withdrawal symptoms (p.1860). However, a systematic review[1] was unable to find evidence to support the use of antidepressants in the treatment of cocaine dependence although the efficacy of desipramine was suggested in some individual studies.

1. Lima MS, *et al.* Antidepressants for cocaine dependence. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2003 (accessed 24/11/05).

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (see p.2148) tricyclic antidepressants such as imipramine or desipramine[1-4] are usually reserved for patients who fail to respond to, or who are intolerant of, stimulants. They may also be of use for selected patients with co-existing disorders such as Tourette's syndrome, anxiety, and enuresis.

1. Rapport MD, *et al.* Methylphenidate and desipramine in hospitalized children: I. separate and combined effects on cognitive function. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 333–42.
2. Pataki CS, *et al.* Side effects of methylphenidate and desipramine alone and in combination in children. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 1065–72.
3. Singer HS, *et al.* The treatment of attention-deficit hyperactivity disorder in Tourette's syndrome: a double-blind placebo-controlled study with clonidine and desipramine. *Pediatrics* 1995; **95:** 74–81.
4. Spencer T, *et al.* A double-blind comparison of desipramine and placebo in children and adolescents with chronic tic disorder and comorbid attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry* 2002; **59:** 649–56.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2) when given in subantidepressant doses.

References to the use of desipramine.

1. Kishore-Kumar R, *et al.* Desipramine relieves postherpetic neuralgia. *Clin Pharmacol Ther* 1990; **47:** 305–12.
2. Max MB, *et al.* Effects of desipramine, amitriptyline, and fluoxetine on pain in diabetic neuropathy. *N Engl J Med* 1992; **326:** 1250–6.
3. Coquoz D, *et al.* Central analgesic effects of desipramine, fluvoxamine, and moclobemide after single oral dosing: a study in healthy volunteers. *Clin Pharmacol Ther* 1993; **54:** 339–44.
4. Gordon NC, *et al.* Temporal factors in the enhancement of morphine analgesia by desipramine. *Pain* 1993; **53:** 273–6.

Preparations

BP 2008: Desipramine Tablets;
USP 31: Desipramine Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Nebril†; ***Austria:*** Pertofran; ***Belg.:*** Pertofran†; ***Canad.:*** Norpramin; ***Chile:*** Distonal; ***Fr.:*** Pertofran†; ***Ger.:*** Pertofran†; Petylyl; ***Israel:*** Deprexan; ***Ital.:*** Nortimil; ***Mex.:*** Norpramin†; ***NZ:*** Pertofran†; ***Pol.:*** Petylyl; ***USA:*** Norpramin.

Multi-ingredient: ***Arg.:*** Plafonyl†.

Desvenlafaxine Succinate *(BANM, USAN, rINNM)*

O-Desmethylvenlafaxine succinate; Dèsvenlafaxine, Succinate de; Desvenlafaxini Succinas; DVS-233 (base or succinate); Succinato de desvenlafaxina; Wy-45233. 1-[(1*RS*)-2-(Dimethylamino)-1-(4-hydroxyphenyl)ethyl]cyclohexanol hydrogen butanedioate monohydrate.

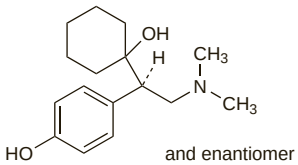
Десвенлафаксина Суксинат

$C_{16}H_{25}NO_2.C_4H_6O_4.H_2O$ = 399.5.

CAS — 93413-62-8 (desvenlafaxine); 386750-22-7 (desvenlafaxine succinate).

ATC — N06AX23.

ATC Vet — QN06AX23.



(desvenlafaxine)

Profile

Desvenlafaxine, the major active metabolite of venlafaxine, is a serotonin and noradrenaline reuptake inhibitor (SNRI) (see Venlafaxine, p.427). It is given orally as the succinate but doses are expressed in terms of the base; desvenlafaxine succinate 75.8 mg is equivalent to about 50 mg of desvenlafaxine. The succinate is given in the treatment of depression (p.373) as a modified-release preparation providing a dose equivalent to desvenlafaxine 50 mg once daily. Higher doses of up to 400 mg daily have been studied, but provide no additional benefit and are associated with more frequent adverse effects. The dose may need to be reduced in patients with renal impairment (see below).

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

Desvenlafaxine is under investigation in the management of menopausal vasomotor symptoms, neuropathic pain, and fibromyalgia.

◊ References.

1. DeMartinis NA, *et al.* A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *J Clin Psychiatry* 2007; **68:** 677–88.
2. Septien-Velez L, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol* 2007; **22:** 338–47.
3. Liebowitz MR, *et al.* A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in adult outpatients with major depressive disorder. *J Clin Psychiatry* 2007; **68:** 1663–72.

Administration in renal impairment. The usual desvenlafaxine oral dose of 50 mg daily may be given to patients with mild to moderate renal impairment. In severe impairment (creatinine clearance less than 30 mL/minute) a dose of 50 mg may be given on alternate days. Supplemental doses should not be given after dialysis.

Preparations

Proprietary Preparations (details are given in Part 3)
USA: Pristiq.

Dibenzepin Hydrochloride *(BANM, USAN, rINNM)*

Dibenzépine, Chlorhydrate de; Dibenzepini Hydrochloridum; HF-1927; Hidrocloruro de dibenzepina. 10-(2-Dimethylaminoethyl)-5,10-dihydro-5-methyl-dibenzo[*b*,*e*][1,4]diazepin-11-one hydrochloride.

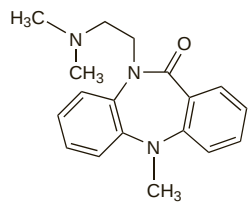
Дибензепина Гидрохлорид

$C_{18}H_{21}N_3O.HCl$ = 331.8.

CAS — 4498-32-2 (dibenzepin); 315-80-0 (dibenzepin hydrochloride).

ATC — N06AA08.

ATC Vet — QN06AA08.



(dibenzepin)

Profile

Dibenzepin hydrochloride is a tricyclic antidepressant (see Amitriptyline, p.376).

In the treatment of depression dibenzepin hydrochloride is given in oral doses of 480 mg daily; higher doses of up to 720 mg daily may be required in some patients with severe depression. Elderly patients should be given reduced doses of 240 mg daily initially, increased to a maximum of 480 mg daily if required.

Dibenzepin hydrochloride has also been given by intravenous infusion.

In some countries it has also been used for nocturnal enuresis.

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

◊ References.

1. Wirtheim E, Bloch Y. Dibenzepin overdose causing pulmonary edema. *Ann Pharmacother* 1996; **30:** 789–90.

Preparations

Proprietary Preparations (details are given in Part 3)
Austria: Noveril; ***Cz.:*** Noveril; ***Ger.:*** Noveril†; ***Hung.:*** Noveril; ***Israel:*** Noveril; Victoril†; ***Pol.:*** Noveril; ***Switz.:*** Noveril.

Dosulepin Hydrochloride *(BANM, rINNM)*

Dosulepiinihydrokloridi; Dosulépine, chlorhydrate de; Dosulepin-hydrochlorid; Dosulepinhydroklorid; Dosulepini hydrochloridum; Dosulepino hidrochloridas; Doszulepin-hidroklorid; Dothiepin Hydrochloride *(USAN)*; Hidrocloruro de dosulepina. 3-(Dibenzo[*b*,*e*]thiepin-11-ylidene)propyldimethylamine hydrochloride.

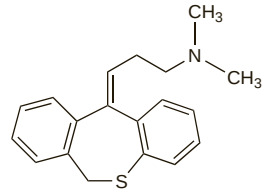
Досулепина Гидрохлорид

$C_{19}H_{21}NS.HCl$ = 331.9.

CAS — 113-53-1 (dosulepin); 897-15-4 (dosulepin hydrochloride).

ATC — N06AA16.

ATC Vet — QN06AA16.



(dosulepin)

Pharmacopoeias. In *Eur.* (see p.vii).
Ph. Eur. 6.2 (Dosulepin Hydrochloride). A white or faintly yellow crystalline powder. It consists chiefly of the *E*-isomer. Freely soluble in water, in alcohol, and in dichloromethane. A 10% solution in water has a pH of 4.2 to 5.2. Protect from light.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376).

Breast feeding. For comments on the use of tricyclic antidepressants in breast feeding patients, see under Precautions for Amitriptyline, p.378.

Effects on the cardiovascular system. For reference to an increased risk of ischaemic heart disease in patients treated with dosulepin, see under Amitriptyline, p.376.

Overdosage. After an overdose of 1 g of dosulepin, the ECG of a 41-year-old man showed cardiac abnormalities mimicking an acute myocardial infarction.[1] However, as cardiac enzymes did not confirm an ischaemic event, the abnormalities were thought to be due to either the quinidine-like effect of dosulepin or changes in potassium membrane permeability.

1. Steeds RP, Muthusamy R. Abnormal ventricular conduction following dothiepin overdose simulating acute myocardial infarction. *Heart* 2000; **83:** 289.

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

Interactions

For interactions associated with tricyclic antidepressants, see Amitriptyline, p.379.

Pharmacokinetics

Dosulepin hydrochloride is readily absorbed from the gastrointestinal tract, and extensively demethylated by first-pass metabolism in the liver to its primary active metabolite, desmethyldothiepin (also termed northiaden). Paths of metabolism also include *S*-oxidation.

Dosulepin is excreted in the urine, mainly in the form of its metabolites; small amounts are also excreted in the faeces. Elimination half-lives of about 14 to 24 and 23 to 46 hours have been reported for dosulepin and its metabolites, respectively.

Dosulepin is distributed into breast milk (see Breast Feeding under Precautions in Amitriptyline, p.378).

◊ References.

1. Maguire KP, *et al.* Clinical pharmacokinetics of dothiepin: single-dose kinetics in patients and prediction of steady-state concentrations. *Clin Pharmacokinet* 1983; **8:** 179–85.
2. Yu DK, *et al.* Pharmacokinetics of dothiepin in humans: a single dose dose-proportionality study. *J Pharm Sci* 1986; **75:** 582–5.
3. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; **33:** 635–9.

Uses and Administration

Dosulepin hydrochloride is a tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is one of the more sedating tricyclics. In the UK, the MHRA suggests that the use of dosulepin for depression should be limited, because of the small margin of safety between the maximum therapeutic dose and potentially fatal overdose. It advises that treatment should only be started by a specialist-care prescriber, and that the quantity issued per prescription should be limited. In patients with increased risk factors for suicide at the start of treatment, during dose adjustment, and until improvement occurs, the MHRA suggests a maximum supply equivalent to 2 weeks of treatment with 75 mg daily.

In the treatment of depression, dosulepin hydrochloride is given in oral doses of 25 mg three times daily initially, gradually increased to 50 mg three times daily if necessary; alternatively a single dose at night may be given. Higher doses of up to 225 mg daily have been given to severely depressed patients in hospital. The recommended initial dose for the elderly is 50 to 75 mg daily.

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