Venlafaxine: a new class of antidepressant

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Venlafaxine represents a new class of antidepressant, the serotonin and noradrenaline re-uptake inhibitor (or SNRI). This article discusses its evolution, pharmacological properties and role in the treatment of depression and related disorders, beginning with an outline of the biology of depression.

Depression constitutes a major health issue. Its importance has come to the fore in recent years. The World Health Organization predicts that depression will be the second most prevalent single cause of illness and disability worldwide by 2020 (Murray and Lopez, 1997). Despite knowledge of the extent of depressive symptoms in medical settings, clinically significant symptoms may be under-treated, with cost implications for the health service and the patient. Reasons include ineffective prescribing and reluctance on the part of the patient or clinician to enter into discussion about psychological wellbeing. However, simple questions (such as 'How is your sleep?') can reveal the degree to which any apparent psychological distress is associated with the biological disturbances suggestive of a depressive illness. This illness is quite often responsive to antidepressant treatment.

DIAGNOSIS OF DEPRESSION

Key neurotransmitters involved in the regulation of mood, sleep, appetite and drive are serotonin and noradrenaline. Noradrenergic and serotonergic cell bodies are concentrated in the locus coerulus and raphe nuclei respectively, in the brainstem, with projections to the frontal and limbic cortex. Imbalance of these is thought to underlie the symptoms of depression. These include sleep disruption with persistent early morning wakening, often associated with diurnal variation in mood, whereby there is noticeable improvement in the patient's demeanour (such as less agitated or retarded) later in the day, anhedonia (an inability to experience pleasure), loss of libido, and significant weight loss. Such marked biological changes are less likely in milder depressive disorders.

Depression is diagnosed by the presence of at least 2 weeks of depressed mood (although some patients may experience more of a flattening or numbing of emotions rather than feeling desperately miserable), loss of interest and/or enjoyment, and fatiguability. In addition, patients may experience varying degrees of sleep disruption (such as initial insomnia and frequent awakening), appetite disturbance, poor concentration, lowered confidence or self-esteem, unreasonable self-reproach or guilt, and recurrent thoughts of death or suicide.

The extent to which such biological disturbance develops may depend on an individual's vulnerability, from inherited and acquired factors (e.g. post-viral infection, post-partum depression). Precipitating factors for developing a depressive illness may therefore vary from a seemingly minimal stressor to a more prolonged stressor, of psychological and/or biological origin. With repeated episodes depression may become independent of external stressors (Brown, 1992). Antidepressants are indicated for depression of at least moderate severity, which if untreated lasts, on average, 6–9 months. By contrast, early effective antidepressant treatment may reduce this period of suffering to 6 weeks.

Links with anxiety

Anxiety is commonly associated with depression, and there is growing evidence to suggest that the neurochemical changes are related (Ressler and Nemeroff, 2000). With the development of a depressive illness, patients previously free from anxiety may develop marked physical and psychological manifestations of anxiety. Patients with primary anxiety disorders such as panic disorder, generalized anxiety and obsessive compulsive disorder also appear more vulnerable to developing depression which may not be attributable solely to the psychological stress imposed by the condition.

Patients with anxiety conditions alone have a significantly reduced quality of life, associated

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with impaired functioning, particularly where there is behavioural avoidance of anxiety-provoking stimuli. For example, in generalized anxiety disorder, which has a lifetime prevalence around 5%, sufferers experience 6 months or more of excessive, uncontrollable worry and apprehension over everyday concerns, with poor concentration, fatigue and somatic symptoms (associated with unpleasant autonomic arousal). Not surprisingly, if left untreated, these patients present frequently to health-care services.

THE EVOLUTION OF ANTIDEPRESSANTS AND VENLAFAXINE

Man has probably sought to alter the mind's functioning through physical means for millennia. The psychotropic effects of alcohol and cocaine have been known for thousands of years. However, the refinement of modern psychopharmacology appears unsurpassed. Conventional antidepressants came into existence with the discovery that some of the drugs used to treat tuberculosis in the 1950s, namely the monoamine oxidase inhibitors, had mood-elevating effects. Similarly, imipramine, a tricyclic antidepressant, was originally investigated as a potential antipsychotic but it showed mood-elevating properties.

Further research led to the monoamine hypothesis of depression, implicating deficiencies in levels of the monoamine neurotransmitters serotonin and noradrenaline. Three methods for increasing monoamine levels include the inhibition of the enzyme (monoamine oxidase) that breaks down monoamines, blockade of autoreceptors that generate negative feedback on the release of the transmitter and blockade of the reuptake of the transmitter back into the nerve cell.

The 1980s saw the development of the selective serotonin re-uptake inhibitors (SSRIs), such as fluoxetine, which act by inhibiting the neuronal re-uptake of serotonin from the synaptic cleft back to the nerve ending, thereby increasing its availability in the synaptic cleft. With fewer side effects than pre-existing treatments, and relative safety in overdose, they soon became popular first-line treatment for moderate depression. However, some evidence suggests that for more severe depression SSRIs alone may not be as effective as the older tricyclics (Barbui and Hotopf, 2001; Smith et al, 2002). A reason for this may be that the tricyclics also act on noradrenaline receptors. In severe depression, the symptoms appear to be a manifestation of profound disturbance in noradrenergic as well as serotonergic functioning. Other neurotransmitters such as dopamine may also contribute. A drawback of the tricyclics, however, is their lack of receptor selectivity, with troublesome side-effects arising from their blockade of alpha-1 noradrenergic, cholinergic and histaminergic receptors. Furthermore, these drugs are dangerous in overdose.

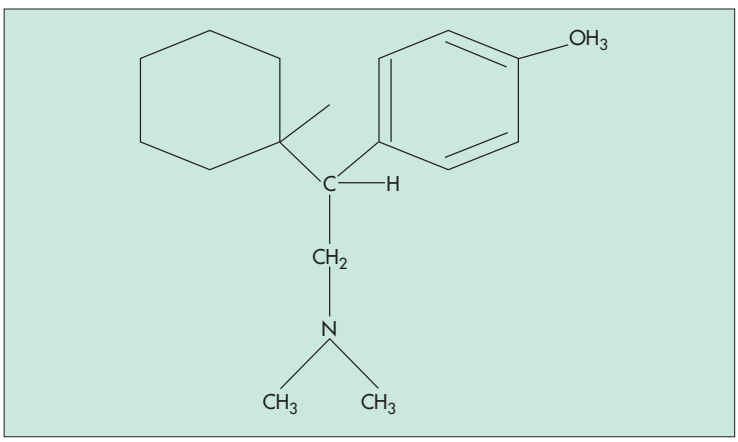
The potential advantage of the dual action is borne out in some of the venlafaxine *vs* SSRI studies. For example, in some studies the remission rates appear to be higher with venlafaxine than with an exclusively serotonergic drug (Poirier and Boyer, 1999; Mehtonen et al, 2000; Thase et al, 2001) and some meta-analytic studies have also suggested the superiority of the dual action over the pure serotonergic agents in depression (Einarson et al, 1999).

PROPERTIES OF VENLAFAXINE

Venlafaxine (*Figure 1*) was developed to selectively inhibit the reuptake of both serotonin and noradrenaline (hence the abbreviation to SNRI) (*Figure 2*) and has no effects on monoamine oxidase activity.

Venlafaxine is licensed from 75 mg to 375 mg daily, with 75 mg being the recommended starting dose for otherwise healthy adults. At low doses it exerts mainly serotonergic activity. As the dose is increased, particularly from 150 mg upwards, significant effects on the noradrenergic system are seen. This binding profile is confirmed with a positron emission tomography (PET) imaging study (Melichar et al, 2001). In clinical practice generally 75 mg is efficacious in treating depression, but higher doses may be needed in more severe cases and in cases with comorbid anxiety. Venlafaxine has a low affinity for brain muscarinic, cholinergic, histaminergic or alpha-adrenergic receptors. It has a fairly rapid onset of action although, in common with other antidepressants, if a patient is going to respond to the drug at the right dose it takes about 6 weeks for symptom resolution.

Figure 1. The structure of venlafaxine.



Venlafaxine, like many other antidepressants, inhibits some CYP enzyme systems. However, its potential for drug interaction is low to negligible. Consideration is needed when using drugs that are substrates for CYP2D6, such as cisapride and astemazole. Concomitant use with monoamine oxidase inhibitors should be avoided. Alcohol is not contraindicated, and venlafaxine is relatively safe in overdose. It can be withdrawn over a week or so, although as with other serotonergic antidepressants, patients may experience transient discontinuation symptoms including low mood and anxiety, flu-like symptoms and insomnia. Patients need to be reassured that this does not represent a relapse of their illness. Like all new antidepressants, venlafaxine is not licensed in pregnancy or lactation.

PHARMACOKINETIC PROPERTIES

These have been reviewed by Ereshefsky and Dugan (2000). Venlafaxine is well absorbed orally, with or without food, and is widely distributed with limited protein binding. It undergoes extensive first pass metabolism in the liver, primarily by O-desmethylation, mediated by the cytochrome P450 enzyme, CYP2D6. The relatively short elimination half-life of the standard formulation of venlafaxine is about 5 hours, with 11 hours for its active metabolite, O-desmethylvenlafaxine, meaning that twice-daily dosing is required. An extended release (microsphere-encapsulated) formulation exists for once-daily dosing, with an elimination half-life of about 15 hours (for the 75 mg dose). The extended release (XL) form of the medication is at least as effective as the standard formulation (Cunningham, 1997). It can be taken at any time during the day. The standard formulation has a peak plasma concentration about 2.5 hours after dosing, compared with about 6 hours for venlafaxine XL. The latter delivers an equivalent total daily exposure to venlafaxine and its metabolite, although without the initial rapid rise in plasma concentration, so it may reduce side effects.

Studies suggest that venlafaxine is well tolerated (Thase, 1997), with common side effects similar to SSRIs, including nausea in the first few weeks, dizziness, insomnia and sexual dysfunction. A small proportion of patients experience hypertension, headache and agitation at higher doses. This relatively benign side effect profile persists in long-term treatment (Shrivastava et al, 1994).

Plasma levels generally correlate well with dose levels. Venlafaxine is mainly excreted via the kidneys, and in patients with moderate renal impairment the dose should be reduced by 50%. This should also be the case if patients have liver disease. The elderly may be able to tolerate the normal adult dose (Khan et al, 1995). Venlafaxine appears relatively safe in overdosage. In 14 reports of overdosage up to approximately 6750 mg, there were few symptoms, including somnolence, mild tachycardia and convulsions. However, in one case, thyroxine and naproxen had been also ingested, and these drugs may have contributed to the emergence of fits.

ANXIETY INDICATION FOR VENLAFAXINE

Newer antidepressants, such as venlafaxine, are also emerging as effective treatment for a range of anxiety disorders. Venlafaxine has been extensively investigated in generalized anxiety disorder and it has shown good efficacy, both in the short and long term (Gelenberg et al, 2000; Allgulander et al, 2001) (*Table 1*). This is important because, until venlafaxine was licensed for the treatment of generalized anxiety disorder, the benzodiazepines remained the principal pharmacological treatment of this group of patients, with the associated problem of under-treatment for the fear of dependence. Studies of venlafaxine in panic disorder and post-traumatic stress disorder are currently under way.

CONCLUSION

Venlafaxine has demonstrable effects on the serotonin and noradrenaline system, and appears to be an effective treatment for depression, anxiety and related conditions. It also appears to be well tolerated by patients, and evidence suggests it has the potential to improve the quality of life and functioning of a significant proportion of health-care users (Boyer et al, 2001), the ultimate goal of medicine. HM

Conflict of interest: Professor Nutt has received grants and honoraria from Wyeth, as well as other pharmaceutical companies.

Allgulander C, Hackett D, Salinas E (2001) Venlafaxine extended release (ER) in the treatment of generalized anxiety disorder. *Br J Psychiatry* **179:** 15–22

Barbui C, Hotopf M (2001) Amitriptyline *vs* the rest: still the leading antidepressant after 40 years of randomised con-

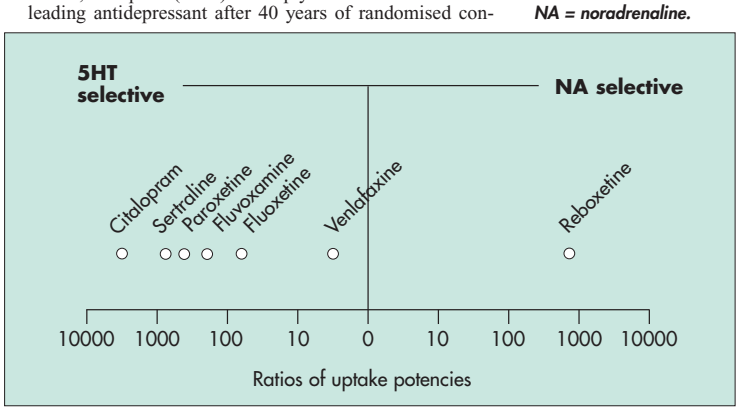


Figure 2. Uptake selectivity ratios for new uptake inhibiting antidepressants. 5HT = 5-hydroxytryptamine; NA = noradrenaline.

TABLE 1.
Relevant studies showing the efficacy of venlafaxine in treating depression and anxiety

Problem	Reference	Study	Findings
Depression	Thase (1997)	Efficacy and tolerability of venlafaxine XL (75–225 mg) *vs* placebo in multi-centre study of 197 outpatients with major depressive disorder	Venlafaxine significantly better than placebo and well tolerated (mean dose about 175 mg/day)
	Salinas (1997)	Venlafaxine XL *vs* paroxetine, in 322 outpatients (double blind, placebo controlled)	Venlafaxine 75 mg XL is more effective and better tolerated than paroxetine 20 mg. Venlafaxine 150 mg XL is more effective and equally well tolerated with paroxetine 20 mg
	Clerc et al (1994)	Venlafaxine (200 mg/day) *vs* fluoxetine (40 mg/day) in 68 inpatients	Venlafaxine superior in efficacy at weeks 4 and 6, and as well tolerated
	Guelfi et al (1995)	Venlafaxine *vs* placebo in 93 inpatients with major depression and melancholia	Venlafaxine (average 350 mg/day) significantly better than placebo, with 65% response, and well tolerated
	Poirier and Boyer (1999)	Venlafaxine (200–300 mg daily) and paroxetine (30–40 mg daily) in treatment-resistant depression	About half on venlafaxine and a third on paroxetine responded, with remission in about 40% and 20% respectively
Depression with anxiety	Feighner et al (1998)	Efficacy of venlafaxine XL (75–225 mg/day) for symptoms of anxiety in depressed outpatients	Venlafaxine significantly more effective than placebo (double-blind) for moderate–severe anxiety
Generalized anxiety disorder (GAD)	Allgulander et al (2001)	Venlafaxine XL in the treatment of GAD: 24-week placebo controlled dose ranging study (529 patients)	At week 8 both 75 mg and 150 mg were significantly efficacious compared with placebo, and this was sustained over 24 weeks
	Gelenberg et al (2000)	Efficacy of venlafaxine XL in non-depressed outpatients with GAD: 6-month randomized, double blind, placebo controlled	Venlafaxine significantly better than placebo, reflected in scores on HAM-A, which improved as early as first week on 75mg/day
	Davidson et al (1999)	Efficacy, safety, and tolerability of venlafaxine XL (75 mg and 150 mg) and buspirone (30 mg) in 365 patients with GAD	Venlafaxine XL was well tolerated, and significantly better than placebo on HAM-A and HAM-D anxiety subscale. It was also significantly better than buspirone on HAM-D anxiety subscale

HAM-A = Hamilton Anxiety Scale; HAM-D = Hamilton Depression Scale; XL = extended release

trolled trials. *Br J Psychiatry* **178:** 129–44

Boyer P, Mahe V, Hackett D, Haudiquet V (2001) Efficacy of venlafaxine ER in social adjustment in patients with generalised anxiety disorder. Poster presented at the VIII Word Congress of Biological Psychiatry, Berlin, July 1–6

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Clerc GE, Ruimy P, Verdeau–Pailles J (1994) A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. *Int Clin Psychopharmacol* **9**(3): 139–43

Cunningham LA (1997) Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. *Analysis Clin Psychiatry* **9**(3): 157–64

Davidson RT, DuPont RL, Hedges D, Haskins JT (1999) Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalised anxiety disorder. *J Clin Psychiatry* **60**(8): 528–35

Einarson TR, Arikian SR, Casciano J, Doyle JJ (1999) Comparison of extended-release venlafaxine, selective serotonin reuptake inhibitors, and tricyclic antidepressants in the treatment of depression: A meta-analysis of randomised controlled trials. *Clin Ther* **21**(2): 296–308

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KEY POINTS

- Venlafaxine is a new, well tolerated, antidepressant that combines serotonin and noradrenaline reuptake inhibition.
- Venlafaxine appears to be more effective than the selective serotonin reuptake inhibitors in severe or chronic forms of depression.
- Venlafaxine is also effective in generalized anxiety disorder.

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Thase ME (1997) Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. *J Clin Psychiatry* **58:** 1–6

Thase ME, Entsuah AR, Rudolph RL (2001) Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry* **178:** 234–41