Duloxetine for the Treatment of Recurrent Major Depressive Disorder in Elderly Patients: Treatment Outcomes in Patients With Comorbid Arthritis

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Background: *Evaluation and treatment of major depression (MDD) in elderly patients is frequently complicated by the presence of comorbid medical conditions, which can reduce the effect of depression treatment, leading to lower rates of depressive-symptom improvement and higher rates of relapse.* **Objective:** *The authors investigated results of antidepressant concurrent with arthritis pain treatment in elderly patients.* **Method:** *Patients age 65 and over with recurrent MDD were stratified by arthritis status and randomized to duloxetine (a dual reuptake-inhibitor of serotonin and norepinephrine) or placebo treatment for 8 weeks (duloxetine, N=117; placebo, N=55).* **Results:** *Duloxetine significantly reduced MDD symptom severity in elderly patients with and without arthritis, and produced significant reduction in several pain measures in those patients with comorbid arthritis.* **Discussion:** *The magnitude and time-course of depressive symptom improvement did not differ significantly between patients with and without arthritis. Some studies have suggested that the severity of pain in arthritis patients may be linked to depression severity.*
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Musculoskeletal diseases, especially arthritis, are among the most common chronic diseases in elderly persons. Whereas the prevalence of osteoarthritis (OA) and rheumatoid arthritis (RA) in the overall United States population has been estimated to be 15% and 1%, respectively,[1] the prevalence in cohorts of older subjects is considerably higher: up to 30% for OA and 10% for RA.[2–4] In one community-based survey, the incidence and prevalence of OA in the knee, hip, and hand increased between two- and ten-fold in subjects from age 30 to 65 years.[5]

Another disease entity with high prevalence in this population is major depressive disorder (MDD), affecting up to 5% of individuals over age 65 in community settings.[6] An additional 8% to 16% of the elderly population have clinically significant depressive symptoms.[7] Evaluation and treatment of depression in elderly patients is frequently complicated by the presence of comorbid medical conditions, which can reduce the effect of depression treatment, leading to lower rates of depressive-symptom improvement and higher rates of relapse.[8]

The presence of arthritis in older patients has been associated with poor depression-treatment outcomes. In a

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study of patients age 60 years and over who received inpatient treatment for depression, those with arthritis had significantly higher depression rating scores and significantly lower rates of treatment response at the study's 3-month follow-up when compared with those without arthritis.[9]

A number of studies have assessed the efficacy of antidepressant treatment in depression patients with arthritis, and these have yielded mixed results. Whereas Sarzi Puttini and colleagues found a significant improvement in depressive symptoms in RA patients treated with dothiepin,[10] a subsequent study showed no significant difference between dothiepin and placebo.[11] Other placebo-controlled studies of tricyclic antidepressants (TCAs) in RA yielded negative or mixed results, possibly due to low baseline depression severity and small sample sizes.[12–15] In a non-placebo-controlled comparison study, Bird and colleagues[16] found paroxetine and amitriptyline to be similarly effective in the treatment of depression in patients with RA, and an open-label study of sertraline in the treatment of patients with MDD and RA found that significantly fewer patients were depressed at 6- and 15-month follow-up visits as compared with the baseline assessment.[17] The same group also found that a pharmacologic and cognitive-behavioral combination approach to the treatment of MDD and RA offered no significant benefit over antidepressant monotherapy.[18]

Most of these studies also assessed changes in pain severity during antidepressant treatment. Again, results were mixed, with some studies showing significant decrease in pain severity over the course of treatment[10,11,13,16] and others showing no significant improvement when compared with placebo.[15–18] However, a recent study found that enhanced care for depression also improved pain and functional outcomes in patients with depression and arthritis. In a study of older adults (age ≥60 years) with depression, an intervention comprising antidepressant medications or six-to-eight sessions of psychotherapy, or both, produced significant improvement in pain severity as well as improved functional status and quality of life in conjunction with less depression at the study's 12-month follow-up.[19]

Duloxetine is a dual reuptake-inhibitor of serotonin (5-HT) and norepinephrine (NE) with demonstrated efficacy and safety in the treatment of MDD.[20–23] Results from both placebo-controlled[24] and open-label studies[25] suggest that duloxetine is safe and effective in the treatment of MDD in older patients. Here, we present the results of a pre-specified secondary analysis of outcomes in depression and pain for elderly patients (age ≥65 years) with recurrent MDD and with or without self- or investigator-reported arthritis, in order to measure the effect of duloxetine on pain and MDD outcomes. No formal measures beyond self-reporting of arthritis pain severity are available because the primary study objective (presented elsewhere) was to test the effect of duloxetine on cognition in this patient population.[26]

Because of the stratification for secondary analyses, the samples sizes in the treatment groups being compared are small; therefore, we consider the results presented here as a pilot analysis that may be useful as a basis for further studies.

METHOD

Study Design

This was a randomized, multicenter, double-blind, placebo-controlled clinical trial of duloxetine (60 mg once daily [qd]) in elderly patients with recurrent MDD. The study protocol was reviewed and approved by the ethical review board at each center, in accordance with the principles of the Declaration of Helsinki, and all patients were provided written informed consent documents before the administration of any study procedures or study drug. The primary safety and efficacy results from the study have been presented previously.[26]

Patients (N=467) were screened for eligibility over a 1-week period. After the 1-week screening phase, all patients meeting entry criteria (N=311) entered a 1-week, double-blind, placebo lead-in phase, after which they were randomized in a 2:1 ratio to treatment with duloxetine 60 mg qd (N=207) or placebo (N=104) for 8 weeks. At the conclusion of the 8-week acute-treatment phase, patients entered a 1-week, double-blind discontinuation phase, at which time the dose of study drug was tapered.

The analysis presented here was pre-specified in the study protocol and is based on a secondary stratification of patients with and without self- or investigator-reported comorbid arthritis. The primary study results, examining the effects of duloxetine treatment on cognition in elderly patients with MDD, have been published elsewhere.[26] Patients were defined as having arthritis on the basis of the investigator evaluation, which included patient report, physical exam, and evaluation of concomitant medications. Preliminary subgroup analyses of patients with and without comorbid arthritis were specified a priori within the study protocol. However, given that the number of