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Is There an Advantage to Venlafaxine in Comparison with Other Antidepressants?

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The purpose of this article s to compare and contrast the benefits and limitations of antidepressant drugs. Several different classes of antidepressants are available for treatment of major depressive disorder, each with its own benefits and limitations as a result of its pharmacological profile. Tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors are effective in a large proportion of depressed patients, but their use is often limited by short- and long-term safety/tolerability problems. Selective serotonin reuptake inhibitors (SSRIs) exhibit comparable efficacy to TCAs in most patients, but may be less effective in certain patients. Additionally, SSRI use may by impacted by clinically significant drug interactions. Venlafaxine is a selective serotonin-noradrenaline reuptake inhibitor (SNRI) with unique pharmacological properties that may enhance its efficacy as well as its safety profile. In clinical trials, venlafaxine exhibits antidepressant activity in a broad range of patients with major depression, including those with melancholia, agitated or retarded symptoms, anxiety symptoms, and refractory or resistant depression. Venlafaxine has shown potential for an early onset of action and offers dose flexibility that may allow recruitment of additional responders at higher dosages. Because of its lack of affinity for muscarinic cholinergic, histaminergic, and alpha$_1$-adrenergic receptors, venlafaxine has a safety profile that is superior to that of TCAs. Venlafaxine also is devoid of the drug interactions characteristic of SSRIs.

KEY WORDS — venlafaxine; tricyclic antidepressants; SSRIs; MAOIs; onset of action; adrenoceptors

INTRODUCTION

While the tricyclic antidepressants (TCAs) are effective antidepressants in many patients, 30 per cent to 40 per cent of patients may not respond. In addition, the incidence of side-effects associated with TCAs may be an important cause of poor compliance (Anderson and Tomenson, 1995), use of low and ineffective doses (McCombs *et al*., 1990; Katon *et al*., 1992), and a widespread perception that antidepressant therapy is not satisfactory. Similarly, the monoamine oxidase (MAO) inhibitors are effective antidepressants, but potentially severe drug–drug and drug–food interactions limit their use (Potter *et al*., 1991). The introduction of selective serotonin reuptake inhibitors (SSRIs) represented an important advance in antidepressant drug therapy with respect to an improved safety profile (Stark and Hardison, 1985; Montgomery *et al*., 1994a; Anderson and Tomenson, 1995). Although there are no direct comparisons of compliance rates with antidepressants, the decreased discontinuation rates with SSRIs indirectly suggest an increase in compliance versus the TCAs (Anderson and Tomenson, 1995). Further, the risk of death from overdose is of much less concern with SSRIs than with TCAs (Freemantle *et al*., 1994). However, questions remain about the efficacy of SSRIs in severely depressed patients with melancholia and those with refractory depression (Danish University Antidepressant Group, 1986, 1990; Roose *et al*., 1994). Also, clinically relevant side-effects and potential drug interactions remain problems (Preskorn, 1994). Thus, a need exists for antidepressants with a broader spectrum of activity than the SSRIs but with an improved safety and tolerability profile.

Venlafaxine, a structurally novel antidepressant is a serotonin–noradrenaline reuptake inhibitor (SNRI) (Muth *et al*., 1986, 1991). Clinical studies suggest that venlafaxine's pharmacological profile contributes to its efficacy in a broad range of patients, and dosage flexibility allows the option to increase the dose to enhance the clinical response and potentially to produce an earlier onset of activity. In this report, we will compare the pharmacological and clinical properties of venlafaxine

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Table 1. Receptor affinity of antidepressant drugs at different *in vitro* concentrations (adapted from Bolden-Watson and Richelson, 1993; Cusack *et al*, 1994)

Receptor	Venlafaxine	Fluoxetine	Sertraline	Nefazodone	Amitriptyline	Desipramine
5-HT	39	14	3·4	137	84	180
NE	210	143	220	570	13·9	0·61
DA	5300	3050	260	2380	8600	11000
H_1	>35000	5400	24000	24000	0·95	60
ACh	>35000	590	630	11000	9·6	66
$alpha_1$	>35000	3800	380	48	24	100
$alpha_2$	>35000	13900	4100	640	690	5500
$5\text{-}HT_{1a}$	>35000	32400	>35000	80	450	6400
$5\text{-}HT_{2a}$	>35000	280	9900	26	18	350
DA_2	>35000	12000	10700	910	1460	3500

Values for 5-HT, NE, and DA are inhibition constants (K_i).
All other values are dissociation constants (K_d) presented as geometric means in nanomolar units.

with those of other antidepressants for the treatment of major depressive disorder.

CLINICAL PHARMACOLOGY

Nearly all TCAs are characterized pharmacologically by non-selective activity on a number of neurotransmitters or receptor sites (Table 1). As a class, TCAs are potent inhibitors of noradrenaline and/or serotonin reuptake, the putative mechanism for antidepressant activity. However, they also non-selectively bind to a number of receptor sites probably not associated with antidepressant activity, including muscarinic, adrenergic, and histaminergic, receptors, as well as produce inhibition of sodium fast channels (Bolden-Watson and Richelson, 1993; Cusack *et al*., 1994). Based on the pharmacological profile of TCAs, a patient may be subjected to a large number of pharmacological effects associated with typical TCA side-effects in order to have an antidepressant response (Preskorn, 1994). The MAO inhibitors also are characterized by non-specific activity on monoamines, including noradrenaline, serotonin, and dopamine. Despite the documented efficacy of MAO inhibitors as antidepressants, their use may be limited by safety and tolerability problems.

In contrast, the SSRIs produce their antidepressant activity by selectively inhibiting reuptake of serotonin, but with little or no effect on noradrenergic reuptake. In addition, the SSRIs generally have much lower binding affinities for receptor sites associated with anticholinergic effects, antihistaminic effects, or cardiac-conduction disturbances that are typical of the TCAs (Bolden-Watson and Richelson, 1993; Cusack *et al*., 1994). The selective activity of SSRIs only on serotonin may make these drugs less effective in severely depressed patients with melancholia and in refractory depression (Roose *et al*., 1994; Anderson and Tomenson, 1995). Another consequence of the SSRIs' potent and selective effects on serotonin is their side-effect profile, namely nausea, sexual dysfunction, insomnia, anxiety, and drug interactions (Gram, 1994).

Venlafaxine is the first of the SNRI class of antidepressants, which also includes duloxetine and milnacipran. The SNRIs differ pharmacologically from other antidepressants, first, by potently inhibiting reuptake of serotonin and noradrenaline and, second, by demonstrating no binding affinity for muscarinic cholinergic, histaminergic, and $alpha_1$-adrenergic receptors at clinically relevant doses (Muth *et al*., 1986, 1991). Thus, at doses used in clinical practice, venlafaxine is expected to exert potent antidepressant activity without the side-effects typically associated with TCAs. The benefits of this pharmacological profile may include an early onset of antidepressant activity, dose flexibility, activity in a broader range of patients, and an improved safety/tolerability profile.

EARLY ONSET OF ANTIDEPRESSANT ACTIVITY

The potential benefits of an antidepressant with an early onset of action include more rapid resolution of the debilitating symptoms of depression, a potential reduction in the risk of suicide and comorbid disease, and a reduction in hospitalization with the associated cost savings.

The onset of improvement with TCAs was evaluated using survival analysis in two meta-analyses of

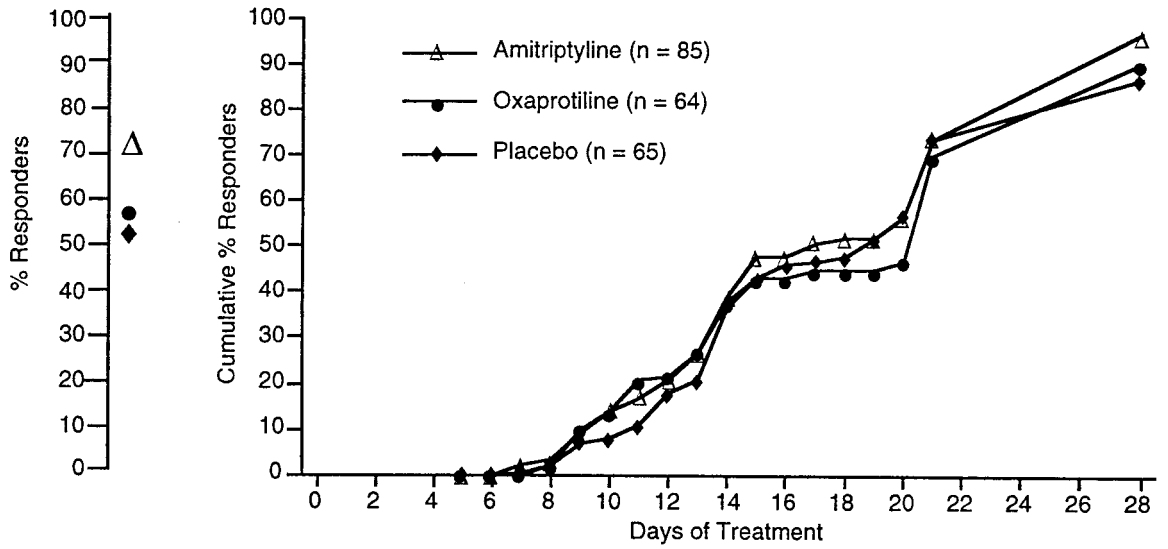

Figure 1. Time to onset of improvement in depressed patients (adapted with permission from Stassen *et al.*, 1993)

double-blind, placebo-controlled trials of oxaprotiline, amitriptyline, maprotiline, and moclobemide (Stassen *et al.*, 1993, 1994). In both reports, the authors found that the time course of improvement among responders was identified for active drugs and for placebo (Figure 1). However, another study found a significant reduction in the HAM-D score as early as day 4 following intravenous or oral clomipramine in patients with major depression (Pollock *et al.*, 1993). Furthermore, this early improvement was predictive of a response at the end of 4 weeks in these patients, which is consistent with the findings of Stassen. This discrepancy may relate to the ability or lack thereof to rapidly titrate the dose of TCAs as was the case with clomipramine.

Results from a number of meta-analyses indicate an early onset of actin with different antidepressants. In an analysis of five double-blind, placebo-controlled studies of fluoxetine and imipramine, Stark and Hardison (1985) found a significant ($P \leqslant 0{\cdot}05$) improvement with imipramine as early as 2 weeks on the CGI improvement scale and 3 weeks on the HAM-D. In contrast fluoxetine did not demonstrate an improvement until the fourth week. A meta-analysis of six studies observed that the probability of a response was greater with fluoxetine than with placebo from week 2 onward; however, the differences tended to be slight (Tollefson and Holman, 1994). Dunbar and colleagues (1991) found a significant ($P < 0{\cdot}05$) improvement in the MADRS as early as week 1 with paroxetine and week 2 with imipramine, although the difference between placebo and both active drugs only exceeded four points at week 4. In a meta-analysis of nine studies with citalopram, Montgomery and associates (1994b) found an improvement in the HAM-D sleep disturbance factor at week 3. However, there was no other evidence of an early improvement, and the results confirmed the flat dose response of citalopram.

A rapid onset of action has been observed with venlafaxine (Rudolph *et al.*, 1991; Guelfi *et al.*, 1995; Benkert *et al.*, 1996). Possible mechanisms for this early onset of action with venlafaxine include a rapid desensitization of beta-adrenergic receptors (Baron *et al.*, 1988), a short half-life and time to steady-state, the ability to rapidly titrate the dose to high levels, or its broad range of monoamine reuptake inhibition. In preclinical studies, venlafaxine produced rapid desensitization of beta-adrenergic receptors after both acute and chronic administration (Muth *et al.*, 1991). In addition, rapid desensitization was observed during acute treatment with combined use of an SSRI and a noradrenaline reuptake inhibitor (Baron *et al.*, 1988). The combination of an SSRI and a noradrenaline reuptake inhibitor produced a rapid onset in patients with major depression (Nelson *et al.*, 1991). Further studies are needed to fully elucidate the mechanisms for and clinical benefits of an early onset of action.

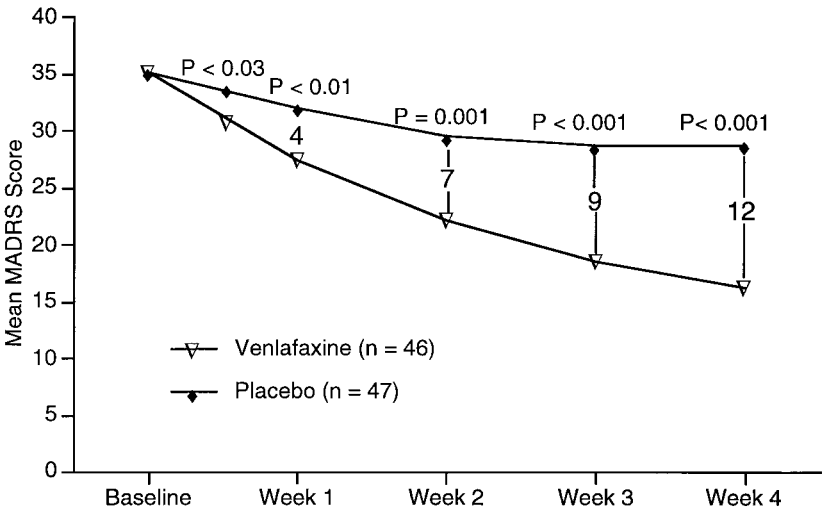

Figure 2. Response on the MADRS scores in a double-blind, randomized trial of venlafaxine and placebo (adapted with permission from Guelfi *et al.*, 1995)

In one trial, 358 depressed outpatients received venlafaxine 75 mg, 150 to 225 mg, or 300 to 375 mg daily for up to 6 weeks (Rudolph *et al.*, 1991). A significant ($P \leqslant 0{\cdot}05$) response was observed at week 1 in the high-dose group (300–375 mg/day) and at week 2 in both the middle- (150–225 mg/day) and high-dose groups compared with the placebo group. In a second study, of 93 hospitalized patients with melancholia, the dose of venlafaxine was titrated rapidly from 150 to 375 mg in the first week (Guelfi *et al.*, 1995). After the first week, the mean daily dose was 350 mg. Significant differences from placebo were observed beginning at 4 days on the MADRS (Figure 2) at 1 week on the HAM-D

In an active-control study, venlafaxine and imipramine were compared in 167 hospitalized patients with a minimum MADRS score of 30. Venlafaxine and imipramine were rapidly titrated over 5 days to a maximum of 375 mg/day for venlafaxine or 200 mg/day for imipramine (Benkert *et al.*, 1996). Both drugs are comparable with respect to the response on the HAM-D total or MADRS total at 6 weeks. However, among the subset of patients who responded by week 6 on the HAM-D, the onset of response was significantly ($P = 0{\cdot}036$) greater with venlafaxine. The median time to response on the HAM-D was 14 days with venlafaxine and 21 days with imipramine.

Thus, while not definitive, these studies do suggest an earlier onset of activity with venlafaxine compared with placebo and imipramine. Of note, two of these studies were designed to evaluate the efficacy of venlafaxine and not the onset of action. While TCAs in particular have the potential for a rapid escalation of the dosage that could result in an earlier onset of activity, rapid dosage escalation is usually limited by dose-related adverse effects.

COMPARISONS OF ANTIDEPRESSANT EFFICACY

Clinical studies with TCAs and with SSRIs demonstrate the clinical efficacy of these drugs for patients with major depression. However, certain subgroups of depressed patients may respond less well to some classes of antidepressants. Thus, MAO inhibitors and SSRIs may be especially effective and TCAs less effective in patients with atypical depression (Reimherr *et al.*, 1984; Quitkin *et al.*, 1990, 1991). In contrast, patients with psychotic depression often respond best to a TCA combined with a neuroleptic (Spiker *et al.*, 1985, 1986). Others have found response rates as low as 21 per cent with fluoxetine in elderly depressed patients compared with 55–70 per cent with TCAs (Gerson *et al.*, 1988; Tollefson and Holman, 1993).

Results from placebo-controlled and comparator-controlled clinical trials have shown venlafaxine to be equivalent or superior to both TCAs and SSRIs for treating major depression (Clerc *et al.*, 1994. Cunningham *et al.*, 1994; Schweizer *et al.*, 1994; Shrivastava *et al.*, 1994;

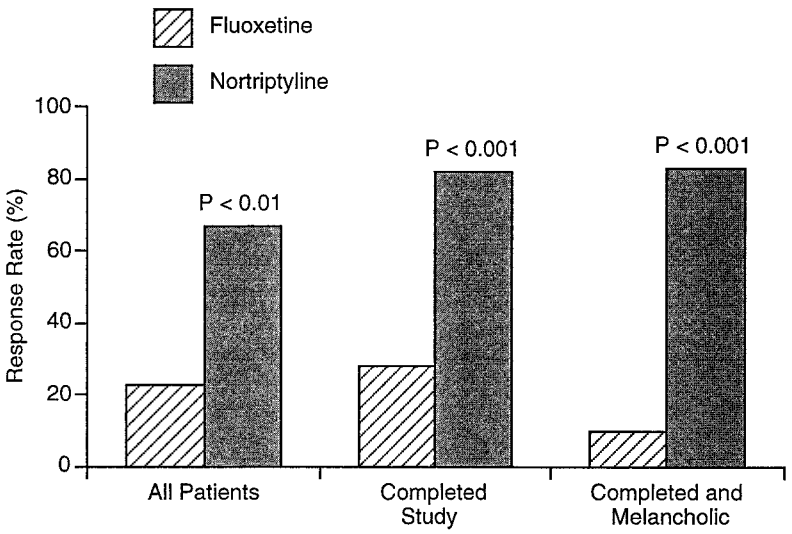

Figure 3. Response rates to nortriptyline and fluoxetine in patients with major depression (adapted with permission from Roose *et al.*, 1994)

Dierick *et al.*, 1996). Venlafaxine has been shown to be effective in both hospitalized patients and outpatients with major depression, and in the elderly and those with melancholia, agitated or retarded symptoms, and refractory or resistant depression.

Major depression with melancholia

TCAs and MAO inhibitors are generally found to be effective in patients with major depression and melancholia (McGrath *et al.*, 1984; Roose *et al.*, 1994). In contrast, several reports now suggest that the SSRIs may be less effective than other antidepressants in patients with major depression and melancholia (Danish University Antidepressant Group, 1986, 1990; Roose *et al.*, 1994; Anderson and Tomenson, 1995). Roose *et al.* (1994) observed that fluoxetine was significantly less effective than nortriptyline in treating elderly hospitalized depressed patients, especially those with melancholia (Figure 3).

Venlafaxine has been evaluated in two double-blind, randomized, comparative studies of hospitalized patients with major depression and melancholia. In one study already discussed (Benkert *et al.*, 1996), the dose of venlafaxine was rapidly titrated over 5 days to a maximum of 375 mg/day for 10 days and then reduced to 150 mg/day for the remainder of the 6-week trial. Imipramine was rapidly titrated over 5 days to 200 mg/day and maintained at that level. Mean HAM-D and MADRS scores were significantly reduced in both treatment groups at 6 weeks, indicating comparable efficacy. In the second study, venlafaxine 200 mg/day and fluoxetine 40 mg/day were compared in 67 inpatients with major depression and melancholia (Clerc *et al.*, 1994). Mean HAM-D and MADRS scores were significantly ($P < 0{\cdot}05$) improved with venlafaxine compared with fluoxetine at 4 and 6 weeks. A response to therapy, defined as at least a 50 per cent decrease from baseline in the MADRS or HAM-D score, was achieved by significantly ($P < 0{\cdot}05$) more venlafaxine-treated patients than fluoxetine-treated patients. The results from these two comparative studies and those from Guelfi *et al.* (1995) suggest that venlafaxine is effective in depressed patients with melancholia and may be superior to fluoxetine, but the influence of dosage on the response must be evaluated.

Retarded/agitated depression

Depressed patients with symptoms of agitation/retardation represent a treatment challenge because of the additional symptomatic complaints. A study of high-dose fluoxetine (80 mg/day) and imipramine showed comparable efficacy in depressed outpatients irrespective of baseline psychomotor activity (Beasley *et al.*, 1991).

To determine the effects of venlafaxine in depressed patient with agitation/retardation, a meta-analysis was conducted of 1122 patients with symptoms of agitation or retardation (Entsuah *et al*., 1995). Patients were included if they had baseline agitation or retardation scores greater than zero on the 21-item HAM-D. By week 3 of treatment, the HALM-D score had decreased significantly more with venlafaxine than with placebo. Venlafaxine also was significantly superior to imipramine at weeks 1 to 6 in depressed patients with psychomotor retardation.

Refractory/resistant depression

Despite an adequate trial of antidepressant therapy at optimal doses, 20–30 per cent of depressed patients fail to obtain clinical improvement (Lydiard, 1985). Patients who are refractory to adequate doses of TCAs often respond to substitution of an MAO inhibitor (McGrath *et al*., 1987; Thase *et al*., 1992). However, it should be noted that many reports of non-response to TCAs include patients who received sub-therapeutic doses (Roose *et al*., 1986). Often patients with refractory depression require combinations of antidepressant drugs, augmentation therapy, or electroconvulsive therapy (ECT) to obtain even a partial response (de Montigny *et al*., 1981; Weilburg *et al*. 1989). These drug combinations must be used with caution because of the risks of clinically significant drug interactions (Bergstrom *et al*., 1992). A meta-analysis of patients who participated in double-blind comparisons of fluoxetine and TCAs found a remission rate of only 17 per cent among non-responders to TCAs who were switched to fluoxetine (Beasley *et al*., 1993).

An open-label evaluation of venlafaxine was undertaken in 82 patients with treatment-resistant depression who had not responded to an adequate trial of at least three antidepressants from two different drug classes or to ECT plus at least one attempt at augmentation or at least two antidepressants plus augmentation and a course of ECT (Nierenberg *et al*., 1994). Complete response was defined as a HAM-D score $\leqslant 8$, a MADRS score $\leqslant 12$, and a CGI improvement score of 1 or 2. Among these patients with documented refractory depression, a complete response was observed in 33 per cent, and the majority of these experienced a sustained response lasting for 6 months or longer.

Long-term response

A second episode of depression will occur in 50–80 per cent of remitted patients (NIH Consensus Development Panel, 1985; Frank *et al*., 1990). An antidepressant that demonstrates efficacy in these patients offers an advantage. The efficacy of imipramine for long-term maintenance therapy in patients with major depression has been demonstrated (Frank *et al*., 1990). However, information on long-term response is not available for most other antidepressants.

The long-term efficacy of venlafaxine was evaluated in a double-blind, randomized trial of venlafaxine and imipramine (Shrivastava *et al*., 1994). The dosage of venlafaxine and imipramine ranged from 75–225 mg daily. At 2, 6, and 12 months, the clinical response was significantly ($P \leqslant 0{\cdot}05$) greater with venlafaxine than with imipramine. In a meta-analysis of four controlled studies the relapse rate was evaluated in 185 patients who continued on venlafaxine for up to 12 months (Rudolph *et al*., 1994). Relapse was defined as withdrawal or lack of efficacy or a CGI severity score of 4 or more. At 1 year, the cumulative probability of relapse was 20 per cent with venlafaxine, 34 per cent with placebo, 31 per cent with imipramine, and 29 per cent with trazodone ($P < 0{\cdot}05$ for venlafaxine versus placebo, Kaplan–Meier analysis). The relapse rate with imipramine in this study was higher than that reported during a 3-year follow-up by Frank and colleagues (1990). The mean imipramine dose in the meta-analysis was 168–179 mg/day versus 216 mg/day in the study of Frank *et al*. Results from a number of other long-term, open-label studies indicate that venlafaxine maintains its efficacy for up to 1 year of therapy (Magni and Hackett, 1992; Khan *et al*., 1995; Lecable *et al*., 1995).

DOSE-RESPONSE EFFECTS OF ANTIDEPRESSANTS

The TCAs demonstrate a dose–antidepressant-response effect; however, dosage titration is frequently limited by dose-related side-effects that, in effect, limit the potential for a true dose response (Preskorn, 1994). The SSRIs as a class are characterized by a relatively flat dose–response curve (Altamura *et al*., 1988; Dornseif *et al*., 1989; Beasley *et al*., 1990; Fickinger *et al*., 1994; Preskorn and Lane, 1995; Figure 4). Thus, if a patient fails to

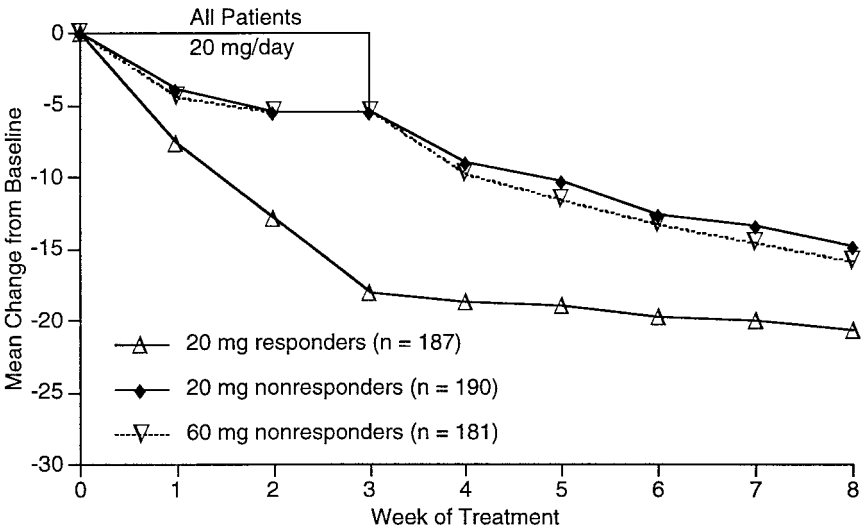

Figure 4. Dose–response effects of fluoxetine on the HAM-D total score from fixed-dose studies (adapted with permission from Dornseif *et al*,. 1989)

respond to the usual dose of an SSRI, a further dosage increase is unlikely to improve the response but may increase the incidence of side-effects, which is dose related (Dornseif *et al*., 1989). The dose–effect relationships with SSRIs may impact the drop-out rate due both to efficacy and adverse effects. The results from controlled trial of fluoxetine in Europe showed a drop-out rate due to adverse effects of 13 per cent with fluoxetine and 9 per cent with comparator drugs. The drop-out rate for all reasons, including lack of efficacy, was 26 per cent with fluoxetine and 22 per cent with comparators (Gram, 1994).

In contrast, there is evidence that venlafaxine demonstrates an improved therapeutic response with increasing doses. The efficacy of venlafaxine given twice daily was evaluated in a double-blind, randomized, placebo-controlled trial of outpatients with major depression (Mendels *et al*., 1993). Patients received placebo or venlafaxine 25–50 mg, 50–75 mg, or 150–200 mg daily. A significant ($P < 0{\cdot}05$) improvement with increasing doses was observed on the HAM-D, MADRS, and CGI severity scores. In another double-blind, placebo-controlled trial, the efficacy of venlafaxine was evaluated in 358 depressed outpatients (Rudolph *et al*., 1991). The venlafaxine dose was rapidly titrated upward from 75 mg daily to the target dose of 75 mg, 150–225 mg, or 300–375 mg daily during the first week. At weeks 1 and 2, a significantly ($P \leqslant 0{\cdot}05$) greater response was observed in the high-dose group (300–375 mg/day) compared with the placebo group (Preskorn, 1994; Figure 5).

A double-blind, randomized study compared venlafaxine and fluoxetine in outpatients with major depression (Dierick *et al*., 1996). Patients were started on either venlafaxine 37·5 mg twice daily or fluoxetine 20 mg once daily; however, the dosage of venlafaxine could be increased to 75 mg twice daily for an inadequate response. Overall, venlafaxine was comparable to fluoxetine. However, among the 54 per cent of patients who increased their venlafaxine dose at week 2, venlafaxine was significantly ($P < 0{\cdot}05$) superior to fluoxetine on the HAM-D from week 3 onward (Figure 6). This study design may be criticized for the use of a fixed dose of fluoxetine.

SAFETY PROFILE

The safety profile of TCAs is well known (Potter *et al*., 1991). Most common are dose-limiting adverse effects such as anticholinergic effects, but intracardiac conduction abnormalities are an important cause of toxicity even at therapeutic dosages (Preskorn and Fast, 1992). In addition, the TCAs are the class of antidepressants most commonly associated with accidental or intentional overdosage among patients treated for

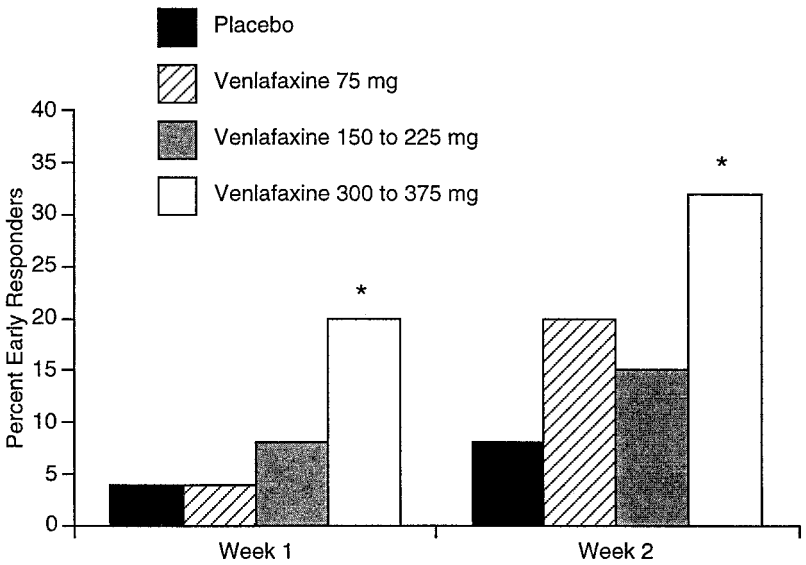

Figure 5. Response rate among patients treated with venlafaxine in a double-blind, placebo-controlled trial in depressed patients (adapted with permission from Preskorn, 1994). $^{*}P \leqslant 0{\cdot}05$ versus placebo

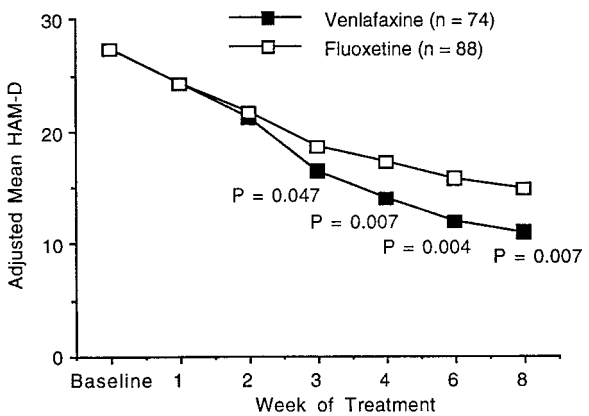

Figure 6. Mean HAM-D total scores for venlafaxine and fluoxetine in patients who increased their dose at week 2 (adapted with permission from Dierick *et al.*, 1996)

depression. The safety and tolerability of TCAs may be a factor contributing to poor compliance and undertreatment of depression (McCombs *et al.*, 1990; Anderson and Tomenson, 1995).

The most common adverse effects with SSRIs, occurring in up to 30 per cent of patients, are nausea, anorexia, nervousness, insomnia, and diarrhoea (Potter *et al.*, 1991; Gram, 1994). Unfortunately, while SSRIs exhibit a flat dose–response curve, both the incidence of adverse effects and the drop-out rate due to adverse effects are dose related (Montgomery *et al.*, 1994a; Table 2). Sexual dysfunction manifested as delayed orgasm or ejaculation, or anorgasmy is a common adverse effect that may be underreported (Gitlin, 1994)

Overall, the most common adverse effects with venlafaxine are nausea, somnolence, dizziness, dry mouth, and sweating. Many of these adverse effects are attributed to venlafaxine's potent effects on serotonin and norepinephrine reuptake. The incidence of nausea, somnolence, and dizziness decreased after 1–2 weeks of treatment (Danjou and Hackett, 1995). In a comparative trial with imipramine, nausea occurred significantly more often with venlafaxine, while dry mouth occurred significantly more often with imipramine (Schweizer *et al.*, 1994). During long-term treatment, no side-effects occurred more frequently with venlafaxine than with comparator antidepressants, and there was a significantly lower rate of discontinuations from venlafaxine than from comparator antidepressants (Danjou and Hackett, 1995). In a long-term, double-blind trial, the incidence of anticholinergic-type side-effects was significantly higher with imipramine than with venlafaxine beginning at the first week of therapy (Shrivastava *et al.*, 1994).

Rapid escalation of the dose of venlafaxine, not unexpectedly, appears to be associated with an

Table 2. Discontinuation rates by dose with fluoxetine, paroxetine, and sertraline from double-blind, controlled trials (adapted with permission from Montgomery *et al.*, 1994a)

	Fluoxetine			Sertraline			Paroxetine		
Dose (mg)	20	40	60	50	100	200	20	30	40
Patients (%)	8	12	30	11	16	36	26	33	26

increased incidence of side-effects. Dose-related side-effects include headache, insomnia, nausea, somnolence, dry mouth, and sexual dysfunction (Danjou and Hackett, 1995). Interestingly, in the study of Benkert and associates (1996), the incidence of adverse effects remained low and relatively constant throughout the study despite rapid dosage escalation, and few patients discontinued for adverse effects.

A small, but significant, rise in blood pressure occurred with venlafaxine in clinical trials, most often at doses above 200 mg daily, but hypertensive patients were not at increased risk for elevated blood pressure (Ferguson *et al.*, 1994). At the usual venlafaxine dose of 75 mg twice daily, no differences in the frequency of clinically significant blood pressure changes were observed between venlafaxine and placebo. Gründer and colleagues (1996), using 24-h ambulatory monitoring, found no difference in blood pressure changes with venlafaxine and imipramine. In a comparative trial of 314 patients treated with venlafaxine 75–150 mg daily or fluoxetine 20 mg daily, the incidence of clinically significant increases in blood pressure was similar with venlafaxine and fluoxetine (Dierick *et al.*, 1996). Clinically important postural hypotension, electrocardiographic changes, and cardiac conduction abnormalities occur rarely with venlafaxine.

The SSRIs are potent inhibitors of cytochrome P450 enzymes, which are responsible for the metabolism of many drugs, including antidepressants, antihypertensives, antiarrhythmics, and neuroleptics (Crewe *et al.*, 1992). Clinically significant and potentially serious pharmacodynamic and pharmacokinetic drug interactions have been reported with all SSRIs (Bergstrom *et al.*, 1992; Härtter *et al.*, 1993; Brosen *et al.*, 1993; Lydiard *et al.*, 1993). Unlike the SSRIs, venlafaxine has no effect *in vitro* on the P450 enzyme system (Otton *et al.*, 1996). Consequently, it is unlikely that venlafaxine will effect the metabolism of other drugs metabolized via these enzymes. However, venlafaxine is dependent on the P450 system for its metabolism. Thus, co-administration with other drugs such as fluoxetine may inhibit its metabolism to increase plasma levels of venlafaxine. Conversely, it is likely that drugs such as carbamazepine and phenytoin, which are potent enzyme inducers, will decrease plasma levels of venlafaxine (Preskorn, 1994). The clinical relevance of these *in vitro* findings can only be confirmed with *in vivo* drug interaction studies and long-term observations.

SUMMARY

TCAs and MAO inhibitors are characterized by non-specific activity on noradrenaline and serotonin in addition to a number of receptors that are unrelated to antidepressant activity. In contrast, SSRIs exert targeted activity primarily on serotonin reuptake. Venlafaxine is the first of the SNRI class of antidepressants with a pharmacological profile characterized by specific inhibition of serotonin and noradrenaline, but with no effect at clinically useful doses on muscarinic, adrenergic, or histaminergic receptors. While TCAs are widely effective in treating major depressive disorder, their use often is limited by adverse effects. The SSRIs demonstrate an improved safety/tolerability profile but may show reduced efficacy in patients with serious or refractory depression. Venlafaxine may differ from other antidepressants because of its activity in a broad range of patients, the option for an improved response wih dosage escalation resulting in the potential for an early onset of action, and a safety profile that is comparable to the SSRIs.

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