A Randomized, Double-Blind Study of Increasing or Maintaining Duloxetine Dose in Patients Without Remission of Major Depressive Disorder After Initial Duloxetine Therapy

Susan G. Kornstein, M.D.; David L. Dunner, M.D.; Adam L. Meyers, M.S.; Virgil G. Whitmyer, Ph.D.; Craig H. Mallinckrodt, Ph.D.; Madelaine M. Wohlreich, M.D.; Michael J. Detke, M.D.; Millie S. Hollandbeck, B.S.; and John H. Greist, M.D.

Objective: To compare efficacy of remaining on duloxetine 60 mg to increasing to 120 mg q.d. in patients without remission of major depressive disorder (MDD) after 6 weeks at 60 mg.

Method: This double-blind, parallel study was conducted in adults with MDD (DSM-IV-TR criteria). Patients initially randomly assigned to duloxetine 60 mg for 6 weeks with a 17-item Hamilton Rating Scale for Depression (HAM-D-17) score > 7 (nonremitters) were randomly reassigned to 60 mg or 120 mg duloxetine for 8 weeks. Patients with a HAM-D-17 score ≤ 7 (remitters) continued on duloxetine 60 mg. The primary objective was to compare time to remission (HAM-D-17 score ≤ 7) between rerandomized groups. Secondary objectives included evaluation of HAM-D-17 and Inventory of Depressive Symptomatology assessments and safety and tolerability evaluations in nonremitters and remitters. Patients were enrolled from November 2004 to January 2006.

Results: Nonremitters randomly reassigned to 60 mg and 120 mg achieved similar time to remission and similar improvements on efficacy measures. Remission was achieved in 30.0% and 30.5% in the 60-mg and 120-mg groups, respectively. Of the remitters, 85.5% continued to be in remission at study end. Other than a greater incidence of hyperhidrosis and chest pain in the 120-mg group, adverse events were similar between groups, as were discontinuations due to adverse events.

Conclusion: Nonremitters to 60 mg of duloxetine for 6 weeks randomly reassigned to 60 mg or 120 mg of duloxetine demonstrated continued symptom improvement in the 8-week extension. Patients randomly reassigned to 120 mg showed no advantage over those who continued on 60 mg. Duloxetine was well tolerated at both doses and had similar safety profiles.

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Corresponding author and reprints: Madelaine M. Wohlreich, M.D., Eli Lilly and Co., Lilly Corporate Center, Indianapolis, IN 46285 (e-mail: mwmd@lilly.com).

Patients with major depressive disorder (MDD) often do not fully respond to antidepressant therapy. Approximately 12% to 15% of patients are partial responders, and approximately 19% to 34% are nonresponders.[1] In such cases, clinicians and patients must decide whether the treatment regimen should be maintained, whether a higher dose is warranted, or whether switching to or augmenting with a new agent is the best choice. To that end, treatment algorithms for enhancing or predicting treatment response have been evaluated.[2–4] While considering many factors such as symptom change and tolerability to drug, clinicians commonly increase the dose as a first-line strategy when dealing with patients who have achieved minimal or partial responses to the initial antidepressant therapy or who have relapsed after initial therapy.[5,6] Quite often, a dose increase is carried out in practice without evidence-based data to suggest that it is warranted or would be efficacious.

Duloxetine, a potent dual reuptake inhibitor of serotonin and norepinephrine, at the recommended dose of 60 mg once daily (q.d.) has been shown to be efficacious for MDD.[7–11] Safety and tolerability for duloxetine doses

ranging from 60 mg to 120 mg have been demonstrated in both acute and long-term (up to 24 months) studies.[12,13] More recently, a study specifically evaluating dose escalation of duloxetine from 60 mg q.d. to 120 mg q.d. over a period of 7 weeks found that adverse events (with the exception of abdominal pain and upset stomach) and rates of discontinuation due to adverse events were not significantly greater for those titrated to 120 mg q.d. than for those who remained on 60 mg q.d.[14]

The rationale behind the present study was to compare the efficacy of duloxetine at a maintained dose of 60 mg q.d. versus an increased dose of 120 mg q.d. in patients with MDD who were nonremitters after 6 weeks of treatment with duloxetine 60 mg. An additional objective of the study was to determine if those patients who achieved remission during acute treatment remained in remission after an additional 8 weeks of treatment. Although previous studies with duloxetine have examined doses between 60 mg and 120 mg, these studies did not specifically evaluate the effectiveness of increasing the dose in patients who had not achieved remission.[14,15] A recent review article of dose-escalation studies indicates that the ideal study design would escalate doses after a minimum of 6 to 8 weeks of therapy.[16] To that end, the present extension phase study design was an adequately powered, double-blind, prospective, 8-week assessment of the effects of maintaining versus raising the dose in those patients who had an inadequate response to initial duloxetine treatment. To optimize the design, patients were treated for 6 weeks, following a 2-week placebo lead-in period, with duloxetine 60 mg q.d. After the initial therapy period, patients not achieving remission were randomly reassigned to either remain on 60 mg or escalate to 120 mg of duloxetine therapy, while those who achieved remission were maintained at the 60-mg q.d. dose.

METHOD

Study Design

This study was a randomized, parallel, double-blind, variable-expected duration, placebo lead-in study conducted in 2 phases over 16 weeks at 33 sites (psychiatric clinical settings) in the United States. Patients were enrolled in the study from November 2004 to January 2006. This article focuses on the results of the extension phase of the study; the acute phase results have been reported separately.[17,18]

The protocol for this study (F1J-US-HMDR), including the statistical analysis plan, was filed with the U.S. Food and Drug Administration prior to study initiation. The clinical trial number is NCT00191061 (clinicaltrials.gov). The study protocol was approved in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent after the procedure(s), and possible adverse events were fully explained. Patients and investigative sites were blinded to certain details of the study design. The full protocol was provided to the investigators' ethical review boards as part of the initial protocol review.

Patients meeting entry criteria were initially randomly assigned to starting doses of 30 mg q.d., 30 mg twice daily (b.i.d.), or 60 mg q.d. of duloxetine and further stratified by instructions to take the study drug with food or not within 1 hour of eating. After 1 week at the starting doses, all patients received 60 mg q.d. for 5 weeks. After acute treatment, patients who failed to achieve remission were randomly reassigned in the extension phase to double-blind duloxetine therapy for an additional 8 weeks. Specifically, at the end of the acute phase, patients with a 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score greater than 7 were randomly reassigned (1:1 ratio) to either remain at 60 mg q.d. or escalate to 120 mg q.d. of duloxetine. Patients with a HAM-D-17 total score less than or equal to 7 continued on duloxetine 60 mg q.d. Investigators and patients were blinded to the rerandomization criteria and to the timing of the rerandomization. Rerandomization occurred via an automated system that determined whether rerandomization criteria had been met based on the HAM-D-17 total score. During the extension phase, study drug decreases were not allowed. Patients requiring a dose decrease due to safety or tolerability issues were discontinued from the study. Efficacy and safety assessments including adverse event reporting and vital signs in the extension phase occurred approximately every 2 weeks, whereas laboratory safety measures were collected at the end of participation in the extension phase.

Placebo capsules and matching duloxetine capsules were utilized in a double-dummy fashion to maintain the integrity of the blind design during the study. All patients received 4 capsules of study drug to be taken orally q.d. during the 8-week extension phase.

Selection of Patients

Study participants were adult male and female outpatients at least 18 years of age. All patients met diagnostic criteria for MDD, as defined by the *Diagnostic and Statistical Manual for Mental Disorders,* Fourth Edition, Text Revision (DSM-IV-TR).[19] The diagnosis of MDD was confirmed by the Mini-International Neuropsychiatric Interview.[20] Patients were required to have a HAM-D-17 score greater than 15[21,22] at the screening and baseline study visits in the acute phase. Patients were required to have completed the acute phase to continue into the extension phase.

Patients were excluded for the following reasons: any current Axis I disorder other than MDD, dysthymia, or any anxiety disorder (obsessive-compulsive disorder excluded); any previous diagnosis of mania, bipolar disorder, or psychosis; serious suicidal risk; serious medical

illness or clinically significant laboratory abnormalities that, in the judgment of the investigator, would be likely to require intervention, hospitalization, or use of an excluded medication during the course of the study; lack of response of the current depressive episode to 2 or more adequate courses of antidepressant therapy at a clinically appropriate dose for a minimum of 4 weeks or treatment-resistant depression (defined as lack of response to 2 or more adequate courses of antidepressant therapy); a history of a lack of response at any time to an adequate trial of duloxetine (≥ 60 mg/day for ≥ 4 weeks); a current Axis II disorder that could interfere with compliance with the study protocol; a history of substance abuse or dependence within the past 6 months, excluding nicotine and caffeine; a positive urine drug screen for any substances of abuse; electroconvulsive therapy or transcranial magnetic stimulation within the past year; initiating, stopping, or changing psychotherapy after study entry; treatment with a monoamine oxidase inhibitor within 14 days prior to baseline; and treatment with fluoxetine within 30 days prior to baseline.

Concomitant medications with primarily central nervous system activity were not allowed. Chronic use of cough and cold medications containing pseudoephedrine or the sedating antihistamine diphenhydramine were not allowed. Chronic use of certain prescription medications, such as angiotensin converting enzyme inhibitors, alpha- and beta-blockers, antiarrhythmics, and calcium channel blockers, were permitted provided the patient had been on a stable dose for a minimum of 3 months prior to study enrollment. Patients were encouraged not to alter their intake of nicotine or caffeine during the course of the study. Narcotic use was allowed only upon approval of the Eli Lilly physician or designee.

Efficacy Measures

The primary objective of the study was to compare time to remission (as measured by the number of days from the end of the acute phase to the first visit in the extension phase in which the HAM-D-17 total score was ≤ 7) for patients who were nonremitters in the acute phase and subsequently randomly reassigned to either 60 mg q.d. or 120 mg q.d. in the extension phase. Only patients with a postextension phase baseline HAM-D-17 score were included in analyses. Efficacy measures included the HAM-D-17 total score,[21,22] HAM-D-17 subscales (core: items 1, 2, 3, 7, and 8; Maier: items 1, 2, 7, 8, 9, and 10; anxiety: items 10, 11, 12, 13, 15, and 17; retardation: items 1, 7, 8, and 14; sleep: items 4, 5, and 6), 30-item Inventory of Depressive Symptomatology-Clinician Rated[23] (IDS-C-30), 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated[24] (QIDS-C-16), Brief Pain Inventory-Short Form[25] (BPI-SF), visual analog scales (VAS) for pain,[26] Clinical Global Impressions-Severity of Illness (CGI-S) scale,[27] and Patient Global Impression-Improvement (PGI-I) scale.[28] Response was a priori defined as a greater than or equal to 50% reduction in the HAM-D-17 total score from the initiation of duloxetine treatment. Remission was defined as a HAM-D-17 total score less than or equal to 7.

Efficacy measures were assessed at all regularly scheduled clinic visits, except for the PGI-I, which was assessed at postbaseline visits only. Analyses included comparing the dose groups in regard to mean changes from baseline (postbaseline means for the PGI-I), both on total scores and various subscales of the measures. Patients who remitted during the acute phase and remained on 60 mg q.d. of duloxetine were analyzed in a separate analysis of mean change from baseline on total scores and various subscales of the measures.

Safety Measures

Safety measures recorded at every visit included spontaneously reported treatment-emergent adverse events (TEAEs), blood pressure, and heart rate. Blood for chemistry and hematology laboratory analyses was collected at baseline for the extension phase and after 8 weeks of treatment with duloxetine. Treatment-emergent elevated pulse was defined as greater than or equal to 100 beats per minute (bpm) and at least 10 bpm greater than baseline.

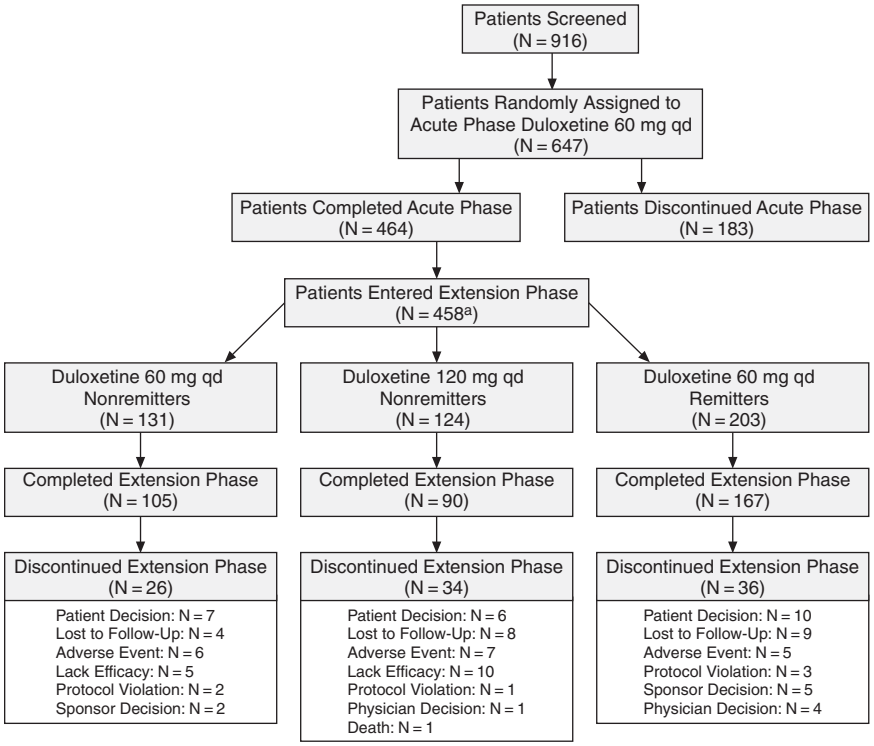
Changes in sexual function were assessed at every visit by means of the self-rated Patient Global Impression-Sexual Function (PGI-SF) scale.[28] The PGI-SF is a 4-question instrument that assesses sexual interest/desire, erection (for men) or vaginal lubrication (for women), ability to achieve orgasm, and an overall rating of sexual function. Each question is rated on a 5-point scale ranging from 1 (no impairment) to 5 (severely impaired).

Statistical Analyses

Patient demographics and baseline illness characteristics were compared by dose groups using pairwise t tests for continuous variables and Fisher exact test for categorical variables. The frequency of TEAEs and the incidence of TEAEs leading to discontinuation were compared by dose. The proportion of patients achieving response as well as those reporting improved, same, or worsened sexual function (PGI-SF) were compared by dose group. Fisher exact test was used to compare frequencies at the $\alpha = .05$ significance level.

Time to remission was analyzed using the Kaplan-Meier Product-Limit method with strata defined by treatment group. Mean changes in the HAM-D-17 total score and subscale scores, IDS-C-30 total score, QIDS-C-16 total score, VAS item scores, BPI-SF item scores, and vital signs were analyzed using a mixed-effects model repeated-measure (MMRM) approach with fixed, categorical effects of extension dose group, visit, and investigator, as well as the continuous, fixed covariate of baseline score and the 2-way interactions between extension

Figure 1. Disposition of Patients With Major Depressive Disorder Treated With Duloxetine



[a]Six patients did not have HAM-D-17 scores entered for the extension phase and were excluded from analyses of extension therapy phase data. Of 458 patients, only 441 had post–extension phase baseline HAM-D-17 scores and were included in subsequent analyses.

dose group and visit and baseline score and visit. Mean CGI-S and PGI-I scores were analyzed using a similar approach. Efficacy and vital sign analyses for acute phase remitters were analyzed using the same model but with the extension dose group term removed. In each case, the within-patient errors were modeled using an unstructured covariance structure. The Kenward-Roger approximation was used to estimate denominator degrees of freedom. Significance tests were based on least-squares means and type 3 sum of squares using a 2-sided $\alpha = .05$ (2-sided 95% confidence intervals). Mean changes from baseline in laboratory analytes were analyzed using a last-observation-carried-forward (LOCF) approach. An analysis of covariance was conducted on rank-transformed data with investigator, baseline value, and extension dose group in the model.

RESULTS

Patient Disposition

A total of 916 patients were screened, of whom 269 failed to meet entry criteria or declined to participate in the study. The remaining 647 patients were randomly assigned to 1 of 3 starting dose groups (60 mg q.d., 30 mg q.d., or 30 mg b.i.d. for the first week, then 60 mg q.d.) in the acute phase. Response rates for the acute phase ranged from 42.6% to 47.7% and remission rates from 35.9% to 42.1% among the 3 duloxetine starting dose groups.[18] A total of 464 patients completed the acute phase and 458 patients entered the extension phase, but only 441 patients had at least 1 postbaseline measurement to be included for analyses. Patients who did not achieve protocol-defined remission of a HAM-D-17 total score less than or equal to 7 (nonremitters) were randomly reassigned to either remain on 60 mg duloxetine (N = 131) or escalate to 120 mg duloxetine (N = 124). Of the patients who achieved remission (remitters) in the acute phase, 203 continued on 60 mg duloxetine in the extension phase (Figure 1).

Baseline Characteristics

The overall patient cohort for the extension phase was predominantly female (62.4%) and white (79.8%), with a mean age of 45 years. The HAM-D-17 mean total baseline score at acute phase baseline was 21.5. After rerandomization for the extension phase, the HAM-D-17 mean total baseline scores were 14.3 and 14.2 for the 60-mg and 120-mg duloxetine groups, respectively, and 3.8 for the remitters remaining on 60 mg. Extension phase

Table 1. Extension Phase Baseline Characteristics of Patients With Major Depressive Disorder Treated With Duloxetine[a]

Characteristic	Duloxetine 60-mg Nonremitters (N = 130)	Duloxetine 120-mg Nonremitters (N = 118)	Duloxetine 60-mg Remitters (N = 193)[b]
Gender, female, N (%)	69 (53.1)	82 (69.5)*	124 (64.2)
Age, mean (SD), y	47.0 (12.9)	43.8 (12.3)	43.3 (13.1)*
Age, range (minimum–maximum), y	20.7–77.9	18.6–82.7	18.9–82.2
Ethnic origin, N (%)			
White	107 (82.3)	95 (80.5)	150 (77.7)
Black	13 (10.0)	12 (10.2)	16 (8.3)
Hispanic	6 (4.6)	11 (9.3)	17 (8.8)
Other	4 (3.1)	0 (0.0)	10 (5.2)
HAM-D-17 total score, mean (SD)	14.3 (4.9)	14.2 (4.8)	3.8 (2.3)†
IDS-C-30 total score, mean (SD)	22.3 (8.9)	22.9 (9.2)	6.9 (4.5)†
QIDS-C-16 total score, mean (SD)	9.3 (3.6)	9.4 (3.7)	3.2 (2.1)†
CGI-S score, mean (SD)	3.2 (0.8)	3.3 (0.9)	1.6 (0.7)†

[a]Defined as visit 7 when patients completed the acute phase and entered the extension phase.
[b]Post–12 weeks of duloxetine at 60 mg q.d.
*$p \leq .05$ vs. 60-mg nonremitters.
†$p < .001$ vs. 60-mg and 120-mg nonremitters.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-C-30 = 30-item Inventory of Depressive Symptomatology-Clinician Rated, QIDS-C-16 = 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated.

baseline characteristics among the 3 groups (60-mg and 120-mg nonremitter and 60-mg remitter) were not statistically significantly different with the following exceptions: there were more women in the 120-mg nonremitter group than in the 60-mg nonremitter group ($p = .01$), the remitter group mean age was statistically significantly lower than that for the 60-mg nonremitter group ($p < .05$), and the total baseline scores for all efficacy measures were statistically significantly lower for the remitter group compared to both nonremitter groups ($p < .001$). Table 1 summarizes the extension phase baseline characteristics.

Efficacy

The primary outcome measure of the extension phase was time to remission. There were no differences in time to remission between the acute phase nonremitters randomly reassigned to 60-mg (median of 72 days) and 120-mg groups (median unestimable) over 8 weeks. However, of those patients who did not remit in the acute phase, remission was achieved in 30.0% and 30.5% of patients when randomly reassigned to 60 mg and 120 mg ($p = .92$), respectively. To clarify these findings, a post hoc analysis of the remission rates achieved by nonremitters in the acute phase revealed that most patients who were responders but not remitters to treatment in the acute phase achieved remission by the end of the extension phase, whereas few patients who were nonresponders in the acute phase achieved remission in the extension phase. Increasing the dose to 120 mg or maintaining the dose at 60 mg was not statistically significantly different ($p \geq .35$) regardless of acute phase response. Of the patients who achieved remission in the acute phase and continued into the extension phase, 85.5% continued to be in remission at the end of the extension phase with a mean ± SD HAM-D-17 total score of 4.09 ± 0.35. Table 2 presents data on remission and remission rates and efficacy measures.

Response to extension phase treatment, as evidenced by a 50% or greater reduction in HAM-D-17 scores, was achieved in 44.6% and 40.7% of nonremitter patients randomly reassigned to the 60-mg and 120-mg groups, respectively, and in 87.1% of 60-mg remitters. There were no differences in response rates between the 60-mg and 120-mg dose groups ($p = .46$). Of the patients who were responders but not remitters in the acute phase and randomly reassigned, 78.1% and 65.2% remained responders and 53.1% and 56.5% became remitters at extension phase endpoint taking 60 mg and 120 mg, respectively.

A summary of mean change from end of acute phase baseline for a priori–specified efficacy measures is presented in Table 2. Although statistically significant improvements were observed for nonremitters randomly reassigned to the 60-mg and 120-mg duloxetine dose groups for all efficacy measures by study endpoint, there were no statistically significant differences between the dose groups. Improvements in mean HAM-D-17 total and a priori–specified scores (core, Maier, anxiety, retardation, and sleep subscales) from the rerandomization baseline were statistically significant for both dose groups after 2 weeks into the extension phase, and improvements were sustained as evidenced by statistical significance at subsequent visits throughout the 8-week extension period. The 1 exception was the HAM-D-17 sleep subscale score, which reached statistical significance after 4 weeks of treatment in the extension phase and continued to be statistically significant at each visit for the remaining 4 weeks of treatment. Figure 2 presents

Table 2. Summary of Efficacy Measures Among Patients With Major Depressive Disorder Treated With Duloxetine

Measure	Duloxetine 60-mg Nonremitters (N = 130)	Duloxetine 120-mg Nonremitters (N = 118)	Duloxetine 60-mg Remitters (N = 193)
Remission, N (%)[a]	39 (30.0)	36 (30.5)	165 (85.5)
Acute responders	17/32 (53.1)	13/23 (56.5)	NA
Acute partial responders	10/36 (27.8)	12/37 (32.4)	NA
Acute nonresponders	12/62 (19.4)	11/58 (19.0)	NA
Response, N (%)[b]	58 (44.6)	48 (40.7)	155/178 (87.1)
Acute responders	25/32 (78.1)	15/23 (65.2)	NA
HAM-D-17 total score change, mean (SE)[c]	–3.46 (0.52)*	–3.38 (0.55)*	0.33 (0.35)
HAM-D-17 subscale score change, mean (SE)[c]			
Anxiety	–1.10 (0.21)*	–0.82 (0.22)*	0.24 (0.13)
Core	–1.37 (0.26)*	–1.63 (0.27)*	0.16 (0.17)
Maier	–1.83 (0.31)*	–1.99 (0.33)*	0.19 (0.20)
Retardation	–1.25 (0.22)*	–1.35 (0.24)*	0.05 (0.15)
Sleep	–0.54 (0.18)*	–0.47 (0.19)*	0.02 (0.11)
IDS-C-30 total score change, mean (SE)[c]	–5.03 (0.87)*	–5.77 (0.93)*	0.18 (0.56)
QIDS-C-16 total score change, mean (SE)[c]	–1.91 (0.38)*	–2.49 (0.40)*	–0.21 (0.25)
VAS overall pain score change, mean (SE)[c]	–5.51 (1.95)*	–4.37 (2.09)*	1.99 (1.61)
BPI average pain score change, mean (SE)[c]	–0.27 (0.16)	–0.10 (0.17)	0.01 (0.12)
CGI-S score, mean (SE)	2.66 (0.10)*	2.50 (0.11)*	1.54 (0.07)
PGI-I score, mean (SE)[d]	2.63 (0.11)*	2.39 (0.11)*	1.83 (0.07)*

[a]HAM-D-17 total score ≤ 7. Acute phase response types were defined as follows: full response was a ≥ 50% reduction in HAM-D-17 total score during the acute phase, partial response was a ≥ 25% but < 50% reduction in HAM-D-17 total score during the acute phase, and nonresponse was a < 25% reduction in HAM-D-17 total score during the acute phase.
[b]HAM-D-17 total score reduction ≥ 50% from acute phase baseline.
[c]Least-squares mean change score.
[d]Least-squares mean score.
*p ≤ .05 (within-group change).
Abbreviations: BPI = Brief Pain Inventory, CGI-S = Clinical Global Impressions-Severity of Illness scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IDS-C-30 = 30-item Inventory of Depressive Symptomatology-Clinician Rated, NA = not applicable, PGI-I = Patient Global Impression-Improvement, QIDS-C-16 = 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated, VAS = visual analogue scale.

HAM-D-17 total scores over the entire study (acute and extension periods).

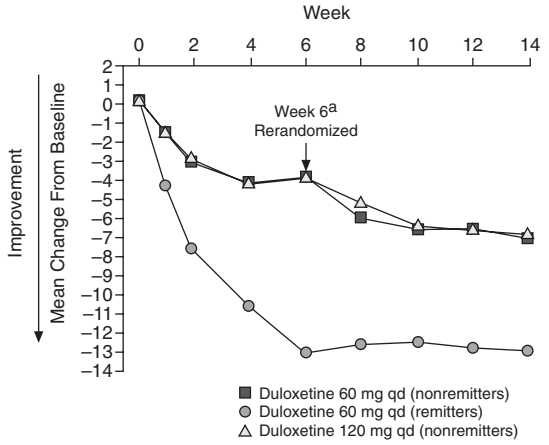
The IDS-C-30 efficacy measure during the extension phase showed statistically significant improvement for nonremitters in both the 60-mg and 120-mg dose groups after 2 weeks of additional treatment in the extension phase. The improvement was maintained at both 60 mg and 120 mg at every visit during the 8-week extension phase, although there were no differences between groups. A post hoc analysis of the QIDS-C-16, a subset of the IDS-C-30, also supported the finding of sustained improvements for both groups at every visit in the extension phase, with no differences between the dose groups.

Clinician-rated (CGI-S) and patient-rated (PGI-I) severity and improvement measures demonstrated continued improvement in nonremitters in both the 60-mg and 120-mg groups at every time point within the 8 weeks of the extension phase, with no differences detected between groups. For remitters in the 60-mg dose group, there were no statistically significant changes in efficacy measures in the extension phase with the exception of the PGI-I, in which continued improvement was demonstrated.

At the end of the extension phase, the average of the BPI interference scores and the interference with mood, relationships, sleep, and enjoyment scores were statistically significantly improved for nonremitters in both the 60-mg and 120-mg dose groups. The worst pain and pain right now scores were only statistically significant for the nonremitters in the 60-mg dose group. Differences between the 60-mg and 120-mg nonremitter dose groups were not statistically significant for any of the BPI measures.

Improvement on the VAS severity of overall pain score and interference with daily activities score for nonremitters in both the 60-mg and 120-mg dose groups was statistically significant at the end of the extension phase. The 60-mg nonremitter dose group experienced improvement on the severity of headache score ($p < .05$), while the 120-mg nonremitter dose group experienced improvement on the severity of shoulder pain and pain

Figure 2. HAM-D-17 Mean Change in Total Score Time Course From Acute Phase Baseline to Phase Endpoint



[a]Week 6 = rerandomization point after 6 weeks of active treatment with 60 mg q.d. duloxetine during the acute phase of the study.

while awake scores. Greater improvement on the severity of shoulder pain score was demonstrated for the 120-mg nonremitter group compared to those in the 60-mg nonremitter dose group (p = .033). Patients in the 60-mg remitter dose group did not experience any statistically significant changes for either the BPI or the VAS.

Safety

Extension phase safety analyses included both acute phase nonremitters and remitters for the 60-mg group and acute phase nonremitters for the 120-mg group. Of all the patients randomly reassigned to the extension phase, a total of 18 patients (3.9%) discontinued due to adverse events. Events leading to discontinuation in both treatment groups included nausea (1–60 mg and 2–120 mg) and somnolence (1 patient in each group). Events leading to discontinuation occurring only in the 60-mg group included single reports of blunted affect, diarrhea, drug exposure during pregnancy, hypertension, pneumonia, sedation, sinus headache, suicidal ideation, and uterine leiomyoma. Events leading to discontinuation occurring only in the 120-mg group included single reports of eye pain, hypomania, memory impairment, and orthostatic hypotension. Discontinuation rates due to adverse events were not statistically significantly different between the 60-mg group (3.3%) and the 120-mg group (5.6%).

Table 3 presents a summary of TEAEs occurring in patients dosed at 60 mg or 120 mg during the extension phase. The incidence of adverse events was similar between the 2 groups with the exception of a greater incidence in the 120-mg group compared to the 60-mg group of hyperhidrosis, tremor, and chest pain. Common adverse events occurring in greater than or equal to 5% of patients in the extension phase in the 60-mg and 120-mg groups included headache and upper respiratory tract infection.

Table 3. Summary of Adverse Events in Extension Phase Among Patients With Major Depressive Disorder Treated With Duloxetine

Adverse Event, N (%)[a]	Duloxetine 60 mg (N = 333)[b]	Duloxetine 120 mg (N = 125)	p Value
Headache	19 (5.7)	6 (4.8)	.82
Upper respiratory tract infection	18 (5.4)	4 (3.2)	.46
Nausea	9 (2.7)	6 (4.8)	.25
Diarrhea	10 (3.0)	3 (2.4)	1.0
Abnormal dreams	9 (2.7)	3 (2.4)	1.0
Vomiting	6 (1.8)	6 (4.8)	.10
Insomnia	6 (1.8)	4 (3.2)	.47
Pharyngolaryngeal pain	8 (2.4)	2 (1.6)	.74
Dry mouth	6 (1.8)	3 (2.4)	.71
Hyperhidrosis	3 (0.9)	6 (4.8)	.02*
Fatigue	5 (1.5)	3 (2.4)	.46
Sinusitis	5 (1.5)	3 (2.4)	.46
Nasopharyngitis	7 (2.1)	0 (0.0)	.20
Shoulder pain	7 (2.1)	0 (0.0)	.20
Libido decreased	3 (0.9)	3 (2.4)	.35
Tremor	2 (0.6)	4 (3.2)	.05*
Back pain	2 (0.6)	3 (2.4)	.13
Chest pain	1 (0.3)	4 (3.2)	.02*
Tooth abscess	1 (0.3)	3 (2.4)	.06

[a]Adverse events occurring in > 2% of either group in the extension phase.
[b]The 60-mg nonremitter and 60-mg remitter groups were combined.
*p ≤ .05.

A total of 7 patients (1.5%) experienced serious adverse events defined as any event resulting in or prolonging hospitalization or death, life-threatening experience, or severe or permanent disability during the study. Among the serious adverse events reported as reasons for discontinuation, 1 death occurred in a patient in the 120-mg dose group due to cardiac arrest secondary to asthma exacerbation. The death and the associated adverse events were judged by the investigator to be unrelated to study drug or protocol procedures. Serious adverse events occurring in the 60-mg dose group included 1 patient reporting suicidal ideation, 1 patient reporting uterine leiomyoma, and 1 patient reporting ongoing events of concussion, rib fracture, and upper limb fracture as a result of a fall that occurred in the acute phase of the study and were judged by the investigator to be unrelated to study drug or protocol procedures. Serious adverse events occurring in the 120-mg dose group included single reports of angina, increased blood pressure, chest pain, nausea, extremity pain, and suicidal ideation. These events were classified as serious, as they resulted in hospitalization. All events with the exception of nausea were judged by the investigator to be unrelated to study drug or protocol procedures. There were no significant differences in the occurrence of serious adverse events between the dose groups.

Baseline-to-endpoint values for laboratory analytes measured in the extension phase for the 120-mg group compared to the 60-mg group revealed a statistically significant mean decrease in direct bilirubin (–0.34 μmol/L vs. –0.17 μmol/L, respectively; p = .017) and a statistically significant mean increase in high-density lipoprotein cholesterol (0.11 mmol/L vs. 0.04 mmol/L, respectively; p = .006). All other laboratory analyte values were similar between groups. Further, after 2 weeks in the extension phase, compared to the 60-mg dose group, repeated-measures analyses revealed that patients in the 120-mg dose group had a statistically significant decrease in sitting systolic blood pressure (–1.88 mmHg vs. 1.18 mmHg for 60 mg; p = .004), and after 4 weeks, had a statistically significant decrease in sitting diastolic blood pressure (–0.88 mmHg vs. 1.01 mmHg for 60 mg; p = .021), an increase in sitting pulse (1.39 bpm vs. –0.36 bpm for 60 mg; p = .042), and a decrease in weight (–0.43 kg vs. 0.26 kg for 60 mg; p = .044). However, the changes in the vital sign measures observed early in the extension phase in the 120-mg group were not statistically significantly different between the 2 groups by study endpoint.

Categorical change analyses of PGI-SF overall score of randomly reassigned patients entering the extension phase showed that sexual function relative to baseline (beginning of the extension phase) was reported as being the same for 63.6% versus 58.1%, worse for 26.4% versus 28.2%, or better for 10.1% versus 13.7% by patients dosed at 60 mg and 120 mg, respectively. There were no statistically significant differences between groups on the overall score or on any of the individual items. However, when evaluated by gender, there was a statistically significant difference between the 60-mg and 120-mg groups in overall scores for men (the same for 65.6% vs. 36.1%, worse for 24.6% vs. 33.3%, or better for 9.8% vs. 30.6% for 60 mg and 120 mg, respectively; p = .01); whereas for women, there were no differences between groups (the same for 61.8% vs. 67.9%, worse for 27.9% vs. 25.9%, or better for 10.3% vs. 6.2% for 60 mg and 120 mg, respectively; p = .59).

DISCUSSION

This study assessed the efficacy of remaining on duloxetine 60 mg compared with increasing to 120 mg in patients who had not achieved remission after 6 weeks of treatment with duloxetine 60 mg. The study results demonstrated that while there were no differences between groups in time to remission, both dose groups evidenced sustained improvement on efficacy measures without a substantially greater adverse event burden for those dosed at 120 mg. In the acute phase of this study, following 6 weeks of treatment, 39.2% of patients achieved remission (HAM-D-17 score ≤ 7) and 45.5% achieved at least a 50% reduction in HAM-D-17 score from acute phase baseline to acute phase endpoint. From the subset of patients who did not remit and were randomly reassigned, 44.6% of the 60-mg dose group and 40.7% of the 120-mg dose group achieved response criteria (50% reduction of total HAM-D-17 score from acute phase baseline score), and 30% in both treatment groups achieved remission by the end of the 8-week extension phase. Of the acute phase remitters, 86% remained in remission at extension phase study end. While dose escalation may not have provided significant differences in response, remission, or efficacy improvements over time compared with standard dose, continuation of duloxetine therapy for either dose group yielded remission for 30% of patients not achieving remission with the initial 6-week 60-mg regimen. Further, these additional improvements in nonremitters were generally realized on most efficacy measures after 2 weeks of additional treatment during extension phase with improvements maintained until study endpoint.

A recent systematic review evaluating dose-escalation studies comparing standard dose to escalated dose with selective serotonin reuptake inhibitors (SSRIs) concluded that dose escalation after 6 weeks is less effective than continuing the same dose.[16] Of the studies reviewed, most had an acute period of only 3 weeks, and the authors concluded that therapy for at least 6 weeks is ideal.[16]

Our study employed a design that allowed for 6 weeks on acute therapy and a blinded rerandomization scheme not reported in the review.[16] The recent review also alluded to the possibility that the type of responder may factor into efficacy of dose escalation for patients who do not initially remit during initial therapy with an antidepressant.[16] To that end, we conducted post hoc analyses of patients who did not remit during the acute phase to compare the remission rates to type of response achieved during the acute phase (full, partial, or nonresponse). A numerically greater percentage of patients who fully responded to treatment at the end of the acute phase tended to achieve remission in the extension phase compared to those who partially responded. Fewer patients achieved remission in the extension phase if they were nonresponders during the acute phase.

From these results, it appears that responders are more likely to achieve remission with additional time on therapy, although there seems to be no advantage in increasing the dose to 120 mg over maintaining therapy at 60 mg. In patients who responded to acute therapy in the 60-mg nonremitter, 120-mg nonremitter, and 60-mg remitter groups, response criteria were maintained at the end of the extension phase. Although no differences were seen between the standard dose and the dose-escalation groups in this study, it appears that our results are consistent with studies of SSRIs that have evaluated dose escalation.[16]

A limitation in our study design may be the use of changes in the HAM-D-17 total score as an indicator of which patients will respond or achieve remission and whether dose adjustment is warranted. Clinicians may consider many factors other than the HAM-D-17 to determine dose increases or change in treatment for patients not responding to initial therapy.[3] The blinded rerandomization design for the extension phase did not allow clinicians to have any impact on determining if a particular patient was a good candidate for dose escalation. Many factors, including weekly assessment and pattern of symptom changes during the course of treatment as well as medication tolerability, may be taken under consideration by clinicians when determining whether a dose change is appropriate. While a flexible dose design allowing patients to move from 60 mg to 120 mg based on physician discretion may have resulted in better overall outcomes, this design would not have allowed for a direct comparison of the 60-mg to the 120-mg dose. Although this study design minimizes the likelihood of a placebo response, not allowing for clinician input is not consistent with clinical practice.[3]

Continued time on duloxetine therapy, regardless of whether the dose was maintained or increased, resulted in remission for 30% of patients entering the extension phase as a "nonremitter" and demonstrated that improvements could still be realized. Further, it is important to note that 86% of patients achieving remission in the acute phase stayed in remission throughout the extension phase. The results of this study suggest that the HAM-D-17 score alone may not be sufficient to determine whether increasing or maintaining duloxetine dose is warranted. Despite the findings from this study and some others indicating that dose escalation may not be beneficial, clinicians may still prefer to increase the dose because of the belief and experience that individual patients do respond to a higher dose. The safety profile in this study between the 60-mg and 120-mg dose groups demonstrated that there were no medically relevant differences in safety measures. Further, there were also no statistically significant differences between the 2 groups in terms of discontinuation rates due to adverse events or in the overall incidence of adverse events emerging over the course of the 2 months. The safety results from this study support previous studies conducted with duloxetine at doses ranging from 60 mg/day to 120 mg/day.[14,15]

CONCLUSIONS

Nonremitters treated with duloxetine 60 mg q.d. for approximately 6 weeks randomly assigned to either 60 mg or 120 mg q.d. for 8 additional weeks demonstrated continued improvement in efficacy measures. No advantage was shown for the 120-mg dose group over nonremitters who continued on 60 mg. The data suggest that duloxetine was well tolerated at both doses and had similar safety profiles.

Drug names: duloxetine (Cymbalta), fluoxetine (Prozac and others), diphenhydramine (Benadryl and others).

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