statistically significant, but clinically trivial, increase in heart rate (about 2 bpm different from placebo). Such heart rate changes may be the most sensitive peripheral sign of NE enhancement. This finding is consistent with the hypothesis that duloxetine produces dual reuptake inhibition at 60 mg/day.

In summary, the present results confirm and extend those of previous clinical trials (reference 22 and Goldstein DJ, Detke MJ, Lu Y, et al., manuscript submitted) by demonstrating that duloxetine in a once-daily dose of 60 mg is efficacious, safe, and well tolerated in the treatment of MDD and the painful physical symptoms

that are a common part of depression. Duloxetine's mechanism of action as a potent and balanced dual 5-HT and NE reuptake inhibitor is thought to underlie its high efficacy in treating traditional symptoms of depression as well as its efficacy in the treatment of painful physical symptoms. Consistent with 2 prior studies, duloxetine was well tolerated, with a low discontinuation rate and no significant safety risks. Collectively, the present results indicate that duloxetine 60 mg/day may represent a valuable new treatment for MDD. In addition, duloxetine may be the treatment of choice for patients with MDD and associated painful physical symptoms.

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

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