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

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