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Research report

Treatment of generalized anxiety disorder with escitalopram: Pooled results from double-blind, placebo-controlled trials

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Abstract

Background: Escitalopram 10 mg/day is an effective and well-tolerated antidepressant. Three randomized controlled trials recently evaluated the safety and efficacy of escitalopram in the treatment of generalized anxiety disorder (GAD).
Methods: The trial designs were virtually identical, allowing data to be pooled across studies. Male and female outpatients, ages 18–80 years, with DSM-IV-defined GAD were randomized to double-blind treatment with escitalopram or placebo for 8 weeks. Escitalopram dose was fixed at 10 mg/day for the first 4 weeks, after which increases to 20 mg/day were permitted. The primary efficacy variable was the mean change from baseline in total Hamilton Anxiety Scale (HAMA) score.
Results: Approximately 850 patients were randomized to double-blind treatment. In each individual study, escitalopram was significantly superior to placebo ($p<0.05$) as measured by change from baseline in HAMA score. By-visit analyses of data pooled across studies revealed significantly greater improvement ($p<0.05$) in the escitalopram group beginning at week 1 or 2 and continuing through week 8 for all primary and secondary efficacy variables. The mean change in HAMA total score from baseline to endpoint also was significantly greater for patients maintained at escitalopram 10 mg/day than for those receiving placebo. Escitalopram was generally well tolerated.
Limitations: The studies included in this analysis were of short-term duration and excluded patients with significant medical and psychiatric comorbidities, such as major depressive disorder.
Conclusion: Results from the individual trials and the pooled analysis demonstrate that escitalopram is effective and well tolerated for the treatment of GAD.

Keywords: Escitalopram; Anxiety; GAD; Pooled; Placebo-controlled

1. Introduction

Generalized anxiety disorder (GAD) is a common disorder characterized by excessive, persistent and uncontrollable worry, nervousness or anxiety, with

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attendant somatic symptoms that may include fatigue, irritability, tension, insomnia, dry mouth, increased sweating and cognitive difficulties (DSM-IV, 1994). GAD patients frequently present with a secondary psychiatric diagnosis, especially depression, and serotonin reuptake inhibitor (SRI) antidepressants are increasingly being considered as first-line agents (Kent et al., 1998).

Escitalopram is a single isomer component of citalopram and is essentially responsible for the serotonin reuptake inhibitory activity of the racemate (Hyttel et al., 1992). Based on a comparative analysis of binding affinities and uptake inhibition at monoaminergic transporters, escitalopram was found to be the most selective SRI available (Owens et al., 2001). Escitalopram has been shown in several placebo-controlled trials to be effective and well tolerated in treating depression at a dose of 10 mg/day (Burke et al., 2002; Wade et al., 2002). At this dose, escitalopram is at least as effective as citalopram 40 mg/day (Burke et al., 2002). Escitalopram also has been shown to be rapidly effective in treating symptoms of anxiety associated with depression (Gorman et al., 2002), and to be active in a number of animal models of anxiety (Miczek et al., 2003; Sánchez, 2003; Sánchez et al., 2003).

The clinical development program to evaluate the efficacy and safety of escitalopram in the treatment of GAD comprised three randomized, double-blind, placebo-controlled trials of similar design, all of which were positive (Davidson et al., 2002, 2004; Forest Pharmaceuticals, data on file, 2002). In this report we present pooled efficacy and safety data across the three studies to examine the effectiveness of the starting dose (10 mg/day), and the overall tolerability, of escitalopram in the acute treatment of GAD.

2. Methods

The safety and efficacy of escitalopram in the treatment of GAD have been evaluated in three randomized, double-blind, placebo-controlled, multicenter studies of 8 weeks duration. The design of these three trials differed only in the method by which dose titration was blinded. All three trials were conducted in the U.S. between July 2000 and February 2002.

2.1. Patients

In each of the three studies, male or female outpatients between the ages of 18 and 80 years who met DSM-IV criteria for GAD and had baseline scores ≥18 on the Hamilton Anxiety Scale (HAMA) (Hamilton, 1959) with a minimum score of 2 on the tension and anxiety items were eligible for inclusion.

Exclusion criteria included a score ≥17 on the Hamilton Depression Rating Scale (HAMD) (Hamilton, 1960), or a lower score on the Covi Anxiety Scale (Lipman, 1982) than the Raskin Depression Scale (Raskin et al., 1969). Also excluded, were patients with a principal diagnosis of any Axis I disorder other than GAD (including major depressive disorder), or who met DSM-IV criteria for bipolar disorder, schizophrenia or any psychotic disorder, obsessive compulsive disorder, mental retardation, or any pervasive developmental disorder or cognitive disorder. A history of psychotic features or disorder, or substance abuse or dependence within the past 6 months also was grounds for exclusion.

Use of any of the following psychoactive medications prior to study entry precluded participation: depot neuroleptics within 6 months; any neuroleptic, antidepressant, or anxiolytic within 2 weeks (5 weeks for fluoxetine); or daily benzodiazepine therapy within 1 month. Use of concomitant treatment with any psychotropic drug (except zolpidem as needed for sleep) was prohibited. Women who were pregnant or breastfeeding, or of child-bearing potential and not practicing a medically reliable method of birth control, also were excluded.

All participants provided written informed consent prior to study entry, and the study protocols were approved by each site's respective Institutional Review Board (IRB), or by a central IRB.

2.2. Dosing

Following a 1-week, single-blind, placebo lead-in period, patients who continued to meet all entry criteria were randomized to 8 weeks of double-blind treatment with escitalopram or matching placebo. During the first 4 weeks of treatment, patients randomized to active drug received a fixed dose of 10 mg/day escitalopram. If the therapeutic response was judged by the investigator to be insufficient at the