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USE OF VENLAFAXINE IN CHILDREN AND ADOLESCENTS: A REVIEW OF CURRENT LITERATURE

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Pediatric psychopharmacology is hindered by the relative lack of controlled, empirical clinical trials [Shatzberg and Nemeroff, 1998: Washington, D.C.: The American Psychiatric Press, Inc. p 301–306]. Psychiatric disorders in children and adolescents carry considerable morbidity, impede development, and carry a significant mortality by suicide. Therefore, there is a need for studies of antidepressants and other psychotropics in children and adolescents. This article reviews the preliminary evidence that venlafaxine (Effexor™), a novel antidepressant, may be useful in children and adolescents with a variety of psychiatric disorders. Depression and Anxiety, Volume 12, Supplement 1:85–89, 2000. *© 2000 Wiley-Liss, Inc.*

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INTRODUCTION

Venlafaxine is a bicyclic phenyl and ethylamine derivative, which received FDA approval for release as an antidepressant in 1994. Its novel chemical structure distinguishes it from commonly prescribed classes of antidepressants such as selective serotonin reuptake inhibitor (SSRIs) and tricyclic antidepressants (TCAs). Venlafaxine was identified as having possible antidepressant activity when it was observed to displace [^{3}H]imipramine from rat cortical binding receptors, which is a standard measure of a compound's ability to inhibit serotonin uptake. In vitro, it was observed that venlafaxine blocks the reuptake of both norepinephrine and serotonin. Thus it can be described as a serotonin-norepinephrine reuptake inhibitor (SNRI). Venlafaxine is also a weak inhibitor of dopamine but does not inhibit monoamine oxidase. Muth [1986] showed that Venlafaxine has antidepressant activity similar to the TCAs but lacks their characteristic side effects. Additional preclinical studies found that it does not bind to the neuroreceptors associated with these adverse effects. However, venlafaxine's in vivo activity is consistent with the behavioral effects of other antidepressants.

Venlafaxine and its active metabolite, O-desmethylvanlafaxine (ODV), strongly inhibit neuronal reuptake of serotonin, norepinephrine, and, to a lesser extent, inhibit reuptake of dopamine in in vitro studies. Venlafaxine and ODV do not have substantial affinity for muscarinic, cholinergic, histamine-H_1, or α-adrenergic receptors in vitro, nor do they inhibit monoamine oxidase A (MAO-A) or monoamine oxidase B (MAO-B). Because of its more selective biochemical activity, venlafaxine is associated with fewer anticholinergic, central nervous system, and cardiac side effects [Schatzberg and Nemeroff, 1998] compared to the TCAs.

VENLAFAXINE STUDIES IN ADULTS

Venlafaxine's efficacy in the treatment of depressed adults has been demonstrated in several clinical trials. In a placebo-controlled trial of venlafaxine treatment of major depression, 60 outpatients meeting DSM-III criteria for major depression were randomized to one of three 6-week treatment regimens (25 mg tid, 75 mg tid, or 125 mg tid). Sixty-eight per cent of all the venlafaxine treatment groups achieved a moderate or marked improvement on the Clinical Global Impression scale, compared to 31% of the placebo group. Venlafaxine was well tolerated. The only side effects observed more frequently with venlafaxine than placebo were nervousness, sweating, and nausea [Schweizer et al., 1991].

Guilfi et al. [1991] investigated the short-term efficacy and safety of venlafaxine in 93 depressed inpatients. Subjects receiving venlafaxine (average daily dose = 350 mg

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during weeks 2–4) had significant improvement in their mood symptoms compared to those receiving placebo. Response rate was rate 65% for venlafaxine and 28% for placebo. Significantly more placebo-treated patients (40%) than venlafaxine-treated patients (9%) discontinued treatment early because of lack of efficacy. Also in 1991, Khan et al. published a double-blind, placebo-controlled study of 93 depressed outpatients. There was significantly greater improvement in patients receiving venlafaxine versus those receiving placebo. Furthermore, this clinical trial suggested that venlafaxine may have antidepressant activity within the first 2 weeks of treatment. Side effects associated with TCAs (anticholinergic, histaminergic, and cardiovascular) were not experienced by these patients on venlafaxine, which is compatible with the preclinical pharmacological profile of the compound predicted by Muth [1991].

In a more recent study, Lenderking et al. [1999] reported the effect of venlafaxine on social activity level, daily functioning, and quality of life in depressed outpatients from two placebo-controlled trials. The General Life Functioning Questionnaire (GLF) and a ten-item Activities Questionnaire (AQ) were used to assess these variables. Subjects were 600 outpatients who met DSM-III-R criteria for major depression. In both studies, venlafaxine had been shown to significantly improve depressive symptoms. Venlafaxine also appeared to improve total AQ scores, social interaction, task-related activity, and GLF scores even when effects of improvement in depressive symptoms were controlled for.

Venlafaxine has been studied in the treatment of other psychiatric disorders but not as extensively as for depression. In 1996 Findling et al. treated ten subjects diagnosed with ADHD in an 8-week open-label trial of venlafaxine and reported significant improvement in ADHD symptomatology. A chart review of nine patients treated with venlafaxine for social phobia found eight patients were markedly improved with venlafaxine [Kelsey 1995].

Some isolated reports of venlafaxine treatment of adults with obsessive-compulsive disorder (OCD) have been described as well. Annanth et al. [1995] reported on two middle-aged men with severe symptoms of OCD who were both treated with 150 mg/day of venlafaxine after they had failed trials of fluoxetine, paroxetine, and clomipramine. In both patients, symptom improvement was rapid and dramatic [Annanth 1995]. One of the patients stopped taking venlafaxine after 4 weeks because his insurance company would not pay for it. Subsequently, he experienced an exacerbation of his obsessions and compulsions. In 1996, Grossman et al. reported the case of a patient whose occupational and social functioning greatly improved after beginning venlafaxine. In a 12-week open trial of venlafaxine described by Rauch et al. [1996], overall improvement in OCD was significant, suggesting antiobsessional effects for venlafaxine.

VENLAFAXINE STUDIES IN CHILDREN AND ADOLESCENTS

Because of its low side-effect profile and early onset of action, efficacy observed in clinical trials in adults, venlafaxine has been suggested as medication that might be used in children and adolescents. Although the efficacy and tolerability of venlafaxine in children and adolescents have not yet been adequately demonstrated, preliminary data suggests that venlafaxine may be useful in a variety of psychiatric disorders in this age group. To date, only a limited number of double blind, placebo-controlled studies of venlafaxine in children and adolescents have been conducted. However, some early reports of venlafaxine in treatment of depression, ADHD, autism spectrum disorder, and conduct disorder in children and adolescents have yielded promising results.

VENLAFAXINE IN CHILDREN AND ADOLESCENTS WITH DEPRESSION

As mentioned earlier, there are only a few double-blind, placebo-controlled trials of venlafaxine in children and adolescents. In one such study, Mandoki et al. [1997] treated 33 subjects, 8 to 17 years of age, who met DSM-IV criteria for major depression based on a baseline evaluation using a set of standardized depression and behavioral inventories. These inventories included the Children's Depression Inventory (CDI), the Child Behavior Checklist (CBCL), the Hamilton Scale for Depression (HAM-D), and the Child Depression Rating Scale (CDRS). Subjects were treated for 6 weeks with either venlafaxine and cognitive behavioral psychotherapy or placebo and cognitive behavioral psychotherapy. The CDI, CBCL, HAM-D, and CDRS were used to assess weekly patient progress. Subjects in both medication and control groups improved over time. However, there was no significant difference between the two groups. Because of the concerns about the safety of venlafaxine in children and adolescents, the investigators used low doses (ranging from 12.5 mg qd to 25 mg tid), which may be suboptimal doses of venlafaxine [Mandoki et al., 1997]. The authors also proposed that the short duration of treatment in this study may not have been sufficient for the venlafaxine to manifest its full effect. Regarding the rate of onset of action of venlafaxine, results indicated that pattern of improvement was the same for both the venlafaxine and placebo groups. The investigators suggested that venlafaxine was not associated with rapid onset of action and rapid improvement compared to placebo. However, they found a low side-effect profile of venlafaxine in children and adolescents. Observed side effects included nausea in both children and adolescents and increased appetite in adolescents. In general, venlafaxine was well-tolerated by all subjects.

There have also been two case reports of depressed adolescents that suggest a combination of venlafaxine and lithium may be beneficial in the treatment of depression. Walter et al. [1998] reported that when two 16-year-old depressed patients being treated with venlafaxine were augmented with lithium, there was rapid marked improvement in mood and function. The first patient had a 3-month history of low mood, early insomnia, irritability, reduced concentration, social withdrawal, and suicidal thoughts when sertraline was started soon after the onset of illness. However, after 3 months of treatment with a maximum dose of 150 mg daily, there was only fleeting improvement. Sertraline was then stopped and venlafaxine was started and titrated to 112.5 mg per day. Two weeks later, the adolescent remained profoundly depressed and began to self-mutilate. With continued deterioration, lithium carbonate was added (1,250 mg daily; serum level 0.63 mmol/L). After 2 days of lithium augmentation, the boy's mood improved significantly, and he described himself as being "free of mental turmoil."

The second patient was a 16-year-old female with a 5-month history of depression. Symptoms included sadness, bouts of anger, hypersomnia, loss of interest in activities, poor concentration, and suicidal thoughts. Treatment with supportive psychotherapy and fluoxetine 40 mg daily was unsuccessful. Fluoxetine was stopped and venlafaxine was prescribed at a dose of 150 mg daily for 8 weeks without improvement. Then Lithium carbonate 500 mg daily was added (serum level 0.40). Within 7 days, her mood was markedly improved, and she was no longer suicidal. A month later she reported being almost back to her normal self. These two cases suggest combining lithium and venlafaxine may be helpful in some children and adolescents with depression.

VENLAFAXINE IN CHILDREN AND ADOLESCENTS WITH ADHD

Use of venlafaxine for attention-deficit/hyperactivity disorder was first reported in 1995. Pleak and Gormly described an 11-year-old African American girl with severe ADHD (combined type), with comorbid conduct and obsessive-compulsive disorders. Her ADHD symptoms had not responded to methylphenidate and clonidine. After a trial of lithium (serum levels 0.8–1.3), the patient's impulse control improved markedly. Her obsessive-compulsive symptoms included rituals of collecting used tissue, collecting hair, counting, and repeated washing in the bathroom. These symptoms had failed to respond to psychotherapy or pharmacotherapy with fluoxetine, paroxetine, and sertraline. Finally, the patient and family agreed to a trial of venlafaxine, which was gradually increased from 37.5 mg t.i.d. to 100 mg t.i.d. After 6 weeks of treatment, she showed a moderate to marked response with improved attention, reduced intrusiveness, less fidgetiness, improved organization, and reduced obsessive-compulsive symptoms. The authors hypothesized that venlafaxine improved the ADHD symptoms through inhibition of norepinephrine reuptake and improved impulsivity and OCD symptoms through inhibition of serotonin reuptake.

In 1996, Olvera et al. published results of a 5-week open trial of venlafaxine in 16 children and adolescents with ADHD. The mean daily venlafaxine dose was 60 mg (1.4 mg/kg) administered in 2–3 divided doses. Of the 14 patients who completed the study, 7 showed a decrease of at least 1 standard deviation from baseline on one of the Conners Parent Rating Scale (CPRS) subscale scores with subjective report of improved behavior by their parent. However, cognitive performance or reaction time on the Conners version of the Continuous Peformance Test (CPT) did not improve. Three subjects had a worsening of their hyperactivity and venlafraxine was discontinued. Nausea led to the discontinuation of venlafaxine in one subject. No adverse effects on blood pressure or heart rate were observed. Two of the patients were lost to follow-up.

Based on their sample, the investigators argued that low doses of venlafaxine reduced the behavioral symptoms, but not the cognitive symptom, of ADHD in 7 of these 16 subjects (44%) by the fifth week of treatment. Four subjects (25%) had intolerable adverse effects. Olvera et al. [1996] noted that due to the small sample size, open-label design, and low doses of venlafaxine used in this study, controlled trials with higher maximum doses are needed to further investigate the effectiveness of venlafaxine for the treatment of ADHD in this age group.

VENLAFAXINE IN CHILDREN AND ADOLESCENTS WITH AUTISM SPECTRUM DISORDER

Hollander et al. [2000] published findings from an open-label, retrospective clinical report of venlafaxine in children, adolescents, and young adults with autism spectrum disorder. Ten subjects who met DSM-IV diagnostic criteria for an autism spectrum disorder were treated with a flexible dose of venlafaxine. Age ranged from 3 to 21 years. There were 8 children and adolescents and 2 young adults. The mean length of treatment was 4.77 ± 2.46 months. Minimum treatment duration was 1 month and maximum treatment duration was 10 months. Four patients met criteria for autism, five for Asperger's Syndrome, and one for pervasive developmental disorder not otherwise specified. Five patients had comorbid diagnoses which included ADHD, body dysmporphic disorder, separation anxiety, obsessive-compulsive disorder, and Tourette's Disorder. Seven of the patients had IQ testing performed at baseline. Range was 65–115. Although several patients had been on psychotropic medications prior to venlafaxine treatment, all subjects had been off medications for at least 1 week before receiving venlafaxine.

Two subjects took concomitant medication during the study. One received clomipramine 75 mg q.d. and diazepam 2 mg p.r.n., and the other was on divalproex sodium 250 mg q.d. and dextroamphetamine 15 mg q.d.

Patients were started on 12.5 mg of venlafaxine once daily. Dose was increased as clinical response and side effects were monitored. Six subjects were judged as sustained treatment responders, since they scored 1 (very much improved) or 2 (much improved) on the Clinical Global Impression improvement scale. The authors noted improvement in each of the core dimensions in autism, i.e., social deficits, communication and language impairment, restricted interests, and repetitive behaviors. There were decreased repetitive behaviors and fewer obsessional symptoms. In the social interaction domain, improvement in eye contact, socialization, and an increased complexity of play was noted. Improvements were also noted in contextual language usage and abnormal vocalizations. The investigators observed improvement in "features" of ADHD in five of the six responders, i.e., better focus or attention in four patients and improved impulse control in two patients.

This report is limited by its small sample size, open retrospective design, and inclusion of two patients on concomitant medications. However, the improvement noted in six of ten patients treated with venlafaxine for autism spectrum disorders suggests that prospective, placebo-controlled trials of venlafaxine in these patients are indicated.

VENLAFAXINE IN CHILDREN AND ADOLESCENTS WITH CONDUCT DISORDER

Derivan et al. [1997] used venlafaxine to treat children and adolescents with conduct disorder. Design was a randomized, double-blind, third party unblind, placebo lead-in study. 13 children and 12 adolescents (6–15 years of age) who met DSM-III-R diagnosis of conduct disorder with or without comorbid ADHD were treated with venlafaxine. Medication was started at 12.5 mg and increased to 25 mg q.d. Duration of treatment was 6 weeks with a 2 year treatment extension period for responders. Subjects were assessed with the Child Behavior Rating Form and the Children's Depression Rating Scale. The authors reported significant clinical improvement in children and adolescents with conduct disorder both with and without ADHD. Venlafaxine appeared to be well-tolerated in these children and adolescents.

This study also sought to obtain preliminary pharmacokinetic data on the appropriate dosing of venlafaxine in children and adolescents. The investigators found that key pharmacokinetic parameters, Area Under the Curve (AUC) and clearance, were different in children and adolescents compared to adults. A given dose in children and adolescents resulted in a lower mean plasma concentration of venlafaxine and O-desmethyl-venlafaxine than the same dose in adults. Based on these preliminary pharmacokinetic data, children and adolescents would need to receive venlafaxine doses approximately 1.5 times the doses given to adults (on per kilogram basis) in order to achieve similar blood levels.

ADVERSE EFFECTS OF VENLAFAXINE IN CHILDREN AND ADOLESCENTS

Reports of the adverse side effects associated with venlafaxine in children and adolescents are fairly consistent in the literature. In a study of venlafaxine treatment of depression, Mandoki et al. [1997] reported a relatively low side-effect profile in children and adolescents. Nausea in both children and adolescents and increased appetite in adolescents were the most frequently reported adverse effects. However, these side effects were not severe enough to discontinue medication. It should be noted that a relatively low dose of venlafaxine was used in this study (maximum dose was 25 mg t.i.d.).

As mentioned previously, Olvera [1997] suggested that behavioral activation may be a relatively common side effect of venlafaxine in children and adolescents with ADHD. In this study three of the four subjects who discontinued medication did so because of increased "hyperactivity." Drowsiness, irritability, and nausea were also significant adverse effects. However, they were mild in severity.

In the previously discussed study of youth with conduct disorder [Derivan 1995], the most reported venlafaxine side effect was nausea, which occurred in 38% of children and 25% of adolescents. Other side effects included nasal congestion (23% in children, 17% in adolescents), insomnia (15% in children, 8% in adolescents), and dizziness (8% in children, 17% in adolescents).

Adverse effects of venlafaxine in children and adolescents have also been documented in case reports. Samuel [2000] reported priapism possibly associated with venlafaxine treatment in a 16-year-old white male with depressive symptoms, alcohol abuse, and intermittent cannabis use. He had been free of all psychotropic medications for over a year before starting a trial of venlafaxine. Dose was started at 37.5 mg/day and increased to 150 mg/day with good response. Two and a half months after starting venlafaxine, the patient reported prolonged erections on four separate occasions of sexual intercourse. There were no problems with libido, erection, or ejaculation. However, after ejaculating the patient maintained an erection for at least 3 hours on one occasion and for 8 hours on another occasion. The patient had not experienced such prolonged erections prior to taking venlafaxine. He denied using drugs or alcohol. The only other

medications he was taking were over-the-counter ibuprofen and guaifenesin (Robitussin®). He was advised to reduce the venlafaxine to 112.5 mg/day and obtain a urine drug screen. The patient did not follow-up as advised. When he returned to treatment 3 months later, he had stopped taking venlafaxine 6 weeks previously and had not experienced any prolonged erections subsequently.

Another case report found diastolic hypertension as a possible side-effect of venlafaxine in children and adolescents. In treating an 11-year-old African-American girl for ADHD, Pleak and Gormly [1995] observed a steady increase in the patient's diastolic blood pressure as venlafaxine was increased from 37.5 mg t.i.d to 100 mg t.i.d. The patient's diastolic blood pressure was 84–94 mm Hg at the maximum dose. After tapering venlafaxine to 75 mg t.i.d., the patient's blood pressure normalized. The authors suggested that the blood pressure of all children and adolescents treated with venlafaxine should be monitored, and if diastolic hypertension develops the dose should be reduced.

FUTURE DIRECTIONS OF VENLAFAXINE TRIALS IN CHILDREN AND ADOLESCENTS

Based on the preliminary data obtained in these case reports, open-label studies, and controlled studies, further study of the safety and efficacy of venlafaxine in children and adolescents is needed. Currently, two large multi-center studies of venlafaxine in children and adolescents are underway.

A double-blind, placebo-controlled study of venlafaxine-ER in children and adolescents with major depression was started in 1997. Projected enrollment for this multicenter study is approximately 158 outpatients. Subjects are 7–17 years of age and meet DSM-IV criteria for major depressive disorder. Subjects are being randomized to venlafaxine or placebo in a 1:1 ratio for 8 weeks of treatment. This is followed by a 2-week period of tapering venlafaxine. The initial dose of venlafaxine for this study begins at 37.5 mg/day for the first week of treatment and increases to 75 mg/day for weeks 2–8. Results from the study are not yet available.

There is also a double-blind, placebo-controlled study of venlafaxine treatment underway of adolescents with social anxiety disorder. In this study, it is planned to treat approximately 290 patients, 12–17 years of age, who meet DSM-IV criteria for social anxiety disorder. Patients are randomized to venlafaxine or placebo in a 1:1 ratio for a 16-week trial. Dose of study medication will vary from 37.5 mg/day to 150 mg/day, depending on clinical response. These studies, combined with further individual case reports, large case series, and controlled studies will provide more information about the safety and efficacy of venlafaxine in children and adolescents.

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