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REVIEW

Venlafaxine. Pharmacology and Therapeutic Potential in the Treatment of Depression

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Venlafaxine is the first available antidepressant of the structurally novel SNRI (serotonin noradrenaline-reuptake inhibitor) class of drugs. It resembles the tricyclics in its ability to inhibit presynaptic reuptake of both serotonin and noradrenaline to a clinically significant degree. However, it does not cause appreciable effects at other receptor sites, including cholinergic, adrenergic and histaminergic, which are responsible for most of the unwanted side effects and toxicity associated with antidepressant treatment. It has the unusual ability to reduce β-noradrenergic responsiveness after a single dose, which has led to the suggestion that it may have an earlier onset of therapeutic effect than traditional antidepressants. Clinical trials provide evidence that venlafaxine is of comparable efficacy to reference antidepressants, but may have a faster onset of antidepressant effect when given in high dosage. © 1998 John Wiley & Sons, Ltd.

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KEY WORDS — depression; serotonin-noradrenaline reuptake inhibitor; venlafaxine; β-adrenergic receptor

INTRODUCTION

Progress in the field of antidepressant development has produced drugs with improved side effect and toxicity profiles, although a delay of 2–3 weeks before the onset of a clinical response remains a standard feature of antidepressant treatment. It has been claimed that various new products have a faster onset of antidepressant effect than the traditional antidepressants. Lack of well defined criteria for onset of action, and factors such as placebo response, inadequate dosage comparison and heterogeneous methods of data analysis, have made such claims difficult to substantiate (Lydiard *et al*., 1984). Studies designed to examine antidepressant potency indicate that the new products are no more effective than tricyclics in the treatment of depression of moderate severity, and may be less effective in the treatment of severe melancholic depression (Danish University Antidepressant Group, 1986, 1990; Roose *et al*., 1994; Anderson *et al*., 1994).

The serotonin and noradrenaline reuptake inhibitors (SNRIs) are a structurally novel group of drugs that, like the tricyclics, have clinically significant effects at both serotonergic and noradrenergic reuptake sites, but their relative specificity gives them a side effect and toxicity profile which resembles that of the SSRIs. Venlafaxine is the only SNRI which is currently licensed for the treatment of depression, however two new SNRIs, duloxetine and milnacipran, are currently under development.

As the search continues for an antidepressant product which offers clear therapeutic advantages, this paper reviews the role of venlafaxine in antidepressant therapy.

PHARMACOLOGY

Venlafaxine is a phenethylamine bicyclic compound (chemical name: 1-[2-(dimethyl-amino)-1-(4-methoxyphenyl)-ethyl]cyclohexanol hydrochloride). The molecule exists as a racemic mixture of R (−) and S (+) enantomers in approximately equal proportions (Wang *et al*., 1992; Howell *et al*., 1994).

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A series of *in vivo* and *in vitro* animal studies provided preclinical evidence that venlafaxine had potential antidepressant properties. In common with classical antidepressants, it suppresses histamine induced ACTH release in rats, and antagonises reserpine-induced hypothermia suggesting an ability to block noradrenaline uptake at sympathetic nerve terminals (Moyer *et al*., 1984). It also reduces noradrenergic neuronal firing rates in the rat locus coeruleus (Haskins *et al*., 1985). Many effective antidepressant treatments cause desensitisation and down-regulation of β-adrenergic receptors in rodents after repeated administration and this has been correlated with the onset of antidepressant effect (Vetulani and Sulser, 1975; Sulser, 1982). Venlafaxine causes a reduction of the cyclic AMP response to isoproterenol (2 μμmol/kg) in the rat pineal gland, an effect that is mediated by the activation of β-adrenergic receptors. The response was reduced by 51 per cent after a single injection of venlafaxine (10 mg/kg i.p.), and by 43 per cent after repeated injections (10 mg/kg i.p. twice daily for 5 days). This contrasts with the delayed onset of this effect observed with other antidepressants. Desipramine, which was used as the standard in this study, reduced cAMP responsiveness by 81 per cent, but only after repeated administration. The unusual property of venlafaxine to reduce noradrenergic responsiveness after a single dose led to the suggestion that it might have a more rapid onset of clinical effects than other antidepressants (Moyer *et al*., 1984).

The antidepressant effects of venlafaxine were studied in animal models of depression. In the behavioural despair (forced swim model), venlafaxine significantly lengthened the time of activity exhibited by mice treated with both 15 and 30 mg/kg s.c. without producing stimulation or sedation (Lloyd *et al*., 1992). Chronic treatment with venlafaxine markedly increased the aggressive behaviour of resident rats that were confronted with an intruder rat, and decreased the flight time of the residents (Mitchell and Fletcher, 1992).

The ability of a drug to displace [^{3}H] imipramine from rat brain cortical binding sites *in vitro* has been correlated with its potency to inhibit 5HT reuptake. Although this property is not universal amongst the new generation of antidepressant, it is used as a screening test for the antidepressant potential of a drug (Raisman *et al*., 1980; Langer *et al*., 1980). Venlafaxine inhibits [^{3}H] imipramine binding with slightly greater potency than does desipramine. It inhibits the reuptake of serotonin, noradrenaline and, to a lesser extent, dopamine at the presynaptic membrane. Both the enantomers of venlafaxine inhibit reuptake of noradrenaline and 5HT, but the S enantomer is relatively more selective for 5HT reuptake inhibition (Muth *et al*., 1986; Yardley *et al*., 1990).

Table 1 shows the relative uptake blockade of [^{3}H] noradrenaline, [^{3}H] serotonin, and [^{3}H] dopamine into rat brain synaptosomes by various antidepressants using the measurement of the inhibitor constants (K_i). Venlafaxine has approximately five times greater potency to inhibit the reuptake of serotonin than noradrenaline.

Venlafaxine has no significant affinity for the rat brain muscarinic cholinergic, α-1, α-2 or β-adrenergic receptors, nor does it have appreciable effects at serotonin-1, serotonin-2, dopamine-2, histamine or benzodiazepine or μ-opiate receptors. Venlafaxine is not a monoamine oxidase A or B inhibitor because it does not inhibit the oxidation of [^{14}C] tryptamine, a non-specific monoamine oxidase substrate (Muth *et al*., 1986; Yardley *et al*., 1990).

The potency of an antidepressant to block specific human brain receptors is predictive of certain side effects and drug interactions. The equilibrium dissociation constant (K_d) measures the potency of a drug for a specific receptor using radioligand binding assays and post mortem human brain tissue. In a study designed to compare the binding potencies of 17 antidepressants, including fluoxetine, sertraline and paroxetine, at seven different receptors (muscarinic, histamine H_1, α_1-adrenergic, α_2-adrenergic, D_2, $5HT_{1A}$, $5HT_2$), most of the newer compounds were shown to have only weak ability to block neurotransmitter receptors. Venlafaxine produced the least blockade of all the drugs tested, with essentially no activity at any of the receptor sites (Cusack *et al*., 1994).

ABSORPTION AND METABOLISM

Venlafaxine is well absorbed after oral administration, reaching peak serum level 1–2 h after oral administration. It undergoes extensive first pass metabolism in the liver via the 2D6 isoenzyme of cytochrome P450 to a major active metabolite *O*-demethylvenlafaxine (56 per cent), and two less active metabolites, *N*-demethylvenlafaxine (1 per cent) and *N*,*O*-didemethylvenlafaxine (16 per cent) (Klamerus *et al*., 1992). *O*-desmethylvenlafaxine (ODV) shares the same biochemical properties as

Table 1. Monoamine reuptake inhibition by various antidepressants; K_i (geometric mean ± S.E.M.) in nM

Drug	NA	5HT	Dopamine
Venlafaxine	210 ± 20	39 ± 3	5300 ± 600
Fluoxetine	143 ± 6	14 ± 3	3050 ± 70
Paroxetine	33 ± 2	0·73 ± 0·04	1700 ± 300
Sertraline	220 ± 40	3·4 ± 0·4	260 ± 40
Desipramine	0·61 ± 0·07	180 ± 10	11 000 ± 1000
Imipramine	14 ± 1	41 ± 3	3050 ± 70
Dothiepin	28 ± 1	170 ± 10	5000 ± 1000
Lofepramine	1·9 ± 0·1	2400 ± 100	1800 ± 200
Trazodone	9500 ± 2000	490 ± 60	25 900 ± 700

K_i = inhibitor constant; lower numbers indicate higher potency.
NA = noradrenaline, DA = dopamine.
Adapted from Bolden-Watson *et al.* (1993).

Table 2. Monoamine uptake inhibition of venlafaxine and metabolites; uptake inhibition, IC_{50} μM

Compound	NE	5HT	DA
Venlafaxine	0·64	0·21	2·8
O-desmethylvenlafaxine	1·16	0·18	13·4
N-desmethylvenlafaxine	4·7	1·6	21·1
N,*O*-didesmethylvenlafaxine	> 10	2·8	30

IC_{50} = concentration that inhibits 50 per cent of amine reuptake.
Table adapted from Muth *et al.* (1991).

the parent compound, i.e. reversal of reserpine induced hypothermia, rapid induction of β-adrenergic subsensitivity, and the same general pattern of monoamine reuptake inhibition. These properties predict that ODV has antidepressant effects in its own right. None of the metabolites exhibit significant binding at neuroreceptor sites likely to give rise to side effects (Muth *et al.*, 1991).

Both venlafaxine and ODV are approximately 30 per cent protein bound, leading to extensive tissue binding and a high volume of distribution (Klamerus *et al.*, 1992). Excretion is primarily by the renal route, in man 87 per cent of a single dose appears in the urine after 48 h, less than 10 per cent of this is as unchanged venlafaxine (Howell *et al.*, 1993). Although the metabolic pathway of venlafaxine has been reported to have a saturable component, this is probably clinically unimportant as the rate of clearance of venlafaxine and ODV together does not differ significantly with dose (Klamerus *et al.*, 1992). At a dose of 75 mg 8-hourly the half life of venlafaxine is 4·1 h and that of the active metabolite ODV is 10·4 h. Their combined short half lives result in steady-state conditions within 10 doses, and because ODV has virtually the same antidepressant ability as the parent drug, its longer half life permits twice daily dosage regimes.

ADMINISTRATION AND TOLERABILITY

The usual recommended starting dose of venlafaxine of 75 mg/day probably confers the same degree of efficacy as the standard dose of an SSRI. Unlike the SSRIs, there is some evidence for a positive dose response effect (Dierick *et al.*, 1996). Severely depressed patients can be started on 150 mg/day and the dose titrated up at intervals of 4 days to a maximum daily dose of 375 mg/day. Higher doses are more likely to cause side effects, however the incidence of nausea can be reduced if the drug is given with food (Fabre and Putham, 1987). In most instances, 75–225 mg/day is adequate to produce a clinical response. There is no significant difference in the steady state pharmacokinetics of venlafaxine 150 mg/day administered in two or three divided doses in healthy volunteers (Troy *et al.*, 1995), and the use of twice daily regimes in the treatment of depressed patients is supported in clinical trials (Mendels *et al.*, 1993; Clerc *et al.*, 1994; Dierick *et al.*, 1996).

Table 3. Comparison of mean pharmacokinetic parameters for venlafaxine, fluoxetine, paroxetine and sertraline (adapted from Morton *et al.*, 1995)

Parameter	Venlafaxine	Fluoxetine	Paroxetine	Sertraline
Mean elimination half life (h)	5	84	21	26
Time to peak plasma conc. (h)	2	4–8	3–8	6–10
Protein binding (%)	27	95	95	98
Time to steady state (days)	2–3	14–28	4–14	10
Mean plasma clearance (l/h/kg)	1·3	0·29	0·76	NA
Mean volume of distribution (l/kg)	7·5	25	13	25
Active metabolite half life	*O*-desmethylvenlafaxine 11 h	norfluoxetine 4–16 days	none	*N*-desmethylsertraline 62–104 h
P450 2D6 inhibition	low	high	high	moderate

References: Klamerus *et al.* (1992); Crewe *et al.* (1992); DeVane (1992).

Adverse effects

In a meta analysis of 19 studies involving 2181 patients treated with venlafaxine, the side effects experienced by $\geqslant 10$ per cent of subjects were nausea, headache, insomnia, somnolence, dry mouth, dizziness, constipation, asthenia, sweating, and nervousness (Danjou and Hackett, 1995). Of these, nausea was the most common, occurring in 32 per cent of subjects and leading to discontinuation of the drug in 6 per cent. The incidence of nausea fell by 50 per cent after the first week and continued to decrease rapidly with time. Other side effects, such as insomnia, and sexual dysfunction, which occurs in about 9 per cent of patients receiving high dose therapy, do not appear to ameliorate with time (Danjou and Hackett, 1995; Mendels *et al.*, 1993). Venlafaxine is about half as likely to produce anticholinergic-type side effects in comparison with the tricyclics, and overall venlafaxine produces a very similar side effect profile to the SSRIs. The pooled results from long term studies (up to one year) indicate that venlafaxine is relatively well tolerated compared with reference antidepressants and placebo, with significantly fewer withdrawals due to side effects and lack of efficacy (Danjou and Hackett, 1995).

In the entire cohort of venlafaxine-treated patients in the meta-analysis, there was a mean increase in supine diastolic blood pressure of 2 mmHg. This was dose dependent, at doses of >200 mg/day 5·1 per cent of patients met the criteria for potentially significant increase in diastolic blood pressure, but at smaller doses the rise was no greater than that produced by placebo. In premarketing studies, the maximal mean increase was 1 mmHg in patients on a dose of 75 mmHg/day, 2 mmHg on 225 mmHg/day, and 7·5 mmHg on 375 mmHg/day. The presence of treated hypertension at baseline does not seem to predispose patients to further rises during treatment. Venlafaxine has no direct effect on cardiac conduction and is a relatively safe choice of an antidepressant in people at risk of cardiac arrythmias (Danjou and Hackett, 1995). Venlafaxine does not appear to be epileptigenic. In premarketing studies, seizures were reported in 0·26 per cent of 3082 patients on venlafaxine, which is a similar rate to those observed with the SSRIs and other new antidepressants (data on file, Wyeth-Ayerst Research; Davidson, 1989). There is some evidence to suggest that a single dose of venlafaxine produces improvements in attention, concentration, memory, subjective drive and wakefulness in normal volunteers, and this is supported by EEG, psychometric and psychophysiological tests leading to the suggestion that venlafaxine may have a particular role in the treatment of cognitive disturbances associated with depression (Saletu *et al.*, 1992; Semlitsch *et al.*, 1993). Venlafaxine has been observed to have an early effect on the cognitive symptoms of depression (Derivan and Rudolph, 1988).

Sudden discontinuation of venlafaxine has been associated with fatigue, dizziness, insomnia, nausea and nervousness (Clerc *et al.*, 1994). The Efexor Data Sheet recommends that patients who have been taking venlafaxine for more than 1 week have their dose gradually reduced over a few days, and those on venlafaxine for 6 weeks should have the

dose tapered over at least 1 week before discontinuation.

There are anecdotal reports of the use of venlafaxine with ECT without apparent ill effect (Farah *et al*., 1995), however there are as yet no clinical data establishing the benefit of the combination. In addition there are no data about possible pharmacodynamic interactions between venlafaxine and the anaesthetic agents commonly used with ECT. The manufacturer recommends that venlafaxine be discontinued at least 1 week before ECT.

Venlafaxine appears to be safe and well tolerated in elderly patients. No dosage reduction is recommended despite an approximate 15 per cent reduction in steady state clearance (Parker *et al*., 1990). Venlafaxine can be administered to patients with renal impairment, however dosage reductions and once daily administration are recommended in patients with creatinine clearance of 30 ml/min or less (Troy *et al*., 1994). Dose reductions are also recommended in patients with moderate to severe hepatic impairment [Troy *et al*., data on file. Wyeth-Ayerst Research].

SAFETY AND TOXICITY

Venlafaxine shares the low toxicity potential of the SSRIs. In the premarketing evaluation there were 14 reports of overdose with venlafaxine, either alone or in combination with other drugs or alcohol. The highest overdose was 6·75 g (equivalent to a 90 day supply of the starting dose of 75 mg/day). An increased QT interval on ECG, and two generalised epileptic seizures were reported in a patient who had ingested 2·75 g, but in most cases somnolence was the only effect and all patients made a full recovery (data on file, Wyeth-Ayerst Research).

There has been limited information about the safety of venlafaxine in pregnancy. Animal studies suggest that foetal exposure to the drug does not cause congenital malformations, however there was an increased incidence of stillbirths and neonatal deaths, and birth weights were reduced when exposure was begun in early pregnancy and continued after weaning. These animals were exposed to up to the equivalent of 10 times the maximum daily dose for humans. In the UK there have been 46 reports of women who have been exposed to venlafaxine during pregnancy since its launch. Twenty-seven of these women are not yet at term and six are lost to follow up. Of the remainder, three women have delivered healthy babies at term, six women have had elective abortions, and three women have had miscarriages. One woman had an abortion and the foetus was found to have a congenital abnormality. There was a family history of spina bifida, and no causality has been assigned to venlafaxine as yet (data on file, Wyeth-Ayerst Research). The excretion of venlafaxine in breast milk has not been studied.

Studies of potential carcinogenic effect of venlafaxine have been negative. Mice and rats exposed to as much as six times the maximum human dose did not have an increased rate of tumour development (data on file, Wyeth-Ayerst Research).

Drug interactions

Antidepressants and most antipsychotics are metabolised primarily in the liver by a group of microsomal enzymes collectively known as the cytochrome pigment 450 (CYP) isoenzyme system. Enzymes of the CYP system are classified into various families and subfamilies based on similarities in the sequences of their amino acids. CYP2D6 and CYP3A3/4 are particularly important in clinical psychopharmacology because they are the principle metabolic pathway of most psychotropic drugs. Substrates for CYP2D6 include the antipsychotics, tricyclics, paroxetine and fluoxetine, and CYP3A3/4 metabolises tricyclics, sertraline, benzodiazepines, anticonvulsants and steroids. Some drugs are metabolised by more than one pathway. Venlafaxine is metabolised by CYP2D6 to its active metabolite ODV, and by CYP3A3/4 to an inactive metabolite (*N*-desmethylvenlafaxine) (Ereshefsky, 1996). Some drugs inhibit specific isoenzymes causing delayed clearance of substrates metabolised by that pathway, and potential drug interactions. The SSRIs, particularly paroxetine and fluoxetine, have been shown to be potent inhibitors of CYP2D6 *in vivo* and *in vitro* (Crewe *et al*., 1992; Otton *et al*., 1996; Lam *et al*., 1996). In clinical practice, co-administration of fluoxetine can cause serum tricyclic levels to reach toxic levels (Westermeyer, 1991). Venlafaxine is 17–300 times less potent an inhibitor of CYP2D6 than the SSRIs, and has no significant capacity to inhibit CYP3A4, CYP1A2 or CYP2C9 (Sellers *et al*., 1993; Otton *et al*., 1996; Ball *et al*., 1996). It is therefore unlikely that venlafaxine would inhibit the clearance of a drug metabolised by these pathways, although possible that the clearance of

venlafaxine could be inhibited by a drug which potently inhibits the CYP isoenzymes, e.g. cimetidine. This is born out by the results from clinical studies using normal human subjects. Venlafaxine inhibits the metabolism of the CYP2D6 marker significantly less than fluoxetine *in vivo* (Amchin *et al*., 1996). No significant pharmacodynamic or pharmacokinetic interactions could be demonstrated between venlafaxine and a single dose of diazepam 10 mg or a single dose of ethanol 0·5/kg (a CYP2E1 substrate) (Troy *et al*., 1992). In addition, the psychomotor and psychometric effects of these drugs were not exaggerated by venlafaxine. No significant interaction between venlafaxine and lithium or carbamazepine have been demonstrated (Parker *et al*., 1991; Wiklander *et al*., 1995). Venlafaxine has recently been evaluated for the inhibition of the CYP3A3/4 substrate alprazolam *in vivo*. Although no inhibition was demonstrated, there was an observed <30 per cent decrease in the plasma concentration of alprazolam which requires further evaluation (Amchin and Zarycranski, 1996). Cimetidine decreases the clearance of venlafaxine by 43 per cent due to inhibition of first pass metabolism, although it does not affect the formation or elimination of ODV. Dose adjustments are probably unnecessary in otherwise healthy adults, but the combined use of venlafaxine and cimetidine may produce a clinically relevant interaction in patients with hypertension or reduced clearance for other reasons (data on file, Wyeth-Ayerst Research).

In common with other drugs which potently inhibit serotonin reuptake, there is the potential for a toxic interaction when the drug is given with an MAOI. Venlafaxine should not be used with or within 14 days of discontinuing an MAOI, and at least 7 days should elapse before an MAOI is started after discontinuation of venlafaxine.

Overall, the low plasma protein binding, and low potential to inhibit CYP2D6 and 3A3/4 activity give venlafaxine a relatively low potential for drug–drug interactions compared with tricyclics and SSRIs.

CLINICAL EFFICACY

Evidence that 75 mg/day, the usual effective dose of venlafaxine, comes from various placebo controlled trials in depressed outpatients (Rudolph *et al*., in press; Mendels *et al*., 1993; Shrivastava *et al*., 1994). Each study indicated that venlafaxine was superior to placebo on at least one measure of efficacy. In an open label trial of venlafaxine in a general practice setting, 300 depressed patients were treated with doses of 75–150 mg, and 75 per cent responded adequately to a dose of 75 mg/day (Lecable *et al*., 1995). Comparator studies of fluoxetine indicate that venlafaxine 75 mg/day is comparable in tolerability and efficacy to fluoxetine 20 mg in depressed outpatients (Tylee *et al*., 1997; Dierick *et al*., 1996). However, unlike the SSRIs, there is some evidence for a positive dose response effect. Venlafaxine in doses of $\geqslant 150$ mg is statistically superior, or at least there is a trend towards superiority, compared with standard doses of fluoxetine, fluvoxamine, and imipramine (Lecrubier *et al*., in press; Shrivastava *et al*., 1994; Dierick *et al*., 1996; Clerc *et al*., 1994; Schweizer *et al*., 1994; Blanchard *et al*., 1995). Patients who had their dose of venlafaxine increased to 150 mg/day after 2 weeks of treatment, demonstrated a statistically superior response on the HAM-D scale by week 3 compared with patients treated with fluoxetine 20 mg/day (Dierick *et al*., 1996). Venlafaxine has been shown to be effective in the treatment of severe melancholic depression. Venlafaxine 200 mg/day was superior to fluoxetine 40 mg/day at weeks 4 and 6 on the HAM-D and MADRAS scales in hospitalised depressed patients with melancholia (Clerc *et al*., 1994). A clinically meaningful response was observed as early as 4 days after the initiation of treatment in one study (Guelfi *et al*., 1995).

A trend towards early clinical response (within 2 weeks) with high dose treatment was detected in several placebo controlled trials (Mendels *et al*., 1993; Khan *et al*., 1991; Schweizer *et al*., 1991). In a study designed specifically to assess onset of response, a rapidly escalated dose of venlafaxine (375 mg in 5 days) was compared to imipramine (200 mg in 5 days) in 167 severely depressed inpatients with melancholia. The venlafaxine treated group had a median time to response on HAM-D of 14 days compared with 21 days for imipramine. Maximal tolerated doses of venlafaxine and imipramine were comparable for overall efficacy (Benkert *et al*., 1996).

Clomipramine has a ratio of serotonin to noradrenaline reuptake inhibition of approximately 1:1. Results from some clinical studies suggest that the benefits of this pharmacological profile may be greater antidepressant activity in severely depressed patients with a more rapid onset of activity (Danish University Antidepressant Group, 1986, 1990; Pollock *et al*., 1993). In

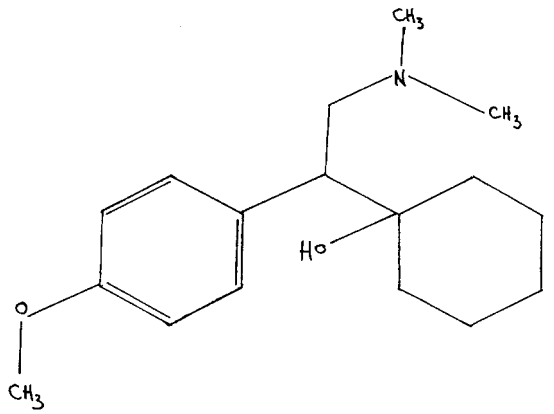

Figure 1. The chemical structure of venlafaxine

depressed outpatients, venlafaxine was equivalent to clomipramine in efficacy. Their tolerability profiles were similar, although there was a trend towards more clomipramine treated patients discontinuing because of side effects (Samuelian and Hackett *et al*., 1992).

Venlafaxine may have a role in the treatment of resistant depression. Seventy patients who had failed to respond to a trial of three different antidepressants from at least two different classes, or two different antidepressants and a course of ECT, were treated with venlafaxine 150–375 mg/day. One third of them experienced a complete or partial response after 12 weeks treatment, and half of the complete responders maintained their response for at least 3 months (Nierenberg *et al*., 1994).

Venlafaxine is effective in the prevention of relapse. In a meta analysis of four double blind placebo controlled trials involving 304 patients, venlafaxine 50–300 mg/day for an additional 12 months after the end of the 6-week study period significantly reduced the incidence of relapse (20 per cent) compared with the placebo group (34 per cent) (Entsuah *et al*., 1993).

CONCLUSION

The mechanism of action of antidepressants is certainly more complex than the simple 'monoamine hypothesis' originally proposed. Although most antidepressant drugs share the property of increasing availability of serotonin, noradrenaline, and in some cases dopamine, at the synapse, some drugs, such as cocaine, are potent monoamine reuptake inhibitors but are not antidepressants. In addition, monoamine reuptake inhibition occurs within hours of exposure to an antidepressant drug, and this does not correlate with the time to onset of therapeutic effect, which takes days or weeks to detect clinically. It is likely that the potentiation of monoaminergic neurotransmission causes gradual adaptive changes resulting a subsensitivity of the neurotransmitter receptors which underlies the clinical response. Attention has focused on the down-regulation of β-adrenergic receptors coupled to adenylate cyclase because this is a common effect of a wide variety of antidepressant treatments and the time frame correlates well with the clinical response (Manji and Brown, 1987). Such long term adaptive changes require interaction with a functional serotonergic system. Removal of cortical serotonergic input by administration of serotonin synthesis inhibitors (Manier *et al*., 1984) or by lesioning serotonergic terminals (Janowsky *et al*., 1982; Brunello *et al*., 1982) prevents or reverses desipramine-induced down-regulation of β-adrenoreceptor number and noradrenaline stimulated cyclic AMP production. The decrease in β-adrenergic sensitivity is believed to be due to the inhibition of reuptake of both noradrenaline and serotonin. The dual action of drugs which specifically inhibit the reuptake of both noradrenaline and serotonin may result in a more rapid onset of antidepressant action (Nelson *et al*., 1991). Rapid down-regulation of β-adrenoreceptors has been demonstrated after the combined administration of desipramine and fluoxetine (Baron *et al*., 1988). Preclinical reports have suggested that venlafaxine may cause a more rapid onset of clinical effects based on the data that both single and repeated doses can induce a rapid subsensitivity of β-receptors in the rat brain. The significance of β-receptor down-regulation remains unclear, however, since it is not a universal property of all effective antidepressants. Potent and selective inhibitors of 5HT reuptake, such as paroxetine or citalopram do not cause β-receptor down-regulation (Nelson *et al*., 1991; Hyttel *et al*., 1984). Nevertheless, to some extent the clinical studies have provided evidence that venlafaxine does have a rapid onset of clinical effects when used in high dosage (Guelfi *et al*., 1995; Benkert *et al*., 1996). It may be that the observed effect is simply a dose response effect. More studies specifically designed to measure the onset of response in comparison to a range of antidepressants are needed to support these findings.

It is evident that venlafaxine is of comparable efficacy to the tricyclics and SSRIs in the treatment

of a broad range of depressed patients. It shows a dose response relationship over a wide range of doses, and steady state levels can be reached rapidly. In contrast to the tricyclics, high doses are relatively well tolerated. The dose of venlafaxine can therefore be adjusted quickly when an early response is important. It has been shown to be effective in a small percentage of treatment resistant patients. The low risk of drug–drug interactions make it a good choice for patients on several different medications. Overall, venlafaxine is a useful alternative to the tricyclics and SSRIs.

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