A Randomized, Placebo-Controlled Study of Duloxetine for the Treatment of Children and Adolescents With Generalized Anxiety Disorder

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Objective: To evaluate the efficacy, safety, and tolerability of the selective serotonin norepinephrine inhibitor duloxetine in children and adolescents with generalized anxiety disorder (GAD).

Method: Youth aged 7 through 17 years with a primary diagnosis of GAD were treated with flexibly dosed duloxetine (30–120 mg daily, n = 135) or placebo (n = 137) for 10 weeks, followed by open-label duloxetine (30–120mg daily) for 18 weeks. Efficacy measures included the Pediatric Anxiety Rating Scale (PARS), Clinical Global Impression–Severity (CGI-Severity) scale, and Children's Global Assessment Scale (CGAS). Safety measures included the Columbia–Suicide Severity Rating Scale (C-SSRS) as well as vital signs and electrocardiographic and laboratory monitoring.

Results: On the primary efficacy measure (PARS severity for GAD), mean improvement from baseline to 10 weeks was statistically significantly greater for duloxetine (–9.7) compared with placebo (–7.1, $p \leq .001$, Cohen's d: 0.5). Symptomatic response (50% improvement on the PARS severity for GAD), remission (PARS severity for GAD ≤8), and functional remission (CGAS >70) rates for the duloxetine group (59%, 50%, 37%, respectively) were statistically significantly greater than for the placebo group (42%, 34%, 24%, respectively, $p \leq .05$) during acute treatment. Changes in systolic and diastolic blood pressure and discontinuation because of adverse events did not statistically differ between the duloxetine and placebo groups, although gastrointestinal-related adverse events, oropharyngeal pain, dizziness, cough, and palpitations were reported with a statistically significantly greater incidence for the duloxetine group compared with the placebo group. Mean changes in pulse and weight for the duloxetine group (+6.5 beats/min, –0.1 kg, respectively) were statistically different from the placebo group (+2.0 beats/min, +1.1 kg, respectively, $p \leq .01$).

Conclusion: In this study, duloxetine was superior to placebo on the primary efficacy analysis of mean change from baseline to week 10 on the PARS severity for GAD score, and safety results were consistent with the known safety profile of duloxetine in pediatric and adult patients.

Clinical trial registration information—A Study in Pediatric Participants With Generalized Anxiety Disorder; http://clinicaltrials.gov; NCT01226511.

Key Words: selective serotonin norepinephrine reuptake inhibitor, generalized anxiety disorder, duloxetine

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Generalized anxiety disorder (GAD) is common in children and adolescents, with prevalence rates ranging from 2% to 6%.[1-3] Moreover, GAD is characterized by uncontrollable, diffuse anxiety and a myriad of somatic and cognitive symptoms.[4] In youth, this chronic relapsing disorder increases the risk of secondary mood disorders,[5,6] other anxiety disorders,[6] and substance use disorders,[7] as well as suicide attempts and suicidal ideation.[8,9] However, in children and adolescents, anxiety disorders, including GAD, are underrecognized and often untreated.[10]

Accumulating evidence suggests that selective serotonin reuptake inhibitors (SSRIs) are effective psychopharmacologic treatments for youth with GAD and other anxiety disorders and are generally well tolerated.[11] Most prior studies, however, have evaluated these SSRIs and selective serotonin norepinephrine reuptake inhibitors (SSNRIs) in the treatment of "mixed" anxiety disorders, including GAD, social phobia, and separation anxiety disorder because of the extensive symptomatic overlap among these disorders.[11] Two large, randomized, controlled trials have examined the psychopharmacologic treatment of anxiety disorders in youth in a broader sense (including GAD among other diagnoses),[12,13] and 3 double-blind, placebo-controlled studies have evaluated the efficacy of SSRI/SNRIs specifically in youth with a primary diagnosis of GAD.[14,15] In the first study of youth with a primary diagnosis of GAD, fixed-dose sertraline (50 mg/day) was superior to placebo in youth aged 5 to 17 years (n = 22) and was efficacious and well tolerated.[14] In a pooled analysis of 2 studies, children and adolescents aged 6 to 17 years with a primary diagnosis of GAD (n = 320) were treated with flexibly dosed venlafaxine, which was superior to placebo in reducing anxiety

CG Clinical guidance is available at the end of this article.

symptoms, but was associated with statistically significant hemodynamic changes, height and weight effects, and increased serum cholesterol levels.[15] In addition, despite the efficacy of current psychopharmacologic and psychotherapeutic interventions in youth with GAD,[12-15] many children and adolescents with anxiety disorders, including GAD, fail to respond to available treatments,[13,16] and residual, or subsyndromal, symptoms are associated with significant disability and functional impairment in youth.[17] Moreover, given that some youth with anxiety disorders who do not respond to one antidepressant may respond to a second antidepressant,[18] the psychopharmacologic armamentarium is in need of new medications, particularly given that emerging data suggest that the efficacy of antidepressants in pediatric anxiety disorders may vary as a function of the serotonergic potency or selectivity.[19]

Duloxetine, a serotonin and norepinephrine reuptake inhibitor, is efficacious in treating adults with GAD,[20] yet its efficacy in youth with GAD remains unknown. Nonetheless, pharmacokinetic evaluations of duloxetine in the pediatric patient population have suggested that there is no need to modify daily dose based on body weight or age, and that similar daily doses may be used in pediatric and adult patients.[21] In addition, previous studies of duloxetine in children and adolescents with major depressive disorder (MDD) do not suggest any new safety concerns in the pediatric population and are consistent with the known safety and tolerability profile of duloxetine in adults.[21-24] With these considerations in mind, the current study was designed to evaluate the efficacy and tolerability of flexibly dosed duloxetine in pediatric patients with a primary diagnosis of GAD. The current study supported United States regulatory authorization of duloxetine for the treatment of children and adolescents with GAD.[22]

METHOD

Study Design

The protocol for this study (F1J-MC-HMGI) was filed with the United States Food and Drug Administration before study initiation, was approved by the ethics review boards for each study site, and was conducted in accordance with Good Clinical Practice guidelines. Written informed consent and assent (as appropriate) were provided by parents/legal guardians and patients, respectively. The study was conducted at 32 psychiatric clinical sites in 3 countries (United States, Mexico, and South Africa) from June 2011 to June 2013.

The primary objective of the study was to assess the efficacy of flexibly dosed duloxetine compared with placebo in the acute treatment of children (aged 7–11 years) and adolescents (aged 12–17 years) who met criteria for GAD as defined in the *DSM-IV-TR*.[4] This objective was evaluated by assessing the mean change from baseline to endpoint (10 weeks) on the Pediatric Anxiety Rating Scale (PARS)[25] severity score for GAD between duloxetine and placebo. The PARS severity for GAD was the severity assessment specifically for the subset of GAD symptoms identified on the PARS symptom checklist.

For this phase 3, randomized, double-blind, placebo-controlled study, patients were randomly assigned (1:1) to either flexibly dosed duloxetine (30–120 mg once daily [QD]) or placebo via Interactive Voice Response System (IVRS). The study design incorporated a 1- to 4-week screening period, a 10-week double-blind (flexible dose), placebo-controlled, acute treatment period, an 18-week extension treatment period (of which 16 weeks were open label) in which all patients received duloxetine (30–120 mg QD), and a 2-week double-blind dose tapering period.

This study used a flexible dosing strategy in which investigators could make duloxetine dose adjustments in the range of 30 to 120 mg QD based on their assessment of tolerability and response. The study protocol gave the following guidance regarding dose changes: Patients who could tolerate the current dose and whose CGI-S score was >2 should have a dose escalation within the allowed range, and patients who could tolerate the current dose and whose CGI-S score was ≤2 should be maintained at the current dose (a more specific dosing algorithm was not used). All patients received blinded capsules of study drug (duloxetine or matching placebo) to be taken once daily throughout the 10-week double-blind acute treatment period. During the acute treatment period, requests for dose changes were made using the study IVRS. To maintain the blind, the IVRS assigned a study drug package number but did not confirm whether a dose change occurred or did not occur, and all patients, regardless of treatment group (i.e., drug or placebo), took the same number of blinded study drug capsules during the acute treatment period. Patients randomized to duloxetine initiated treatment at 30 mg QD for 2 weeks before dose escalations could occur. Duloxetine could be increased to 60 mg QD at the 2-week time point or later, 90 mg QD at the 4-week time point or later, and 120 mg QD at the 7-week time point or later, up to the 12-week time point. Patients randomized to placebo remained on placebo throughout the 10-week acute treatment period and were then automatically transitioned to duloxetine 30 mg QD for 2 weeks. To complete the transition from the double-blind period to the open-label period, all study patients were transitioned to duloxetine 60 mg QD at the 12-week time point for 2 weeks. At the 14-week time point and thereafter, open-label flexible dosing (30, 60, 90, 120 mg QD) was allowed during extension treatment. Dose escalations throughout the study were required to be sequential with increases in 30-mg increments. Dose decreases because of tolerability issues were permitted. Patients discontinuing from the studies (early termination or 28-week completers) entered a 2-week, drug-tapering phase based on investigators' determination of patient safety. Drug tapering was conducted under double-blind conditions if the patient discontinued during the placebo-controlled acute phase. Patients receiving duloxetine 90 or 120 mg QD at last study visit had their doses reduced to 60 mg QD in the first week of the tapering phase and 30 mg QD in the second week; patients receiving duloxetine 60 mg QD at last study visit had their doses reduced to 30 mg QD in the first week of the tapering phase and received placebo in the second week; and patients receiving duloxetine 30 mg QD or placebo at last study visit received placebo for both weeks of the tapering phase. Tapering was not required for patients discontinuing from duloxetine 30 mg QD during the open-label phase.

Selection of Patients

Study participants were outpatient youth aged 7 through 17 years who met *DSM-IV-TR* criteria for GAD, assessed using the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-Kid),[26] and had the following: a PARS[25] severity for GAD score ≥15 at 2 screening visits; presence of ≥4 symptoms identified on the generalized anxiety subsection of the PARS symptom checklist at 2 screening visits (2 of which were "excessive worry" and "dread or fearful anticipation" [nonspecific]); a Clinical Global Impression of Severity (CGI-Severity)[27] score ≥4 at the 2 screening visits; and significant social, academic, and/or familial dysfunction as determined by the Children's Global Assessment Scale (CGAS)[28] score of ≤60 at 2 screening visits. Patients were required to be medically stable based on the physical examination, laboratory tests, and