Venlafaxine ER for the Treatment of Pediatric Subjects With Depression: Results of Two Placebo-Controlled Trials

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ABSTRACT

Objective: The safety, efficacy, and tolerability of venlafaxine extended release (ER) in subjects ages 7 to 17 years with major depressive disorder were evaluated in two multicenter, randomized, double-blind, placebo-controlled trials conducted between October 1997 and August 2001. **Method:** Participants received venlafaxine ER (flexible dose, based on body weight; intent to treat, $n = 169$) or placebo (intent to treat, $n = 165$) for up to 8 weeks. The primary efficacy variable was the change from baseline in the Children's Depression Rating Scale-Revised score at week 8. **Results:** There were no statistically significant differences between venlafaxine ER and placebo on the Children's Depression Rating Scale-Revised in either study. A post hoc age subgroup analysis of the pooled data showed greater improvement on the Children's Depression Rating Scale-Revised with venlafaxine ER than with placebo (−24.4 versus −19.9; $p = .022$) among adolescents (ages 12–17), but not among children (ages 7–11). The most common adverse events were anorexia and abdominal pain. Hostility and suicide-related events were more common in venlafaxine ER–treated participants than in placebo-treated participants. There were no completed suicides. **Conclusions:** Venlafaxine ER may be effective in depressed adolescents. However, its safety and efficacy in pediatric patients has not been established. Prescribers should monitor for signs of suicidal ideation and hostility in pediatric patients taking venlafaxine ER. *J. Am. Acad. Child Adolesc. Psychiatry,* 2007;46(4):479–488. **Key Words:** depression, serotonin norepinephrine reuptake inhibitor, venlafaxine, randomized, controlled trial, pediatric.

Major depressive disorder (MDD) is a common and recurrent disorder in pediatric populations, with a prevalence of approximately 2% in children and 4% to 8% in adolescents (Birmaher et al., 1998; Emslie et al., 1997a). The National Comorbidity Survey of 1,769 adolescents and young adults reports a lifetime prevalence rate of 15.3% for MDD (Kessler and Walters, 1998). Prepubertal patients with MDD have significantly worse psychosocial outcomes than age-matched normal control subjects (Geller et al., 2001), and depressed adolescents are at continued risk of recurrences with persistence of depressive episodes and psychosocial morbidity into adulthood (Rao et al., 1995).

Pharmacological approaches to treating MDD in pediatric populations have been based on small, underpowered studies or on extrapolation of data from adult studies (Weller et al., 2004). Recent controlled clinical trials in depressed pediatric populations evaluated the efficacy of antidepressants, including fluoxetine (Emslie et al., 1997b, 1998, 2002), paroxetine (Braconnier et al., 2003; Keller et al., 2001), sertraline (Wagner et al., 2003), and citalopram (Sood et al., 2004; Wagner et al., 2004), but with mixed

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results. Selective serotonin reuptake inhibitors (SSRIs) may be considered for use in pediatric patients with depression because of relatively favorable safety profiles and ease of use (Cheung et al., 2005; DeVane and Sallee, 1996; Leonard et al., 1997). However, fluoxetine is the only SSRI approved by the U.S. Food and Drug Administration (FDA) for use in children and adolescents with depression (U.S. Food and Drug Administration, 2006).

Venlafaxine extended release (ER), a serotonin norepinephrine reuptake inhibitor, is approved for treatment in adults with MDD, generalized anxiety disorder, social anxiety disorder, or panic disorder (Effexor XR package insert, Wyeth Pharmaceuticals, Collegeville, PA, 2005). We report the results of two controlled trials designed to evaluate the safety and efficacy of venlafaxine ER treatment in outpatient children and adolescents with MDD.

METHOD

Study Design

Two similarly designed multicenter, randomized, double-blind, placebo-controlled, flexible-dose trials were conducted between October 1997 and August 2001 at a total of 50 clinical sites in the United States. Study 1 was performed at 14 predominantly academic sites, and study 2 at 37 sites (one site participated in both studies). The institutional review board for each center approved the study protocol(s). Written informed consent was obtained from the parents of all subjects before enrollment. Subjects provided signed and witnessed assent.

After a single-blind, placebo lead-in period (14 ± 3 days in study 1, 7 ± 3 days in study 2), eligible subjects were randomly assigned to receive venlafaxine ER or placebo once daily for 8 weeks, followed by a taper period of up to 14 days. Dose-finding studies of venlafaxine ER in children and adolescents have not been conducted. Subjects received 37.5 mg/day during the first week of treatment. For subjects weighing 25 to 39 kg, the dose could be increased to 75 mg beginning on day 8, and to 112.5 mg on day 29. For subjects weighing 40 to 49 kg, the dose was increased to 75 mg on day 8 (mandatory increase) and could be increased to 112.5 mg beginning on day 15 and to 150 mg beginning on day 29. For subjects weighing ≥50 kg, the dose was increased to 75 mg on day 8 (mandatory increase) and could be increased to 150 mg beginning on day 15 and to 225 mg beginning on day 29. Subjects visited the clinic at screening (prestudy), baseline, and days 4 (study 1 only), 7,14,21,28,42, and 56 and at the end of the taper period.

Study Participants

Diagnosis and Inclusion Criteria. Participants were outpatient children and adolescents ages 7 to 17 years who met *DSM-IV* (American Psychiatric Association, 1994) and Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime version (Kaufman et al., 1997) criteria for MDD, had prestudy and baseline scores >40 on the Childhood Depression Rating Scale-Revised (CDRS-R; Poznanski et al., 1985) with ≤30% decrease between prestudy and baseline, had Clinical Global Impression-Severity (CGI-S; Guy, 1976) score ≥4 at prestudy and baseline, and had depressive symptoms for at least 1 month before study entry.

Exclusion Criteria. Participants were excluded if any of the following criteria were met: history of any psychotic disorder or bipolar disorder; MDD with psychotic features, anorexia or bulimia, conduct disorder, panic disorder, or obsessive-compulsive disorder; first-degree relative with bipolar disorder; recent drug or alcohol dependence or abuse; acute suicidality; serious medical problem or mental disorder caused by general medical condition; use of venlafaxine/venlafaxine ER within 6 months or fluoxetine within 21 days; use of investigational drugs, antipsychotics, or electroconvulsive therapy within 30 days; use of monoamine oxidase inhibitors, triptans, or herbal products within 14 days; and use of any other antidepressants, anxiolytics, sedative-hypnotics, stimulants, other psychotropic drugs or substances or nonpsychopharmacologic drugs with psychotropic effects (except if on stable dose for more than 1 month) within 14 days from the start of double-blind treatment. Females with a positive β-human chorionic gonadotropin test result at prestudy were excluded.

Outcome Measures and Schedule of Assessments

The primary outcome measure was the CDRS-R score. Secondary outcome measures were the 21-Item Hamilton Rating Scale for Depression ($HAM\text{-}D_{21}$) (Hamilton, 1960), Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), and CGI-S and CGI-Improvement scales. The CDRS-R, HAM-D, and MADRS were administered at prestudy, baseline, and days 4 (study 1 only), 7, 14, 21, 28, 42, and 56; the CGI was administered at baseline (CGI-S only), and days 4 (study 1 only), 7, 14, 21, 28, 42, and 56.

Safety Assessments and Schedule

Safety assessments included reports of adverse events (AEs), results of routine physical examinations, vital sign and weight recordings, laboratory determinations, and electrocardiogram (ECG) readings. Vital signs and body weight were evaluated at prestudy, baseline, each on-therapy visit, and poststudy. Height and oral temperature were measured at prestudy and on day 56.

AEs were defined as any untoward, undesired, or unplanned clinical event in the form of signs, symptoms, or laboratory or physiological observations, regardless of causal relationship. AEs were based on signs or symptoms detected during the physical examination and clinical evaluation of the subject, and from subject responses to the nonspecific question: "How have you been feeling since your last visit?" Standard COSTART dictionary terminology was used to classify reported events. Treatment-emergent AEs were defined as those not seen before the first dose of double-blind study medication was taken or those that worsened during treatment. Serious AEs (SAEs) were defined as AEs that were fatal or life threatening; required or prolonged hospitalization; resulted in persistent disability, cancer, or congenital anomaly; or events that, based on appropriate medical judgment, may have jeopardized the subject or required medical or surgical intervention to prevent one of the above outcomes.