Tryptophan *(USAN, rINN)*

Triptofán; Triptofanas; Triptófano; Tryptofaani; Tryptofan; L-Tryptophan; Tryptophane; Tryptophanum; W. L-2-Amino-3-(indol-3-yl)propionic acid.

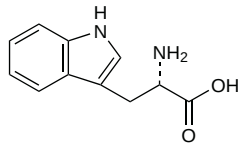
Триптофан

$C_{11}H_{12}N_2O_2$ = 204.2.

CAS — 73-22-3.

ATC — N06AX02.

ATC Vet — QN06AX02.



Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Jpn*, and *US*.

Ph. Eur. 6.2 (Tryptophan). A white or almost white crystalline or amorphous powder. Sparingly soluble in water; slightly soluble in alcohol; dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides. Protect from light.

USP 31 (Tryptophan). White to slightly yellowish-white crystals or crystalline powder. Soluble in hot alcohol and in dilute hydrochloric acid. pH of a 1% solution in water is between 5.5 and 7.0.

Adverse Effects

Tryptophan-containing products have been associated with the eosinophilia-myalgia syndrome; for further details, see below.

Other adverse effects that have been reported include nausea, headache, lightheadedness, and drowsiness.

An increased incidence of bladder tumours has been reported in *mice* given L-tryptophan orally as well as in cholesterol pellets embedded in the bladder lumen. However, there was no increase in tumour incidence when only high-dose, oral tryptophan was given.

Eosinophilia-myalgia syndrome. In late 1989 the first notification linking the eosinophilia-myalgia syndrome with the use of tryptophan-containing products was made in the USA.[1] There followed a number of similar published case reports from the USA, Europe, and Japan. Reviews of tryptophan-associated eosinophilia-myalgia syndrome have noted that by early 1990 over 1500 cases were known in the USA.[2,3]

In early 1990 the CDC in the USA summarised the features and known reports concerning the syndrome.[4] As the name implies the characteristic features are an intense eosinophilia together with disabling fatigue and muscle pain, although multisystem organ involvement and inflammatory disorders affecting the joints, skin, connective tissue, lungs, heart, and liver have also been recorded. Symptoms have generally developed over several weeks and the syndrome has occurred in patients who had been receiving tryptophan for many years previously with no untoward effect. In most patients slow and gradual improvement in the degree of eosinophilia and other clinical manifestations has followed the withdrawal of tryptophan, but in some patients the disease has progressed despite withdrawal and there have been fatalities.[5-7] The inflammatory condition has necessitated the use of corticosteroids in some patients.

The eosinophilia-myalgia syndrome has been reported in patients taking both tryptophan-containing prescription products for depression and non-prescription dietary supplements for a number of disorders including insomnia, the premenstrual syndrome, and stress; it does not appear to have occurred in patients receiving amino-acid preparations containing tryptophan as part of total parenteral nutrition regimens. The recognition of this syndrome led to the withdrawal of tryptophan-containing products or severe restrictions being imposed upon their use in many countries during 1990.

Various theories were proposed as to the reason for the association of tryptophan with this syndrome. Confusion existed because the reports implicated a very wide range of products from different manufacturers. However, later evidence appeared to have confirmed that contaminated tryptophan had originated from a single manufacturer in Japan.[8-10] Bulk tryptophan was imported from Japan for manufacture into finished pharmaceutical dosage forms and it was noted in one of these reports[9] that a single product was often found to contain two or more lots of powdered tryptophan that were blended together during the production of tablets or capsules. Many trace contaminants have been found in batches of tryptophan associated with the syndrome.[11] One contaminant has been identified as 1,1′-ethylidenebis(tryptophan).[12] Its inclusion in bulk tryptophan powder appeared to coincide with alterations in the manufacturing conditions that involved a change in the strain of *Bacillus amyloliquefaciens* used in the fermentation process and a reduction in the amount of charcoal used for purification.[9] Other investigations indicated the presence of bacitracin-like peptides in batches of the contaminated tryptophan.[13] However, further work[14] has provided only weak support for an association between the syndrome and any one particular contaminant and the causative agent remains to be confirmed. Nonetheless, since the syndrome only appeared to be associated with tryptophan from one manufacturer, tryptophan preparations were reintroduced in the UK in 1994 for restricted use under carefully monitored conditions.[15] In January 2005, the UK requirement for patient registration and monitoring was removed.

1. Anonymous. Eosinophilia-myalgia syndrome—New Mexico. *MMWR* 1989; **38:** 765–7.
2. Troy JL. Eosinophilia-myalgia syndrome. *Mayo Clin Proc* 1991; **66:** 535–8.
3. Milburn DS, Myers CW. Tryptophan toxicity: a pharmacoepidemiologic review of eosinophilia-myalgia syndrome. *DICP Ann Pharmacother* 1991; **25:** 1259–62.
4. Kilbourne EM, *et al.* Interim guidance on the eosinophilia-myalgia syndrome. *Ann Intern Med* 1990; **112:** 85–6.
5. Anonymous. Eosinophilia-myalgia syndrome associated with ingestion of -tryptophan—United States, through August 24, 1990. *JAMA* 1990; **264:** 1655.
6. Kaufman LD, *et al.* Clinical follow-up and immunogenetic studies of 32 patients with eosinophilia-myalgia syndrome. *Lancet* 1991; **337:** 1071–4.
7. Hertzman PA, *et al.* The eosinophilia-myalgia syndrome: status of 205 patients and results of treatment 2 years after onset. *Ann Intern Med* 1995; **122:** 851–5.
8. Slutsker L, *et al.* Eosinophilia-myalgia syndrome associated with exposure to tryptophan from a single manufacturer. *JAMA* 1990; **264:** 213–17.
9. Belongia EA, *et al.* An investigation of the cause of the eosinophilia-myalgia syndrome associated with tryptophan use. *N Engl J Med* 1990; **323:** 357–65.
10. Varga J, *et al.* The cause and pathogenesis of the eosinophilia-myalgia syndrome. *Ann Intern Med* 1992; **116**: 140–7.
11. Hill RH, *et al.* Contaminants in L-tryptophan associated with eosinophilia myalgia syndrome. *Arch Environ Contam Toxicol* 1993; **25:** 134–42.
12. Mayeno AN, *et al.* Characterization of "peak E", a novel amino acid associated with eosinophilia-myalgia syndrome. *Science* 1990; **250:** 1707–8.
13. Barnhart ER, *et al.* Bacitracin-associated peptides and contaminated -tryptophan. *Lancet* 1990; **336:** 742.
14. Philen RM, *et al.* Tryptophan contaminants associated with eosinophilia-myalgia syndrome. *Am J Epidemiol* 1993; **138:** 154–9.
15. CSM/MCA. L-Tryptophan (Optimax): limited availability for resistant depression. *Current Problems* 1994; **20:** 2. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024457&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Precautions

Tryptophan has been associated with eosinophilia-myalgia syndrome (see above); caution is advised in patients receiving the drug who develop some, but not all, of the symptoms of this syndrome. It should not be used in those with a history of eosinophilia-myalgia syndrome associated with tryptophan treatment.

Patients taking tryptophan may experience drowsiness and, if affected, they should not drive or operate machinery. For further details of the effects of antidepressant therapy on driving see under Amitriptyline, p.379.

Abnormal metabolism of tryptophan may occur in patients with pyridoxine deficiency and tryptophan is thus sometimes given with pyridoxine supplements.

Interactions

Although tryptophan has been given to patients receiving MAOIs in the belief that clinical efficacy may be improved, it should be noted that the adverse effects may also be potentiated. For further details, see Antidepressants under Interactions of Phenelzine, p.418.

Use of tryptophan with drugs that inhibit the reuptake of serotonin may exacerbate the adverse effects of the latter and precipitate the serotonin syndrome (p.416).

There have been occasional reports of sexual disinhibition in patients taking tryptophan with phenothiazines or benzodiazepines.

For a report of tryptophan reducing blood concentrations of levodopa, see Nutritional Agents under Interactions of Levodopa, p.808.

Pharmacokinetics

Tryptophan is readily absorbed from the gastrointestinal tract. Tryptophan is extensively bound to plasma albumin. It is metabolised in the liver by tryptophan pyrrolase and tryptophan hydroxylase. Metabolites include hydroxytryptophan, which is then converted to serotonin, and kynurenine derivatives. Some tryptophan is converted to nicotinic acid and nicotinamide. Pyridoxine and ascorbic acid are cofactors in the decarboxylation and hydroxylation, respectively, of tryptophan; pyridoxine apparently prevents the accumulation of the kynurenine metabolites.

◊ References.

1. Green AR, *et al.* The pharmacokinetics of -tryptophan following its intravenous and oral administration. *Br J Clin Pharmacol* 1985; **20:** 317–21.

Uses and Administration

Tryptophan is an amino acid that is an essential constituent of the diet. Tryptophan and DL-tryptophan have been used as dietary supplements.

Tryptophan is a precursor of serotonin. Because CNS depletion of serotonin is considered to be involved in depression, tryptophan has been used in its treatment. Although it has been given alone, evidence of effectiveness is scant and tryptophan has generally been used as adjunctive therapy in depression. It has sometimes been given with pyridoxine and ascorbic acid, which are involved in its metabolism to serotonin (see Pharmacokinetics, above).

In many countries preparations containing tryptophan have either been withdrawn from the market or their availability severely restricted or limited because of its association with the eosinophilia-myalgia syndrome. In the UK, tryptophan is restricted to use as an adjunct to other antidepressant medication or in patients who have failed to respond to an adequate trial of standard antidepressant drug treatment. Therapy should be started by hospital specialists; thereafter tryptophan may be prescribed in the community.

In the treatment of depression the usual oral dose of tryptophan is 1 g given three times daily, but some patients may require up to 6 g daily in divided doses. Lower doses may be required in the elderly especially those with renal or hepatic impairment.

Depression. Evidence of benefit for tryptophan when given alone for depression (p.373) is lacking, though there is some suggestion of a weak antidepressant effect.[1] It has therefore mainly been used with other antidepressants in the belief that it would potentiate their effects. Although beneficial effects have been reported in some patients given tryptophan with SSRIs, tricyclic antidepressants, or MAOIs, either alone or with lithium, evidence of efficacy is mainly limited to case reports and small controlled studies.[2-4]

After the publication of reports linking the use of tryptophan with the eosinophilia-myalgia syndrome (see under Adverse Effects, above) preparations containing tryptophan for depression were withdrawn from the market or their use restricted. For details of UK restrictions see Uses and Administration, above.

1. Shaw K, *et al.* Tryptophan and 5-hydroxytryptophan for depression. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2002 (accessed 24/11/05).
2. Barker WA, *et al.* The Newcastle chronic depression study: results of a treatment regime. *Int Clin Psychopharmacol* 1987; **2:** 261–72.
3. Smith S. Tryptophan in the treatment of resistant depression—a review. *Pharm J* 1998; **261:** 819–21.
4. Levitan RD, *et al.* Preliminary randomized double-blind placebo-controlled trial of tryptophan combined with fluoxetine to treat major depressive disorder: antidepressant and hypnotic effects. *J Psychiatry Neurosci* 2000; **25:** 337–46.

Dietary supplementation. The use of tryptophan as a dietary supplement has been reviewed.[1] However, because of its association with the eosinophilia-myalgia syndrome (see under Adverse Effects, above), the addition of tryptophan to food intended for human consumption is prohibited in some countries.

1. Li Wan Po A, Maguire T. Tryptophan: useful dietary supplement or a health hazard? *Pharm J* 1990; **244:** 484–5.

Insomnia. Tryptophan, sometimes in the form of dietary supplements, has enjoyed some popularity for the treatment of insomnia (p.957). However, in comparison with other hypnotics such as the benzodiazepines, the effects of tryptophan have been difficult to substantiate, and enthusiasm for tryptophan has waned considerably amongst sleep researchers.[1] It should also be noted that since the publication of reports linking the use of tryptophan with the eosinophilia-myalgia syndrome (see under Adverse Effects, above) preparations indicated for insomnia have been withdrawn from the market in many countries.

1. Lahmeyer HW. Tryptophan for insomnia. *JAMA* 1989; **262:** 2748.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Kalma; ***Canad.:*** Tryptan; ***Ger.:*** Ardeydorm; Ardeytropin; Kalma; ***UK:*** Optimax.

Multi-ingredient: ***Fr.:*** Vita-Dermacide; ***Ital.:*** Brioplus; Fisioreve; ***USA:*** PDP Liquid Protein.

Venlafaxine Hydrochloride

(BANM, USAN, rINNM)

Hidrocloruro de venlafaxina; Venlafaxine, chlorhydrate de; Venlafaxin-hydrochlorid; Venlafaxini hydrochloridum; Venlafaxinum hydrochloridum; Wenlafaksyny chlorowodorek; Wy-45030. (*RS*)-1-(2-Dimethylamino-1-*p*-methoxyphenylethyl)cyclohexanol hydrochloride.

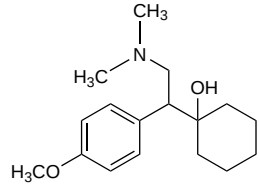
Венлафаксина Гидрохлорид

$C_{17}H_{27}NO_2$,HCl = 313.9.

CAS — 93413-69-5 (venlafaxine); 99300-78-4 (venlafaxine hydrochloride).

ATC — N06AX16.

ATC Vet — QN06AX16.



(venlafaxine)

Pharmacopoeias. In *Eur.* (see p.vii).

Ph. Eur. 6.2 (Venlafaxine Hydrochloride). A white or almost white powder. It exhibits polymorphism. Freely soluble in water and in methyl alcohol; soluble in dehydrated alcohol; slightly soluble or practically insoluble in acetone.

Adverse Effects and Treatment

Adverse effects that have been reported most frequently with venlafaxine include nausea, headache, insomnia, somnolence, dry mouth, dizziness, constipation, sexual dysfunction, asthenia, sweating, and nervousness. Other common adverse effects have included anorexia, diarrhoea, dyspepsia, abdominal pain, anxiety, urinary frequency, visual disturbances, mydriasis, vasodilatation, vomiting, tremor, paraesthesia, hypertonia, chills or fever, palpitations, weight gain or loss, increased serum-cholesterol, agitation, abnormal dreams, confusion, arthralgia, myalgia, tinnitus, pruritus, dyspnoea, yawning, and skin rashes. Dose-related increases in blood pressure have also been observed in some patients.

Less common effects have included reversible increases in liver enzymes, orthostatic hypotension, syncope, arrhythmias, tachycardia, mucous membrane bleeding, ecchymosis, hallucinations, bruxism, muscle spasm, myoclonus, alopecia, altered taste, urinary retention, menorrhagia, angioedema, and photosensitivity reactions.

Convulsions, galactorrhoea, haemorrhage including gastrointestinal bleeding, anaphylaxis, hepatitis, erythema multiforme, Stevens-Johnson syndrome, ataxia, dysarthria, extrapyramidal disorders including psychomotor restlessness and akathisia, and activation of mania or hypomania have been reported rarely. Other rare adverse effects include blood dyscrasias such as agranulocytosis, aplastic anaemia, neutropenia, pancytopenia, and thrombocytopenia, prolongation of the QT interval and torsade de pointes, ventricular tachycardia or fibrillation, rhabdomyolysis, delirium, pancreatitis, and pulmonary eosinophilia.

Aggressive behaviour has developed with venlafaxine treatment particularly at the start and when stopping therapy. Suicidal ideation has been reported, particularly in children (see under Effects on Mental State, below).

Hyponatraemia possibly due to inappropriate secretion of antidiuretic hormone has been associated with the use of antidepressants, particularly in the elderly.

In overdosage, symptoms such as sweating, dizziness, somnolence, ECG changes, cardiac arrhythmias, and seizures may be noted. Treatment of overdosage includes consideration of the use of activated charcoal if more than 12.5 mg/kg has been ingested and the patient presents within 1 hour; this should be followed by symptomatic and supportive therapy. Dialysis, haemoperfusion, exchange perfusion, and measures to increase urine production are considered unlikely to be of benefit.

Effects on the endocrine system. The syndrome of inappropriate antidiuretic hormone secretion (SIADH) with hyponatraemia may be more likely to occur with serotonergic antidepressants such as venlafaxine than with other antidepressants; for further details, see under Fluoxetine p.392.

Effects on the eyes. Acute angle-closure glaucoma developed in a 45-year-old woman 3 days after starting venlafaxine;[1] she recovered after iridotomy. In another case, a 35-year-old man presented with bilateral acute angle-closure glaucoma 10 days after starting venlafaxine.[2] The patient had also experienced visual disturbances while on mirtazapine and sertraline.

1. Ng B, *et al.* Venlafaxine and bilateral acute angle closure glaucoma. *Med J Aust* 2002; **176:** 241.
2. de Guzman MHP, *et al.* Bilateral acute angle closure caused by supraciliary effusions associated with venlafaxine intake. *Med J Aust* 2005; **182:** 121–2.

Effects on the hair. Hair loss has been described in 3 women given venlafaxine. The effect was noticed by the patients within a few weeks[1] to 5 months[2] after starting treatment. One patient who noticed hair loss within 1 week of starting venlafaxine had experienced the same problem during previous fluoxetine treatment.[3] In all 3 cases, hair loss abated soon after stopping venlafaxine. In 2 cases hair regrowth was reported within a few weeks,[2,3] but the third report was unclear as to whether regrowth occurred.[1]

1. Pitchot W, Ansseau M. Venlafaxine-induced hair loss. *Am J Psychiatry* 2001; **158:** 1159–60.
2. Pereira CE, Goldman-Levine JD. Extended-release venlafaxine-induced alopecia. *Ann Pharmacother* 2007; **41:** 1084.
3. O'Bryan EC, Albanese RP. A case report of fluoxetine- and venlafaxine-induced hair loss. *Prim Care Companion J Clin Psychiatry* 2004; **6:** 181.

Effects on the liver. Acute hepatitis developed in a 44-year-old woman about 6 months after starting venlafaxine;[1] she recovered once venlafaxine was withdrawn. In another report,[2] acute hepatitis developed in a 78-year-old man about a month after venlafaxine was added to therapy. Again, symptoms resolved when the drug was stopped. Hepatitis was noted in a 60-year-old woman about a month after starting low-dose venlafaxine (75 mg daily); symptoms resolved when the drug was stopped and recurred on rechallenge.[3] Hepatitis has also been attributed to low-dose venlafaxine (37.5 mg daily) in a patient with chronic hepatitis B; other causes of hepatitis and relapse of viral hepatitis were excluded.[4]

For a report of hepatotoxicity in patients taking venlafaxine subsequent to an attempted overdose with sertraline, see p.392.

1. Horsmans Y, *et al.* Venlaxafine-associated [sic] hepatitis. *Ann Intern Med* 1999; **130:** 944.
2. Cardona X, *et al.* Venlafaxine-associated hepatitis. *Ann Intern Med* 2000; **132:** 417.
3. Phillips BB, *et al.* Hepatitis associated with low-dose venlafaxine for postmenopausal vasomotor symptoms. *Ann Pharmacother* 2006; **40:** 323–7.
4. Sencan I, *et al.* Low-dose venlafaxine-associated liver toxicity in chronic hepatitis. *Ann Pharmacother* 2004; **38:** 352–3.

Effects on mental state. An expert working group was convened in May 2003 by the UK CSM to consider the ongoing safety concerns of the SSRIs and, in particular, the risk of suicidal behaviour in children; the safety of venlafaxine (another serotonergic antidepressant) was also considered. An interim report issued in September 2003 concluded that data from trials received by the CSM failed to show that venlafaxine was effective in the treatment of depressive illness in **children under 18 years old** and indicated that the risk of harmful outcome including self-harm and suicidal ideation was increased in those receiving venlafaxine when compared with placebo.[1] The CSM recommended that venlafaxine should not be used to treat depressive illness in children under 18 years old. Similar warnings have also been issued in Canada,[2] the EU,[3] and the USA. (The final report[4] of the CSM's expert working group was published in December 2004.)

The risk of suicide and suicide-related events with antidepressant treatment in **adults** including young adults is discussed under Fluoxetine, p.392.

1. MHRA. Safety of venlafaxine in children and adolescents under 18 years in the treatment of depressive illness. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 19th September, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019501.pdf (accessed 14/08/08)
2. Wyeth Canada. Important safety information regarding the use of Effexor (venlafaxine HCl) tablets and Effexor XR (venlafaxine HCl) capsules in children and adolescents (issued 10th September, 2003). Available at: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/medeff/effexor_hpc-cps-eng.pdf (accessed 14/08/08)
3. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/12891805en.pdf (accessed 14/08/08)
4. Weller IVD. *Report of the CSM expert working group on the safety of selective serotonin reuptake inhibitor antidepressants.* London: The Stationery Office, 2005. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)

Effects on the skin. Stevens-Johnson syndrome developed in a patient 12 days after beginning treatment with venlafaxine for recurrent depression.[1] She had also been taking several other drugs for at least 6 months. Symptoms resolved on withdrawal of all medication and treatment with an intravenous corticosteroid.

1. Weiss NT, *et al.* A possible case of venlafaxine-induced Stevens-Johnson syndrome. *J Clin Psychiatry* 2004; **65:** 1431–3.

Overdosage. Rare serious events including seizures and ECG changes[1-3] have occurred after venlafaxine overdoses; in some cases, death has ensued.[4,5] Symptoms suggestive of serotonin toxicity may also develop.[6,7]

Venlafaxine may not be as safe in overdose as some other serotonergic antidepressants. A review[8] of UK data recording the number of deaths due to acute poisoning by a single drug, with or without alcohol, found the number of fatalities per million prescriptions (the fatal toxicity index) was higher for venlafaxine than for other serotonergic antidepressants, and was similar to that for some of the less toxic tricyclic antidepressants.

1. White CM, *et al.* Seizure resulting from a venlafaxine overdose. *Ann Pharmacother* 1997; **31:** 178–80.
2. Coorey AN, Wenck DJ. Venlafaxine overdose. *Med J Aust* 1998; **168:** 523.
3. Blythe D, Hackett LP. Cardiovascular and neurological toxicity of venlafaxine. *Hum Exp Toxicol* 1999; **18:** 309–13.
4. Banham NDG. Fatal venlafaxine overdose. *Med J Aust* 1998; **169:** 445, 448.
5. Mazur JE, *et al.* Fatality related to a 30-g venlafaxine overdose. *Pharmacotherapy* 2003; **23:** 1668–72.
6. Oliver JJ, *et al.* Venlafaxine poisoning complicated by a late rise in creatine kinase: two case reports. *Hum Exp Toxicol* 2002; **21:** 463–6.
7. Whyte IM, *et al.* Relative toxicity of venlafaxine and selective serotonin reuptake inhibitors in overdose compared to tricyclic antidepressants. *QJM* 2003; **96:** 369–74.
8. Buckley NA, McManus PR. Fatal toxicity of serotoninergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ* 2002: **325:** 1332–3.

Serotonin syndrome. The serotonin syndrome (p.416) is most often due to the additive adverse effects of two or more drugs that enhance serotonin activity at central receptors; rarely, a single serotonergic drug may cause the syndrome. One such case[1] was reported to have occurred in a 29-year-old woman who developed symptoms suggestive of serotonin syndrome 3 days after starting low-dose venlafaxine. However, this patient had been switched to venlafaxine the day after stopping imipramine treatment; it is usually recommended that at least 3 weeks should elapse after stopping imipramine before starting another drug with serotonergic properties.

1. Pan J-J, Shen WW. Serotonin syndrome induced by low-dose venlafaxine. *Ann Pharmacother* 2003; **37:** 209–11.

Precautions

Venlafaxine should not be used in patients with an identified very high risk of a serious ventricular arrhythmia or uncontrolled hypertension. Caution is advised in those with a recent history of myocardial infarction or whose condition might be exacerbated by an increase in heart rate. Due to the risk of dose-related increases in blood pressure, blood pressure measurement should be performed regularly during therapy. Measurement of serum-cholesterol levels should also be considered with long-term treatment.

Venlafaxine should be used with caution in patients with moderate to severe hepatic or renal impairment and dosage adjustment may be necessary. It should also be used with caution in patients with a history of epilepsy and avoided in those with unstable disease; it should be stopped in any patient developing a seizure or if there is an increase in seizure frequency. Caution is also advised in patients with a history of bleeding disorders or of hypomania or mania. Patients with raised intra-ocular pressure or at risk of angle-closure glaucoma should be monitored closely. Patients who develop a rash, urticaria, or related allergic reaction with venlafaxine should be advised to contact their doctor.

Patients should be closely monitored during early antidepressant therapy until a significant improvement in depression is observed because suicide is an inherent risk in depressed patients. For further details, see under Depression, p.373. Suicidal thoughts and behaviour may also develop during early treatment with antidepressants for other disorders; the same precautions observed when treating patients with depression should therefore be observed when treating patients with other disorders.

As with other antidepressants, venlafaxine may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery. Patients, especially the elderly, should be warned of the risk of dizziness or unsteadiness due to orthostatic hypotension.

Symptoms reported on abrupt withdrawal or dose reduction of venlafaxine include fatigue, somnolence, headache, nausea, vomiting, anorexia, palpitations, dizziness, dry mouth, diarrhoea, insomnia, agitation, anxiety, nervousness, confusion, hypomania, paraesthesia, sweating, and vertigo. It is therefore recommended that venlafaxine should be withdrawn gradually over at least one week after more than one week's therapy; patients receiving high-dose venlafaxine for longer than 6 weeks should be tapered over at least 2 weeks. All patients should also be monitored to minimise the risk of withdrawal reactions.

Abuse. A patient had an amfetamine-like "high" after taking crushed modified-release tablets of venlafaxine in doses of up to 3600 mg daily.[1] He continued to ingest increasing amounts of venlafaxine until a 4050-mg dose produced chest pain. On evaluation he had a raised pulse and blood pressure but these returned to normal within a few days.

1. Sattar SP, *et al.* A case of venlafaxine abuse. *N Engl J Med* 2003; **348:** 764–5.

Breast feeding. Licensed product information recommends that venlafaxine should not be used in women who are breast feeding.

Venlafaxine and its metabolite *O*-desmethylvenlafaxine were both detected in breast milk in significant quantities in 3 women;[1] there were also measurable concentrations of desmethylvenlafaxine in the infants' plasma. In another study[2] by the same group the mean milk-to-plasma ratio in 6 breast-feeding women was calculated to be 2.5 for venlafaxine and 2.74 for *O*-desmethylvenlafaxine. Detectable plasma concentrations of venlafaxine were found only in 1 of 7 breast-fed infants while 4 had detectable *O*-desmethylvenlafaxine levels; no adverse effects were reported in the infants. Nonetheless, the authors recommended caution when giving venlafaxine to breast-feeding women particularly for those feeding premature or very young neonates. The distribution of venlafaxine into breast milk and the presence of *O*-desmethylvenlafaxine in the serum of a further 5 breast-fed infants has also been reported.[3,4] There were no detectable adverse effects in the infants, and the authors of 1 report[4] suggested that women being treated for postpartum depression should not be generally discouraged from breast feeding. It has been suggested that venlafaxine in breast milk might alleviate a withdrawal syndrome in the neonate (see Pregnancy, below).

1. Ilett KF, *et al.* Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. *Br J Clin Pharmacol* 1998; **45:** 459–62.
2. Ilett KF, *et al.* Distribution of venlafaxine and its *O*-desmethyl metabolite in human milk and their effects in breastfed infants. *Br J Clin Pharmacol* 2002; **53:** 17–22.
3. Hendrick V, *et al.* Venlafaxine and breast-feeding. *Am J Psychiatry* 2001; **158:** 2089–90.
4. Berle JØ, *et al.* Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome P450 genotypes. *J Clin Psychiatry* 2004; **65:** 1228–34.

Children. Venlafaxine is associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State, above.

US licensed product information also refers to studies that suggest that venlafaxine may adversely affect weight and height changes in children. In particular, the difference between the observed and the expected growth rate was larger for those children under 12 years of age than for older children.

Pregnancy. Licensed product information recommends that venlafaxine should not be used during pregnancy unless clearly necessary.

In a study of 150 women who took venlafaxine in the first trimester of pregnancy there were 125 live births, 18 spontaneous abortions, 7 therapeutic abortions, and 2 reports of major malformations (hypospadias and neural tube defect with club foot).[1] Although the rate of spontaneous abortions was non-significantly higher in the venlafaxine group than in historical controls, the rate of major malformations was not greater than the baseline rate of 1 to 3%.

A neonatal withdrawal syndrome developed in the infant of a mother who had taken venlafaxine throughout her pregnancy;[2] symptoms included restlessness, hypertonia, irritability, and poor feeding. The infant recovered within 8 days. Seizures have been described in 2 neonates whose mothers were taking venlafaxine.[3] Lip smacking and extensor limb posturing began at 30 minutes of age in 1 case, and multifocal myoclonic seizures occurred at 24 hours of age in the other; both recovered and were well at 1 year of age. Serum-venlafaxine concentrations had not been measured and the authors were unsure whether the adverse effects in the neonates were due to withdrawal or toxicity. In a retrospective study[4] of women who had taken SSRIs or venlafaxine during the third trimester (9 had taken venlafaxine), there were reports of adverse effects on the CNS and respiratory tract in the neonates, such as abnormal movements, tonus abnormalities, irritability, insomnia, indrawing, apnoea/bradycardia, and tachypnoea. The signs usually appeared on the first day of life and lasted for about 3 days in full-term neonates and about 5 days in those born prematurely.

Venlafaxine and its metabolite *O*-desmethylvenlafaxine are distributed into breast milk (see Breast Feeding, above), and it has been suggested that breast feeding might have helped to alleviate symptoms of a withdrawal syndrome in a neonate whose mother took venlafaxine throughout her pregnancy.[5]

1. Einarson A, *et al.* Pregnancy outcome following gestational exposure to venlafaxine: a multicenter prospective controlled study. *Am J Psychiatry* 2001; **158:** 1728–30.
2. de Moor RA, *et al.* Withdrawal symptoms in a neonate following exposure to venlafaxine during pregnancy. *Ned Tijdschr Geneeskd* 2003; **147:** 1370–2.
3. Pakalapati RK, *et al.* Neonatal seizures from in utero venlafaxine exposure. *J Paediatr Child Health* 2006; **42:** 737–8.
4. Ferreira E, *et al.* Effects of selective serotonin reuptake inhibitors and venlafaxine during pregnancy in term and preterm neonates. *Pediatrics* 2007; **119:** 52–9.
5. Koren G, *et al.* Can venlafaxine in breast milk attenuate the norepinephrine and serotonin reuptake neonatal withdrawal syndrome? *J Obstet Gynaecol Can* 2006; **28:** 299–301.

Renal impairment. The mean terminal disposition half-life of venlafaxine was prolonged from a mean of 3.8 hours in 18 healthy subjects to 5.8 hours in 12 patients with mild to moderate renal impairment (creatinine clearance 10 to 70 mL/minute) and 10.6 hours in patients requiring haemodialysis;[1] corresponding values for *O*-desmethylvenlafaxine, the active major metabolite of venlafaxine, were 11.8, 16.8, and 28.5 hours, respectively. Because of the large intersubject variability, the change in disposition for venlafaxine and its active metabolite was evident only in patients with a creatinine clearance of less than 30 mL/minute; drug clearance in these patients was reduced by about 55% and half-life more than doubled. It was calculated that for these patients half the usual daily dose could be given once daily.

Similar recommendations are made in licensed drug information, see under Uses and Administration, below.

1. Troy SM, *et al.* The effect of renal disease on the disposition of venlafaxine. *Clin Pharmacol Ther* 1994; **56:** 14–21.

Surgery. Serotonergic antidepressants such as venlafaxine may be associated with an increased risk of blood loss during surgery; for further details, see under Fluoxetine, p.396.

Withdrawal. Withdrawal reactions may be more common with venlafaxine than with some other serotonergic antidepressants; for further details, see under Fluoxetine, p.396. Withdrawal reactions may also be seen in neonates after maternal venlafaxine use, see under Pregnancy above.

Some cases[1,2] of withdrawal reactions to venlafaxine have been reported.

1. Anonymous. Venlafaxine withdrawal reactions. *Med J Aust* 1998; **169:** 91–2.
2. Johnson H, *et al.* Withdrawal reaction associated with venlafaxine. *BMJ* 1998; **317:** 787.

Interactions

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions including the *serotonin syndrome* (see p.416) may occur. Sequential prescribing of different types of antidepressant may also produce adverse reactions, and an appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. Venlafaxine should not be used with MAOIs and at least 14 days should elapse between stopping an MAOI and starting treatment with venlafaxine. At least 7 days should elapse between stopping venlafaxine and starting any drug liable to provoke a serious reaction (e.g. phenelzine). For further details, see Antidepressants under Interactions of Phenelzine, p.418. Adverse effects such as the serotonin syndrome may also occur when venlafaxine is given with other drugs known to act on the same neurotransmitter, a consequence of synergistic interaction.

Venlafaxine has occasionally been associated with bleeding disorders and other effects on the blood; caution is advised when giving venlafaxine with other drugs known to affect platelet function.

Although cimetidine inhibits the first-pass hepatic metabolism of venlafaxine, it has no effect on the active metabolite *O*-desmethylvenlafaxine, which is present in the plasma in much greater concentrations. Licensed product information therefore considers that when cimetidine and venlafaxine are used together, clinical monitoring may only be necessary in elderly patients and in those with hepatic impairment or pre-existing hypertension.

◊ Conversion of venlafaxine to its equally active metabolite *O*-desmethylvenlafaxine is mediated by the cytochrome P450 isoenzyme CYP2D6. Therefore the potential exists for drugs that inhibit or act as a substrate for this enzyme to affect plasma concentrations of venlafaxine and its active metabolite. However, the US product information indicates that, as the total amount of active compounds is unaffected, no dosage adjustment is usually necessary for venlafaxine. Venlafaxine is also metabolised by CYP3A4 to the less active metabolite *N*-desmethylvenlafaxine. This is a relatively minor pathway and the potential for clinically significant interactions between venlafaxine and CYP3A4 inhibitors is considered to be small. However, potent inhibitors of CYP3A4 or drugs that inhibit both CYP2D6 and CYP3A4 could significantly increase venlafaxine concentrations in patients who are poor CYP2D6 metabolisers; such combinations should therefore be used with caution.

Venlafaxine itself is considered to be a relatively weak inhibitor of CYP2D6.

Antiarrhythmics. Psychosis with raised serum concentrations of venlafaxine and its metabolite *O*-desmethylvenlafaxine developed when *propafenone* therapy was started in a 67-year-old woman. There was improvement when venlafaxine was stopped and restarted at a reduced dose; 50 mg daily was sufficient to maintain therapeutic serum concentrations.[1]

1. Pfeffer F, Grube M. An organic psychosis due to a venlafaxine-propafenone interaction. *Int J Psychiatry Med* 2001; **31:** 427–32.

Antibacterials. Tingling in the tip of the tongue, intense paraesthesia in the fingers, severe abdominal cramps, profuse diarrhoea, cold sweats, and uncontrolled shivering and tremor occurred when *co-amoxiclav* was started in a man taking venlafaxine.[1] The reaction lasted for about 6 hours. It occurred again 2 months later after a single dose of co-amoxiclav. The patient reported that he had taken co-amoxiclav in the past without any reaction at a time when he was not taking venlafaxine. The mechanism for an interaction between venlafaxine and co-amoxiclav causing this serotonin syndrome is unknown. The author also suggested that many patients must have taken this combination without adverse effect, and found no other reports.

Serotonin syndrome has been reported in an elderly patient taking venlafaxine, after 20 days of antibacterial treatment including *linezolid*.[2] In another report, serotonin syndrome developed 8 days after starting treatment with intravenous linezolid in a patient taking venlafaxine.[3]

1. Connor H. Serotonin syndrome after single doses of co-amoxiclav during treatment with venlafaxine. *J R Soc Med* 2003; **96:** 233–4.
2. Jones SL, *et al.* Serotonin syndrome due to co-administration of linezolid and venlafaxine. *J Antimicrob Chemother* 2004; **54:** 289–90.
3. Bergeron L, *et al.* Serotonin toxicity associated with concomitant use of linezolid. *Ann Pharmacother* 2005; **39:** 956–61.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of serotonin and noradrenaline reuptake inhibitors (SNRIs) with serotonin (5-HT_1) agonists such as *sumatriptan* (see p.626).

Antipsychotics. For mention of neuroleptic malignant syndrome developing in patients who received venlafaxine with antipsychotics see under Interactions in Chlorpromazine, p.974.

Gastrointestinal drugs. Signs suggestive of the serotonin syndrome that occurred after intravenous *metoclopramide* were attributed to an interaction with venlafaxine.[1] The 32-year-old woman experienced confusion, agitation, generalised shaking, myoclonus, facial twitching, diaphoresis, horizontal nystagmus, and dilated pupils, that resolved within 2 days after stopping both drugs and treatment with diazepam.

1. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* 2002; **36:** 67–71.

Selegiline. Although it is generally recommended that venlafaxine should not be started for at least 14 days after stopping an MAOI, there is a report[1] of serotonin syndrome developing when a patient began venlafaxine treatment 15 days after stopping selegiline, an MAO type B inhibitor.

1. Gitlin MJ. Venlafaxine, monoamine oxidase inhibitors, and the serotonin syndrome. *J Clin Psychopharmacol* 1997; **17:** 66–7.

Pharmacokinetics

Venlafaxine is readily absorbed from the gastrointestinal tract. After oral doses it undergoes extensive first-pass metabolism in the liver mainly to the active metabolite *O*-desmethylvenlafaxine; formation of *O*-desmethylvenlafaxine is mediated by the cytochrome P450 isoenzyme CYP2D6. The isoenzyme CYP3A4 is also involved in the metabolism of venlafaxine. Other metabolites include *N*-desmethylvenlafaxine and *N,O*-didesmethylvenlafaxine. Peak plasma concentrations of venlafaxine and *O*-desmethylvenlafaxine appear about 2 and 4 hours after a dose, respectively. Venlafaxine is 27% and *O*-desmethylvenlafaxine 30% bound to plasma proteins. The mean elimination half-life of venlafaxine and *O*-desmethylvenlafaxine is about 5 and 11 hours, respectively. Venlafaxine is excreted mainly in the urine, mainly in the form of its metabolites, either free or in conjugated form; about 2% is excreted in the faeces. Venlafaxine and *O*-desmethylvenlafaxine have been detected in amniotic fluid and umbilical cord blood, and are distributed into breast milk.

◊ References.

1. Troy SM, *et al.* The pharmacokinetics of venlafaxine when given in a twice-daily regimen. *J Clin Pharmacol* 1995; **35:** 404–9.
2. Troy SM, *et al.* Pharmacokinetics and effect of food on the bioavailability of orally administered venlafaxine. *J Clin Pharmacol* 1997; **37:** 954–61.
3. Ball SE, *et al.* Venlafaxine: in vitro inhibition of CYP2D6 dependent imipramine and desipramine metabolism; comparative studies with selected SSRIs, and effects on human hepatic CYP3A4, CYP2C9 and CYP1A2. *Br J Clin Pharmacol* 1997; **43:** 619–26.

Pregnancy. Venlafaxine and its metabolite, *O*-desmethylvenlafaxine, have been detected in amniotic fluid[1,2] and umbilical cord blood.[1,3] For adverse effects that have occurred in neonates of women who were taking venlafaxine during the third trimester, see Pregnancy, under Precautions, above.

1. Hostetter A, *et al.* Amniotic fluid and umbilical cord blood concentrations of antidepressants in three women. *Biol Psychiatry* 2000; **48:** 1032–4.

2. Loughhead AM, *et al.* Antidepressants in amniotic fluid: another route of fetal exposure. *Am J Psychiatry* 2006; **163:** 145–7.
3. Rampono J, *et al.* A pilot study of newer antidepressant concentrations in cord and maternal serum and possible effects in the neonate. *Int J Neuropsychopharmacol* 2004; **7:** 329–34.

Uses and Administration

Venlafaxine, a phenylethylamine derivative, is a serotonin and noradrenaline reuptake inhibitor (SNRI); it also weakly inhibits dopamine reuptake. It is reported to have little affinity for muscarinic, histaminergic, or α_1-adrenergic receptors *in vitro*. Venlafaxine is given orally as the hydrochloride although doses are expressed in terms of the base; venlafaxine hydrochloride 28.3 mg is equivalent to about 25 mg of venlafaxine.

Venlafaxine is used in the treatment of **depression**. The initial daily dose is equivalent to venlafaxine 75 mg in two or three divided doses with food. In the USA, it is suggested that some patients may be best started on 37.5 mg daily for the first 4 to 7 days before increasing the dose to 75 mg daily. The dose may be increased, if necessary, after several weeks to 150 mg daily. Further increases, to a maximum daily dose of 375 mg, may be made in increments of up to 75 mg at intervals of at least 2 to 4 days. Such doses may be required in severely depressed or hospitalised patients and should be gradually reduced to the minimum effective dose. Modified-release preparations are available for once-daily dosing.

Venlafaxine is also used, as a modified-release preparation, in the treatment of **generalised anxiety disorder**. The recommended initial dose is 75 mg once daily. In the USA it is suggested that some patients may be best begun with 37.5 mg daily for 4 to 7 days initially; dosage may subsequently be adjusted in increments of up to 75 mg, at intervals of at least 4 days, to a maximum of 225 mg daily. Venlafaxine should be withdrawn gradually if there is no response after 8 weeks.

In the USA, modified-release venlafaxine is licensed for the treatment of **social anxiety disorder** in doses similar to those used for generalised anxiety disorder. It is also licensed in the USA for **panic disorder** with or without agoraphobia in doses of 37.5 mg once daily for the first 7 days, then increasing to 75 mg daily. Subsequent increases in increments of up to 75 mg may be made at intervals of at least 7 days, to a maximum dose of 225 mg daily.

Reduced doses may need to be given in hepatic or renal impairment, see below.

Venlafaxine should be withdrawn gradually to reduce the risk of withdrawal symptoms (see Precautions, above).

Administration in hepatic impairment. UK licensed product information considers that patients with mild hepatic impairment do not require a change in dose of venlafaxine. For those with moderate impairment, the dose should be reduced by half and given once daily. There are insufficient data to make any recommendations for patients with severe impairment.

Administration in renal impairment. The UK licensed product information states that, based on glomerular filtration rate (GFR), patients with mild renal impairment (GFR above 30 mL/minute) do not require a change in dose of venlafaxine. For those with moderate impairment (GFR 10 to 30 mL/minute), the dose should be reduced by 50% and once-daily dosage may be appropriate. There are insufficient data to make any recommendations for patients with severe impairment (GFR less than 10 mL/minute).

In the USA, it is recommended that patients with a GFR of 10 to 70 mL/minute reduce the dose of immediate-release venlafaxine by 25% and of modified-release venlafaxine by 25 to 50%; regardless of preparation, in those undergoing haemodialysis, the dose should be reduced by 50% and withheld until the dialysis is completed.

Anxiety disorders. Venlafaxine is used in the treatment of generalised anxiety disorder and social anxiety disorder (see under Phobic Disorders, p.953); it may also be of use in a variety of other types of anxiety disorders (p.952) including the treatment of obsessive-compulsive disorder (p.952), panic disorder (p.952), and post-traumatic stress disorder (p.953).

References.
1. Altamura AC, *et al.* Venlafaxine in social phobia: a study in selective serotonin reuptake inhibitor non-responders. *Int Clin Psychopharmacol* 1999; **14:** 239–45.
2. Gelenberg AJ, *et al.* Efficacy of venlafaxine extended-release capsules in nondepressed outpatients with generalized anxiety disorder: a 6-month randomized controlled trial. *JAMA* 2000; **283:** 3082–8.
3. Sheehan DV. Attaining remission in generalized anxiety disorder: venlafaxine extended release comparative data. *J Clin Psychiatry* 2001; **62** (suppl 19): 26–31.
4. Katz IR, *et al.* Venlafaxine ER as a treatment for generalized anxiety disorder in older adults: pooled analysis of five randomised placebo-controlled clinical trials. *J Am Geriatr Soc* 2002; **50:** 18–25.
5. Hollander E, *et al.* Venlafaxine in treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry* 2003; **64:** 546–50. Correction. *ibid.*; 972.
6. Lenox-Smith AJ, Reynolds A. A double-blind, randomised, placebo controlled study of venlafaxine XL in patients with generalised anxiety disorder in primary care. *Br J Gen Pract* 2003; **53:** 772–7.
7. Boyer P, *et al.* Social adjustment in generalised anxiety disorder: a long-term placebo-controlled study of venlafaxine extended release. *Eur Psychiatry* 2004; **19:** 272–9.
8. Denys D, *et al.* A double-blind switch study of paroxetine and venlafaxine in obsessive-compulsive disorder. *J Clin Psychiatry* 2004; **65:** 37–43.
9. Liebowitz MR, *et al.* Venlafaxine extended release vs placebo and paroxetine in social anxiety disorder. *Arch Gen Psychiatry* 2005; **62:** 190–8.
10. Liebowitz MR, *et al.* A randomized controlled trial of venlafaxine extended release in generalized social anxiety disorder. *J Clin Psychiatry* 2005; **66:** 238–47.
11. Phelps NJ, Cates ME. The role of venlafaxine in the treatment of obsessive-compulsive disorder. *Ann Pharmacother* 2005; **39:** 136–40.
12. Bradwejn J, *et al.* Venlafaxine extended-release capsules in panic disorder: flexible-dose, double-blind, placebo-controlled study. *Br J Psychiatry* 2005; **187:** 352–9.
13. Davidson J, *et al.* Venlafaxine extended release in posttraumatic stress disorder: a sertraline- and placebo-controlled study. *J Clin Psychopharmacol* 2006; **26:** 259–67. Correction. *ibid.*; 473. [dose]
14. Davidson J, *et al.* Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. *Arch Gen Psychiatry* 2006; **63:** 1158–65.
15. Ferguson JM, *et al.* Relapse prevention of panic disorder in adult outpatient responders to treatment with venlafaxine extended release. *J Clin Psychiatry* 2007; **68:** 58–68.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. In December 2004 the UK CSM recommended that, because of the risk of adverse cardiovascular effects and toxicity in overdosage (see above), venlafaxine treatment should be begun and maintained under specialist supervision only. After an assessment of further safety evidence, these restrictions were revised in May 2006 and specialist supervision was considered only necessary when starting venlafaxine treatment in severely depressed or hospitalised patients who require doses of 300 mg daily or above. However, it was also advised that venlafaxine should be considered a second-line treatment, after the SSRIs.

The *O*-desmethyl metabolite of venlafaxine, desvenlafaxine (p.388), is also used in depression.

References.
1. Morton WA, *et al.* Venlafaxine: a structurally unique and novel antidepressant. *Ann Pharmacother* 1995; **29:** 387–95.
2. Derivan A, *et al.* Venlafaxine: measuring the onset of antidepressant action. *Psychopharmacol Bull* 1995; **31:** 439–47.
3. Wellington K, Perry CM. Venlafaxine extended-release: a review of its use in the management of major depression. *CNS Drugs* 2001; **15:** 643–69.
4. Cohen LS, *et al.* Venlafaxine in the treatment of postpartum depression. *J Clin Psychiatry* 2001; **62:** 592–6.
5. Montgomery SA, *et al.* Venlafaxine versus placebo in the preventive treatment of recurrent major depression. *J Clin Psychiatry* 2004; **65:** 328–36.

Hot flushes. For the reference to the use of venlafaxine in the treatment of hot flushes, see under Fluoxetine, p.398.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (p.2148) initial treatment is usually with a central stimulant. Antidepressants may be used for patients who fail to respond to, or who are intolerant of, central stimulants; in open studies venlafaxine has been reported to be effective in both adults[1-3] and children[4,5] although in one study[4] some patients experienced a worsening of symptoms.

1. Hedges D, *et al.* An open trial of venlafaxine in adult patients with attention deficit hyperactivity disorder. *Psychopharmacol Bull* 1995; **31:** 779–83.
2. Adler LA, *et al.* Open-label trial of venlafaxine in adults with attention deficit disorder. *Psychopharmacol Bull* 1995; **31:** 785–8.
3. Findling RL, *et al.* Venlafaxine in adults with attention-deficit/hyperactivity disorder: an open clinical trial. *J Clin Psychiatry* 1996; **57:** 184–9.
4. Olvera RL, *et al.* An open trial of venlafaxine in the treatment of attention-deficit/hyperactivity disorder in children and adolescents. *J Child Adolesc Psychopharmacol* 1996; **6:** 241–50.
5. Motavalli Mukaddes N, Abali O. Venlafaxine in children and adolescents with attention deficit hyperactivity disorder. *Psychiatry Clin Neurosci* 2004; **58:** 92–5.

Migraine. Retrospective analysis[1] in patients with tension-type headache (p.617) or migraine (p.616) indicated that venlafaxine, as a modified-release preparation, had potential for headache prophylaxis. A more recent randomised placebo-controlled study[2] also supports the use of modified-release venlafaxine in the prophylaxis of migraine.

1. Adelman LC, *et al.* Venlafaxine extended release (XR) for the prophylaxis of migraine and tension-type headache: a retrospective study in a clinical setting. *Headache* 2000; **40:** 572–80.
2. Ozyalcin SN, *et al.* The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache* 2005; **45:** 144–52.

Pain. Venlafaxine may be of benefit in the treatment of neuropathic pain syndromes (p.8)[1,2] including painful diabetic neuropathy (p.6).[3-5] It has also shown some promise in the treatment of fibromyalgia (see Soft-tissue Rheumatism, p.13).[6]

1. Sumpton JE, Moulin DE. Treatment of neuropathic pain with venlafaxine. *Ann Pharmacother* 2001; **35:** 557–9.
2. Grothe DR, *et al.* Treatment of pain syndromes with venlafaxine. *Pharmacotherapy* 2004; **24:** 621–9.
3. Davis JL, Smith RL. Painful peripheral diabetic neuropathy treated with venlafaxine HCl extended release capsules. *Diabetes Care* 1999; **22:** 1909–10.
4. Kiayias JA, *et al.* Venlafaxine HCl in the treatment of painful peripheral diabetic neuropathy. *Diabetes Care* 2000; **23:** 699.
5. Rowbotham MC, *et al.* Venlafaxine extended release in the treatment of painful diabetic neuropathy: a double-blind, placebo-controlled study. *Pain* 2004; **110:** 697–706. Correction. *ibid.* 2005; **113:** 248.
6. Sayar K, *et al.* Venlafaxine treatment of fibromyalgia. *Ann Pharmacother* 2003; **37:** 1561–5.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Efexor; Elafax; Ganavax; Mezine; Quilarex; Sesaren; ***Austral.:*** Efexor; ***Austria:*** Efectin; ***Belg.:*** Efexor; ***Braz.:*** Efexor; Venlaxin; Venlift; ***Canad.:*** Effexor; ***Chile:*** Depurol; Efexor; Nervix; Norpilen; Senexon; Sentidol; Sesaren; Subelan; Venlax; ***Cz.:*** Argofan; Convalemin; Efectin; Elify; Faxiprol; Lafaxon; Mollome; Olvexya; Velaxin; ***Denm.:*** Efexor; ***Fin.:*** Efexor; ***Fr.:*** Effexor; ***Ger.:*** Trevilor; ***Gr.:*** Arvifax; Efexor; ***Hong Kong:*** Efexor; ***Hung.:*** Efectin; Olwexya; Velaxin; ***India:*** Flavix; Venlor; Vexor; ***Indon.:*** Efexor; ***Irl.:*** Efexor; ***Israel:*** Efexor; Venla; Viepax; ***Ital.:*** Efexor; Faxine; ***Malaysia:*** Efexor; ***Mex.:*** Efexor; Odven SBK; ***Neth.:*** Efexor; ***Norw.:*** Efexor; ***NZ:*** Efexor; ***Philipp.:*** Efexor; ***Pol.:*** Efectin; Velafax; Velaxin; ***Port.:*** Desinax; Efexor; Genexin; Venxin; Xapnev; Zarelix; ***Rus.:*** Efevelone (Эфевелон); Velafax (Велафакс); Velaxin (Велаксин); ***S.Afr.:*** Efexor; Venlor; ***Singapore:*** Efexor; ***Spain:*** Dobupal; Vandral; ***Swed.:*** Efexor; ***Switz.:*** Efexor; ***Thai.:*** Efexor; ***Turk.:*** Efexor; ***UK:*** Efexor; ***USA:*** Effexor; ***Venez.:*** Efexor; Idoxen; Sesaren.

Viloxazine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de viloxazina; ICI-58834; Viloxazine, Chlorhydrate de; Viloxazini Hydrochloridum. 2-(2-Ethoxyphenoxymethyl) morpholine hydrochloride.

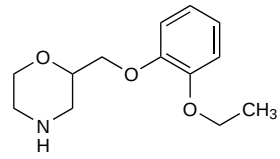
Вилоксазина Гидрохлорид

$C_{13}H_{19}NO_3$,HCl = 273.8.

CAS — 46817-91-8 (viloxazine); 35604-67-2 (viloxazine hydrochloride).

ATC — N06AX09.

ATC Vet — QN06AX09.



(viloxazine)

Profile

Viloxazine is a bicyclic antidepressant. Like the tricyclic antidepressants (see Amitriptyline, p.376), viloxazine is an inhibitor of the reuptake of noradrenaline; it may also enhance the release of serotonin from neuronal stores. However, it does not have marked antimuscarinic, cardiotoxic, or sedative properties.

Viloxazine is given for the treatment of depression (p.373) as the hydrochloride although doses are expressed in terms of viloxazine; viloxazine hydrochloride 57.7 mg is equivalent to about 50 mg of viloxazine. The usual oral dose is equivalent to viloxazine 200 to 300 mg daily in 2 or 3 divided doses. This may be increased, if necessary, to 600 mg daily as tolerated. The initial dose for the elderly or patients with hepatic or renal impairment is 100 mg daily cautiously increased if necessary. A modified-release preparation is also available for once daily use. Viloxazine hydrochloride has also been given by intravenous infusion.

Viloxazine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Porphyria. Viloxazine hydrochloride is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *animals*.

Preparations

Proprietary Preparations (details are given in Part 3)
Belg.: Vivalan†; ***Cz.:*** Vivalan†; ***Fr.:*** Vivalan†; ***Ger.:*** Vivalan†; ***Port.:*** Vivalan†.