

## Original Research Reports

# A Randomized, Placebo-Controlled, Double-Blinded Trial of Duloxetine in the Treatment of General Fatigue in Patients With Chronic Fatigue Syndrome

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**Objective:** To assess the efficacy and safety of duloxetine in patients with chronic fatigue syndrome.

**Methods:** A 12-week, randomized, double-blind study was designed to compare duloxetine 60–120 mg/d ( $n = 30$ ) with placebo ( $n = 30$ ) for efficacy and safety in the treatment of patients with chronic fatigue syndrome. The primary outcome measure was the Multidimensional Fatigue Inventory general fatigue subscale (range: 4–20, with higher scores indicating greater fatigue). Secondary measures were the remaining Multidimensional Fatigue Inventory subscales, Brief Pain Inventory, Medical Outcomes Study Short Form-36, Hospital Anxiety and Depression Scale, Centers for Disease Control and Prevention Symptom Inventory, Patient Global Impression of Improvement, and Clinical Global Impression of Severity. The primary analysis of efficacy for continuous variables was a longitudinal analysis of the intent-to-treat sample, with treatment-by-time interaction as the measure of effect.

**Results:** The improvement in the Multidimensional

Fatigue Inventory general fatigue scores for the duloxetine group was not significantly greater than for the placebo group ( $P = 0.23$ ; estimated difference between groups at week 12 =  $-1.0$  [95% CI:  $-2.8, 0.7$ ]). The duloxetine group was significantly superior to the placebo group on the Multidimensional Fatigue Inventory mental fatigue score, Brief Pain Inventory average pain severity and interference scores, Short Form-36 bodily pain domain, and Clinical Global Impression of Severity score. Duloxetine was generally well tolerated. **Conclusion:** The primary efficacy measure of general fatigue did not significantly improve with duloxetine when compared with placebo. Significant improvement in secondary measures of mental fatigue, pain, and global measure of severity suggests that duloxetine may be efficacious for some chronic fatigue syndrome symptom domains, but larger controlled trials are needed to confirm these results.

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## INTRODUCTION

Chronic fatigue syndrome (CFS) is characterized by severe disabling fatigue of at least 6 months duration that cannot be fully explained by an identifiable medical condition.<sup>1</sup>

Pain symptoms are also a part of the diagnostic criteria for CFS and include muscle pain, multijoint pain, and headaches.<sup>1</sup> Patients with CFS have 2–4

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times the rate of depression and anxiety when compared with the general population.<sup>2</sup> CFS is also commonly comorbid with fibromyalgia, a disorder characterized by chronic widespread pain, tenderness, fatigue, sleep, and mood disturbances.<sup>2-5</sup> The prevalence of CFS ranges from 0.007%–2.8% in the general adult population and 0.006%–3.0% in primary care practice.<sup>6</sup> Although most of those who are diagnosed with CFS are 30–40 years of age, white, and female, CFS affects women and men, adults and children, and all racial and socioeconomic classes.<sup>6</sup>

There are currently no Food and Drug Administration–approved treatments for CFS. There have been several randomized, placebo-controlled trials of antidepressant treatment of CFS. The monoamine oxidase inhibitor phenelzine administered at a dose of 15 mg/d was found to improve fatigue, functional status, and mood states in a 6-week, randomized, double-blind, placebo-controlled phase-in trial.<sup>7</sup> A subjective sense of vigor and energy was improved in 51% of patients with CFS who were taking 600 mg/d of moclobemide, a reversible monoamine oxidase inhibitor, compared with 33% of those receiving placebo in a 6-week trial.<sup>8</sup> The selective serotonin reuptake inhibitor fluoxetine was evaluated in 2 randomized controlled trials. In the first trial, administration of 20 mg/d of fluoxetine over 8 weeks had no beneficial effect on any of the characteristics of CFS studied.<sup>9</sup> In the second study that examined the effect of 20 mg/d of fluoxetine over 6 months, it improved depression only, with no improvements in work capacity or fatigue.<sup>10</sup> Mirtazapine, an antidepressant that enhances central noradrenergic and serotonergic activity, was evaluated in a 24-week mixed cross-over combination design.<sup>11</sup> Patients initially undergoing cognitive-behavioral treatment for 12 weeks followed by mirtazapine for 12 weeks reported significant improvement in fatigue compared with other treatment groups. These results suggest that CFS may respond to a combination of pharmacologic and nonpharmacologic therapies, with the sequence and timing of the interventions having potential importance for their effectiveness. In a recent review of antidepressant trials in CFS, Pae *et al.*<sup>12</sup> concluded that antidepressants may be an option for treating symptoms of CFS regardless of whether comorbid depression is present. However, they noted that more trials are needed to assess the efficacy of antidepressants in the treatment of CFS.<sup>12</sup> The antidepressants

phenelzine, moclobemide, and mirtazapine that were found to have efficacy in the CFS trials reviewed earlier enhance neurotransmission of both serotonin and norepinephrine. These results suggest that increasing both norepinephrine and serotonin in the central nervous system may be more effective in treating CFS than increasing serotonin alone.

Based on the findings in clinical trials of antidepressants with effects on serotonin and norepinephrine, we hypothesized that duloxetine hydrochloride (hereafter referred to as duloxetine), a potent serotonin and norepinephrine reuptake inhibitor, would be safe and efficacious in reducing the symptoms of CFS. To test this hypothesis, we conducted a 12-week, randomized, double-blinded, placebo-controlled, parallel-group, flexible-dose study to assess the safety and efficacy of duloxetine (dosage range: 60–120 mg/d, administered once daily) in 60 outpatients who met the Centers for Disease Control and Prevention (CDC)–defined guidelines for CFS. To our knowledge, this is the first randomized controlled study of duloxetine in the treatment of CFS.

## PATIENTS AND METHODS

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### Overview

The study was conducted in a single outpatient research center in the United States. Enrollment began in October 2006, and the study was completed in June 2012. The institutional review board approved the protocol, and all patients provided written informed consent after the study was explained and their questions were answered and before study procedures were initiated. Patients were identified by physician referral (from both community primary care and tertiary care centers that were made aware of the study through outreach efforts of the investigators) or response to an advertisement for a chronic fatigue medication trial. An institutional review board–approved prescreening phone interview was conducted to identify potential patients for screening.

### Entry Criteria

Female or male patients were eligible for the study if they were between 18 and 65 years of age and met the following criteria for revised CDC definition of CFS: at least 6 months of persistent fatigue that

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