DEPRESSION AND ANXIETY, VOLUME 12, SUPPLMENT 1:90–94 (2000)

USE OF VENLAFAXINE IN OTHER PSYCHIATRIC DISORDERS

Philip T. Ninan, M.D.*

Venlafaxine is a medication available by prescription in the U.S. both in an immediate release and an extended release formulation. Preclinical studies indicate it has the effect of potently blocking the serotonin and norepinephrine transporters. Venlafaxine is approved by the FDA for the treatment of major depressive disorder and generalized anxiety disorder. Suggestive evidence, mostly from open label case series, indicates efficacy of venlafaxine in several other conditions including panic disorder, social anxiety disorder, obsessive compulsive disorder, trichotillomania, ADHD, chronic pain, and fibromyalgia. The limited evidence supporting efficacy in these conditions is reviewed. Additional randomized clinical trials with placebo controls are indicated. Depression and Anxiety, Volume 12, Supplement 1:90–94, 2000. *© 2000 Wiley-Liss, Inc.*

Key words: ***serotonin; norepinephrine; venlafaxine; major depressive disorder; anxiety; panic disorder***

INTRODUCTION

Venlafaxine is a medication available by prescription in the U.S. for the past 5 years. It has received regulatory approval by the FDA for the indications of major depressive disorder and generalized anxiety disorder. Originally available in an immediate release formulation, it was subsequently manufactured in an extended release form. Extended release venlafaxine, marketed under the trade name Effexor XR, has a similar bioavailability profile but without the peaks and valleys of the immediate release formulation [Troy et al., 1997]. The clinical significance of these characteristics is the possibility of once daily dosing and better tolerability from reduced side effects.

The efficacy of a pharmacological compound for a diagnosis is best documented by randomized clinical trials with placebo controls. However, such efficacy trials are complex and costly to conduct and in the U.S. are largely performed for regulatory purposes to obtain approval from the FDA for marketing purposes. These studies involve patients with limited co-morbid conditions and a moderate degree of symptoms, who often respond to advertisements. Consequently, a medication may be effective for many diagnostic conditions, but evidence to support their efficacy is not gathered because such studies are not funded or performed. In the absence of randomized clinical trials, case reports, particularly a large series, provide the clinician suggestive evidence of efficacy. However, such reports are open to bias, which should diminish the weight clinicians provide to these reports [Schulz et al., 1995].

This article examines the literature on the suggestive efficacy of venlafaxine in conditions not otherwise covered in this supplement. A medline search of the literature was conducted to examine reports of studies with venlafaxine in the treatment of disorders other than major depression and generalized anxiety disorder. This manuscript reviews mostly case series examining efficacy but does not include isolated single case reports. All of the reports reviewed involve the immediate release formulation of venlafaxine.

With the increasing recognition that co-morbidity is the rule rather than the exception, efficacy of venlafaxine in a condition may be the result of benefit in general anxiety or depressive symptoms. Thus, a certain caution is necessary prior to stating definitely that the benefit is independent of the antidepressant or anti-anxiety effects of venlafaxine.

PANIC DISORDER

Panic Disorder is characterized by sudden repetitive attacks of intense anxiety-labeled panic attacks. It can result in anticipatory anxiety and avoidance (phobias) of places or situations associated with the panic attacks. Several pharmacological agents as well as psychotherapeutic treatments have documented the efficacy in the treatment of panic disorder with or without phobic avoidance. Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine and sertraline have documented efficacy in controlled studies for the treatment of panic disorder. Similarly, benzodiazepines, such as alprazolam and clonazepam, have also documented efficacy, as well as tricyclic antidepressants such as imi-

Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia

*Correspondence to: Dr. Philip T. Ninan, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1841 Clifton Road, Room 401, Atlanta, GA 30322. E-mail: philninan@learnlink.emory.edu

pramine and clomipramine [American Psychiatric Association. Practice Guidelines, 1998].

Pollack et al. [1996] reported a double-blind placebo controlled study of venlafaxine in panic disorder. Twenty-five patients with panic disorder were randomized with 13 receiving venlafaxine (average dose 156 mg/day) for 8 weeks of treatment. Venlafaxine was statistically superior to placebo on the Clinical Global Impressions (CGI) scale. A numerical decrease, short of statistical significance, was evident with venlafaxine over placebo on panic, generalized anxiety, phobic fear, and avoidance as well as depressive symptoms. The results are encouraging since the small sample size raises the potential for a type II statistical error: a failure to detect a real difference because of limited subjects.

A case series by Papp et al. [1998] report an open label trial of venlafaxine in 13 patients (10 female) treated for 10 weeks. Seven met criteria for agoraphobia; nine completed the study, and two dropped out because of side effects, while another two dropped out for non-study-related reasons. The average dose of venlafaxine was 93 mg/day. All patients were panic free by the end of the trial. In addition there was a statistically significant decrease in the CGI and the HAM-A scores.

Geracioti [1995] reported another case series of four patients with panic disorder (with at least two suffering from agoraphobic avoidance). They were treated with open label venlafaxine (between 50 and 75 mg daily) and all four responded with complete cessation of panic attacks.

These reports provide suggestive evidence of the efficacy of venlafaxine in the treatment of panic disorder. However, caution is indicated because of the high potential for placebo response in panic disorder. Of interest, these reports indicate efficacy at times, with relatively low doses of venlafaxine. Assessment of benefit for avoidance behavior is in need of additional study, since a considerable amount of disability results from the phobic components of the illness. If supported by additional placebo-controlled randomized clinical trials, venlafaxine would be a useful addition to the choices clinicians have for the pharmacological management of panic disorder.

SOCIAL ANXIETY DISORDER

Social anxiety disorder (or social phobia) is characterized by intense anxiety and often avoidance of situations where the individual is the focus of attention. These could involve both social and/or performance situations. The individual fears embarrassment or humiliation. SSRIs such as paroxetine, benzodiazepines such as clonazepam, irreversible MAO inhibitors such as phenelzine, and reversible MAO inhibitors such as brofaramine have documented efficacy in social anxiety disorder [Liebowitz, 1999]. Additionally, cognitive behavior therapy has also documented efficacy in social anxiety disorder.

Altamura et al. [1999] reported 12 patients (7 women) with social anxiety disorder who had previously failed to respond to an SSRI and were treated with venlafaxine (average dose 171.9 mg/day). Treatment lasted for 15 weeks and all patients completed the trial. Social anxiety symptoms were reduced on average by 60.4% ($P < 0.05$) from baseline. Eleven (92%) scored much or very much improved on the CGI for fear and ten (83%) for avoidance.

In another case series, Kelsey [1995] in a retrospective chart review of nine patients with Social Anxiety Disorder assessed outcome after 4 to 12 weeks of treatment. The average dose of venlafaxine was 146.5 mg/day The fear questionnaire post treatment scores were reduced by 62.9% ($P < 0.02$) from baseline, with a concomitant reduction in Beck Depression Inventory scores ($P < 0.05$) in patients who scored more than 14. These data are suggestive of efficacy, but placebo-controlled randomized clinical trials are indicated.

OBSESSIVE COMPULSIVE DISORDER (OCD)

Obsessive compulsive disorder (OCD) is characterized by repetitive, intrusive, senseless ideas, which induce anxiety (obsessions) triggering mental or overt behavioral rituals (compulsions) to reduce the anxiety. Serotonin reuptake inhibitors are the only class of medications consistently shown to be effective in the treatment of obsessive compulsive disorder. These include nonselective SRIs such as clomipramine as well as selective SRIs such as fluvoxamine, fluoxetine, paroxetine, and sertraline [Greist et al., 1995]. Norepinephrine reuptake inhibitors such as desipramine do not appear to be effective in OCD. Additionally cognitive behavioral treatment that focuses on exposure and response prevention is an effective treatment modality.

Yaryura-Tobias and Neziroglu [1996] reported the only double-blind placebo controlled study of venlafaxine in OCD. Thirty outpatients with OCD without depression were randomized to either venlafaxine or placebo for 8 weeks. Sixteen patients received venlafaxine (maximum 225 mg/day). The number of patients who dropped out were 2/16 on venlafaxine and 6/14 on placebo. Symptom scores and CGI scores were not significantly different between the two groups at the end of 8 weeks. However, none of the patients who received placebo responded while 6 of the 14 patients on venlafaxine improved (criteria not reported). The authors recognized the limitations of the study including the limited number of subjects, the dose of venlafaxine limited to 225 mg/day, and the short duration of treatment (8 weeks).

Rauch et al. [1996] reported a case series of ten clinic outpatients with OCD treated with open label venlafaxine for 12 weeks at a maximum dose of 375 mg/day. The average dose achieved was 308.3 mg/day. Responders were defined as having a 35% reduction

in obsessive compulsive symptoms or a CGI score of much/very much improved. Nine of the ten patients completed the study (one dropped out because of nausea) and the average reduction in OCD symptoms was 24.1% ($P < 0.05$). Three patients met both response definitions and four met at least one. The authors report the degree of benefit comparable to other serotonin reuptake inhibitors in OCD.

These reports are interesting because the dual serotonin and norepinephrine reuptake inhibitor, clomipramine, may have a superior degree of benefit compared to selective serotonin reuptake inhibitors [Greist et al., 1995]. If venlafaxine has a similar degree of benefit, it would have the advantage of a more benign side-effect profile than clomipramine. Additional placebo-controlled randomized clinical trials are indicated.

TRICHOTILLOMANIA

Trichotillomania is characterized by irresistible impulses to pull out one's hair resulting in noticeable hair loss. It occurs predominantly in women, usually starting in childhood. There is high co-morbidity of anxiety and depressive disorders with trichotillomania. Trichotillomania is classified as an impulse control disorder, though it is also considered within the spectrum of obsessive compulsive disorder. Treatments reported effective in the short term include clomipramine [Swedo et al., 1989] and cognitive-behavior therapy [Ninan et al., 2000].

A single study of venlafaxine in the treatment of trichotillomania has been reported [Ninan et al., 1998, Ninan, 2000]. Twenty patients were treated with venlafaxine (average dose 322.5 mg/day) for up to 12 weeks. Eleven were considered responders based on a ≥50% reduction in symptom scores and a CGI of much/very much improved. Eight of the responders entered a double-blind discontinuation trial where half were randomized to continue venlafaxine and the other half to placebo. All patients except one (who was on placebo) relapsed within the next 24 weeks [Ninan, 2000].

Randomized clinical trials with placebo controls in a larger number of patients are clearly indicated prior to any definite conclusions. This study suggests that venlafaxine is effective in the short-term management of trichotillomania, though the benefit is not durable.

ATTENTION DEFICIT HYPERACTIVITY DISORDER

Attention Deficit Hyperactivity Disorder is a well-validated diagnosis in children. It is characterized by hyperactivity, impulsivity, and inattention. The majority of children with ADHD continue to have similar symptoms in adulthood, though the symptom profile shifts away from motoric hyperactivity to inattention [Faraone et al., 2000]. Co-morbidity of anxiety, mood disorders, and chemical dependency is high in adults with ADHD. ADHD in adults appears to be responsive to pharmacological agents effective in childhood ADHD. Placebo-controlled studies document efficacy of stimulants like methylphenidate [Spencer et al., 1995] and noradrenergic agents such as desipramine [Wilens et al., 1996] in the short-term treatment of adult AHDH.

There are no placebo-controlled studies of venlafaxine in adult ADHD. Findling et al. [1996] reported a study of ten clinic patients (five women) with adult ADHD with a history of symptoms present before the age of 7. There symptoms were at least of moderate severity with dysfunction in at least two settings. The patients did not have any anxiety disorders, major depression, or dysthymia at study entry. Venlafaxine was started at 37.5 mg b.i.d. with the option of increasing it to 75 mg b.i.d. at week 4. One patient discontinued at week 2 because of sedation; the other nine completed the study. Seven of the nine were categorized as responders. Symptom scores of ADHD improved significantly, with the greatest improvement occurring in the first 2 weeks. The CGI also improved significantly. Among the nine completers, eight chose to continue venlafaxine clinically (one discontinued because of sexual side-effects).

Adler et al. [1995] reported efficacy of venlafaxine in 16 clinic patients with ADHD. Three patients had current co-morbid panic disorder and one had past major depression. Three patients were on concomitant stimulants: one on clonazepam and one on trazadone. Venlafaxine was started at a minimum of 25 mg/day and raised based on efficacy and side-effects to a maximum of 225 mg/day. The mean final dose was not reported. Four patients discontinued venlafaxine because of side-effects. Symptoms were reduced on average by 48% ($P < 0.0001$). Ten of twelve patients had a greater than 30% reduction in symptoms and all patients chose to continue venlafaxine clinically after the trial.

Hedges et al. [1995] reported 18 clinic patients (6 women) who met the UTAH criteria for ADHD with a childhood history of the same, and scoring less than 20 on the HAM-D scale. The venlafaxine trial lasted 8 weeks (average dose 96 mg/day). Seven (39%) of the patients had significant side-effects. Nine (50%) were much or very much improved on the CGI on an intent-to-treat analysis. Among the completers, 8 of 11 (73%) were responders.

These reports are encouraging. Efficacy of venlafaxine in adult ADHD, if supported by placebo controlled studies, would have the advantage of freedom from the concerns associated with stimulants like methylphenidate and a more benign side effect profile than tricyclic antidepressants like desipramine.

CHRONIC PAIN

Antidepressant medications have some degree of efficacy in pain management [Ansari, 2000]. The majority of reports have focused on tricyclic antidepressants. Diamond [1995] reported a retrospective chart review

of the use of venlafaxine in a specialty headache clinic; 97 patients (79 women) were diagnosed by the International Headache Society criteria [1988]. Their average age was 44.5 years (range 15–78); 12 had tension headaches, 20 had migraines, and 65 had a combination of the two. All patients suffered from headaches for at least 2 years and were refractory to previous pharmacological treatments. They were treated with venlafaxine 75 mg b.i.d.. Response was categorized as improved (less than two headaches/week), unchanged, or worse: 36 patients had headaches improved, 44 had no change, and 17 had an increased frequency of headaches. Forty-eight patients reported side-effects, described as mild and transient. The author considered the response to venlafaxine as "very good" given the nature of the population.

Taylor and Rowbotham [1996] report on 12 patients (8 women) with chronic pain, which was primarily neuropathic pain. Outcome was assessed combining a patient self rating with the CGI after a minimum period of 4 weeks. All had failed or been intolerant to a previous antidepressant trial (average trials, 2.6). Three patients had mild relief, eight had moderate relief, and one had complete relief.

There is considerable clinical heterogeneity under the rubric of chronic pain. These initial reports of the efficacy of venlafaxine are promising and worthy of follow-up with placebo-controlled randomized clinical trials.

FIBROMYALGIA

Fibromyalgia is a condition characterized by symptoms of chronic diffuse muscular pain and fatigue [Parziale, 1999]. The diagnostic validity of fibromyalgia is debated. Patients with fibromyalgia have a high incidence of co-morbidity with anxiety and depressive disorders.

No placebo-controlled studies have been reported with venlafaxine in fibromyalgia. In the single report of venlafaxine in fibromyalgia, 15 patients recruited through advertisement entered an 8 week trial [Dwight et al., 1996]. The majority had current co-morbid diagnoses, mainly depressive and anxiety disorders (66%), as well as 5 (33%) with irritable bowel syndrome. Five patients (33%) did not have a co-morbid psychiatric diagnosis. Four patients failed to complete the trial: one because of insomnia, and three because of non-compliance with visits. Eleven patients completed the trial and six (55%) were categorized as responders (≥50% reduction in symptoms). The average final dose of venlafaxine was 167 (± 14 S.D.) mg/day.

This report is suggestive evidence of efficacy of venlafaxine for fibromyalgia, though further placebo-controlled randomized clinical trials are needed.

CONCLUSION

Venlafaxine is an antidepressant medication with potent inhibitory effects on the serotonin and norepinephrine transporters and a benign side-effect profile, particularly with its extended release formulation. Venlafaxine is effective in the treatment of major depression and generalized anxiety disorder based on several placebo-controlled randomized clinical trials. This review suggests that venlafaxine has a broad range of efficacy in multiple disorders beyond those currently approved by the FDA. Further studies in these areas are critical to confirm such efficacy and also to examine the relative value of venlafaxine over other pharmacological choices in these conditions.

REFERENCES

Adler LA, Resnick S, Kunz M, Devinsky O. 1995. Open-label trial of venlafaxine in adults with attention deficit disorder. Psychophamacol Bull 31:785–788.

Altamura AC, Piolo R, Vitto M, Mannu P. 1999. Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. Int Clin Psychophamacol 14:239–245.

American Psychiatric Association. 1998. Practice guidelines for the treatment of patients with panic disorder. Am J Psychiatry 155:5.

Ansari A. 2000. The efficacy of newer antidepressants in the treatment of chronic pain: a review of current literature. Harv Rev Psychiatry 7:257–277.

Diamond S. 1995. Efficacy and safety profile of venlafaxine in chronic headache. Headache Quart 6:212–214.

Faraone SV, Biederman J Spences T et al. 2000. Attention-deficit/hyperactivity disorder in adults: An overview. Biol Psychiatry 48:9–20.

Findling RL, Schwartz MA, Flannery DJ, Manos MJ. 1996. Venlafaxine in adults with attention-deficit/hyperactivity disorder: an open clinical trial. J Clin Psychiatry 57:184–189.

Geracioti TD. 1995. Venlafaxine treatment for panic disorder: a case series. J Clin Psychiatry 56:408–410.

Greist JH, Jefferson JW, Kobak KA, Katzelnick DJ, Serlin RC. 1995. Efficacy and tolerability of serotonin transport inhibitors in obsessive-compulsive disorder: a meta-analysis. Arch Gen Psychiatry 52:53–60.

Hedges D, Reimherr FW, Rogers A, Strong R, Wender PH. 1995. An open trial of venlafaxine in adult patients with attention deficit hyperactivity disorder. Psychopharmacol Bull 31:779–783.

International Headache Society. 1988. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Cephalalgia 8:1–96.

Kelsey JE. 1995. Venlafaxine in social phobia. Psychopharmacol Bull 31:767–771.

Liebowitz MR. 1999. Update on the diagnosis and treatment of social anxiety disorder. J Clin Psychiatry 60:22–26.

Ninan PT, Knight B, Kirk L, Rothbaum BO, Kelsey J, Nemeroff CB. 1998. A controlled trial of venlafaxine in trichotillomania: Interim phase I results. Psychopharmacol Bull 34:221–224.

Ninan PT, Rothbaum BO, Marsteller FA, Knight BT, Eccard MB. 2000. A placebo controlled trial of cognitive behavior therapy and clomipramine in trichotillomania. J Clin Psychiatry. 61:47–50.

Ninan PT. 2000. Conceptual issues in trichotillomania, a prototypical impulse control disorder. Current Psychiatry Reports 2:72–75.

Papp LA, Sinha SS, Martinez JM, Coplan JD, Amchin J, Gorman JM. 1998. Low-dose venlafaxine treatment in panic disorder. Psychopharmacol Bull 34:207–209.

Parziale JR. 1999. The clinical management of fibromyalgia. Med Health R I 82:325–328.

Pollack MH, Worthington JJ, Otto MW, Maki KM, Smoler JW, Manfro GG, Rudolph R, Rosenbaum JF. 1996. Venlafaxine for panic disorder: results from a double-blind, placebo-controlled study. Psychopharacol Bull 32:667–670.

Qwight MW, Arnold LM, O'Brien H, Metzger R, Morris-Park E, Keck PE. 1998. An open clinical trial of venlafaxine treatment of fibromyalgia. Psychosomatics 39:14–17.

Rauch SL, O'Sullivan RL, Jenicke MA. 1996. Open treatment of obsessive-compulsive disorder with venlafaxine: a series of ten cases (letter). J Clin Psychophamacol 16:81–84.

Schulz KF, Chalmers J, Hyes RJ, Altman DG. 1995. Empirical evidence of bias. JAMA 273:408–412.

Spencer T, Wilens T, Biederman J, et al. 1995. A double-blind crossover comparison of methylphenidate and placebo in adults with childhood-onset attention-deficit hyperactivity disorder. Arch Gen Psychiatry 52:434–443.

Swedo SE, Leonard HL, Rapaport JL, Lenane MC, Goldgerger B, Cheslow BA. 1989. A double-blind comparison of clomipramine and desipramine in the treatment of trichotillomania (hair pulling). N Engl J Med 321:497–501.

Taylor K, Rowbotham MC. 1996. Venlafaxine hydrochloride and chronic pain. West J Med 165:147–148.

Troy SM, Dilea C, Martin PT, Rosen AS, Fruncillo RJ, Chiang ST. 1997. Bioavailability of once-daily venlafaxine extended release compared with the immediate-release formulation in healthy adult volunteers. Current Therapeutic Research 58:492–503.

Wilens TE, Biederman J, Prince J, et al. 1996. Six-week double-blind placebo-controlled study of desipramine for adult attention-deficit hyperactivity disorder. Am J Psychiatry 153: 1147–1153.

Wilens TE, Biederman J, Spencer TJ. 1995. Venlafaxine for adult ADHD (letter). Am J Psychiatry 152:1099–1100.

Yaryura-Tobias J, Neziroglu FA. 1996.Venlafaxine in obsessive-compulsive disorder (letter). Arch Gen Psychiatry 53:653–654.