Acute and Long-term Treatment of Late-Life Major Depressive Disorder: Duloxetine Versus Placebo

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Objective: *To compare the efficacy of duloxetine with placebo on depression in elderly patients with major depressive disorder.* **Design:** *Multicenter, 24-week (12-week short-term and 12-week continuation), randomized, placebo-controlled, double-blind trial.* **Setting:** *United States, France, Mexico, Puerto Rico.* **Participants:** *Age 65 years or more with major depressive disorder diagnosis (one or more previous episode); Mini-Mental State Examination score ≥20; Montgomery-Asberg Depression Rating Scale total score ≥20.* **Intervention:** *Duloxetine 60 or 120 mg/day or placebo; placebo rescue possible.* **Measurements:** Primary-*Maier subscale of the 17-item Hamilton Depression Rating Scale (HAMD-17) at week 12.* Secondary-*Geriatric Depression Scale, HAMD-17 total score, cognitive measures, Brief Pain Inventory (BPI), Numeric Rating Scales (NRS) for pain, Clinical Global Impression-Severity scale, Patient Global Impression of Improvement in acute phase and acute plus continuation phase of treatment.* **Results:** *Compared with placebo, duloxetine did not show significantly greater improvement from baseline on Maier subscale at 12 weeks, but did show significantly greater improvement at weeks 4, 8, 16, and 20. Similar patterns for Geriatric Depression Scale and Clinical Global Impression-Severity scale emerged, with significance also seen at week 24. There was a significant treatment effect for all BPI items and 4 of 6 NRS pain measures in the acute phase, most BPI items and half of the NRS measures in the continuation phase. More duloxetine-treated patients completed the study (63% versus 55%). A significantly higher percentage of duloxetine-treated patients versus placebo discontinued due to adverse event (15.3% versus 5.8%).* **Conclusions:** *Although the antidepressant efficacy of duloxetine was not confirmed by the primary outcome, several secondary measures at multiple time points suggested efficacy. Duloxetine had significant and meaningful beneficial effects on pain.* (Am J Geriatr Psychiatry 2014; 22:34–45)

Key Words: Duloxetine, elderly depression, pain, symptom severity

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OBJECTIVE

Late-life major depressive disorder (MDD) is common but not a natural part of aging.[1] Approximately 1% to 5% of community-located elderly and 14% to 42% of elderly residents of long-term care facilities have MDD.[2]

Meta-analyses[3,4] evaluating placebo-controlled trials of second-generation antidepressants in patients with MDD of age 60 years or more showed that antidepressants had modest efficacy. Drug−placebo differences were greater in 10- to 12-week studies than in 6- to 8-week studies, suggesting that antidepressant treatment may take longer to become effective in older patients. Nevertheless, with no placebo-controlled trials longer than 12 weeks, it is not known if antidepressant effects increase beyond this point.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor approved for treatment of MDD, generalized anxiety disorder, and management of diabetic peripheral neuropathic pain, fibromyalgia, and chronic musculoskeletal pain in the United States.[5] Raskin and colleagues[6] demonstrated the efficacy of duloxetine in improving cognition, depression, and pain among elderly patients with MDD.

To our knowledge, the current study is the first placebo-controlled study in elderly patients with MDD to examine efficacy over 24 weeks under double-blind conditions. Our primary objective was to compare the efficacy of duloxetine 60 mg/day treatment versus placebo after 12 weeks of treatment. Key secondary objectives included comparison of efficacy of duloxetine 60 to 120mg/day versus placebo after 24 weeks of treatment. Safety and tolerability of duloxetine were examined for the 24-week study.

METHODS

Study Overview

Eligibility criteria included: age 65 years or more; recurrent MDD (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*);[7] Mini-Mental State Examination score ≥20; and Montgomery-Åsberg Depression Rating Scale total score 20 or more.[8,9]

Major exclusion criteria included: history of bipolar, panic, or obsessive-compulsive disorder, psychosis, or schizophrenia; current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*, primary axis I diagnosis other than MDD; judged a serious suicidal risk; lack of response of current MDD episode to two or more adequate doses of antidepressant therapy, or an adequate trial of duloxetine at any time; and serious unstable medical illness or clinically significant laboratory abnormality.

This multicenter, randomized, placebo-controlled, double-blind, phase 4 study compared duloxetine with placebo for treatment of MDD in elderly patients over 24 weeks. A double-blind placebo lead-in period of variable expected duration was used; patients and investigators were informed that assignment to duloxetine could begin anytime between visits 2 and 4. Study drug packaging was blinded and dispensing maintained by an interactive voice response system (IVRS). After lead-in, patients were randomized 2:1 to duloxetine (30 mg/day for 1 week, forced titration to 60 mg/day) or placebo for 12 weeks. At each site, treatment randomization was stratified by age group (<75, 75−84, and ≥85 years). Assignment to treatment groups was determined by a computer-generated random sequence using an automated system that was independent of any recruiting activities. During the acute phase, patients requiring dosage decrease due to safety/tolerability or increase due to efficacy reasons were discontinued. From weeks 12 until 20 (continuation phase), placebo rescue or duloxetine dose optimization was available if the patient had less than 50% improvement from baseline on the 17-item Hamilton Depression Rating Scale (HAMD-17)[10] Total score at week 12 or HAMD-17 total score more than 10 at weeks 16 or 20, and therapy adjustment was deemed appropriate by the investigator. Placebo rescue and dose-optimization were instituted using IVRS (double-blind). Placebo-rescued patients received duloxetine 30 mg/day for 1 week with an increase to 60 mg/day for the remainder of the trial. Duloxetine-treated patients receiving treatment optimization received dose increases from 60 to 120 mg/day. One dose decrease due to safety or tolerability was allowed; if a second was requested the patient was discontinued from the study.

This study planned to enroll 300 patients to yield 80% power to detect an effect size (treatment group difference in baseline-to-endpoint mean change

divided by common SD for the change score) of approximately 0.35. When the study began, the primary outcome measure was the patient-rated HAMD-24, collected via IVRS. As the study progressed, blinded analyses showed that HAMD-24 scores did not sufficiently correspond to clinician-rated Montgomery-Åsberg Depression Rating Scale scores. Study enrollment was halted and assessment methodology re-evaluated. The study resumed under an amended protocol in which the clinician-rated HAMD-17 replaced the HAMD-24, and the Geriatric Depression Scale (GDS)[11] was added to evaluate patient-reported depression. The primary hypothesis and study design remained the same. Only the patients randomized after this change were included in the efficacy analysis. All randomized patients were included in safety analyses.

The protocol was approved by study center ethical review boards. Patients provided written informed consent before initiation of study procedures. The study was conducted in accordance with regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996) and all applicable local regulations. Trial registration: clinicaltrials.gov (NCT00406848).

Outcome Measures

The primary efficacy measure was the Maier Subscale of the HAMD-17.[10] Secondary measures included the GDS,[11] HAMD-17 total score, Clinical Global Impressions-Severity (CGI-S) scale[12] and Patient Global Impression of Improvement (PGI-I) scale.[13] The Memory Enhanced Retrospective Evaluation of Treatment was used in conjunction with PGI-I.[14] The Brief Pain Inventory (BPI)[15] and Numeric Rating Scales (NRS) assessed pain severity and interference. Patient self-report measures were administered via IVRS. Validated translations for patient-rated scales were provided in the native language for France, Mexico, and Puerto Rico.

Cognition was assessed using the Verbal Learning and Recall Test;[16,17] Symbol Digit Substitution Test (Wechsler Adult Intelligence Scale);[18] 2-Digit Cancellation Test;[19,20] and Trail Making Test Part B;[21,22] a composite cognitive score (0−51) was calculated on the basis of these four assessments.

Response rate was defined as 50% or more improvement from baseline on HAMD-17 total score. Remission rates were defined as a HAMD-17 total score $\leq$7 and $\leq$10 (to address the possibility that medically associated somatic symptoms might inflate HAMD-17).[23]

Safety Measures

Blood pressure (BP) (systolic [SBP], diastolic [DBP], and orthostatic), pulse, and weight were evaluated. Laboratory measures included hematology, glycosylated hemoglobin (HbA_{1c}), fasting glucose, lipid profile, clinical chemistry (including electrolytes, renal and hepatic function), urine drug screen, urinalysis, and thyroid function. Post randomization incidence rates of serious adverse events (SAEs), treatment-emergent AEs (TEAEs), and discontinuation due to AEs were assessed.

Statistical Analysis

The statistical methods were prespecified before unblinding of treatment assignment and were performed on an intent-to-treat basis unless otherwise specified. Efficacy analyses were performed on the intent-to-treat sample with a baseline observation and at least one postbaseline observation. All tests of hypotheses considered statistically significant had a two-sided p value of $\leq$0.05. No adjustments were made for multiple comparisons. For patients assigned to placebo and subsequently switched to duloxetine therapy during the continuation period, only data collected up to the point that treatment was switched were included in efficacy and safety comparisons of duloxetine versus placebo.

The primary analysis for the HAMD-17 Maier subscale score was a restricted maximum-likelihood-based, mixed-effects model repeated measures (MMRM) approach. The model included fixed, categorical effects of treatment, investigator, visit, and treatment x visit interaction; and continuous, fixed covariates of baseline score and baseline score x visit interaction. The primary comparison was the difference between duloxetine and placebo in estimated mean changes from baseline to endpoint of the acute period (week 12).

Secondary efficacy variables were analyzed using the following methods: 1) for numerical outcomes collected at each study visit (HAMD-17 total score, GDS, Clinical Global Impressions-Severity, PGI-I, BPI, and NRS), the MMRM model, as described

earlier, was used to analyze visitwise longitudinal observations available. Because pain outcomes (BPI and NRS) were expected to show a relatively rapid onset of treatment effect that afterward remained fairly constant over time, the prespecified principal treatment comparison was based on the contrast of main effect of treatments from the MMRM model, which is averaged mean change from baseline over the course of the study. In addition, an MMRM analysis on BPI pain reduction was applied to a subgroup of patients with at least moderate baseline pain (BPI average pain ≥3); 2) for cognition test scores, collected only once in the acute phase and once at the end of the entire study (last visit if patient dropped out), fixed-effects analysis of covariance (ANCOVA) employing last observation carried forward was utilized for change from baseline to endpoint; the model included treatment, investigator, and baseline score; a likelihood-based MMRM analysis was also conducted to assess the sensitivity of the prespecified ANCOVA; and 3) for visit wise binary outcomes such as response and remission status, categorical MMRM analysis using a pseudo-likelihood-based repeated measures approach was applied to estimate probability of response/remission and compare between treatments at study endpoints. The model included fixed, categorical effects of treatment, investigator, visit, and treatment-by-visit interaction, and the continuous, fixed covariate of baseline score.

Postrandomization incidence rates of study discontinuation, TEAEs, SAEs, and AEs leading to discontinuation were summarized and compared between treatments using Fisher's exact test. Mean changes in BP, pulse, or body weight were analyzed using the MMRM method summarized earlier.

Categorical analyses of BP included patients who met criteria for elevated SBP (≥140 with increase ≥10 from baseline) or DBP (≥90 with increase ≥10 from baseline), sustained elevations in BP (for three consecutive visits), and orthostatic hypotension (supine DBP minus standing DBP ≥10 mm Hg or supine SBP minus standing SBP ≥20 mm Hg); incidence rates were compared between treatments using Fisher's exact test. Baseline-to-endpoint changes in laboratory values were summarized for each group and analyzed by analysis of variance model including terms of treatment and investigator. Incidence of treatment-emergent high, low, and abnormal laboratory values was summarized for each treatment group and compared between treatment groups using Fisher's exact test.

RESULTS

Thirty-eight sites in the United States, France, Mexico, and Puerto Rico participated. The safety analysis included 370 randomized patients (249 duloxetine, 121 placebo). The total number of randomized patients in the efficacy analysis was 299 (204 duloxetine, 95 placebo) (Table 1). Most participants were women, white, with a mean age of 73 years; 2.7% had mild dementia. No statistically significant differences emerged between treatment groups on demographics in either the efficacy or safety populations. Patient disposition is presented in Figure 1. The overall 12-week completion rate was

TABLE 1. Baseline Patient Demographics, Cognition, and Psychiatric and Pain Status[a]

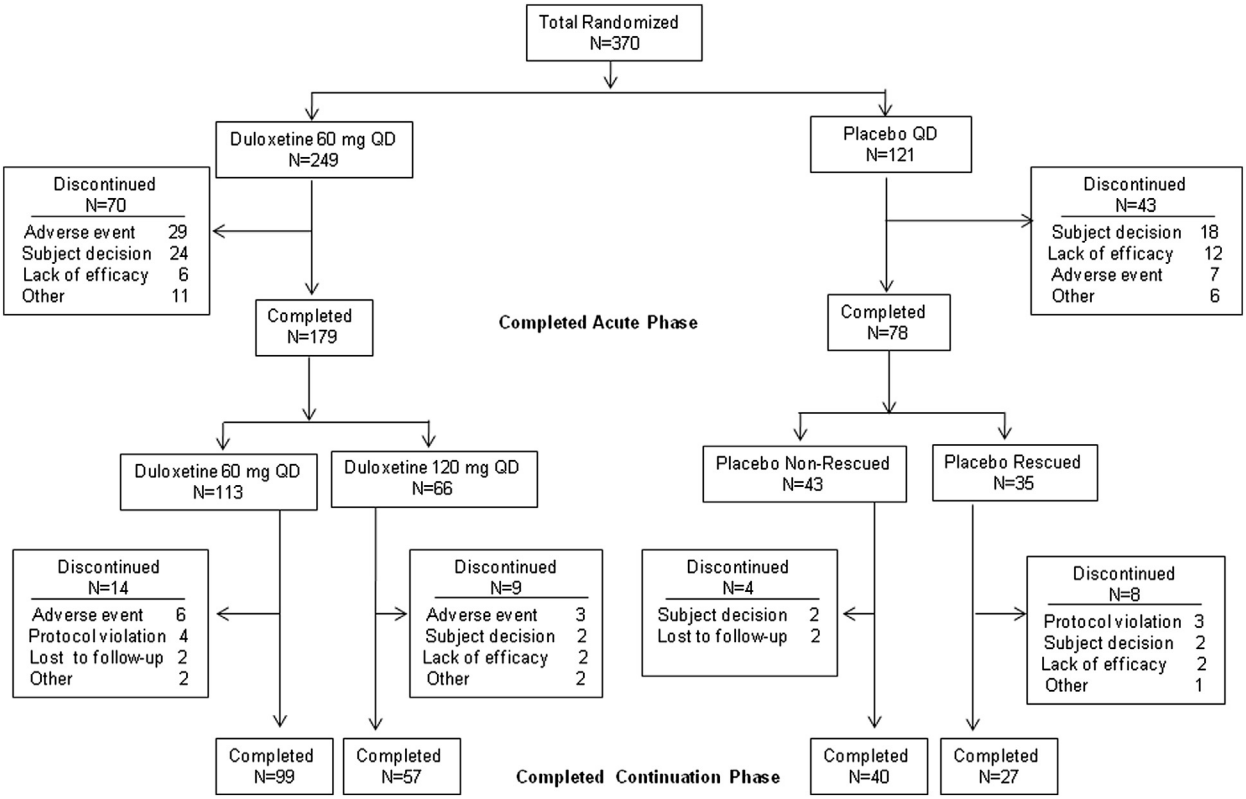
Characteristic	Placebo (N = 95)	Duloxetine (N = 204)
Age, years, mean (SD)	73.1 (5.64)	73.01 (6.26)
[minimum–maximum]	[65.1–89.9]	[65.0–89.5]
Gender, n (%)		
Female	56 (58.9)	135 (66.2)
Male	39 (41.1)	69 (33.8)
Ethnicity, n (%)		
African American	5 (5.3)	3 (1.5)
White	70 (73.7)	160 (78.4)
Hispanic	19 (20.0)	41 (20.1)
Dementia status, mean (%)		
Mild[b]	2 (2.1)	6 (3.0)
Cognitive assessment, mean (SD)		
Mini-Mental State Examination total score	28.4 (1.7)	28.6 (1.8)
Composite Cognitive Score	23.3 (7.3)	23.2 (7.8)
Mood assessment, mean (SD)		
HAMD-17, total score	19.3 (5.8)	19.4 (5.6)
HAMD-17, Maier subscale	10.1 (3.4)	9.96 (3.1)
CGI-S	4.4 (0.8)	4.12 (0.7)
GDS	17.64 (6.7)	18.54 (6.9)
Montgomery-Asberg Depression Rating Scale	28.5 (5.4)	29.3 (5.6)
Pain assessment, mean (SD)		
BPI 24-hour average pain score	3.48 (2.6)	3.48 (2.7)
NRS overall pain score	3.59 (2.7)	3.79 (3.0)

Notes: No. patients per country: United States: 225; Puerto Rico: 28; Mexico: 25; France: 21.

[a]Because many of these measures are efficacy, this includes only those patients in the efficacy analysis (no significant difference compared with safety group).

[b]Defined as a score of 20 to 23 on the Mini-Mental State Examination.

FIGURE 1. Study Consort Diagram. QD: once daily.



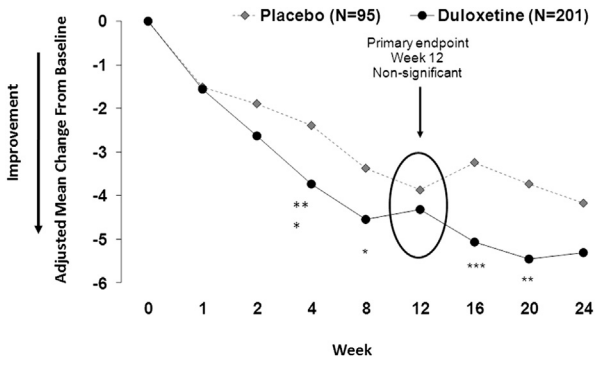
69.5% (placebo 64.5%, duloxetine 71.9%). The completion rate at 24 weeks was 60%, with significantly more duloxetine-treated patients (62.7%) completing than placebo-treated patients who did not receive duloxetine rescue medication (46.5%, Fisher's exact test, $p = 0.01$).

Efficacy Outcomes

After 12 weeks, the estimated mean changes (±SE) in HAMD-17 Maier subscale scores from baseline did not have statistically significant differences between patients treated with duloxetine (-4.34 ± 0.29) versus placebo (-3.90 ± 0.44) ($t = 0.85$, *df*: 243.5; $p = 0.397$). Statistically significant separation favoring duloxetine did occur at weeks 4, 8, 16, and 20, but not at week 24 (-5.31 ± 0.29 versus -4.17 ± 0.54; $t = 1.90$; *df*: 186.7; $p = 0.059$) (Figure 2).

Statistically significant improvement compared with placebo on the estimated mean change (±SE) in GDS was not achieved at week 12 (-6.01 ± 0.53

FIGURE 2. Primary Outcome: Adjusted Mean Changes From Baseline in Maier Subscale of the HAMD-17 via Specified MMRM Model, Acute Plus Continuation Phase.



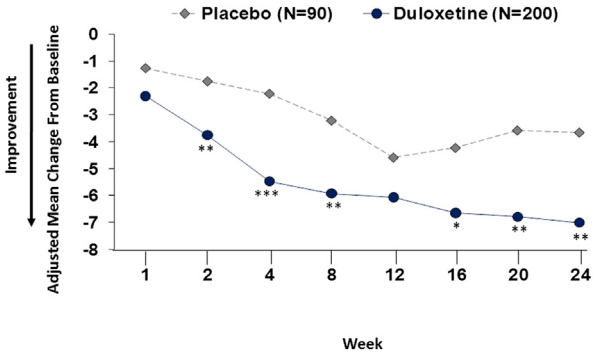
[a]*p ≤0.05; **p ≤0.01; ***p ≤0.001. [†a]Includes only the patients in the efficacy analysis.

versus −4.53 ± 0.79; $t = 1.58$; *df*: 244.8; p = 0.115), but was seen at weeks 2, 4, 8, 16, 20, and 24 (−7.02 ± 0.58 versus −3.66 ± 1.00; $t = 2.95$; *df*: 226.6; p = 0.004) (Figure 3). On the Clinical Global Impressions-Severity, duloxetine-treated patients had significantly greater improvement compared with placebo at weeks 4, 8, 16, 20, and 24 (Figure 4). Duloxetine-treated patients reported significantly greater improvement on the PGI-I compared with placebo at weeks 4 (2.72 ± 0.11 versus 3.36 ± 0.16; $t = 3.39$; *df*: 232.1; p <0.001) and 8 (2.51 ± 0.10 versus 3.21 ± 0.15; $t = 3.96$; *df*: 223.4; p <0.001); no other significant differences emerged on the PGI-I. Duloxetine-treated patients experienced significantly greater improvement compared with placebo-treated patients on the HAMD-17 total score at weeks 4 (−6.40 ± 0.42 versus −4.62 ± 0.60; $t = 2.50$; *df*: 246.7; p = 0.013), 8 (−7.86 ± 0.47 versus −5.99 ± 0.68; $t = 2.33$; *df*: 250.7; p = 0.021), 16 (−8.61 ± 0.52 versus −5.68 ± 0.83; $t = 3.03$; *df*: 220.2; p = 0.003), and 20 (−9.09 ± 0.50 versus −6.44 ± 0.85; $t = 2.74$; *df*: 199.0; p = 0.007). No statistically significantly different mean changes, from baseline to endpoint between treatment groups, occurred for any individual or composite cognitive assessment score (Figure 5), based on both ANCOVA and MMRM methods.

The probability of response (50% or more improvement from baseline on HAMD-17 total score) was significantly greater for patients treated with duloxetine compared with placebo at weeks 2 and 4, but not at week 8 through study end. Probability of remission (HAMD-17 total scores ≤7 and ≤10 throughout the study) is shown in Figure 6. Of randomized duloxetine patients who remained on 60 mg throughout the study, 65.6% and 64.5% were in remission (≤7 on HAMD-17) at 12 weeks and study endpoint, respectively.

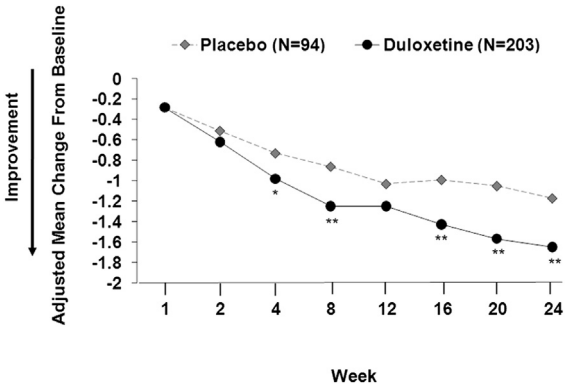
For pain outcomes, prespecified treatment comparisons between duloxetine and placebo were made for all patients regardless of baseline pain levels and for patients with at least moderate pain at baseline (BPI average pain rating ≥3). Among all patients, duloxetine-treated patients reported statistically significant improvement compared with placebo-treated patients on all BPI severity and interference items and on 4 of 6 NRS items in the acute phase (Table 2). During the acute plus continuation phase, the duloxetine group reported statistically significant improvement compared with the placebo group on 7/11 BPI items and 3 of 6 NRS items (Table 2). Among patients with baseline BPI average pain severity rating ≥3, duloxetine-treated patients showed significantly greater improvement on most BPI items in the acute phase (Table 3).

FIGURE 3. Adjusted Mean Changes From Baseline to 24-Week Endpoint in GDS via Specified MMRM Model.



*p ≤0.05; **p ≤0.01; ***p ≤0.001.

FIGURE 4. Adjusted Mean Change From Baseline to 24-Week Endpoint in CGI-S via Specified MMRM model.

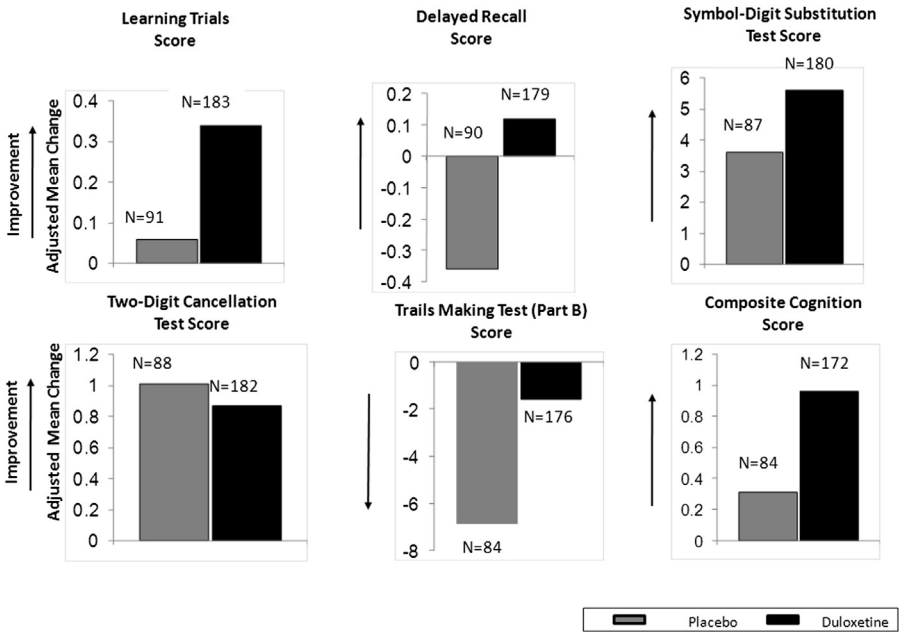


*p ≤0.05; **p ≤0.01.

Safety Outcomes

There were no deaths in the study. During the 24-week period, 17 patients (13 duloxetine, 4 placebo) reported a total of 24 SAEs with no significant between-group differences. One patient who was

FIGURE 5. Adjusted Mean Change From Baseline in Individual and Composite Cognitive Assessments at Study Last Observation via Specified ANCOVA.



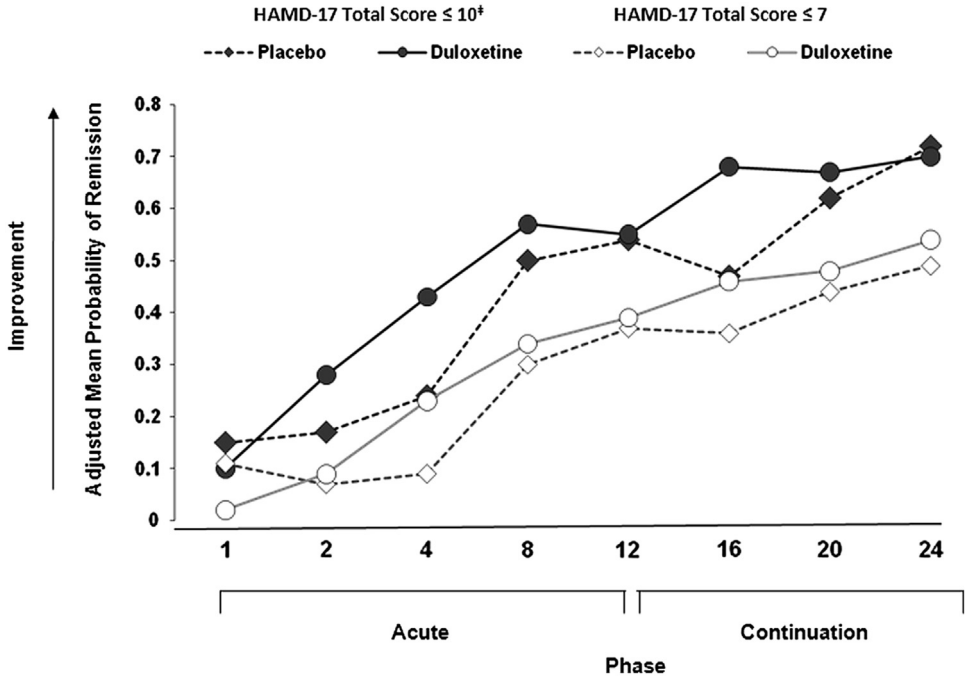
Treatment comparison p values >0.05 for all cognition assessments.

originally assigned to placebo treatment but was rescued to duloxetine therapy during the continuation period experienced a pulmonary embolism after being rescued to duloxetine treatment. Six patients (five duloxetine, one placebo) discontinued because of SAEs. One SAE was judged by the investigator to be related to study drug: hip fracture in a duloxetine-treated patient as a result of a fall. This patient had a history of osteoporosis, was receiving antihypertensive medication, and was noted to be hypotensive at the study visit before the fall. Thirty eight (15.3%) duloxetine-treated versus seven (5.8%) placebo-treated patients discontinued from the study because of an AE (Fisher's exact test; $p = 0.01$). The TEAEs that occurred in 5% or more of the duloxetine treated patients and twice that of placebo are presented in Figure 7. Two duloxetine-treated patients reported suicidal ideation; one remained in the study and the other discontinued.

Vital sign results are presented in Table 4. There were no significant between-group differences at week 12 or 24 in standing/sitting SBP/DBP, or occurrence of sustained hypertension. Significant differences were observed for mean changes in supine DBP and orthostatic change (standing-supine) in DBP at week 12, and supine pulse rate and orthostatic change in DBP at week 24. Incidence of treatment-emergent orthostatic hypotension during the acute phase was not significantly different between duloxetine- versus placebo-treated patients (23.0% versus 22.2%, respectively), and remained nonsignificant for the entire 24 weeks (31.1% versus 23.3%, respectively). There were no significant differences between groups for electrocardiographic changes. A significant difference was observed for mean weight change at week 12, with duloxetine-treated patients experiencing a mean weight loss (−0.86 kg) and placebo-treated patients experiencing a mean weight gain (+0.06 kg). By week 24, no significant differences in weight were noted, with both groups reporting modest weight loss.

No clinically meaningful changes occurred in laboratory analytes at 12- or 24-week endpoints in either treatment group. There was a statistically significant difference in mean change (±SD) in fasting glucose between duloxetine (+0.37 ± 1.88 mmol/L)

FIGURE 6. Estimated Probability of Remission[a] Over 24 Weeks via Specified MMRM Model.



*p ≤0.05; **p ≤0.01; ***p ≤0.001. [a]Remission defined as either HAMD-17 total score ≤7 or ≤10. [b]Main effect of treatment was statistically significant (p ≤0.05) for duloxetine for patients with HAMD-17 total score ≤10.

and placebo (−0.11 ± 1.06 mmol/L); the magnitude of the change was not considered clinically meaningful. There was no significant between-group difference in baseline-to-endpoint change in HbA_{1c} values. There were no reports of alanine aminotransferase levels three or more times the upper limit of normal. During the acute phase, one treatment-emergent abnormal laboratory analyte (low leukocyte count) occurred at a statistically significantly higher frequency in duloxetine-treated patients versus placebo (4.99% versus 0%, Fisher's exact test; p = 0.019), but the difference was not significant at the 12-week endpoint (p = 0.06).

Although TEAE falls (i.e., reported to study investigator at each study visit) did not meet defined criteria for reporting (5% or more of duloxetine-treated patients and twice the rate of placebo), a significantly higher percentage of duloxetine-treated patients reported TEAE falls versus placebo-treated patients (23.7% versus 14.0%; Fisher's exact test; p = 0.04) in the acute plus continuation phase. In the acute phase, the percentage of duloxetine-treated patients who reported TEAE falls was not significantly higher than placebo (16.1% versus 9.9%; p = 0.15).

CONCLUSIONS

In this study, duloxetine-treated patients did not report significantly greater improvement on the Maier subscale of the HAMD-17 at week 12 compared with placebo (primary measure); however, they did report significantly greater improvement at weeks 4, 8, 16, and 20. Furthermore, significantly greater improvement in depressive symptoms as measured by the GDS was achieved in duloxetine-treated patients at weeks 2, 4, 8, 16, 20, and 24. Although these data do not confirm antidepressant efficacy in this population, they do suggest efficacy. The finding of significant improvement for duloxetine-treated patients versus placebo at weeks before and after, but not at, week 12 was surprising. Researchers have suggested that depressive symptoms vary with age, and some instruments, including

TABLE 2. Adjusted Mean Change[a] in BPI and NRS Items During Acute Phase and Acute Plus Continuation Phase Among All Randomized Patients

	Acute Phase				Acute Plus Continuation Phase			
	Mean Change (SE)				Mean Change (SE)			
Measure	Placebo (N = 87)	Duloxetine (N = 191)	*t* (*df*)	p	Placebo (N = 88)	Duloxetine (N = 191)	*t* (*df*)	p
BPI pain severity								
Average pain	−0.14 (0.18)	−0.83 (0.13)	3.35 (254.4)	<0.001	−0.37 (0.18)	−0.87 (0.12)	2.49 (265.0)	0.013
Worst pain	−0.18 (0.19)	−0.66 (0.14)	2.13 (244.8)	0.034	−0.36 (0.20)	−0.74 (0.14)	1.65 (255.5)	0.100
Least pain	0 (0.15)	−0.47 (0.11)	2.62 (247.3)	0.009	−0.26 (0.16)	−0.54 (0.11)	1.53 (258.2)	0.126
Pain right now	−0.26 (0.18)	−0.78 (0.13)	2.42 (258.1)	0.016	−0.46 (0.18)	−0.86 (0.13)	1.90 (259.6)	0.058
BPI pain interference								
General activity	−0.03 (0.19)	−0.58 (0.13)	2.56 (249.1)	0.011	−0.23 (0.19)	−0.65 (0.13)	1.89 (245.6)	0.060
Mood	−0.03 (0.19)	−0.82 (0.14)	3.51 (243.1)	<0.001	−0.25 (0.19)	−0.95 (0.13)	3.21 (246.4)	0.002
Walking	−0.19 (0.20)	−0.74 (0.14)	2.36 (251.8)	0.019	−0.24 (0.21)	−0.75 (0.15)	2.07 (254.8)	0.040
Normal work	−0.01 (0.21)	−0.72 (0.15)	2.99 (251.9)	0.003	−0.19 (0.21)	−0.79 (0.15)	2.47 (253.0)	0.014
Relations	−0.03 (0.19)	−0.6 (0.13)	2.60 (256.6)	0.010	−0.18 (0.19)	−0.73 (0.13)	2.59 (259.2)	0.010
Sleep	−0.17 (0.21)	−0.77 (0.15)	2.45 (252.5)	0.015	−0.26 (0.21)	−0.94 (0.14)	2.85 (262.3)	0.005
Enjoyment of life	0.03 (0.21)	−0.93 (0.15)	3.90 (248.2)	<0.001	0.08 (0.21)	−1.04 (15)	3.90 (250.2)	<0.001
NRS								
Overall pain	−0.05 (0.18)	−0.65 (0.13)	2.82 (244.2)	0.005	−0.40 (0.19)	−0.67 (0.13)	1.27 (248.4)	0.204
Headaches	0.01 (0.16)	−0.32 (0.12)	1.77 (226.8)	0.078	0.01 (0.18)	−0.28 (0.12)	1.46 (227.6)	0.147
Back pain	0 (0.20)	−0.63 (0.14)	2.74 (242.4)	0.007	−0.15 (0.21)	−0.75 (0.14)	2.49 (242.1)	0.013
Shoulder pain	−0.22 (0.17)	−0.54 (0.12)	1.55 (247.8)	0.124	−0.30 (0.18)	−0.55 (0.13)	1.20 (263.3)	0.231
Interference with daily activities	−0.2 (0.20)	−0.84 (0.14)	2.75 (248.7)	0.006	−0.34 (0.21)	−0.91 (0.15)	2.37 (257.7)	0.019
Time in pain while awake	−0.04 (0.19)	−0.75 (0.14)	3.17 (247.6)	0.002	−0.33 (0.20)	−0.80 (0.13)	2.11 (244.0)	0.036

[a]MMRM method.

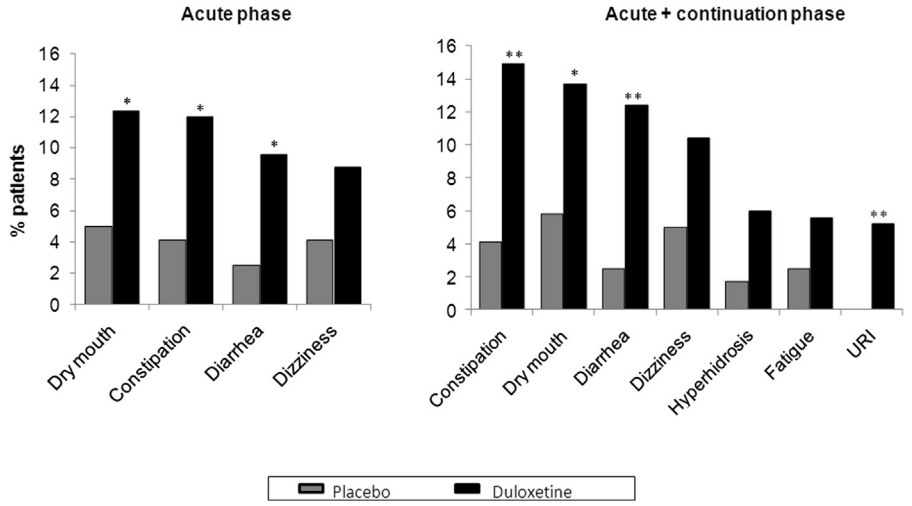
TABLE 3. Adjusted Mean Change[a] in BPI Items During the Acute Phase Among Patients With at Least Moderate Pain at Baseline

	Patients With at Least Moderate Pain Mean Change (SE)			
Measure	Placebo (N = 49)	Duloxetine (N = 112)	*t* (*df*)	p
BPI pain severity				
Average pain	−0.82 (0.29)	−1.66 (0.20)	2.67 (138.0)	0.009
Worst pain	−0.95 (0.30)	−1.46 (0.21)	1.55 (133.4)	0.124
Least pain	−0.34 (0.26)	−1.02 (0.18)	2.41 (132.0)	0.017
Pain right now	−0.77 (0.30)	−1.49 (0.21)	2.19 (138.2)	0.031
BPI pain interference				
General activity	−0.44 (0.28)	−1.28 (0.20)	2.69 (137.5)	0.008
Mood	−0.65 (0.30)	−1.56 (0.21)	2.72 (134.5)	0.007
Walking	−0.79 (0.32)	−1.37 (0.22)	1.63 (135.4)	0.106
Normal work	−0.53 (0.32)	−1.34 (0.22)	2.29 (138.2)	0.024
Relations	−0.39 (0.30)	−1.04 (0.21)	1.96 (140.9)	0.052
Sleep	−0.59 (0.33)	−1.32 (0.23)	2.05 (137.0)	0.043
Enjoyment of life	−0.52 (0.33)	−1.56 (0.23)	2.83 (138.8)	0.005

[a]MMRM method.

the HAMD, may be less sensitive to symptom change in the elderly patients (1). The GDS, validated for elderly patients with more focus on psychological symptoms (1), may have provided greater sensitivity in this population than the HAMD as noted by significant differences at weeks 2 and 24. Also, since the study design allowed for dosage adjustment at week 12, it is possible that scores were influenced by knowledge of a potential rescue/dose optimization. Perhaps completely blinded timing of treatment change would have addressed this possibility. The current trial suggests that patients who remit on

FIGURE 7. TEAEs That Occurred in at Least 5% of Duloxetine-Treated Patients and Twice That of Placebo During the Acute and the Continuation Phases.



*p ≤0.05; **p ≤0.01. URI: upper respiratory infection.

TABLE 4. Adjusted Mean Change[a] in Supine Blood Pressure, Pulse, and Weight at Study Endpoints

	Adjusted Mean Change (SE)			
Measure	**Placebo (N = 118)**	**Duloxetine (N = 246)**	***t* (*df*)**	**p**
SBP, mm Hg				
Week 12	−0.58 (1.39)	0.19 (0.94)	−0.47 (290)	0.64
Week 24	0.54 (1.99)	2.22 (1.09)	−0.75 (230)	0.45
DBP, mm Hg				
Week 12	−1.58 (0.92)	1.89 (0.62)	−3.23 (288)	0.001
Week 24	0.65 (1.23)	2.44 (0.68)	−1.30 (238)	0.19
Orthostatic change (standing-supine)—SBP, mm Hg				
Week 12	2.29 (0.96)	0.27 (0.64)	1.82 (269)	0.07
Week 24	0.50 (1.68)	−1.92 (0.88)	1.30 (211)	0.20
Orthostatic change (standing-supine)—DBP, mm Hg				
Week 12	2.28 (0.78)	−0.94 (0.52)	3.52 (277)	<0.001
Week 24	0.84 (1.08)	−1.53 (0.57)	1.97 (208)	0.05
Pulse rate, beats/minute				
Week 12	−1.56 (0.88)	0.03 (0.60)	−1.55 (300)	0.12
Week 24	−0.87 (1.28)	2.10 (0.69)	−2.09 (220)	0.04
Weight, kg (N = 121) (N = 248)				
Week 12	0.06 (0.26)	−0.86 (0.17)	3.01 (321)	0.003
Week 24	−0.03 (0.38)	−0.69 (0.22)	1.53 (291)	0.13

[a]MMRM method.

60 mg of duloxetine will do so within 12 weeks, and that additional time on the same dose does not increase remission. For example, among patients who stayed on 60 mg/day throughout 24 weeks, 65.6% achieved remission (HAMD-17 score ≤7) by week 12 and 64.5% were in remission at 24 weeks. Alternatively, for 53 duloxetine-treated patients whose dose was increased to 120 mg at week 12 or later, 26% remitted by endpoint. Although a formal comparator group is not available for the 120-mg duloxetine-treated patients, these data suggest that for some elderly patients who have not reached remission after 12 weeks at 60 mg/day, a dose increase to 120 mg may be beneficial.

Baseline pain scores indicated mild to moderate pain for this study population. Compared with placebo, duloxetine-treated patients had significant improvement in pain severity and interference during the acute phase; similar treatment effects were observed among patients with at least moderate pain at baseline. The pain improvement observed in this study is consistent with previous research evaluating the effects of duloxetine on associated pain symptoms in elderly patients with MDD.[24] Considering that an estimated 65% of elderly depressed patients have comorbid pain (in this sample 57.9% had at least moderate pain), and the negative effects of the interaction between pain and depression,[25–27] the pain reduction achieved by duloxetine-treated patients is an important finding that clinicians may consider when assessing and treating this patient population.

Duloxetine 60 or 120 mg daily for up to 24 weeks was well tolerated. The 12-week acute phase completion rates in this study compare favorably with those reported from an 8-week study[6] of duloxetine in elderly depressed patients (78.3% and 76.9% for the duloxetine and placebo groups, respectively). The TEAEs of dry mouth, constipation, diarrhea, and dizziness occurred in 5% or more of duloxetine-treated patients and twice that of placebo in both phases. Statistically significant pulse increase was observed in duloxetine-treated patients. With the exception of falls, the AE profile observed was similar to previous duloxetine trials and consistent with known duloxetine properties. Throughout the study, a higher percentage of duloxetine-treated patients reported TEAE falls than placebo-treated patients. Because falls are understandably a concern in the elderly population, a Falls Assessment Questionnaire was used at every visit to query patients regarding the occurrence of falls. The solicitation of fall history was unique to this study and may have increased TEAE rates of falls reported in both treatment groups; further analyses of the Falls Assessment Questionnaire data are planned.

Previous duloxetine studies of MDD in the general adult population have reported nausea as the most common TEAE.[28–32] Previous data also suggest that among treatment-näıve patients, taking duloxetine with food, or starting at 30 mg for 1 week before increasing to 60 mg, can reduce the risk of nausea.[31] Possibly the lower starting dose in this study (30 mg), and the instruction to take with food, reduced the incidence of nausea. Overall, these data indicate that duloxetine is well tolerated in elderly patients, and that AEs are no worse than those observed in younger populations.[33]

This 24-week study provides longer-term placebo controlled, double-blind data on antidepressant use in the elderly patients, allowing us to address an important question in late-life depression regarding adequate duration of treatment and, at least in part, separate the effects of duration and dose adjustment. The data also demonstrate the beneficial effect of duloxetine on pain in depressed patients, previously demonstrated in short-term trials, with continued treatment.

The study did not replicate previously reported positive cognitive functioning results for duloxetine; however, cognition did not worsen either. Additional studies are needed to better understand antidepressant treatment effects on cognition in elderly depressed patients.

The study has limitations. Patients were mostly white; however, with inclusion of sites in Puerto Rico and Mexico, 20% of them were Hispanic. Most patients were women and had limited baseline cognitive impairment. Also, patients with a primary axis I disorder other than MDD were excluded. Thus, results may not generalize to other subgroups of elderly depressed patients. Moreover, the timing of the shift from acute to optimization phase was not blinded.

In conclusion, although duloxetine did not show significant improvement over placebo in the HAMD-17 Maier subscale score at 12 weeks of treatment, significantly greater improvement was observed at various time points across the 24-week study period, with similar results in both clinician- and patient-rated depression measures. Also, the study documented the beneficial effects of duloxetine on pain in elderly patients with MDD.

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