classical antipsychotics, but the use of thioridazine is now restricted in the treatment of schizophrenia because of the risk of cardiotoxicity.

Substance dependence. ***ALCOHOL***. For advice against the use of antipsychotics for alcohol withdrawal, see p.1626.

OPIOIDS. In a discussion of neonatal abstinence syndrome (p.102), it was observed in 1986 that, although opioids, diazepam, and phenobarbital were widely used in the USA for the management of this condition, chlorpromazine had tended to be the preferred treatment in the UK.[1] This was still true as late as the mid-1990s, although practice varied widely.[2] However, a systematic review[3] found insufficient evidence to support the use of chlorpromazine in the management of neonatal abstinence syndrome. The following dosage schedule has been suggested:[1] chlorpromazine is begun with a loading dose of 3 mg/kg, followed by a total oral maintenance dose of 3 mg/kg daily, divided into 4 or 6 doses. The authors suggested that this dose might be increased by 3 mg/kg daily if withdrawal symptoms were particularly severe. Once stabilised a reduction in the dose of chlorpromazine by 2 mg/kg every third day is attempted.[1] Complications of phenothiazine usage have been notably absent, although rarely seizures may occur.

1. Rivers RPA. Neonatal opiate withdrawal. *Arch Dis Child* 1986; **61:** 1236–9.
2. Morrison CL, Siney C. A survey of the management of neonatal opiate withdrawal in England and Wales. *Eur J Pediatr* 1996; **155:** 323–6.
3. Osborn DA, *et al*. Sedatives for opiate withdrawal in newborn infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2005 (accessed 02/10/07).

Taste disorders. Disturbances of the sense of taste may be broadly divided into either loss or distortion of taste. Loss of taste may be either complete (ageusia) or partial (hypogeusia). Distortion of taste (dysgeusia) may occur as aliageusia in which stimuli such as food or drink produce an inappropriate taste or as phantogeusia in which an unpleasant taste is not associated with an external stimuli and is sometimes referred to as a gustatory hallucination. Taste disturbances have many causes including infections, metabolic or nutritional disturbances, radiation, CNS disorders, neoplasms, drug therapy, or may occur as a consequence of normal ageing.[1] Management primarily consists of treatment of any underlying disorder. Withdrawal of offending drug therapy is commonly associated with resolution but occasionally effects persist and may require treatment.[2] Zinc or vitamin therapy has been used but there is insufficient evidence to indicate efficacy[1,3] for taste disturbances secondary to drug therapy or medical conditions that do not involve low zinc or vitamin concentrations. Phantogeusia might be linked to excessive activity of dopaminergic receptors as it has been reported[4] to respond to short-term treatment with small doses of antipsychotic drugs such as haloperidol or pimozide.

1. Schiffman SS. Taste and smell losses in normal aging and disease. *JAMA* 1997; **278:** 1357–62.
2. Henkin RI. Drug-induced taste and smell disorders: incidence, mechanisms and management related primarily to treatment of sensory receptor dysfunction. *Drug Safety* 1994; **11:** 318–77.
3. Heyneman CA. Zinc deficiency and taste disorders. *Ann Pharmacother* 1996; **30:** 186–7.
4. Henkin RI. Salty and bitter taste. *JAMA* 1991; **265:** 2253.

Preparations

BP 2008: Chlorpromazine Injection; Chlorpromazine Oral Solution; Chlorpromazine Suppositories; Chlorpromazine Tablets;
USP 31: Chlorpromazine Hydrochloride Injection; Chlorpromazine Hydrochloride Oral Concentrate; Chlorpromazine Hydrochloride Syrup; Chlorpromazine Hydrochloride Tablets; Chlorpromazine Suppositories.

Proprietary Preparations (details are given in Part 3)

Arg.: Ampliactil; Conrax; ***Austral.:*** Largactil; ***Braz.:*** Amplictil; Clorpromaz; Longactil; ***Canad.:*** Chlorpromanyl†; Largactil; ***Chile:*** Largactil; ***Cz.:*** Plegomazin; ***Denm.:*** Largactil; ***Fin.:*** Klorpromaan; ***Fr.:*** Largactil; ***Ger.:*** Propaphenin; ***Gr.:*** Largactil; Solidon; Zuledin; ***Hong Kong:*** Largactil†; ***Hung.:*** Hibernal; ***Indon.:*** Cepezet; Meprosetil; Promactil; ***Irl.:*** Clonazine; Largactil†; ***Israel:*** Taroctyl; ***Ital.:*** Largactil; Prozin; ***Malaysia:*** Matcine; ***Mex.:*** Largactil; ***Neth.:*** Largactil; ***Norw.:*** Largactil; ***NZ:*** Largactil; ***Philipp.:*** Laractyl; Psynor; Thorazine; ***Pol.:*** Fenactil; ***Port.:*** Largactil; Largatrex; ***Rus.:*** Aminazin (Аминазин); ***S.Afr.:*** Largactil; ***Singapore:*** Largo; Matcine; ***Spain:*** Largactil; ***Swed.:*** Hibernal; ***Switz.:*** Chlorazin; ***Thai.:*** Chlormazine†; Chlorpromasit; Chlorpromed; Duncan; Matcine; Pogetol; Prozine; ***Turk.:*** Largactil; ***UK:*** Largactil; ***USA:*** Thorazine†; ***Venez.:*** Largactil†.

Multi-ingredient: ***Arg.:*** 6 Copin; ***India:*** Trinicalm Forte; ***Spain:*** Largatrex†; ***Thai.:*** Ama.

Chlorprothixene *(BAN, USAN, rINN)*

Chlorprothixène; Chlorprothixenum; Clorprotixeno; Klooriprotikseeni; Klorprotixen; N-714; Ro-4-0403. (*Z*)-3-(2-Chlorothioxanthen-9-ylidene)-*NN*-dimethylpropylamine.

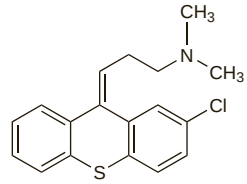
Хлорпротиксен

$C_{18}H_{18}ClNS$ = 315.9.

CAS — 113-59-7.

ATC — N05AF03.

ATC Vet — QN05AF03.



Pharmacopoeias. In *Chin.*

Chlorprothixene Hydrochloride *(BANM, rINNM)*

Chloroprotyksenu chlorowodorek; Chlorprothixène, chlorhydrate de; Chlorprothixen-hydrochlorid; Chlorprothixeni hydrochloridum; Chlorprotikseno hidroclorida; Hidrocloruro de clorprotixeno; Klooriprotikseenihydrokloridi; Klórprotixen-hidroklorid; Klorprotixenhydroklorid.

Хлорпротиксена Гидрохлорид

$C_{18}H_{19}Cl_2NS$ = 352.3.

ATC — N05AF03.

ATC Vet — QN05AF03.

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

Ph. Eur. 6.2 (Chlorprothixene Hydrochloride). A white or almost white, crystalline powder. Soluble in water and in alcohol; slightly soluble in dichloromethane. A 1% solution in water has a pH of 4.4 to 5.2. Protect from light.

Chlorprothixene Mesilate *(BANM, rINNM)*

Chlorprothixène, Mésilate de; Chlorprothixene Mesylate; Chlorprothixeni Mesilas; Chlorprothixenium Mesylicum; Mesilato de clorprotixeno.

Хлорпротиксена Мезилат

$C_{19}H_{22}ClNO_3S_2,H_2O$ = 430.0.

ATC — N05AF03.

ATC Vet — QN05AF03.

Profile

Chlorprothixene is a thioxanthene antipsychotic with general properties similar to those of the phenothiazine, chlorpromazine (p.969). It is used mainly in the treatment of psychoses (p.954). Chlorprothixene is given as the acetate and the hydrochloride. Preparations of chlorprothixene prepared with the aid of lactic acid have been stated to contain chlorprothixene lactate. The citrate and the mesilate have also been used.

Chlorprothixene is usually given orally as the hydrochloride and doses are expressed in terms of this salt. The acetate is given by injection with doses expressed in terms of the base. A usual oral initial dose for the treatment of psychoses is 15 to 50 mg three or four times daily, increased according to response; doses of up to 600 mg or more daily have been given in severe or resistant cases. It may also be given intramuscularly or intravenously in single doses of up to 100 mg. Chlorprothixene should be used in reduced dosage for elderly or debilitated patients.

Adverse effects. A 59-year-old man receiving chlorprothixene (for the second time) for acute mania developed severe obstructive jaundice within a few days; he was also taking chlorpropamide, digoxin, and diuretics.[1] Chlorprothixene was considered the most likely cause of the jaundice, though chlorpropamide could not be excluded.

1. Ruddock DGS, Hoenig J. Chlorprothixene and obstructive jaundice. *BMJ* 1973; **1:** 231.

Breast feeding. The American Academy of Pediatrics[1] considers that, although the effect of chlorprothixene on breast-fed infants is unknown, its use by mothers during breast feeding may be of concern since antipsychotics do appear in breast milk and thus could conceivably alter CNS function in the infant both in the short and long term.

Chlorprothixene and its sulfoxide metabolite were concentrated in the breast milk of 2 mothers given chlorprothixene 200 mg daily but it was calculated that the amount ingested by the nursing infant was only 0.1% of the maternal dose per kg bodyweight.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 28/04/04)
2. Matheson I, *et al*. Presence of chlorprothixene and its metabolites in breast milk. *Eur J Clin Pharmacol* 1984; **27:** 611–13.

Metabolism. Results from studies on the metabolism of chlorprothixene in *animals* and man[1] indicated that in addition to the major metabolite chlorprothixene-sulfoxide, 2 further urinary metabolites were identified, namely *N*-desmethylchlorprothixene-sulfoxide and chlorprothixene-sulfoxide-*N*-oxide.

1. Raaflaub J. Zum Metabolismus des Chlorprothixen. *Arzneimittelforschung* 1967; **17:** 1393–5.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Truxal; Truxaletten; ***Denm.:*** Truxal; ***Fin.:*** Cloxan†; Truxal; ***Ger.:*** Truxal; ***Hung.:*** Truxal; ***Neth.:*** Truxal; ***Norw.:*** Truxal; ***Rus.:*** Truxal (Труксал); ***Swed.:*** Truxal; ***Switz.:*** Truxal; Truxaletten.

Cinolazepam *(rINN)*

Cinolazépam; Cinolazepamum; OX-373. 7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-3-hydroxy-2-oxo-1*H*-1,4-benzodiazepine-1-propionitrile.

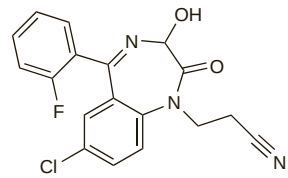
Цинолазепам

$C_{18}H_{13}ClFN_3O_2$ = 357.8.

CAS — 75696-02-5.

ATC — N05CD13.

ATC Vet — QN05CD13.



Profile

Cinolazepam is a benzodiazepine derivative with general properties similar to those of diazepam (p.986) that has been used in the short-term management of sleep disorders in usual oral doses of 40 mg at night.

Preparations

Proprietary Preparations (details are given in Part 3)

Austria: Gerodorm; ***Cz.:*** Gerodorm; ***Hung.:*** Gerodorm.

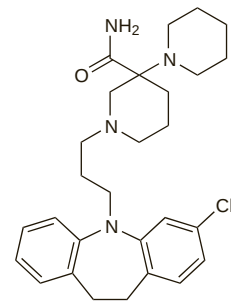
Clocapramine Hydrochloride *(rINNM)*

Chlorcarpipramine Hydrochloride; Clocapramine, Chlorhydrate de; Clocapramini Hydrochloridum; Hidrocloruro de clocapramina; Y-4153. 1′-[3-(3-Chloro-10,11-dihydro-5*H*-dibenz[*b,f*]azepin-5-yl)propyl][1,4′-bipiperidine]-4′-carboxamide dihydrochloride monohydrate.

Клокапрамина Гидрохлорид

$C_{28}H_{37}ClN_4O,2HCl,H_2O$ = 572.0.

CAS — 47739-98-0 (clocapramine); 28058-62-0 (clocapramine hydrochloride).



(clocapramine)

Pharmacopoeias. In *Jpn.*

Profile

Clocapramine is a chlorinated derivative of carpipramine (p.968). The hydrochloride has been given orally in the treatment of schizophrenia.

Clomethiazole *(BAN, rINN)*

Chlormethiazole; Clométhiazole; Clomethiazolum; Clometiazol; Klometiatsoli; Klometiazol. 5-(2-Chloroethyl)-4-methyl-1,3-thiazole.

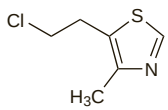
Клометиазол

C_6H_8ClNS = 161.7.

CAS — 533-45-9.

ATC — N05CM02.

ATC Vet — QN05CM02.



Pharmacopoeias. In *Br.*

BP 2008 (Clomethiazole). A colourless to slightly yellowish-brown liquid with a characteristic odour. Slightly soluble in water; miscible with alcohol, with chloroform, and with ether. A 0.5% solution in water has a pH of 5.5 to 7.0. Store at a temperature of 2° to 8°.

Clomethiazole Edisilate *(BANM, rINNM)*

Chlormethiazole Edisylate; Chlormethiazole Ethanedisulphonate; Clométhiazole, Edisilate de; Clomethiazole Edisylate *(USAN)*; Clomethiazoli Edisilas; Edisilato de clometiazol; Klometiazolu edysylan; NEX-002. 5-(2-Chloroethyl)-4-methylthiazole ethane-1,2-disulphonate.

Клометиазола Эдизилат

$(C_6H_8ClNS)_2,C_2H_6O_6S_2$ = 513.5.

CAS — 1867-58-9.

ATC — N05CM02.

ATC Vet — QN05CM02.

Pharmacopoeias. In *Br.* and *Pol.*

BP 2008 (Clomethiazole Edisilate). A white crystalline powder with a characteristic odour. Freely soluble in water; soluble in alcohol; practically insoluble in ether.

Incompatibility. Several studies have shown that clomethiazole edisilate may permeate through or be sorbed onto plastics used in intravenous infusion bags or giving sets.[1-4] The drug may also react with and soften the plastic.[1] The manufacturers of clomethiazole edisilate have suggested that thrombophlebitis, fever, and headache reported in young children during prolonged infusions may have been due to reaction with plastic giving sets and silastic cannulae. Recommendations for intravenous use have therefore included the use of a motor-driven glass syringe in preference to a plastic drip set in small children, changing plastic drip sets at least every 24 hours when used in older patients, and use of teflon intravenous cannulas.

1. Lingam S, *et al.* Problems with intravenous chlormethiazole (Heminevrin) in status epilepticus. *BMJ* 1980; **280:** 155–6.
2. Tsuei SE, *et al.* Sorption of chlormethiazole by intravenous infusion giving sets. *Eur J Clin Pharmacol* 1980; **18:** 333–8.
3. Kowaluk EA, *et al.* Dynamics of clomethiazole edisylate interaction with plastic infusion systems. *J Pharm Sci* 1984; **73:** 43–7.
4. Lee MG. Sorption of four drugs to polyvinyl chloride and polybutadiene intravenous administration sets. *Am J Hosp Pharm* 1986; **43:** 1945–50.

Dependence and Withdrawal

Dependence may develop, particularly with prolonged use of higher than recommended doses of clomethiazole. Features of dependence and withdrawal are similar to those of barbiturates (see Amobarbital, p.962).

Adverse Effects, Treatment, and Precautions

Clomethiazole may produce nasal congestion and irritation, sneezing, and conjunctival irritation sometimes associated with a headache. Nasopharyngeal or bronchial secretions may be increased. Skin rashes and urticaria have also occurred and in rare cases bullous eruptions have been reported. Gastrointestinal disturbances including nausea and vomiting, have been reported after oral doses. Reversible increases in liver enzyme values and blood-bilirubin concentrations have also been noted. Clomethiazole can cause excessive drowsiness, particularly in high doses; drowsiness may persist the next day, and patients affected should not drive or operate machinery. Paradoxical excitation or confusion may occur rarely. Anaphylaxis has also been reported rarely.

Excessive doses may produce coma, respiratory depression, hypotension, and hypothermia; pneumonia may follow increased respiratory secretion. Treatment is as for barbiturate overdose (see Amobarbital, p.962).

Clomethiazole is contra-indicated in patients with acute pulmonary insufficiency, and should be given with care to patients with sleep apnoea syndrome, chronic pulmonary insufficiency, or renal, liver, cerebral, or cardiac disease. Clomethiazole should be given with caution to elderly patients as there may be increased bioavailability and delayed elimination. Paradoxical worsening of epilepsy may occur in the Lennox Gastaut syndrome.

Administration by intravenous infusion. Severe adverse effects have followed the intravenous use of clomethiazole, and intravenous preparations are no longer generally available. Facilities for intubation and resuscitation were required when clomethiazole was given intravenously, with care taken to ensure that the patient's airway was maintained since there is a risk of mechanical obstruction during deep sedation. At too high a rate of infusion, sleep induced with clomethiazole could lapse into deep unconsciousness and patients required close and constant observation. Rapid infusion has also caused transient apnoea and hypotension, and special care was needed in patients susceptible to cerebral or cardiac complications, including the elderly. With prolonged infusion there was also a risk of electrolyte imbalance due to the water load involved with the glucose vehicle. Recovery has been considerably delayed after prolonged infusion.

Effects on the heart. Cardiac arrest in 2 chronic alcoholics might have been associated with clomethiazole infusion.[1]

1. McInnes GT, *et al.* Cardiac arrest following chlormethiazole infusion in chronic alcoholics. *Postgrad Med J* 1980; **56:** 742–3.

Overdosage. A report of clomethiazole poisoning on 16 occasions in 13 patients, some of whom had also taken other drugs and alcohol.[1] There was increased salivation on 7 occasions; otherwise the clinical features were those of barbiturate poisoning (see Adverse Effects of Amobarbital, p.962). The highest plasma-clomethiazole concentration was 36 micrograms/mL, with the highest value in a conscious patient 11.5 micrograms/mL. All the patients survived following intensive supportive treatment as for barbiturate poisoning.

1. Illingworth RN, *et al.* Severe poisoning with chlormethiazole. *BMJ* 1979; **2:** 902–3.

Parotitis. Acute bilateral parotitis has been reported in a patient given clomethiazole.[1] The swelling disappeared after withdrawal of clomethiazole and recurred on rechallenge.

1. Bosch X, *et al.* Parotitis induced by chlormethiazole. *BMJ* 1994; **309:** 1620.

Pregnancy. There have been reports of neonates being adversely affected by clomethiazole given to their mothers for toxaemia of pregnancy.[1,2] Effects included sedation, hypotonia, and apnoea. In a report[1] it was suggested that the effects might have been due to a synergistic interaction between clomethiazole and diazoxide as these drugs were given to most of the mothers with affected infants.

1. Johnson RA. Adverse neonatal reaction to maternal administration of intravenous chlormethiazole and diazoxide. *BMJ* 1976; **1:** 943.
2. Wood C, Renou P. Sleepy and hypotonic neonates. *Med J Aust* 1978; **2:** 73.

Interactions

The sedative effects of clomethiazole are enhanced by CNS depressants such as alcohol, barbiturates, other hypnotics and sedatives, and antipsychotics.

Alcohol. Although clomethiazole has been a popular choice for the treatment of alcohol withdrawal symptoms (p.1626), if it is given long-term, patients readily transfer dependency to it; if they also continue to abuse alcohol this may lead to severe self-poisoning with deep coma and potentially fatal respiratory depression.[1]

1. McInnes GT. Chlormethiazole and alcohol: a lethal cocktail. *BMJ* 1987; **294:** 592.

Beta blockers. Sinus bradycardia developed in an 84-year-old woman taking *propranolol* for hypertension 3 hours after she took a second dose of clomethiazole 192 mg.[1] Her pulse rate increased on stopping propranolol and clomethiazole and later stabilised when she took propranolol with haloperidol.

1. Adverse Drug Reactions Advisory Committee (Australia). *Med J Aust* 1979; **2:** 553.

Diazoxide. For a report of adverse reactions in neonates born to mothers given clomethiazole and diazoxide, see Pregnancy under Adverse Effects, Treatment, and Precautions, above.

Histamine H_2-antagonists. A study of the pharmacokinetics of clomethiazole edisilate 1 g orally in 8 healthy subjects, before and after doses of *cimetidine* 1 g daily for 1 week, showed that mean clearance of clomethiazole was reduced by 31% by cimetidine.[1] This was associated with an increase in the mean peak plasma concentration of the hypnotic from 2.664 to 4.507 micrograms/mL and an increase in the mean elimination half-life from 2.33 to 3.63 hours. After the original dose of clomethiazole subjects slept for 30 to 60 minutes, whereas after cimetidine, most slept for at least 2 hours.

Ranitidine did not significantly affect the pharmacokinetics of clomethiazole in a study in 7 healthy subjects.[2]

1. Shaw G, *et al.* Cimetidine impairs the elimination of chlormethiazole. *Eur J Clin Pharmacol* 1981; **21:** 83–5.
2. Mashford ML, *et al.* Ranitidine does not affect chlormethiazole or indocyanine green disposition. *Clin Pharmacol Ther* 1983; **34:** 231–3.

Pharmacokinetics

Clomethiazole is rapidly absorbed from the gastrointestinal tract, peak plasma concentrations occurring about 15 to 90 minutes after oral doses depending on the formulation used. It is widely distributed in the body and is reported to be 65% bound to plasma proteins. Clomethiazole is extensively metabolised, probably by first-pass metabolism in the liver with only small amounts appearing unchanged in the urine. The elimination half-life has been reported to be about 4 hours but this may be increased to 8 hours or longer in the elderly or in patients with hepatic impairment. Clomethiazole crosses the placenta and is distributed into breast milk.

Hepatic impairment. Studies in 8 patients with advanced cirrhosis of the liver and in 6 healthy men showed that the amount of unmetabolised clomethiazole reaching the circulation after an oral dose was about 10 times higher in the patients than in the controls.[1] Low concentrations in the controls were related to extensive first-pass metabolism in the liver.

1. Pentikäinen PJ, *et al.* Pharmacokinetics of chlormethiazole in healthy volunteers and patients with cirrhosis of the liver. *Eur J Clin Pharmacol* 1980; **17:** 275–84.

Uses and Administration

Clomethiazole is a hypnotic and sedative with anticonvulsant effects. It is used orally in the treatment of agitation and restlessness (see Disturbed Behaviour, p.954) in elderly patients, in the short-term management of severe insomnia (p.957) in the elderly, and in the treatment of acute alcohol withdrawal symptoms (p.1626). It was also given as an intravenous infusion in the management of status epilepticus (p.469) and impending or actual eclampsia (p.470); however, a parenteral formulation of clomethiazole no longer appears to be available.

In the UK, clomethiazole (as *Heminevrin*; *AstraZeneca*) is available as capsules containing 192 mg of clomethiazole base and as syrup containing 250 mg of the edisilate in 5 mL. As a result of differences in the bioavailability of these preparations, 192 mg of the base in the capsules is considered therapeutically equivalent to 250 mg (5 mL) of the edisilate in the syrup, i.e. one capsule or 5 mL of syrup are equivalent in their effects.

The usual hypnotic dose of clomethiazole for **insomnia** is 1 or 2 capsules (192 or 384 mg of the base) or the equivalent. For **restlessness and agitation** in the elderly 1 capsule (192 mg of the base), or the equivalent dose as one of the other dosage forms, may be given 3 times daily.

Various clomethiazole regimens have been suggested for the treatment of **alcohol withdrawal**, usually starting with 9 to 12 capsules, or the equivalent, divided into 3 or 4 doses, on the first day, and gradually reducing the dosage over the next 5 days. Treatment should be carried out in hospital or in specialist centres, and use for longer than 9 days is not recommended because of the risk of dependence (see above).

Porphyria. Clomethiazole is one of the drugs that has been used for seizure prophylaxis in patients with porphyria (p.471) who continue to experience convulsions while in remission.

Stroke. Clomethiazole has been studied[1,2] as a neuroprotective drug in the acute management of patients with stroke, but no beneficial effect on long-term outcome was found.

1. Wahlgren NG, *et al.* CLASS Study Group. Clomethiazole Acute Stroke Study (CLASS): results of a randomized, controlled trial of clomethiazole versus placebo in 1360 acute stroke patients. *Stroke* 1999; **30:** 21–8.
2. Lyden P, *et al.* Clomethiazole Acute Stroke Study in ischemic stroke (CLASS-I): final results. *Stroke* 2002; **33:** 122–8.

Substance dependence. For a discussion of the management of *opioid* withdrawal symptoms, including mention of the use of clomethiazole, see p.101.