Nefazodone and Venlafaxine: Two New Agents for the Treatment of Depression

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Nefazodone and venlafaxine are two new antidepressants with pharmacologic actions and side-effect profiles that differ from those of the selective serotonin reuptake inhibitors (SSRIs). In addition to inhibition of serotonin reuptake, nefazodone exhibits 5-HT2 antagonism. Venlafaxine inhibits the reuptake of both norepinephrine and serotonin. Both appear to be effective and well tolerated in the treatment of major depressive disorder. Nefazodone differs from the SSRIs in that it does not cause sexual dysfunction or sleep impairment. Venlafaxine differs from the SSRIs because of its effects augmenting norepinephrine, as well as its demonstrated efficacy in the treatment of severely depressed, melancholic patients. Both drugs appear to hold significant promise as effective and well-tolerated medications for the treatment of major depression in the primary care setting.

Key words. Nefazodone; venlafaxine; antidepressants; serotonin; norepinephrine; primary health care.
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Depression is a significant problem in the United States. It has been estimated that the lifetime prevalence of depression is 17%.[1] There are approximately 13 million people in the United States who are depressed but not receiving treatment. Of those who are receiving medication, more than 50% are treated by primary care physicians.[2] Until recently, tricyclic antidepressants (TCAs) were the drugs of choice for depression. Over the last few years, however, TCAs have gradually been replaced as first-line therapy by the selective serotonin reuptake inhibitors (SSRIs), which have a better safety and tolerability profile. Nevertheless, there are still some patients who either do not respond well to currently available antidepressants or are unable to tolerate the adverse effects of these drugs.

There are several new alternatives to the SSRIs available to the primary care clinician, including nefazodone (Serzone) and venlafaxine (Effexor). Venlafaxine was introduced in April of 1994 and nefazodone in early 1995. The purpose of this article is to help primary care clinicians understand the basic pharmacology of these new medications and to gain a perspective on how they may be useful in their practices.

Neuropharmacology

Nefazodone and its major metabolite, hydroxynefazodone, exhibit potent antagonist activity at 5-HT2 receptors compared with other antidepressants, with only moderate inhibition of presynaptic serotonin reuptake (Table 1). The inhibitory effect of nefazodone at 5-HT2 receptors may lead to an increase in serotonergic neurotransmission through indirect enhancement of 5-HT1A-mediated transmission[3] and has been reported to coincide with the onset of the therapeutic effect of several antidepressant drugs. Like the SSRIs but in contrast to TCAs, nefazodone exhibits little or no activity at cholinergic, histaminic, beta-adrenergic, dopaminergic, benzodiazepine, GABA, or m-opiate receptors.

Venlafaxine also has a unique pharmacologic profile and is unrelated to either the tricylics or the SSRIs. Like the tricylics, it has combined serotonin and norepinephrine uptake inhibitory effects. However, it is devoid of effects for cholinergic, histaminic, and adrenergic receptors (Table 1). The principal active metabolite of venlafaxine, O-desmethylvenlafaxine {ODV}, has a pharmacologic profile similar to that of its parent compound.

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Table 1. Antidepressant Effects on Neurotransmitters

Neurotransmitter	TCAs	SSRIs	Nefazodone	Venlafaxine
Serotonin	+	+	+	+
Norepinephrine	+	0	0	+
5 HT-2 antagonism	0	0	+	0
Histamine	+	0	0	0
Acetylcholine	+	0*	0	0
Alpha-adrenergic	+	0	0/+†	0

**Paroxetine has weak anti-cholinergic effects.*
†Nefazodone has weak alpha-adrenergic blocking effects.
TCA denotes tricyclic antidepressant; SSRI, serotonin reuptake inhibitor.

Pharmacokinetic Properties

Nefazodone is rapidly absorbed after oral administration, reaching peak-plasma concentrations in approximately 1 hour. Its bioavailability is approximately 20%, and it is highly (>99%) but not tightly protein-bound. Venlafaxine is rapidly absorbed after oral administration, reaching peak-plasma concentrations in approximately 1 hour. Its bioavailability is around 90%, and it has a low percentage (only about 30%) of protein-binding. Therefore, drug interactions caused by protein-binding displacement are unlikely to occur with venlafaxine.

Nefazodone exhibits nonlinear kinetics; therefore, its plasma concentration increases to a greater extent than would be predicted by the increase of oral dose. Unlike some TCAs, which may not reach steady-state plasma concentrations for 1 or 2 weeks, nefazodone reaches a steady-state plasma concentration in approximately 4 to 5 days. Venlafaxine exhibits linear kinetics. Steady-state plasma concentrations for venlafaxine and ODV are reached within 3 days of multiple-dose therapy.

Nefazodone is metabolized primarily in the liver by the cytochrome P450 system, producing three active metabolites. Its primary metabolite, hydroxy-nefazodone, has activity similar to that of the parent compound in terms of its effects on 5-HT2 receptors and serotonin reuptake. A second metabolite, triazoledione, has weak 5-HT2 antagonist effects but exerts no inhibition of serotonin reuptake.[4] The third active metabolite, m-chlorophenylpiperazine (m-CPP), has activity similar to that of the parent compound in terms of inhibition of serotonin reuptake but is present in low concentrations.[5] It also has antagonist effects at 5-HT2 and 5-HT3 receptors and agonist activity at 5-HT1A and 5-HT1C receptors. Venlafaxine is also metabolized primarily in the liver by the cytochrome P450 system, producing one active metabolite, ODV. This primary metabolite possesses activity similar to that of the parent compound.

The plasma elimination half-life of nefazodone ranges from 2 to 4 hours and from 1.5 to 4 hours for its primary metabolite hydroxy-nefazodone. The pharmacokinetic profile of nefazodone is affected somewhat by the age and sex of the patient. In elderly patients, the drug reaches higher plasma concentrations, particularly after single doses, and is eliminated more slowly. Plasma concentrations reach higher levels in patients with hepatic impairment, but renal impairment does not appear to affect the pharmacokinetic profile of nefazodone. The plasma elimination half-life of venlafaxine is approximately 5 hours, and for ODV, approximately 11 hours. The pharmacokinetic profile of venlafaxine does not appear to be affected by patient age or sex. Elimination half-life is prolonged in patients with hepatic impairment and those with renal impairment. It is recommended that doses be decreased 25% in renally impaired patients and 50% in patients on dialysis.

Clinical Antidepressant Efficacy

Nefazodone, in doses from 100 to 600 mg/d, is an effective and well-tolerated agent for the treatment of depression.[6–8] In a 6-week, double-blind, placebo-controlled trial comparing nefazodone with imipramine in 180 outpatients with major depressive disorder,[7] a mean dose of 460 mg/d nefazodone was as effective as a mean dose of 214 mg/d imipramine but was better tolerated. In this study, anxiety subscale scores showed a more rapid (within 1 week) improvement than with imipramine. Adverse events were judged to affect functioning in less than 10% of patients receiving nefazodone compared with more than 30% receiving imipramine, and fewer patients receiving nefazodone withdrew from treatment (1 with nefazodone vs 6 with imipramine). Typical clinical use of nefazodone involves starting at a dose of 100 mg twice daily, with an increase to 150 mg twice daily after 1 week. Patients should be maintained on 150 mg twice daily for 3 to 5 weeks, evaluating response before further increasing dosage. These dosage guidelines should be halved when treating older patients, those with hepatic impairment, and those sensitive to sedating side effects.

Venlafaxine has also been demonstrated to be an effective and well-tolerated agent for the treatment of depression. Efficacy has been demonstrated in both open and placebo-controlled double-blind studies involving moderately depressed outpatients as well as more severely depressed inpatients.[9,10] A double-blind trial in 224 outpatients with major depression[11] found that venlafaxine in doses ranging from 75 to 225 mg/d produced improvement in 90% of patients, compared with 79% who improved while taking a mean maximum dose of 176 mg/d imipramine and 53% who improved on placebo. One study[12] reported that venlafaxine-treated inpatients with major depression and melancholia showed a superior re-

Table 2. Top Five Side Effects of New Antidepressants

	Fluoxetine	Paroxetine	Sertraline	Nefazodone	Venlafaxine
1	Nausea	Nausea	Nausea	Nausea	Nausea
2	Diarrhea	Sedation	Diarrhea	Sedation	Sedation
3	Insomnia	Weakness	Insomnia	Weakness	Insomnia
4	Nervousness	Dry Mouth	Dry Mouth	Dizziness	Dizziness
5	Headache	Headache	Headache	Headache	Sweating

Table 3. Probability of Sustained Elevation in Supine Diastolic Blood Pressure (SDBP) with Venlafaxine

Dose of Venlafaxine, mg/d	Incidence of Sustained Elevation in SDBP, %
Placebo	2
≤100	3
101–200	5
210–300	7
>300	13

sponse rate to that of patients treated with fluoxetine. The typical starting dose for venlafaxine is 37.5 mg twice daily. Higher doses are often not necessary in the treatment of moderately depressed outpatients.

Tolerability and Safety

Neither nefazodone nor venlafaxine exhibit the anticholinergic, antihistaminic, or cardiac conduction adverse effects associated with TCAs, and unlike TCAs, neither appears to have lethal overdose potential. Adverse events occurring more commonly with nefazodone include nausea, drowsiness, asthenia, dizziness, dry mouth, constipation, light-headedness, and headache (Table 2). Most side effects, however, are mild or moderate in severity and duration, rarely lead to discontinuation of treatment, and occur at a rate less than that of TCAs. In contrast to trazodone, SSRIs, and TCAs, no adverse effects on sexual function have been reported with nefazodone. Although nefazodone is chemically related to trazodone, it has a different pharmacological and clinical profile. Nefazodone differs from trazodone in having significantly lower effects on alpha-1 and alpha-2 receptors. Therefore, nefazodone is less sedative than trazodone, is less likely to cause orthostatic hypotension, and has not been reported to cause priapism.

Adverse events associated with venlafaxine resemble those of SSRIs, except for some adrenergic symptoms, such as sweating. Most common side effects include nausea, headache, anxiety, anorexia, nervousness, sweating, dizziness, insomnia, and somnolence (Table 2). Patients often develop tolerance to both nausea and somnolence after a week or two, although it is helpful to lower the dose initially to reduce the severity of these symptoms. The actual incidence of sexual dysfunction may be lower than that associated with SSRIs, although definitive data are not available. Venlafaxine shows some potential to cause increased supine diastolic blood pressure (SDBP). Increase in SDBP appears to be a dose-related phenomenon (Table 3), although there is no way to predict it based on characteristics such as preexisting hypertension, age, sex, race, or concomitant medications. In a dose-to-dose comparison of venlafaxine and imipramine, they appear to be associated with a comparable increased risk of elevated SDBP: the incidence in both is about 4%.

Neither nefazodone nor venlafaxine has demonstrated abuse potential. Seven cases of overdose with nefazodone (up to 11200 mg) have been reported but none has been fatal or life-threatening, and treatment and recovery were usually uneventful (Unpublished data. Food and Drug Administration. Psychopharmacologic Drugs Advisory Committee meeting. Serzone [nefazadone HCl]: safety and effectiveness in use as an antidepressant. Rockville, Md, July 1993). There have been 14 reported cases of overdose with venlafaxine (up to 6750 mg) but none has been fatal or life-threatening. Nausea and vomiting have been noted, and one patient was reported to have developed two generalized convulsions. All patients recovered (data on file, Wyeth-Ayerst Laboratories, Philadelphia, Pa).

Drug Interactions

Nefazodone is an inhibitor of the P450 3A4 isoenzymes in vitro. Because of this, coadministration of nefazodone with terfenadine or astemizole is contraindicated. Studies have also shown interactions during coadministration of nefazodone with triazolam and alprazolam, both of which are P450 3A4 substrates. Doses of these drugs should be reduced by approximately 50% if coprescribed with nefazodone. Lorazepam, which is conjugated, is not affected in this way. Other P450 3A4 substrates include calcium channel blockers, cisapride, and tamoxifen.[13]

Venlafaxine does not appear to be an inhibitor of the P450 system, though it is a substrate of the P450 2D6 system. Drugs that inhibit the cytochrome P450 2D6 system, such as quinidine or SSRIs, may increase the serum concentrations of venlafaxine. There are no systematic data on the interaction of venlafaxine and alcohol. The combination of either nefazodone or venlafaxine with monoamine oxidase inhibitors should be avoided because of possible potentiation of serotonin activity.

Special Issues and Clinical Perspective

There appear to be two clinical situations in which nefazodone can be differentiated from SSRIs. One of these is in the area of sexual dysfunction. The rate of sexual dysfunction reported with the SSRIs has been between 10% and 60%, while there appears to be a rate of only about 5% for nefazodone. One preliminary study[14] has reported the effects of nefazodone on 48 patients with premenstrual syndrome, one half of whom also had major depression. A significant improvement occurred by the end of the first treatment cycle with a mean dose of 245 mg/d nefazodone, and after two cycles of nefazodone treatment, 86% of patients no longer met the criteria for late luteal phase dysphoric disorder. This result is similar to the 90% response to fluoxetine reported in another study.[15] However, the incidence of decreased libido or anorgasmia was approximately 30% in the fluoxetine-treated patients, whereas there were no such reports with nefazodone treatment.

A second area of difference between nefazodone and the SSRIs involves sleep. A significant number of patients treated with SSRIs report sleep impairment. Impaired sleep during SSRI therapy is associated with increased light stage sleep and increased frequency of awakenings on electroencephalogram (EEG) studies. Nefazodone appears to have an opposite effect on sleep and the EEG, causing both a decrease in light stage sleep and decreased frequency of awakenings. Therefore, it is unlikely that a patient taking nefazodone would need an additional sleep medication, as is sometimes the case for patients using an SSRI.

In addition to its effectiveness as a first-line treatment for moderate levels of major depression, venlafaxine appears to have significant potential for the treatment of severely depressed and treatment-resistant patients.[16] SSRIs have been studied mainly in depressed outpatients. The current hypothesis for the underlying biology of depression is that depression is an outcome of dysfunction that can involve serotonin, norepinephrine, or both. Nonresponse to SSRIs may occur because that drug group does not have an effect on norepinephrine. The effect of venlafaxine on both serotonin and norepinephrine may account for the positive results achieved by this drug in the treatment of severely depressed or treatment-resistant patients. One study[17] has demonstrated that venlafaxine, often in doses greater than 300 mg/d, was able to produce a sustained response in about 20% of patients with treatment-resistant disorder. In addition, there is some, at least preliminary, evidence that venlafaxine, particularly at doses exceeding 225 mg/d, has a more rapid onset of action than is typical of other antidepressants.[18,19] However, advantages of earlier response may be offset somewhat by the increased rate of adverse effects associated with the initial use of high doses.

Conclusions

Nefazodone and venlafaxine are two new antidepressants deserving of attention from primary care physicians. They are not SSRI look-alikes. These new additions to our armamentarium in treating depression offer options for clinicians with respect to issues such as sexual side effects, sleep, and spectrum of effectiveness.

References

1. Blazer DG, Kessler RC, McGonagle KA, et al. The prevalence and distribution of major depression in a national community sample: The National Comorbidity Survey. Am J Psychiatry 1994; 15:979-86.
2. Beardsley RS, Gardocki GJ, Larson DB, et al. Prescribing of psychotropic medication by primary care physicians and psychiatrists. Arch Gen Psychiatry 1988; 45:1117–9.
3. Eison AS, Eison MS, Torrente JR, et al. Nefazodone: preclinical pharmacology of a new antidepressant. Psychopharmacol Bull 1990; 26:311–5.
4. Taylor DP, Carter RB, Eison AS, et al. Pharmacology and neurochemistry of nefazadone, a novel antidepressant drug. J Clin Psychiatry 1995; 46(suppl 6):3–11.
5. Hamik A, Peroutka SJ. 1-(M-chlorophenyl)piperazine (m-CPP) interactions with neurotransmitter receptors in the human brain. Biol Psychiatry 1989; 25:569–75.
6. Feighner JP, Pambakian R, Fowler RC, et al. A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression. Psychopharmacol Bull 1989; 25:219–21.
7. Fontaine R, Ontiveros A, Elie R, Kensler TT, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry 1994; 55:234–41.
8. Rickels K, Schweizer E, Clary C, et al. Nefazodone and imipramine in major depression: a placebo-controlled trial. Br J Psychiatry 1994; 164:802–5.
9. Khan A, Fabre LF, Rudolph R. Venlafaxine in depressed outpatients. Psychopharmacol Bull 1991; 27:141–4.
10. Cunningham LA, Borison RL, Carman JS, et al. A comparison of venlafaxine, trazodone, and placebo in major depression. J Clin Psychopharmacol 1994; 14:99–106.
11. Schweizer E, Weise C, Clary C, et al. Placebo-controlled trial of venlafaxine for the treatment of major depression. J Clin Psychopharmacol 1991; 11:233–6.
12. Montgomery SA. Evidence for early onset of action and superior efficacy in controlled trials with venlafaxine. J Clin Psychiatry 1993; 54:126.
13. von Moltke LL, Greenblatt DJ, Harmatz JS, et al. Cytochromes in psychopharmacology. J Clin Psychopharmacol 1994; 14:1–4.
14. Freeman EW, Rickels K, Sondheimer SJ, et al. Nefazodone in the treatment of premenstrual syndrome: a preliminary study. J Clin Psychopharmacol 1994; 14:180–6.
15. Stone AB, Pearlstein TB, Brown WA: Fluoxetine in the treatment of late luteal phase dysphoric disorder. J Clin Psychiatry 1991; 52: 290–3.
16. Guelfi JD, White C, Hackett D, et al. The effectiveness of venlafaxine in patients hospitalized with major depression and melancholia. J Clin Psychiatry. In press, 1996.
17. Nierenberg AA, Feighner JP, Rudolph R, et al. Venlafaxine for treatment-resistant unipolar depression. J Clin Psychopharmacol 1994;14:419–23.
18. Rickels D. Venlafaxine: a new potent antidepressants agents with putative fast onset of action. Biol Psychiatry 1991; 1:345–6.
19. Rudolph R, Entsuah R, Derivan A. Early clinical response in depression to venlafaxine hydrochloride [abstract]. Biol Psychiatry 1991; 29(11s):630S.