2. Stubb S, *et al.* Fixed drug eruptions: 77 cases from 1981 to 1985. *Br J Dermatol* 1989; **120:** 583.
3. Roujeau J-C, *et al.* Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med* 1995; **333:** 1600–7.

Porphyria. Chlormezanone has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Cardiosedantol; Restoril†.

Multi-ingredient: ***Chile:*** Adalgen†; Calmosedan; Diapam; Dioran†; Dolnix; Dolonase; Dolorelax†; Fibrorelax; Mesolona†; Multisedil; Neo Butartrol; Promidan; Sedantol; Sedilit; Silrelax†; Sin-Algin; ***Hong Kong:*** Parazone; ***S.Afr.:*** Myoflex.

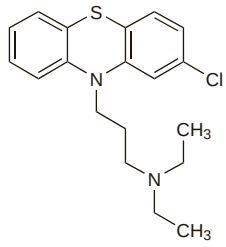
Chlorproethazine Hydrochloride *(rINNM)*

Chlorproéthazine, Chlorhydrate de; Chlorproethazini Hydrochloridum; Hidrocloruro de clorproetazina; RP-4909 (chlorproethazine). 3-(2-Chlorophenothiazin-10-yl)-*NN*-diethylpropylamine hydrochloride.

Хлорпроэтазина Гидрохлорид

$C_{19}H_{23}ClN_2S,HCl$ = 383.4.

CAS — 84-01-5 (chlorproethazine); 4611-02-3 (chlorproethazine hydrochloride).
ATC — N05AA07.
ATC Vet — QN05AA07.



(chlorproethazine)

Profile

Chlorproethazine is a phenothiazine derivative differing chemically from chlorpromazine by the substitution of a diethyl for a dimethyl group. It has general properties similar to those of chlorpromazine (below) but has been used mainly as a muscle relaxant in the management of muscle spasm (p.1887). Although exposure of the skin to phenothiazines has been associated with sensitivity reactions, chlorproethazine hydrochloride has been applied topically with the warning to avoid direct exposure to sunlight. It has also been given orally or by intramuscular or slow intravenous injection.

Preparations

Proprietary Preparations (details are given in Part 3)
Fr.: Neuriplege†.

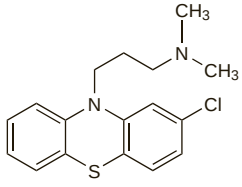
Chlorpromazine *(BAN, rINN)*

Chlorpromazinum; Clorpromazina; Klooripromatsiini; Klorpromazin. 3-(2-Chlorophenothiazin-10-yl)propyldimethylamine.

Хлорпромазин

$C_{17}H_{19}ClN_2S$ = 318.9.

CAS — 50-53-3.
ATC — N05AA01.
ATC Vet — QN05AA01.



Pharmacopoeias. In *Br.* and *US*.

BP 2008 (Chlorpromazine). A white or creamy-white powder or waxy solid; odourless or almost odourless. M.p. 56° to 58°. Practically insoluble in water; freely soluble in alcohol and in ether; very soluble in chloroform. Protect from light.

USP 31 (Chlorpromazine). A white crystalline solid with an amine-like odour. It darkens on prolonged exposure to light. Practically insoluble in water; soluble 1 in 3 of alcohol, 1 in 2 of chloroform, 1 in 3 of ether, and 1 in 2 of benzene; freely soluble in dilute mineral acids; practically insoluble in dilute alkali hydroxides. Store in airtight containers. Protect from light.

Chlorpromazine Embonate *(BANM, rINNM)*

Chlorpromazine, Embonate de; Chlorpromazine Pamoate; Chlorpromazini Embonas; Embonato de clorpromazina.

Хлорпромазина Эмбонат

$(C_{17}H_{19}ClN_2S)_2,C_{23}H_{16}O_6$ = 1026.1.

ATC — N05AA01.
ATC Vet — QN05AA01.

Chlorpromazine Hydrochloride *(BANM, rINNM)*

Aminazine; Chloropromazyny chlorowodorek; Chlorpromazin hydrochlorid; Chlorpromazine, chlorhydrate de; Chlorpromazini hydrochloridum; Chlorpromazino hidrochloridas; Hidrocloruro de clorpromazina; Klooripromatsiinihydrokloridi; Klorpromazin Hidroklorür; Klórpromazin-hidroklorid; Klorpromazinhydroklorid.

Хлорпромазина Гидрохлорид

$C_{17}H_{19}ClN_2S,HCl$ = 355.3.

CAS — 69-09-0.
ATC — N05AA01.
ATC Vet — QN05AA01.

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

Ph. Eur. 6.2 (Chlorpromazine Hydrochloride). A white or almost white crystalline powder. It decomposes on exposure to air and light. Very soluble in water; freely soluble in alcohol. A freshly prepared 10% solution in water has a pH of 3.5 to 4.5. Store in airtight containers. Protect from light.

USP 31 (Chlorpromazine Hydrochloride). A white or slightly creamy-white odourless crystalline powder. It darkens on prolonged exposure to light. Soluble 1 in 1 of water, 1 in 1.5 of alcohol, and 1 in 1.5 of chloroform; insoluble in ether and in benzene. Store in airtight containers. Protect from light.

Dilution. Solutions containing 2.5% of chlorpromazine hydrochloride may be diluted to 100 mL with 0.9% sodium chloride solution provided the pH of the saline solution is such that the pH of the dilution does not exceed the critical range of pH 6.7 to 6.8.[1] With saline of pH 7.0 or 7.2, the final solution had a pH of 6.4.

1. D'Arcy PF, Thompson KM. Stability of chlorpromazine hydrochloride added to intravenous infusion fluids. *Pharm J* 1973; **210:** 28.

Incompatibility. Incompatibility has been reported between chlorpromazine hydrochloride injection and several other compounds; precipitation of chlorpromazine base from solution is particularly likely if the final pH is increased. Compounds reported to be incompatible with chlorpromazine hydrochloride include aminophylline, amphotericin B, aztreonam, some barbiturates, chloramphenicol sodium succinate, chlorothiazide sodium, dimenhydrinate, heparin sodium, morphine sulfate (when preserved with chlorocresol), some penicillins, and remifentanil.

For a warning about incompatibility between chlorpromazine solution (*Thorazine*; *GSK, USA*) and carbamazepine suspension (*Tegretol*; *Novartis, USA*), see p.471.

Sorption. There was a 41% loss of chlorpromazine hydrochloride from solution when infused for 7 hours via a plastic infusion set (cellulose propionate burette with PVC tubing), and a 79% loss after infusion for 1 hour from a glass syringe through silastic tubing.[1] Loss was negligible after infusion for 1 hour from a system comprising a glass syringe with polyethylene tubing.

1. Kowaluk EA, *et al.* Interactions between drugs and intravenous delivery systems. *Am J Hosp Pharm* 1982; **39:** 460–7.

Adverse Effects

Chlorpromazine generally produces less central depression than the barbiturates or benzodiazepines, and tolerance to its initial sedative effects develops fairly quickly in most patients. It has antimuscarinic properties and may cause adverse effects such as dry mouth, constipation, difficulty with micturition, blurred vision, and mydriasis. Tachycardia, ECG changes (particularly Q- and T-wave abnormalities), and, rarely, cardiac arrhythmias may occur; hypotension (usually orthostatic) is common. Other adverse effects include delirium, agitation and, rarely, catatonic-like states, insomnia or drowsiness, nightmares, depression, miosis, EEG changes and convulsions, nasal congestion, minor abnormalities in liver function tests, inhibition of ejaculation, impotence, and priapism.

Hypersensitivity reactions include urticaria, exfoliative dermatitis, erythema multiforme, and contact sensitivity. A syndrome resembling SLE has been reported. Jaundice has occurred, and probably has an immunological origin. Prolonged therapy may lead to deposition of pigment in the skin, or more frequently the eyes; corneal and lens opacities have occurred. Pigmentary retinopathy has occurred only rarely with chlorpromazine. Photosensitivity reactions are more common with chlorpromazine than with other antipsychotics.

Haematological disorders, including haemolytic anaemia, aplastic anaemia, thrombocytopenic purpura, eosinophilia, and a potentially fatal agranulocytosis have occasionally been reported; they may be manifestations of a hypersensitivity reaction. Most cases of agranulocytosis have occurred within 4 to 10 weeks of starting treatment, and symptoms such as sore throat or fever should be watched for and white cell counts instituted should they appear. Mild leucopenia has been stated to occur in up to 30% of patients on prolonged high dosage.

Extrapyramidal dysfunction and resultant disorders include acute dystonia, a parkinsonism-like syndrome, and akathisia; late effects include tardive dyskinesia and perioral tremor. The neuroleptic malignant syndrome may also occur.

Chlorpromazine alters endocrine and metabolic functions. Patients have experienced amenorrhoea, galactorrhoea, and gynaecomastia due to hyperprolactinaemia, weight gain, and hyperglycaemia and altered glucose tolerance. Body temperature regulation is impaired and may result in hypo- or hyperthermia depending on environment. There have also been reports of hypercholesterolaemia.

There have been isolated reports of sudden death with chlorpromazine; possible causes include cardiac arrhythmias or aspiration and asphyxia due to suppression of the cough and gag reflexes.

Pain and irritation at the injection site may occur on injection. Nodule formation may occur after intramuscular injection.

Phenothiazines do not cause dependence of the type encountered with barbiturates or benzodiazepines. However, withdrawal symptoms have been seen on abrupt withdrawal in patients receiving prolonged and/or high-dose maintenance therapy.

Although the adverse effects of **other phenothiazines** are broadly similar in nature to those of chlorpromazine, their frequency and pattern tend to fall into 3 groups:

- group 1 (e.g. chlorpromazine, levomepromazine, and promazine) are generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal effects
- group 2 (e.g. pericyazine, pipotiazine, and thioridazine) are generally characterised by moderate sedative effects, marked antimuscarinic effects, and fewer extrapyramidal effects than groups 1 or 3
- group 3 (e.g. fluphenazine, perphenazine, prochlorperazine, and trifluoperazine) are generally characterised by fewer sedative and antimuscarinic effects but more pronounced extrapyramidal effects than groups 1 or 2

Classical antipsychotics of **other chemical groups** tend to resemble the phenothiazines of group 3. They include the butyrophenones (e.g. benperidol and haloperidol); diphenylbutylpiperidines (e.g. pimozide); thioxanthenes (flupentixol and zuclopenthixol); substituted benzamides (e.g. sulpiride); oxypertine; and loxapine.

Carcinogenicity. See Effects on Endocrine Function, below.

Convulsions. Treatment with antipsychotics can result in EEG abnormalities and lowered seizure threshold.[1] Seizures can be induced particularly in patients with a history of epilepsy or drug-induced seizures, abnormal EEG, previous electroconvulsive therapy, or pre-existing CNS abnormalities. The risk appears to be greatest at the start of antipsychotic therapy, or with high doses, or abrupt increases of dose, or with the use of more than one antipsychotic. The incidence of antipsychotic-induced convulsions is, however, probably less than 1%.

In general, the epileptic potential has been correlated with the propensity of the antipsychotic to cause sedation. Phenothiazines with marked sedative effects [group 1] such as chlorpromazine appear to present a higher risk than those with strong extrapyramidal effects [group 3]. Haloperidol appears to carry a relatively low risk of seizures. The following drugs have been suggested when classical antipsychotic therapy is considered necessary in

patients at risk of seizures or being treated for epilepsy: fluphenazine, haloperidol, pimozide, or trifluoperazine. Antipsychotic dosage should be increased slowly and the possibility of interactions with antiepileptic therapy considered (see under Interactions, below).

The atypical antipsychotic clozapine appears to be associated with a particularly high risk of seizures (see Effects on the Nervous System, under Clozapine, p.982). Risperidone may be preferred if an atypical antipsychotic is to be used in patients at risk of seizures.

1. Pisani F, *et al.* Effects of psychotropic drugs on seizure threshold. *Drug Safety* 2002; **25:** 91–110.

Effects on the blood. The UK CSM provided data on the reports it had received between July 1963 and January 1993 on agranulocytosis and neutropenia.[1] Several groups of drugs were commonly implicated, among them phenothiazines for which there were 87 reports of agranulocytosis (42 fatal) and 33 of neutropenia (22 fatal). The most frequently implicated phenothiazines were chlorpromazine with 51 reports of agranulocytosis (26 fatal) and 12 of neutropenia (2 fatal) and thioridazine with 20 reports of agranulocytosis (9 fatal) and 10 of neutropenia (none fatal).

1. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 18/07/08)

Effects on body-weight. Most antipsychotic drugs are associated with weight gain. A meta-analysis[1] found evidence of weight gain in patients receiving both classical (chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, thioridazine, tiotixene, or trifluoperazine) and atypical (clozapine, olanzapine, quetiapine, risperidone, sertindole, and ziprasidone) antipsychotics. Two drugs, molindone and pimozide, appeared in contrast to be associated with weight loss, although in the case of pimozide this could not be confirmed statistically. Placebo treatment was also associated with weight loss. For further details, see Effects on Body-weight, in Clozapine, p.981.

1. Allison DB, *et al.* Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry* 1999; **156:** 1686–96.

Effects on the cardiovascular system. Orthostatic hypotension is a common problem in patients taking psychotropic drugs and is particularly pronounced with low-potency antipsychotics.[1]

Various **EEG changes** or frank **arrhythmias** have occurred in patients receiving antipsychotics. T-wave changes have been reported with low-potency antipsychotics; they are usually benign and reversible, and subject to diurnal fluctuations. Low-potency antipsychotics, particularly *thioridazine* and *mesoridazine*, and the high-potency drug *pimozide*, prolong the QT interval in a similar manner to class I antiarrhythmics such as quinidine or procainamide; their use is therefore contra-indicated in patients taking such antiarrhythmics. *Droperidol*, another high-potency drug, has also been reported to prolong the QT interval.[2] Thioridazine is most frequently discussed in case reports of psychotropic drug-induced torsade de pointes,[2] which has led to restrictions on its use (see Precautions, and Uses and Administration of Thioridazine, p.1031); *chlorpromazine* and *pimozide* have also been implicated. Torsade de pointes has also been reported after overdosage[3-5] with, or high intravenous[6] doses of, the high-potency antipsychotic *haloperidol*. There are also isolated reports of cardiac arrhythmias after attempts at rapid control with high doses of haloperidol.[7,8] *Melperone*, a butyrophenone antipsychotic related to haloperidol, has been reported to have class III electrophysiologic and antiarrhythmic activity.[9,10]

In the UK, the risk of arrhythmias with antipsychotic treatment has been considered by an expert working group of the CSM;[11] the following recommendations were made regarding ECG monitoring:

- the need for an ECG should be based on a patient's relevant medical history, family history, and clinical examination; the elderly and those with a personal or family history of heart disease or any cardiac abnormalities would benefit the most from a baseline ECG
- during treatment an ECG should be performed in patients who experience palpitations or other symptoms suggestive of cardiac disease; if the QT interval is prolonged then a reduction in dose may be required, if it exceeds 500 milliseconds treatment may need to be stopped
- an ECG should be considered during dose increases
- potassium levels should be monitored before and during treatment and in particular during periods of acute illnesses

Sudden unexpected deaths have long been reported in patients receiving antipsychotics.[12] Whether this is due to the disease being treated or to the treatment is still unclear. However, in a retrospective cohort study[13] involving about 482 000 patients, analysis of 1487 sudden cardiac deaths indicated that patients receiving antipsychotics in doses of more than 100 mg of thioridazine or its equivalent had a 2.4-fold increase in the rate of sudden cardiac death, rising to a 3.53-fold increase in those patients with pre-existing severe cardiovascular disease. A later case-control study[14] in 5 UK psychiatric hospitals found that sudden unexplained death in psychiatric patients was associated with hypertension, ischaemic heart disease, and current treatment with thioridazine. Although several mechanisms have been suggested for the effect, prolongation of the QT interval has been implicated in a proportion of the cases.[12]

Results from a case-control study[15] have suggested that use of classical antipsychotics may be associated with an increased risk of idiopathic **venous thromboembolism.** The risk was most pronounced during the first 3 months of treatment, and was higher for low potency than high potency antipsychotics. This study did not examine the risk of venous thromboembolism with atypical antipsychotics, but see under Clozapine, p.982.

1. DiGiacomo J. Cardiovascular effects of psychotropic drugs. *Cardiovasc Rev Rep* 1989; **10:** 31–2, 39–41, and 47.
2. Reilly JG, *et al.* QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; **355:** 1048–52.
3. Zee-Cheng C-S, *et al.* Haloperidol and torsades de pointes. *Ann Intern Med* 1985; **102:** 418.
4. Henderson RA, *et al.* Life-threatening ventricular arrhythmia (torsades de pointes) after haloperidol overdose. *Hum Exp Toxicol* 1991; **10:** 59–62.
5. Wilt JL, *et al.* Torsade de pointes associated with the use of intravenous haloperidol. *Ann Intern Med* 1993; **119:** 391–4.
6. O'Brien JM, *et al.* Haloperidol-induced torsade de pointes. *Ann Pharmacother* 1999; **33:** 1046–50.
7. Mehta D, *et al.* Cardiac arrhythmia and haloperidol. *Am J Psychiatry* 1979; **136:** 1468–9.
8. Bett JHN, Holt GW. Malignant ventricular tachyarrhythmia and haloperidol. *BMJ* 1983; **287:** 1264.
9. Møgelvang JC, *et al.* Antiarrhythmic properties of a neuroleptic butyrophenone, melperone, in acute myocardial infarction. *Acta Med Scand* 1980; **208:** 61–4.
10. Hui WKK, *et al.* Melperone: electrophysiologic and antiarrhythmic activity in humans. *J Cardiovasc Pharmacol* 1990; **15:** 144–9.
11. CSM/MHRA. Cardiac arrhythmias associated with antipsychotic drugs. *Current Problems* 2006; **31:** 9. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2023860&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
12. Haddad PM, Anderson IM. Antipsychotic-related QTc prolongation, torsade de pointes and sudden death. *Drugs* 2002; **62:** 1649–71.
13. Ray WA, *et al.* Antipsychotics and the risk of sudden cardiac death. *Arch Gen Psychiatry* 2001; **58:** 1161–7.
14. Reilly JG, *et al.* Thioridazine and sudden unexplained death in psychiatric in-patients. *Br J Psychiatry* 2002; **180:** 515–22.
15. Zornberg GL, Jick H. Antipsychotic drug use and risk of first-time idiopathic venous thromboembolism: a case-control study. *Lancet* 2000; **356:** 1219–23.

Effects on endocrine function. Antipsychotics can alter the secretion of prolactin, growth hormone, and thyrotrophin from the anterior pituitary via their ability to block central dopamine-D_2 receptors. Therapeutic doses of classical antipsychotics (and some atypical antipsychotics such as amisulpride and risperidone) increase serum-prolactin concentrations; this effect occurs at lower doses and after shorter latent periods than the antipsychotic effects. However, partial tolerance to the hyperprolactinaemic effect may develop on long-term use.[1] Serum prolactin declines to normal values within 3 weeks of stopping oral antipsychotic therapy but may remain raised for 6 months after an intramuscular depot injection.[1]

The long-term consequences of gonadal hormone deficiency, secondary to raised prolactin concentrations, have caused concern. There is evidence[2] that patients taking long-term prolactin-raising antipsychotics are at high risk of osteoporosis associated with hypogonadism. Long-term antipsychotic treatment has also been shown to increase the incidence of mammary tumours in the *rat*. Although early studies[3,4] found little or no evidence that chronic use in humans alters the risk of breast cancer among women with schizophrenia, a later retrospective cohort study[5] found a modest dose-related increase in the risk of breast cancer in women using antipsychotic dopamine antagonists. A similar increase was seen in women receiving antiemetic dopamine antagonists. Fears that pituitary abnormalities, including pituitary tumours,[6] might develop in patients on long-term phenothiazine therapy have not been confirmed.[7,8]

Antipsychotics can in some circumstances reduce both basal and stimulated growth-hormone secretion but attempts to use them to treat dysfunctions in growth-hormone regulation have not been successful.[9] Although a number of clinical studies show that acute dosage of antipsychotics increased both basal and stimulated thyrotrophin secretion, the majority of studies find either no change or only a small increase in thyrotrophin secretion following long-term use.

A small study[10] has suggested that thioridazine may be more likely than other antipsychotics to decrease serum concentrations of testosterone or luteinising hormone in men. However, concentrations were within the normal range in most patients taking antipsychotics.

See also Effects on Fluid and Electrolyte Homoeostasis, below and Effects on Sexual Function, below.

1. Haddad PM, Wieck A. Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs* 2004; **64:** 2291–2314.
2. Meaney AM, *et al.* Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia. *Br J Psychiatry* 2004; **184:** 503–8.
3. Mortensen PB. The incidence of cancer in schizophrenic patients. *J Epidemiol Community Health* 1989; **43:** 43–7.
4. Mortensen PB. The occurrence of cancer in first admitted schizophrenic patients. *Schizophr Res* 1994; **12:** 185–94.
5. Wang PS, *et al.* Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiatry* 2002; **59:** 1147–54.
6. Asplund K, *et al.* Phenothiazine drugs and pituitary tumors. *Ann Intern Med* 1982; **96:** 533.
7. Rosenblatt S, *et al.* Chronic phenothiazine therapy does not increase sellar size. *Lancet* 1978; **ii:** 319–20.
8. Lilford VA, *et al.* Long-term phenothiazine treatment does not cause pituitary tumours. *Br J Psychiatry* 1984; **144:** 421–4.
9. Gunnet JW, Moore KE. Neuroleptics and neuroendocrine function. *Ann Rev Pharmacol Toxicol* 1988; **28:** 347–66.
10. Brown WA, *et al.* Differential effects of neuroleptic agents on the pituitary-gonadal axis in men. *Arch Gen Psychiatry* 1981; **38:** 1270–2.

Effects on the eyes. Phenothiazines may induce a pigmentary retinopathy which is dependent on both the dose and the duration of treatment.[1] Those phenothiazine derivatives with piperidine side-chains such as thioridazine have a higher risk of inducing retinal toxicity than other phenothiazine derivatives, with relatively few cases reported for those with aliphatic side-chains such as chlorpromazine; the piperazine group does not appear to exert direct ocular toxicity.[2] The retinopathy may present either acutely, (sudden loss of vision associated with retinal oedema and hyperaemia of the optic disc), or chronically, (a fine pigment scatter appearing in the central area of the fundus, extending peripherally but sparing the macula). Chronic paracentral and pericentral scotomas may be found. Although pigmentary disturbances may progress after withdrawal of thioridazine, they are not always paralleled by deterioration in visual function; nonetheless, some cases have led to progressive chorioretinopathy.[3] The critical ocular toxic dose of thioridazine is reported to be 800 mg daily[1] and UK licensed product information has recommended that a daily dose of 600 mg should not usually be exceeded. However, there is a report[4] of pigmentary retinopathy in a patient who received long-term thioridazine in daily doses not exceeding 400 mg; the total dose was 752 g.

Pigmentation may also occur in the cornea, lens, and conjunctiva following use of phenothiazines. It may occur in association with pigmentary changes in the skin and is dose-related. In a study of 100 Malaysian patients, ocular pigmentation was observed in slightly more than half of those who had received a total dose of chlorpromazine of 100 to 299 g and in 13 of 15 who had received 300 to 599 g.[5] All those who had received more than 600 g of chlorpromazine or thioridazine had ocular pigmentation. Cataract formation, mainly of an anterior polar variety, has been observed rarely, mainly in patients on chlorpromazine. It does not appear to be dose-related.[2]

A patient who had received fortnightly injections of fluphenazine 12.5 mg for 10 years (total dose 3.25 g) developed bilateral maculopathy following unprotected exposure of less than 2-minute's duration to a welding arc.[6] It was postulated that accumulation of phenothiazine in the retinal epithelium sensitised the patient to photic damage. However, another patient who had received fortnightly injections of fluphenazine 25 mg for 25 years (total dose 16.25 g) developed bilateral maculopathy without exposure to any extreme photochemical sources.[7] The authors concluded that this was due to a direct effect of fluphenazine secondary to its accumulation in the retinal epithelium.

1. Spiteri MA, James DG. Adverse ocular reactions to drugs. *Postgrad Med J* 1983; **59:** 343–9.
2. Crombie AL. Drugs causing eye problems. *Prescribers' J* 1981; **21:** 222–7.
3. Marmor MF. Is thioridazine retinopathy progressive? Relationship of pigmentary changes to visual function. *Br J Ophthalmol* 1990; **74:** 739–42.
4. Lam RW, Remick RA. Pigmentary retinopathy associated with low-dose thioridazine treatment. *Can Med Assoc J* 1985; **132:** 737.
5. Ngen CC, Singh P. Long-term phenothiazine administration and the eye in 100 Malaysians. *Br J Psychiatry* 1988; **152:** 278–81.
6. Power WJ, *et al.* Welding arc maculopathy and fluphenazine. *Br J Ophthalmol* 1991; **75:** 433–5.
7. Lee MS, Fern AI. Fluphenazine and its toxic maculopathy. *Ophthalmic Res* 2004; **36:** 237–9.

Effects on fluid and electrolyte homoeostasis. There have been occasional reports of water intoxication in patients taking antipsychotics. A review[1] of hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion associated with psychotropics summarised 20 such reports for antipsychotics in the literature. The drugs implicated were thioridazine (8 reports), haloperidol (3 reports), chlorpromazine, trifluoperazine, and fluphenazine (2 reports each), and flupentixol, tiotixene, and clozapine (1 report each). The majority of reports did not permit clear conclusions and, particularly in the cases of prolonged treatment, the role of the medication was unclear. However, at least 3 of the cases were well documented and supported the view that antipsychotics could cause hyponatraemia.

A report not considered by the above review described water retention and peripheral oedema associated with chlorpromazine.[2] A small controlled study[3] found that 5 of 10 evaluated patients receiving haloperidol decanoate had impaired fluid homoeostasis.

1. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
2. Witz L, *et al.* Chlorpromazine induced fluid retention masquerading as idiopathic oedema. *BMJ* 1987; **294:** 807–8.
3. Rider JM, *et al.* Water handling in patients receiving haloperidol decanoate. *Ann Pharmacother* 1995; **29:** 663–6.

Effects on lipid metabolism. Most antipsychotics are associated with hyperlipidaemia. A review[1] found evidence of a higher risk of hyperlipidaemia in patients receiving low-potency classi-

cal antipsychotics, such as chlorpromazine and thioridazine, or the atypical antipsychotics, clozapine, olanzapine, and quetiapine. High-potency classical antipsychotics, such as haloperidol, and the atypical antipsychotics aripiprazole, risperidone, and ziprasidone, appeared to be associated with a lower risk of hyperlipidaemia. Possible mechanisms for dyslipidaemia associated with antipsychotic therapy include the development of glucose intolerance, weight gain, and dietary changes. For further details, see Effects on Body-weight under Adverse Effects of Clozapine, p.981 and Effects on Body-weight, above.

1. Meyer JM, Koro CE. The effects of antipsychotic therapy on serum lipids: a comprehensive review. *Schizophr Res* 2004; **70:** 1–17.

Effects on the liver. Chlorpromazine and other phenothiazines may cause hepatocanalicular cholestasis often with hepatocyte damage suggestive of immunological liver injury.[1] Only a small number of patients taking the drug are affected and the onset is usually in the first 4 weeks of therapy. The drug or one of its metabolites may induce alteration in the liver-cell membrane so that it becomes antigenic; there is also good evidence for direct hepatotoxicity related to the production of free drug radical. There may be an individual idiosyncrasy in the metabolism of chlorpromazine and in the production of these radicals. A study has suggested that patients who have poor sulfoxidation status combined with unimpaired hydroxylation capacity may be most likely to develop jaundice with chlorpromazine.[2]

A preliminary study[3] showing a high incidence of gallstones in psychiatric inpatients in Japan found a correlation between the presence of gallstones and the duration of illness and use of antipsychotics. It was speculated that gallstones could be a consequence of phenothiazine-induced cholestasis.

1. Sherlock S. The spectrum of hepatotoxicity due to drugs. *Lancet* 1986; **ii:** 440–4.
2. Watson RGP, *et al.* A proposed mechanism for chlorpromazine jaundice—defective hepatic sulphoxidation combined with rapid hydroxylation. *J Hepatol* 1988; **7:** 72–8.
3. Fukuzako H, *et al.* Ultrasonography detected a higher incidence of gallstones in psychiatric inpatients. *Acta Psychiatr Scand* 1991; **84:** 83–5.

Effects on sexual function. The phenothiazines can cause both impotence and ejaculatory dysfunction.[1] Thioridazine has been frequently implicated, and in an early report 60% of 57 male patients taking the drug reported sexual dysfunction compared with 25% of 64 men taking other antipsychotics.[2] There are also several reports of priapism with phenothiazines;[1,3-5] alpha-adrenoceptor blocking properties of these compounds may be partly responsible. Male sexual dysfunction, including priapism, has been reported only rarely with other classical antipsychotics such as the butyrophenones, diphenylbutylpiperidines, and thioxanthenes.[6] Priapism has also been reported with clozapine[7] and other atypical antipsychotics. The effects of antipsychotics on female sexual function are less well studied. Orgasmic dysfunction has been reported with thioridazine, trifluoperazine, and fluphenazine.[8]

The effects of hyperprolactinaemia (see Effects on Endocrine Function, above) on sexual function are described on p.2079.

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Kotin J, *et al.* Thioridazine and sexual dysfunction. *Am J Psychiatry* 1976; **133:** 82–5.
3. Baños JE, *et al.* Drug-induced priapism: its aetiology, incidence and treatment. *Med Toxicol* 1989; **4:** 46–58.
4. Chan J, *et al.* Perphenazine-induced priapism. *DICP Ann Pharmacother* 1990; **24:** 246–9.
5. Salado J, *et al.* Priapism associated with zuclopenthixol. *Ann Pharmacother* 2002; **36:** 1016–18.
6. Fabian J-L. Psychotropic medications and priapism. *Am J Psychiatry* 1993, **150:** 349–50.
7. Patel AG, *et al.* Priapism associated with psychotropic drugs. *Br J Hosp Med* 1996; **55:** 315–19.
8. Segraves RT. Psychiatric drugs and inhibited female orgasm. *J Sex Marital Ther* 1988; **14:** 202–7.

Effects on the skin. ***DEPOT INJECTION.*** Of 217 patients who received a combined total of 2354 depot antipsychotic injections 42 (19.4%) had local problems at the site of injection; 18 (8.3%) experienced chronic complications and 30 (13.8%) acute reactions.[1] Acute problems reported included 31 episodes of unusual pain, 21 of bleeding or haematoma, 19 of clinically important leakage of drug from injection site, 11 of acute inflammatory indurations, and 2 of transient nodules. Complications were more common in patients receiving concentrated preparations, higher doses, weekly injections, haloperidol decanoate or zuclopenthixol decanoate, and injection volumes greater than 1 mL and in those treated for more than 5 years. Chronic reactions were more common in patients aged over 50 years.

1. Hay J. Complications at site of injection of depot neuroleptics. *BMJ* 1995; **311:** 421.

PHOTOSENSITIVITY. Testing in 7 subjects taking chlorpromazine revealed that photosensitivity reactions manifested primarily as immediate erythema and that sensitivity was primarily to light in the long ultraviolet (UVA) and visible wavebands. Sensitivity to UVB was normal.[1]

The incidence of photosensitivity reactions to chlorpromazine has been given as 3%. However, a higher incidence of 16-25% has also been reported.[2]

See also Effects on the Eyes, above.

1. Ferguson J, *et al.* Further clinical and investigative studies of chlorpromazine phototoxicity. *Br J Dermatol* 1986; **115** (suppl 30): 35.
2. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Safety* 1996; **14:** 252–9.

PIGMENTATION. The pigment found in the skin of patients treated with chlorpromazine was considered[1] to be a chlorpromazine-melanin polymer formed in a light-catalysed anaerobic reaction. Hydrogen chloride liberated during the reaction could account for the skin irritation. Intracutaneous injection of a preparation of the polymer into 2 volunteers produced a bluish-purple discoloration which faded in 3 days.

1. Huang CL, Sands FL. Effect of ultraviolet irradiation on chlorpromazine II: anaerobic condition. *J Pharm Sci* 1967; **56:** 259–64.

Extrapyramidal disorders. Antipsychotics and a number of other drugs, including antiemetics such as metoclopramide and some antidepressants, can produce a range of dyskinesias or involuntary movement disorders involving the extrapyramidal motor system, including parkinsonism, akathisia, acute dystonia, and chronic tardive dyskinesia.[1-4] Such reactions are a major problem in the clinical management of patients receiving antipsychotics. Reactions of this type can occur with any antipsychotic, but (excluding tardive dyskinesia) are particularly prominent during treatment with high-potency drugs such as the tricyclic piperazines and butyrophenones. Antipsychotics such as clozapine carry a low risk of extrapyramidal effects and are therefore described as atypical antipsychotics. The incidence of tardive dyskinesia does appear to be minimal with clozapine, although there is less evidence for other atypical antipsychotics (p.982; but see also below).

Of 2811 patients studied[5] in the first few months of therapy with prochlorperazine (a drug with a high propensity to cause extrapyramidal reactions), 57 reported adverse effects, 16 of which involved the extrapyramidal system. There were 4 dystonic-dyskinesic reactions (an incidence of 1 in 464 and 1 in 707 for patients aged under and over 30 years respectively), 9 reports of parkinsonism (under 60 years, 1 in 1555; over 60 years, 1 in 159), and 3 reports of akathisia (1 in 562).

One explanation of extrapyramidal disorders is an imbalance between dopaminergic and cholinergic systems in the brain. However, this simple model fails to explain the co-existence of a variety of extrapyramidal effects, and several alternative mechanisms have been proposed.[2,6] Hypotheses based on interactions between different dopamine receptor types may help to explain the decreased tendency of some antipsychotic drugs to induce these reactions (see Action under Uses and Administration, below).

1. CSM/MCA. Drug-induced extrapyramidal reactions. *Current Problems* 1994; **20:** 15–16. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015632&RevisionSelectionMethod=LatestReleased (accessed 08/08/08)
2. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995; **47:** 575–604.
3. Holloman LC, Marder SR. Management of acute extrapyramidal effects induced by antipsychotic drugs. *Am J Health-Syst Pharm* 1997; **54:** 2461–77.
4. Jiménez-Jiménez FJ, *et al.* Drug-induced movement disorders. *Drug Safety* 1997; **16:** 180–204.
5. Bateman DN, *et al.* Extrapyramidal reactions to metoclopramide and prochlorperazine. *Q J Med* 1989; **71:** 307–11.
6. Ereshefsky L, *et al.* Pathophysiologic basis for schizophrenia and the efficacy of antipsychotics. *Clin Pharm* 1990; **9:** 682–707.

AKATHISIA. Akathisia is a condition of mental and motor restlessness in which there is an urge to move about constantly and an inability to sit or stand still. It is the most common motor adverse effect of treatment with antipsychotics.[1] Acute akathisia is dose-dependent, usually develops within a few days of beginning treatment or after a rapid increase in dose, and usually improves if the drug is stopped or the dose reduced. *Antimuscarinic antiparkinsonian drugs* appear to provide only limited benefit, although success may be more likely in patients with concomitant parkinsonism. A low dose of a *beta blocker* such as *propranolol* (although good evidence is lacking[2]) or a *benzodiazepine*[3] may be helpful. Improvement has also been reported with *clonidine* and *amantadine* but the usefulness of these drugs may be limited by adverse effects or development of tolerance, respectively. The tardive form, like tardive dyskinesia (see below), which appears after several months of treatment, does not respond to antimuscarinics and is difficult to treat.

1. Miller CH, Fleischhacker WW. Managing antipsychotic-induced acute and chronic akathisia. *Drug Safety* 2000; **22:** 73–81.
2. Barnes TRE, *et al.* Central action beta-blockers versus placebo for neuroleptic-induced acute akathisia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 21/08/08).
3. Soares-Weiser K, *et al.* Benzodiazepines for neuroleptic-induced acute akathisia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 1999 (accessed 21/08/08).

DYSTONIA. Acute dystonic reactions, which mainly affect the muscles of the face, neck, and trunk and include jaw clenching (trismus), torticollis, and oculogyric crisis are reported to occur in up to 10% of patients taking antipsychotics. Laryngeal dystonia is rare, but potentially fatal.[1] Dystonias usually occur within the first few days of treatment or after a dosage increase but may also develop on withdrawal. They are transitory, and are most common in children and young adults. Dystonic reactions may be controlled by *antimuscarinics* such as *biperiden* or *procyclidine*, or *antihistamines* such as *diphenhydramine* or *promethazine*.[2] *Benzodiazepines* such as *diazepam* can also be used. Prophylactic antimuscarinics can prevent the development of dystonias, but routine use is not recommended as not all patients require them and tardive dyskinesia may be unmasked or worsened (see below); such a strategy should probably be reserved for short-term use in those at high risk of developing dystonic reactions, such as young adults starting treatment with high-potency antipsychotics or in patients with a history of drug-induced dystonias.[3,4] Some patients may develop tardive dystonia. A range of drugs has been tried in this condition but without consistent benefit.[5]

1. Koek RJ, Pi EH. Acute laryngeal dystonic reactions to neuroleptics. *Psychosomatics* 1989; **30:** 359–64.
2. van Harten PN, *et al.* Acute dystonia induced by drug treatment. *BMJ* 1999; **319:** 623–6.
3. WHO. Prophylactic use of anticholinergics in patients on long-term neuroleptic treatment: a consensus statement. *Br J Psychiatry* 1990; **156:** 412.
4. Barnes TRE. Comment on the WHO consensus statement. *Br J Psychiatry* 1990; **156:** 413–14.
5. Raja M. Managing antipsychotic-induced acute and tardive dystonia. *Drug Safety* 1998; **19:** 57–72.

PARKINSONISM. Parkinsonism, often indistinguishable from idiopathic Parkinson's disease (p.791), may develop during therapy with antipsychotics, usually after the first few weeks or months of treatment. It is generally stated to be more common in adults and the elderly, although a retrospective study with haloperidol found an inverse relationship between drug-induced parkinsonism and age.[1] This parkinsonism is generally reversible on drug withdrawal or dose reduction, and may sometimes disappear gradually despite continued drug therapy. *Antimuscarinic antiparkinsonian* drugs are used to suppress the symptoms of parkinsonism.[2] However, they are often minimally effective and commonly cause adverse effects. Routine use for prophylaxis is not recommended because of the risk of unmasking or exacerbating tardive dyskinesia (see below). *Amantadine* is an alternative to the antimuscarinics.[2]

1. Moleman P, *et al.* Relationship between age and incidence of parkinsonism in psychiatric patients treated with haloperidol. *Am J Psychiatry* 1986; **143:** 232–4.
2. Mamo DC, *et al.* Managing antipsychotic-induced parkinsonism. *Drug Safety* 1999; **20:** 269–75.

TARDIVE DYSKINESIA. The central feature of tardive dyskinesia is orofacial dyskinesia characterised by protrusion of the tongue ('fly catching'), lipsmacking, sucking, lateral chewing, and pouting of the lips and cheeks. The trunk and limbs also become involved with choreiform movements such as repetitive 'piano-playing' hand movements, shoulder shrugging, foot tapping, or rocking movements. The prevalence of tardive dyskinesia among those receiving antipsychotics varies widely but up to 60% of patients may develop symptoms. In most cases the condition is mild and not progressive and tends to wax and wane. Although tardive dyskinesia usually develops after many years of antipsychotic therapy no clear correlation has been shown between development of the condition and the length of drug treatment or the type and class of drug. However, *clozapine* does not appear to be associated with the condition and in some cases use has resulted in improvement of established tardive dyskinesia (see Schizophrenia under Clozapine, p.985). Whether other atypical antipsychotics also have a lower incidence of tardive dyskinesia remains to be established, although there are some data to suggest that this may be the case.[1-3] Symptoms of tardive dyskinesia often develop after stopping the antipsychotic or after dose reduction. Risk factors include old age, female sex, affective disorder, schizophrenia characterised by negative symptoms, and organic brain damage.

Suggested causes of tardive dyskinesia include dopaminergic overactivity, imbalance between dopaminergic and cholinergic activity, supersensitivity of postsynaptic dopamine receptors, presynaptic catecholaminergic hyperfunction, and alterations of the gamma-aminobutyric acid (GABA) system.

Options in the management of tardive dyskinesia include attempts at treatment while maintaining antipsychotic therapy, or withdrawal of antimuscarinic therapy, and either withdrawal of the antipsychotic or reduction of the dosage to the minimum required or transfer to an atypical antipsychotic.

Although many drugs have been tried in the **treatment** of tardive dyskinesia there have been relatively few double-blind studies. Reviews of tardive dyskinesia[1,4-6] have concluded that there appeared to be no reliable or safe treatment. Overall, classical antipsychotics appeared to be the most effective in masking symptoms of tardive dyskinesia but tolerance may develop and a worsening of the underlying pathophysiology by antipsychotics had to be assumed on theoretical grounds. Other drugs with anti-

dopaminergic actions which were probably of comparable efficacy included *reserpine, oxypertine, tetrabenazine,* and *metirosine*. The next most effective drugs were considered to be noradrenergic antagonists such as *clonidine*. Some encouraging results had also been obtained with GABAergic drugs such as the *benzodiazepines, baclofen, progabide, valproate,* and *vigabatrin*, although systematic reviews of studies of some GABAergic drugs[7] including benzodiazepines[8] found the evidence inconclusive and/or unconvincing. The efficacy of cholinergics could not be confirmed.[9,10] Dopaminergics and antimuscarinics mostly exacerbated symptoms but others[11] had commented that there was no convincing evidence that long-term use of antimuscarinics increased the risk of developing the condition. Other drugs whose value is unclear include include *vitamin E*[12] and some calcium-channel blockers.[13]

Withdrawal of the causative drug usually worsens the condition although symptoms often diminish or disappear over a period of weeks or sometimes a year or so. Success is most likely in younger patients. During withdrawal, drugs such as *diazepam* or *clonazepam* may be given to alleviate symptoms. Although classical antipsychotics are effective, their routine use to suppress symptoms is not recommended but they may be required for acute distressing or life-threatening reactions or in chronic tardive dyskinesia unresponsive to other treatment. In extremely severe resistant cases some have used an antipsychotic with *valproate* or *carbamazepine* or *reserpine* with *metirosine*.

In view of the unsatisfactory management of tardive dyskinesia, emphasis is placed on its **prevention**. Antipsychotics should be prescribed only when clearly indicated, should be given in the minimum dose, and continued only when there is evidence of benefit. Although drug holidays have been suggested for reducing the risk of tardive dyskinesia, the limited evidence indicates that interruptions in drug treatment may increase the risk of both persistent dyskinesia and psychotic relapse.[14] Increasing the dose of antipsychotic generally improves the condition, but only temporarily.

1. Casey DE. Tardive dyskinesia and atypical antipsychotic drugs. *Schizophr Res* 1999; **35** (suppl): S61–S66.
2. Kane JM. Tardive dyskinesia in affective disorders. *J Clin Psychiatry* 1999; **60** (suppl 5): 43–7.
3. Llorca P-M, *et al.* Tardive dyskinesias and antipsychotics: a review. *Eur Psychiatry* 2002; **17:** 129–38.
4. Haag H, *et al.*, eds. Tardive Dyskinesia. *WHO Expert Series on Biological Psychiatry Volume 1*. Seattle: Hogrefe & Huber, 1992.
5. Egan MF, *et al.* Treatment of tardive dyskinesia. *Schizophr Bull* 1997; **23:** 583–609.
6. Najib J. Tardive dyskinesia: a review and current treatment options. *Am J Ther* 1999; **6:** 51–60.
7. Rathbone J, *et al.* Gamma-aminobutyric acid agonists for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2004 (accessed 12/08/08).
8. Bhoopathi PS, Soares-Weiser K. Benzodiazepines for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 14/03/08).
9. McGrath J, Soares-Weiser K. Cholinergic medication for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 21/08/08).
10. Tammenmaa IA, *et al.* Systematic review of cholinergic drugs for neuroleptic-induced tardive dyskinesia: a meta-analysis of randomized controlled trials. *Prog Neuropsychopharmacol Biol Psychiatry* 2004; **28:** 1099–1107.
11. Barnes TRE. Comment on the WHO consensus statement. *Br J Psychiatry* 1990; **156:** 413–14.
12. McGrath J, Soares-Weiser K. Vitamin E for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 21/08/08).
13. Soares-Weiser K, Rathbone J. Calcium channel blockers for neuroleptic-induced tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2004 (accessed 14/04/05).
14. Soares-Weiser K, Rathbone J. Neuroleptic reduction and/or cessation and neuroleptics as specific treatments for tardive dyskinesia. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2006 (accessed 12/05/06).

Neuroleptic malignant syndrome. The neuroleptic malignant syndrome (NMS) is a potentially fatal reaction to a number of drugs including antipsychotics and other dopamine antagonists such as metoclopramide. The clinical **features** of the classic syndrome are usually considered to include hyperthermia, severe extrapyramidal symptoms including muscular rigidity, autonomic dysfunction, and altered levels of consciousness. Skeletal muscle damage may occur and the resulting myoglobinuria may lead to renal failure. However, there appear to be no universal criteria for diagnosis. Some believe the classic syndrome to be the extreme of a range of effects associated with antipsychotics and have introduced the concept of milder variants or incomplete forms. Others consider it to be a rare idiosyncratic reaction and suggest that the term neuroleptic malignant syndrome should be reserved for the full-blown reaction. Consequently, estimates of the **incidence** vary greatly and recent estimates have ranged from 0.02 to 2.5%. The mortality rate has been substantial; although it has decreased over the years with improved diagnosis and management, this may also be due to the detection and inclusion of the milder or incomplete variants. Possible risk factors include dehydration, pre-existing organic brain disease, and a history of a previous episode; young males have also been reported to be particularly susceptible.

The **pathogenesis** of NMS is still unclear. Blockade of dopaminergic receptors in the corpus striatum is thought to cause muscular contraction and rigidity generating heat while blockade of dopaminergic receptors in the hypothalamus leads to impaired heat dissipation. Peripheral mechanisms such as vasomotor paralysis may also play a role. Also a syndrome resembling NMS has been seen after withdrawal of treatment with dopamine agonists such as levodopa (see p.806). Symptoms develop rapidly over 24 to 72 hours and may occur days to months after starting antipsychotic medication or increase in dosage, but no consistent correlation with dosage or length of therapy has been found. Symptoms may last for up to 14 days after stopping oral antipsychotics, or for up to 4 weeks after stopping depot preparations. All antipsychotics are capable of inducing NMS; depot preparations may, however, be associated with prolonged recovery once it develops, and hence a higher mortality rate. Use with lithium carbonate or antimuscarinics may increase the likelihood of developing the syndrome.

Antipsychotic medication should be withdrawn immediately once the diagnosis of the classic syndrome is made; this should be followed by symptomatic and supportive **therapy** including cooling measures, correction of dehydration, and treatment of cardiovascular, respiratory, and renal complications. Whether antipsychotics should be withdrawn from patients with mild attacks and how they should be managed is a matter of debate.

The efficacy of specific drug therapy remains to be proven, and justification for use is based mainly on case reports.

- *Dantrolene* was first used because of its effectiveness in malignant hyperthermia. It has a direct action on skeletal muscle and may be particularly effective for the reversal of hyperthermia of muscle origin.
- In contrast, dopaminergic agonists may resolve hyperthermia of central origin, restoring dopaminergic transmission and hence alleviating extrapyramidal symptoms. There have been isolated reports of success with *amantadine* and *levodopa* but *bromocriptine* is generally preferred. Any underlying psychosis may, however, be aggravated by dopaminergic drugs.
- Since dantrolene and dopaminergics act in different ways a combination of the two might be useful, but any advantage remains to be demonstrated.
- *Antimuscarinics* are generally considered to be of little use and may aggravate the associated hyperthermia.
- *Benzodiazepines* may be used for sedation in agitated patients and may be of use against concomitant catatonia. ECT may be an alternative in refractory cases of NMS or when catatonic symptoms are present.

Re-introduction of antipsychotic therapy may be possible but is not always successful and extreme caution is advised. It has been recommended that a gap of at least 5 to 14 days should be left after resolution of the symptoms before attempting re-introduction.

References.

1. Wells AJ, *et al.* Neuroleptic rechallenge after neuroleptic malignant syndrome: case report and literature review. *Drug Intell Clin Pharm* 1988; **22:** 475–80.
2. Bristow MF, Kohen D. How "malignant" is the neuroleptic malignant syndrome? *BMJ* 1993; **307:** 1223–4.
3. Kornhuber J, Weller M. Neuroleptic malignant syndrome. *Curr Opin Neurol* 1994; **7:** 353–7.
4. Velamoor VR, *et al.* Management of suspected neuroleptic malignant syndrome. *Can J Psychiatry* 1995; **40:** 545–50.
5. Ebadi M, Srinivasan SK. Pathogenesis, prevention, and treatment of neuroleptic-induced movement disorders. *Pharmacol Rev* 1995; **47:** 575–604.
6. Bristow MF, Kohen D. Neuroleptic malignant syndrome. *Br J Hosp Med* 1996; **55:** 517–20.
7. Velamoor VR. Neuroleptic malignant syndrome: recognition, prevention and management. *Drug Safety* 1998; **19:** 73–82.
8. Adnet P, *et al.* Neuroleptic malignant syndrome. *Br J Anaesth* 2000; **85:** 129–35.

Withdrawal. Stopping treatment with an antipsychotic abruptly may produce withdrawal symptoms, the most common of which are nausea, vomiting, anorexia, diarrhoea, rhinorrhoea, sweating, myalgias, paraesthesias, insomnia, restlessness, anxiety, and agitation.[1] Patients may also experience vertigo, alternate feelings of warmth and coldness, and tremor. Symptoms generally begin within 1 to 4 days of withdrawal and abate within 7 to 14 days. They are more severe and frequent when antimuscarinics are stopped simultaneously.

1. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10:** 103–14.

Treatment of Adverse Effects

After an overdose of chlorpromazine, patients should be managed with intensive symptomatic and supportive therapy. Activated charcoal should be given by mouth if a substantial amount of the phenothiazine has been taken within 1 hour of presentation, provided that the airway can be protected; emptying the stomach by gastric lavage has sometimes been recommended. Dialysis is of little or no value in poisoning by phenothiazines.

Hypotension should be corrected by raising the patient's legs, or in severe cases by intravascular volume expansion. An inotrope such as dopamine may be considered in refractory cases. If a vasoconstrictor is considered necessary in the management of phenothiazine-induced hypotension the use of adrenaline or other sympathomimetics with high beta-adrenergic agonist properties should be avoided since the alpha-blocking effects of phenothiazines may impair the usual alpha-mediated vasoconstriction of these drugs, resulting in unopposed beta-adrenergic stimulation and increased hypotension.

The treatment of neuroleptic malignant syndrome and the difficulties of treating extrapyramidal adverse effects, especially tardive dyskinesia, are discussed above.

Precautions

Chlorpromazine and other phenothiazines are contraindicated in patients with pre-existing CNS depression or coma, bone-marrow suppression, phaeochromocytoma, or prolactin-dependent tumours. They should be used with caution or not at all in patients with impaired liver, kidney, cardiovascular, cerebrovascular, and respiratory function and in those with angle-closure glaucoma, a history of jaundice, parkinsonism, diabetes mellitus, hypothyroidism, myasthenia gravis, paralytic ileus, prostatic hyperplasia, or urinary retention. Care is required in patients with epilepsy or a history of seizures as phenothiazines may lower the seizure threshold. Debilitated patients may be more prone to the adverse effects of phenothiazines as may the elderly, especially those with dementia. For precautions of phenothiazines in pregnancy, see below.

The sedative effects of phenothiazines are most marked in the first few days of treatment; affected patients should not drive or operate machinery.

The effects of phenothiazines on the vomiting centre may mask the symptoms of overdosage of other drugs, or of disorders such as gastrointestinal obstruction. Use at extremes of temperature may be hazardous since body temperature regulation is impaired by phenothiazines.

Regular eye examinations are advisable for patients receiving long-term phenothiazine therapy and avoidance of undue exposure to direct sunlight is recommended. Phenothiazines should be used with caution in the presence of acute infection or leucopenia. Blood counts are advised if the patient develops an unexplained infection or fever.

Patients should remain supine for at least 30 minutes after parenteral doses of chlorpromazine; blood pressure should be monitored.

Abrupt withdrawal of phenothiazine therapy is best avoided.

AIDS. Isolated reports[1,2] have suggested that patients with AIDS may be particularly susceptible to antipsychotic-induced extrapyramidal effects.

1. Hollander H, *et al.* Extrapyramidal symptoms in AIDS patients given low-dose metoclopramide or chlorpromazine. *Lancet* 1985; **ii:** 1186.
2. Edelstein H, Knight RT. Severe parkinsonism in two AIDS patients taking prochlorperazine. *Lancet* 1987; **ii:** 341–2.

Asthma. Findings of a retrospective case-control study[1] appeared to indicate that asthmatic patients given antipsychotics were at an increased risk of death or near death from asthma.

1. Joseph KS, *et al.* Increased morbidity and mortality related to asthma among asthmatic patients who use major tranquillisers. *BMJ* 1996; **312:** 79–82.

Breast feeding. The American Academy of Pediatrics[1] considers that the use of chlorpromazine by mothers during breast feeding may be of concern, since there have been reports of galactorrhoea in the mother and of drowsiness, lethargy, and declines in developmental scores in the infant. The *BNF* considers that the use of antipsychotics such as chlorpromazine should be avoided by breast-feeding mothers unless absolutely necessary.

Chlorpromazine was detected[2] in all milk samples from 4 women at concentrations ranging from 7 to 98 nanograms/mL. Two of the women breast-fed their infants, but one infant showed no effects while the other was noted to be drowsy and lethargic;

milk-chlorpromazine concentrations were 7 and 92 nanograms/mL, respectively.

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 27/10/04)
2. Wiles DH, *et al.* Chlorpromazine levels in plasma and milk of nursing mothers. *Br J Clin Pharmacol* 1978; **5:** 272–3.

Children. Few phenothiazines are recommended for use in children; in particular there have been concerns about the use of phenothiazine derivatives in infants (see Sudden Infant Death Syndrome, p.588). For reference to the use of chlorpromazine in infants suffering neonatal abstinence syndrome see Substance Dependence, Opioids, under Uses and Administration, below.

References.

1. Dyer KS, Woolf AD. Use of phenothiazines as sedatives in children: what are the risks? *Drug Safety* 1999; **21:** 81–90.

Contact sensitisation. The *BNF* warns that because of the risk of contact sensitisation, health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

The elderly. The risk of *hip fracture* has been reported to be increased in elderly patients given antipsychotics. A large case-control study in patients over 65 found that current users of antipsychotics had a twofold increase in the risk of hip fractures.[1] The effect was dose-related and the increased risk was similar for chlorpromazine, haloperidol, and thioridazine. It was suggested that antipsychotic-induced sedation or orthostatic hypotension could increase the risk of falls in elderly persons. A study in 12 schizophrenic patients receiving antipsychotics plus other drugs such as antimuscarinics or benzodiazepines has suggested that long-term treatment with antipsychotics may decrease bone mineralisation.[2] A later study suggested that any increased risk of falls might be due to an effect of antipsychotics on balance as thioridazine was found to increase sway in elderly but not young subjects.[3] A meta-analysis of 40 studies[4] concluded that there was a small, but consistent, association between the use of most classes of psychotropic drugs, including antipsychotics, and falls. However, the evidence from these studies was based solely on observational data, with minimal adjustment for confounders, dosage, or duration of therapy.

There is some evidence[5,6] to suggest that the use of antipsychotics to manage behavioural complications of *dementia* may increase the rate of cognitive decline. Elderly patients with dementia, especially Lewy-body dementia, are reported to be highly susceptible to the extrapyramidal adverse effects of antipsychotic drugs,[7,8] and the reaction can be extremely serious, even fatal. If these drugs are to be used in elderly patients with dementia, then very low doses should be used, and special care should be taken if the dementia is suspected to be of the Lewy-body type since sudden life-threatening deterioration may occur.[9] Depot preparations should not be used and, since dopamine D_2 receptors may be involved, it has been suggested that consideration could be given to using an antipsychotic such as clozapine that does not principally antagonise those receptors;[8] however, the FDA now recommends that atypical antipsychotics should not be used in such patients because of evidence of an increased death rate (see Dementia, p.1024).

An *increased risk of death* has also been noted in elderly patients given classical antipsychotics. A retrospective cohort study,[10] involving nearly 23 000 patients given atypical or classical antipsychotics, found that classical antipsychotics were at least as likely as the atypicals to increase the risk of death in the elderly. The authors also suggested that the greatest increase in risk occurred soon after starting therapy and with higher doses of classical antipsychotics. A similar increase in risk with use of classical antipsychotics was also seen in a large retrospective population-based study[11] in elderly patients with dementia when compared with that seen with use of atypicals in this patient group.

For further discussion of the problems associated with the use of antipsychotics in disturbed behaviour in the elderly, see p.954.

1. Ray WA, *et al.* Psychotropic drug use and the risk of hip fracture. *N Engl J Med* 1987; **316:** 363–9.
2. Higuchi T, *et al.* Certain neuroleptics reduce bone mineralization in schizophrenic patients. *Neuropsychobiology* 1987; **18:** 185–8.
3. Liu Y, *et al.* Comparative clinical effects of thioridazine (THD) on fall risk on young and elderly subjects. *Clin Pharmacol Ther* 1995; **57:** 200.
4. Leipzig RM, *et al.* Drugs and falls in older people: a systematic review and meta-analysis: I. Psychotropic drugs. *J Am Geriatr Soc* 1999; **47:** 30–9.
5. McShane R, *et al.* Do neuroleptic drugs hasten cognitive decline in dementia? Prospective study with necropsy follow up. *BMJ* 1997; **314:** 266–70.
6. Holmes C, *et al.* Do neuroleptic drugs hasten cognitive decline in dementia? Carriers of apolipoprotein E ε4 allele seem particularly susceptible to their effects. *BMJ* 1997; **314:** 1411.
7. McKeith I, *et al.* Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *BMJ* 1992; **305:** 673–8.
8. Piggott MA, *et al.* DRD2 Ser311/Cys311 polymorphism in schizophrenia. *Lancet* 1994; **343:** 1044–5. Correction. *ibid.*; 1170. [Title: Dopamine D2 receptors in demented patients with severe neuroleptic sensitivity.]
9. CSM/MCA. Neuroleptic sensitivity in patients with dementia. *Current Problems* 1994; **20:** 6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 30/05/06)
10. Wang PS, *et al.* Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *N Engl J Med* 2005; **353:** 2335–41.
11. Gill SS, *et al.* Antipsychotic drug use and mortality in older adults with dementia. *Ann Intern Med* 2007; **146:** 775–86.

Epilepsy. See Convulsions under Adverse Effects, above.

Folic acid deficiency. Concentrations of folate in serum and erythrocytes were reduced in 15 patients receiving long-term treatment with chlorpromazine or thioridazine.[1] All the patients had significant induction of hepatic microsomal enzymes. It was suggested that folate deficiency due to the induction of microsomal enzymes might subsequently limit enzyme induction and hence reduce drug metabolism, which could lead to symptoms of toxicity in patients apparently stabilised for a number of years. The dietary intake of patients on long-term treatment with enzyme-inducing drugs might be inadequate.

1. Labadarios D, *et al.* The effects of chronic drug administration on hepatic enzyme induction and folate metabolism. *Br J Clin Pharmacol* 1978; **5:** 167–73.

Hypoparathyroidism. There have been rare reports[1,2] of acute dystonic reactions associated with the use of phenothiazines in patients with untreated hypoparathyroidism. Caution was recommended in giving phenothiazine derivatives to patients with hypoparathyroidism and it was suggested that any acute reaction to such a drug should prompt investigation for some form of latent tetany.

1. Schaaf M, Payne CA. Dystonic reactions to prochlorperazine in hypoparathyroidism. *N Engl J Med* 1966; **275:** 991–5.
2. Gur H, *et al.* Acute dystonic reaction to methotrimeprazine in hypoparathyroidism. *Ann Pharmacother* 1996; **30:** 957–9.

Pregnancy. Licensed product information generally does not recommend the use of phenothiazines in late pregnancy; such use may be associated with intoxication of the neonate. Chlorpromazine may prolong labour and should be withheld until the cervix is dilated 3 to 4 cm. Overall, however, it has been suggested[1] that the criteria for the selection of an antipsychotic for use in pregnant women do not differ from those used in non-pregnant women. It was also concluded that the benefits of continuing antipsychotic treatment at the minimum effective dose would usually outweigh any risks to the fetus.

A review[2] of the use of phenothiazines in pregnancy concluded that there was no clear evidence that these drugs caused a significant increase in fetal malformations. Nevertheless it was considered advisable that if pregnant patients required such treatment, then a single phenothiazine should be used and that it should be one of the established drugs.

A subsequent review[3] of the literature reported that women with schizophrenia are generally at increased risk for poor obstetric outcomes including preterm delivery, low birth-weight, and neonates who are small for their gestational age. It was also considered that there was an increased risk of congenital malformation when the fetus was exposed to phenothiazines during weeks 4 to 10 of gestation but this conclusion and the methods used to select the data to review have been criticised.[4]

See also p.563 for the use of phenothiazines as antiemetics during pregnancy.

1. Trixler M, Tényi T. Antipsychotic use in pregnancy: what are the best treatment options? *Drug Safety* 1997; **16:** 403–10.
2. McElhatton PR. The use of phenothiazines during pregnancy and lactation. *Reprod Toxicol* 1992; **6:** 475–90.
3. Patton SW, *et al.* Antipsychotic medication during pregnancy and lactation in women with schizophrenia: evaluating the risk. *Can J Psychiatry* 2002; **47:** 959–65.
4. Levinson A. Review: women with schizophrenia have poorer pregnancy outcomes than other women, but it is unclear whether antipsychotic medications affect their infants. *Evid Based Ment Health* 2003; **6:** 89.

Renal impairment. Although there do not seem to be specific indications for dosage adjustment of phenothiazines in renal impairment, the *BNF* considers that cerebral sensitivity to antipsychotics may be increased in severe renal impairment. Phenothiazine-induced toxic psychosis occurred in 4 patients with chronic renal failure who had been given chlorpromazine.[1]

1. McAllister CJ, *et al.* Toxic psychosis induced by phenothiazine administration in patients with chronic renal failure. *Clin Nephrol* 1978; **10:** 191–5.

Interactions

The most common interactions encountered with phenothiazines such as chlorpromazine result from use with drugs that have similar pharmacological actions. Symptoms of CNS depression may be enhanced by other drugs with CNS-depressant properties including alcohol, general anaesthetics, hypnotics, anxiolytics, and opioids. When given with other drugs that produce orthostatic hypotension, dosage adjustments may be necessary. However, it should be noted that phenothiazines have been reported to reduce the antihypertensive action of guanethidine and other adrenergic neurone blockers. As many phenothiazines possess antimuscarinic actions they can potentiate the adverse effects of other drugs with antimuscarinic actions, including tricyclic antidepressants and the antimuscarinic antiparkinsonian drugs that may be given to treat phenothiazine-induced extrapyramidal effects. In theory, antipsychotics with dopamine-blocking activity and dopaminergic drugs such as those used to treat parkinsonism may be mutually antagonistic. Use with metoclopramide may increase the risk of antipsychotic-induced extrapyramidal effects.

There is an increased risk of arrhythmias when antipsychotics are used with drugs that prolong the QT interval, including certain antiarrhythmics, other antipsychotics, some non-sedating antihistamines, antimalarials, and cisapride; use with diuretics that cause electrolyte imbalance (particularly hypokalaemia) may also have the same effect. There is also an increased risk of arrhythmias when tricyclic antidepressants are used with antipsychotics that prolong the QT interval.

Because of an increased risk of seizures US licensed product information for chlorpromazine recommends withdrawal before the use of metrizamide for radiographic procedures.

◊ Most interactions with antipsychotics are as a result of additive pharmacological effects.[1] Since tolerance develops to many of these adverse effects, interactions are likely to be most important in the early stages of combination therapy.

1. Livingston MG. Interactions that matter: 11 antipsychotic drugs. *Prescribers' J* 1987; **27** (Dec): 26–9.

Alcohol. Phenothiazines may increase the CNS depressant effects of alcohol. There has been a report of akathisia and dystonia after consumption of alcohol by patients taking antipsychotics;[1] alcohol might lower the threshold of resistance to neurotoxic adverse effects.

1. Lutz EG. Neuroleptic-induced akathisia and dystonia triggered by alcohol. *JAMA* 1976; **236:** 2422–3.

Antacids. Studies in 6 patients showed that chlorpromazine plasma concentrations were significantly lower after giving chlorpromazine with an *aluminium hydroxide* and *magnesium trisilicate* antacid gel (*Gelusil*) than after chlorpromazine alone.[1] *In-vitro* studies indicated that chlorpromazine was highly bound to the gel.

1. Fann WE, *et al.* Chlorpromazine: effects of antacids on its gastrointestinal absorption. *J Clin Pharmacol* 1973; **13:** 388–90.

Antiarrhythmics. There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of pimozide or thioridazine with antiarrhythmics (especially *amiodarone*, *disopyramide*, *procainamide*, and *quinidine*) should be avoided. Use of haloperidol with amiodarone is also not recommended. A study[1] in healthy subjects has suggested that quinidine might increase plasma concentrations of haloperidol.

1. Young D, *et al.* Effect of quinidine on the interconversion kinetics between haloperidol and reduced haloperidol in humans: implications for the involvement of cytochrome P450IID6. *Eur J Clin Pharmacol* 1993; **44:** 433–8.

Antibacterials. Seven schizophrenic patients whose antitubercular therapy included *rifampicin* (in addition to isoniazid, and in some cases also ethambutol) had lower serum concentrations of haloperidol compared with tuberculotic schizophrenic patients receiving no antimycobacterials and with non-tuberculotic schizophrenics.[1] Pharmacokinetic studies involving some of these patients indicated accelerated haloperidol clearance in the presence of rifampicin. Abnormally high serum-haloperidol concentrations were observed in 3 of 18 patients treated with *isoniazid* alone.

Black galactorrhoea occurred in a patient receiving *minocycline*, perphenazine, amitriptyline hydrochloride, and diphenhydramine hydrochloride.[2] Simultaneous occurrence of phenothiazine-induced galactorrhoea and tetracycline-induced pigmentation was considered responsible.

Sudden cardiac deaths have been reported[3] in patients given *clarithromycin* and pimozide. Elevated pimozide plasma concentrations were recorded after pretreatment with clarithromycin.[4] The manufacturer of pimozide has recommended that pimozide should not be used with macrolide antibacterials.

1. Takeda M, *et al.* Serum haloperidol levels of schizophrenics receiving treatment for tuberculosis. *Clin Neuropharmacol* 1986; **9:** 386–97.
2. Basler RSW, Lynch PJ. Black galactorrhea as a consequence of minocycline and phenothiazine therapy. *Arch Dermatol* 1985; **121:** 417–18.
3. Flockhart DA, *et al.* A metabolic interaction between clarithromycin and pimozide may result in cardiac toxicity. *Clin Pharmacol Ther* 1996; **59:** 189.
4. Desta Z, *et al.* Effect of clarithromycin on the pharmacokinetics and pharmacodynamics of pimozide in healthy poor and extensive metabolisers of cytochrome P450 2D6 (CYP2D6). *Clin Pharmacol Ther* 1999; **65:** 10–20.

Anticoagulants. For reference to the effects of some antipsychotics on the activity of anticoagulants, see under Warfarin, p.1430.

Antidepressants. Interactions between antipsychotics and *tricyclic antidepressants* are generally of two forms: additive pharmacological effects such as antimuscarinic effects or hypotension; or pharmacokinetic interactions. Although not commonly reported in the literature, additive antimuscarinic activity may be a significant risk especially in the elderly. Careful drug selection might help to prevent the development of serious adverse effects. Mutual inhibition of liver enzymes involved in the metabolism of both the antipsychotic and the tricyclic antidepressant might result in increased plasma concentrations of either drug. In one study,[1] addition of *nortriptyline* to chlorpromazine therapy produced an increase in plasma concentrations of chlorpromazine but this resulted in a paradoxical increase in agitation and tension.

There is an increased risk of arrhythmias when tricyclic antidepressants are given with other drugs that prolong the QT interval. It has been recommended that the use of pimozide or thioridazine with tricyclic antidepressants should be avoided.

Increased serum concentrations of haloperidol have occurred when patients were also given *fluoxetine*,[2] *fluvoxamine*,[3] or *nefazodone*. Isolated reports[4-9] of extrapyramidal symptoms, psychoneuromotor syndrome, stupor, bradycardia, and urinary retention associated with use of fluoxetine with antipsychotics suggest that fluoxetine might exacerbate the adverse effects of antipsychotics or produce additive toxicity. Similar CNS effects have been noted in subjects given perphenazine and *paroxetine*.[10] There has also been an isolated report of a patient who complained of amenorrhoea and galactorrhoea after fluvoxamine was added to loxapine therapy.[11] Significant increases in the plasma concentrations of thioridazine have occurred after use with fluvoxamine.[12] Paroxetine may also inhibit the metabolism of thioridazine, resulting in increased thioridazine plasma concentrations; UK licensed product information for paroxetine contra-indicates their concomitant use. The US licensed product information for paroxetine states that giving paroxetine with pimozide was associated with a mean increase of 151% in the area under the concentration-time curve of pimozide and 62% in its mean maximum plasma concentration. Due to the narrow therapeutic index of pimozide concomitant use of these 2 drugs is contra-indicated.

Combinations of antipsychotics and *lithium* should be used with care. Lithium can reduce plasma-chlorpromazine concentrations and there is a report of ventricular fibrillation on withdrawal of lithium from a patient also taking chlorpromazine. Chlorpromazine has also been reported to enhance the excretion of lithium. Neurotoxic or extrapyramidal symptoms have been reported rarely in patients taking antipsychotics and lithium; these may be atypical cases of lithium toxicity or neuroleptic malignant syndrome. The above issues are discussed in detail, and references given, on p.405.

A patient on long-term trifluoperazine treatment developed neuroleptic malignant syndrome after a single dose of *venlafaxine*.[13] The authors noted that the manufacturers of venlafaxine have received a small number of similar reports after introduction of venlafaxine in patients receiving antipsychotics including molindone.

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

1. Loga S, *et al.* Interaction of chlorpromazine and nortriptyline in patients with schizophrenia. *Clin Pharmacokinet* 1981; **6:** 454–62.
2. Goff DC, *et al.* Elevation of plasma concentrations of haloperidol after the addition of fluoxetine. *Am J Psychiatry* 1991; **148:** 790–2.
3. Daniel DG, *et al.* Coadministration of fluvoxamine increases serum concentrations of haloperidol. *J Clin Psychopharmacol* 1994; **14:** 340–3.
4. Tate JL. Extrapyramidal symptoms in a patient taking haloperidol and fluoxetine. *Am J Psychiatry* 1989; **146:** 399–400.
5. Ahmed I, *et al.* Possible interaction between fluoxetine and pimozide causing sinus bradycardia. *Can J Psychiatry* 1993; **38:** 62–3.
6. Ketai R. Interaction between fluoxetine and neuroleptics. *Am J Psychiatry* 1993; **150:** 836–7.
7. Hansen-Grant S, *et al.* Fluoxetine-pimozide interaction. *Am J Psychiatry* 1993; **150:** 1751–2.
8. D'Souza DC, *et al.* Precipitation of a psychoneuromotor syndrome by fluoxetine in a haloperidol-treated schizophrenic patient. *J Clin Psychopharmacol* 1994; **14:** 361–3.
9. Benazzi F. Urinary retention with fluoxetine-haloperidol combination in a young patient. *Can J Psychiatry* 1996; **41:** 606–7.
10. Özdemir V, *et al.* Paroxetine potentiates the central nervous system side effects of perphenazine: contribution of cytochrome P4502D6 inhibition in vivo. *Clin Pharmacol Ther* 1997; **62:** 334–47.
11. Jeffries J, *et al.* Amenorrhea and galactorrhea associated with fluvoxamine in a loxapine-treated patient. *J Clin Psychopharmacol* 1992; **12:** 296–7.
12. Carrillo JA, *et al.* Pharmacokinetic interaction of fluvoxamine and thioridazine in schizophrenic patients. *J Clin Psychopharmacol* 1999; **19:** 494–9.
13. Nimmagadda SR, *et al.* Neuroleptic malignant syndrome after venlafaxine. *Lancet* 2000; **354:** 289–90.

Antidiabetic drugs. Since chlorpromazine may cause hyperglycaemia or impair glucose tolerance the dose of *oral hypoglycaemics* or of *insulin* may need to be increased in diabetics.

Antiepileptics. *Carbamazepine*, *phenobarbital*, and *phenytoin* are potent enzyme inducers and use may decrease plasma concentrations of antipsychotics or their active metabolites.[1-5] The clinical effect of any interaction has not been consistent; worsening, improvement, or no change in psychotic symptoms have all been noted. Delirium has been reported in a patient given haloperidol and carbamazepine.[6] Phenytoin might also exacerbate antipsychotic-induced dyskinesia.[7] Care should be taken when withdrawing enzyme-inducing antiepileptics as this may result in a rise in antipsychotic serum concentrations.[8]

The effect of antipsychotics on antiepileptic concentrations is discussed on p.475 (carbamazepine) and p.499 (phenytoin). It should also be remembered that antipsychotics may lower the seizure threshold.

1. Loga S, *et al.* Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* 1975; **2:** 197–208.
2. Linnoila M, *et al.* Effect of anticonvulsants on plasma haloperidol and thioridazine levels. *Am J Psychiatry* 1980; **137:** 819–21.
3. Jann MW, *et al.* Effects of carbamazepine on plasma haloperidol levels. *J Clin Psychopharmacol* 1985; **5:** 106–9.
4. Arana GW, *et al.* Does carbamazepine-induced reduction of plasma haloperidol levels worsen psychotic symptoms? *Am J Psychiatry* 1986; **143:** 650–1.
5. Ereshefsky L, *et al.* Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; **11:** 296–301.
6. Kanter GL, *et al.* Case report of a possible interaction between neuroleptics and carbamazepine. *Am J Psychiatry* 1984; **141:** 1101–2.
7. DeVeaugh-Geiss J. Aggravation of tardive dyskinesia by phenytoin. *N Engl J Med* 1978; **298:** 457–8.
8. Jann MW, *et al.* Clinical implications of increased antipsychotic plasma concentrations upon anticonvulsant cessation. *Psychiatry Res* 1989; **28:** 153–9.

Antihistamines. For the effect of a preparation containing *chlorphenamine maleate* and phenylpropanolamine hydrochloride on thioridazine, see Sympathomimetics (below). There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of pimozide or thioridazine with antihistamines such as *astemizole* or *terfenadine* should be avoided.

Antihypertensives. For discussion of the interaction between phenothiazines and drugs with hypotensive properties, see Interactions, above. For a report of chlorpromazine enhancing the hyperglycaemic effect of *diazoxide*, see p.1258. For reports of hypertension or dementia in patients given *methyldopa* and antipsychotics, see p.1335.

Antimalarials. Pretreatment with single doses of *chloroquine sulfate*, *amodiaquine hydrochloride*, or *sulfadoxine with pyrimethamine* increased the plasma concentrations of chlorpromazine and 7-hydroxychlorpromazine, but not of chlorpromazine sulfoxide, in schizophrenic patients maintained on chlorpromazine.[1] The raised plasma concentrations appeared to be associated with a greater level of sedation.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of antipsychotics, and pimozide in particular, with antimalarials such as *halofantrine*, *mefloquine*, or *quinine* should be avoided. For the possible effects of the use of *quinidine* with antipsychotics see Antiarrhythmics, above.

1. Makanjuola ROA, *et al.* Effects of antimalarial agents on plasma levels of chlorpromazine and its metabolites in schizophrenic patients. *Trop Geogr Med* 1988; **40:** 31–3.

Antimigraine drugs. A report[1] of a patient receiving loxapine who had a dystonic reaction within 15 minutes of subcutaneous *sumatriptan* suggests that these two drugs might interact or potentiate each other's adverse effects. However, the patient had a previous history of dystonic reactions associated with haloperidol and was receiving benzatropine prophylactically. Furthermore, the dose of loxapine had been increased 2 days before the event and this may have predisposed the patient to dystonia.

1. Garcia G, *et al.* Dystonic reaction associated with sumatriptan. *Ann Pharmacother* 1994; **28:** 1199.

Antiparkinsonian drugs. Antiparkinsonian drugs are sometimes given with antipsychotics for the management of antipsychotic-induced adverse effects including extrapyramidal disorders (see under Adverse Effects, above). Theoretically, dopaminergics such as *levodopa* and *bromocriptine* might induce or exacerbate psychotic symptoms. A study in 18 subjects and review of the literature suggested that bromocriptine can be used safely in patients at risk of psychotic illness provided they are clinically stable and maintained on antipsychotics.[1] Conversely, antipsychotics might antagonise the effects of dopaminergics; diminished therapeutic effects of levodopa have been noted with several antipsychotics (see p.808) and thioridazine has been reported to oppose the prolactin-lowering action of bromocriptine (see p.800).

Additive antimuscarinic adverse effects are obviously a risk when antimuscarinic antiparkinsonian drugs are given with antipsychotics. Although these are generally mild, serious reactions have occurred. *Trihexyphenidyl*[2] and *orphenadrine*[3] have both been reported to decrease plasma concentrations of chlorpromazine, possibly by interfering with absorption from the gastrointestinal tract. Reports suggesting that antimuscarinics may antagonise the antipsychotic effects of antipsychotics at the neurotransmitter level require substantiating.

1. Perovich RM, *et al.* The behavioral toxicity of bromocriptine in patients with psychiatric illness. *J Clin Psychopharmacol* 1989; **9:** 417–22.
2. Rivera-Calimlim L, *et al.* Effects of mode of management on plasma chlorpromazine in psychiatric patients. *Clin Pharmacol Ther* 1973; **14:** 978–86.
3. Loga S, *et al.* Interactions of orphenadrine and phenobarbitone with chlorpromazine: plasma concentrations and effects in man. *Br J Clin Pharmacol* 1975; **2:** 197–208.

Antipsychotics. Elevated plasma levels of haloperidol were reported[1] in a patient being treated for schizophrenia when *chlorpromazine* or *clozapine* were also given.

1. Allen SA. Effect of chlorpromazine and clozapine on plasma concentrations of haloperidol in a patient with schizophrenia. *J Clin Pharmacol* 2000; **40:** 1296–7.

Antivirals. *Ritonavir* may increase the plasma concentration of some antipsychotics. The increases expected for pimozide were considered in licensed product information for ritonavir to be large enough to recommend that these drugs should not be used together. Other classical antipsychotics predicted to have increases include haloperidol, perphenazine, and thioridazine; it was recommended that monitoring of drug concentrations and/or adverse effects were required when used with ritonavir.

Beta blockers. Chlorpromazine and *propranolol* may mutually inhibit each other's hepatic metabolism. Propranolol has been reported to increase plasma concentrations of chlorpromazine[1] and thioridazine,[2,3] and *pindolol* to increase plasma-thioridazine concentrations.[4] Neither beta blocker tested had a significant effect on haloperidol concentrations,[3,4] although there is a report of severe hypotension or cardiopulmonary arrest occurring on 3 occasions in a schizophrenic patient given haloperidol with propranolol.[5] The clinical significance of antipsychotic-beta blocker interactions is unclear.

For the effect of chlorpromazine on propranolol, see Anxiolytics and Antipsychotics, under Interactions of Beta Blockers, p.1228.

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. The use of antipsychotics, and pimozide in particular, with *sotalol* should be avoided.

1. Peet M, *et al.* Pharmacokinetic interaction between propranolol and chlorpromazine in schizophrenic patients. *Lancet* 1980; **ii:** 978.
2. Silver JM, *et al.* Elevation of thioridazine plasma levels by propranolol. *Am J Psychiatry* 1986; **143:** 1290–2.
3. Greendyke RM, Kanter DR. Plasma propranolol levels and their effect on plasma thioridazine and haloperidol concentrations. *J Clin Psychopharmacol* 1987; **7:** 178–82.
4. Greendyke RM, Gulya A. Effect of pindolol administration on serum levels of thioridazine, haloperidol, phenytoin, and phenobarbital. *J Clin Psychiatry* 1988; **49:** 105–7.
5. Alexander HE, *et al.* Hypotension and cardiopulmonary arrest associated with concurrent haloperidol and propranolol therapy. *JAMA* 1984; **252:** 87–8.

Buspirone. The use of haloperidol with buspirone has resulted in increased serum haloperidol concentrations. However, while some[1] found the mean rise in serum-haloperidol concentrations to be 26%, that observed by others[2] was not statistically significant.

1. Goff DC, *et al.* An open trial of buspirone added to neuroleptics in schizophrenic patients. *J Clin Psychopharmacol* 1991; **11:** 193–7.
2. Huang HF, *et al.* Lack of pharmacokinetic interaction between buspirone and haloperidol in patients with schizophrenia. *J Clin Pharmacol* 1996; **36:** 963–9.

Cimetidine. Despite expectations that cimetidine might reduce the metabolism of chlorpromazine, mean steady-state plasma concentrations of chlorpromazine fell rather than rose in 8 patients given cimetidine for 7 days in addition to regular chlorpromazine therapy.[1] The explanation was probably that cimetidine interfered with chlorpromazine absorption. Excessive sedation, necessitating a reduction in chlorpromazine dosage, has been reported[2] after addition of cimetidine to the drug therapy of 2 chronic schizophrenics.

1. Howes CA, *et al.* Reduced steady-state plasma concentrations of chlorpromazine and indomethacin in patients receiving cimetidine. *Eur J Clin Pharmacol* 1983; **24:** 99–102.
2. Byrne A, O'Shea B. Adverse interaction between cimetidine and chlorpromazine in two cases of chronic schizophrenia. *Br J Psychiatry* 1989; **155:** 413–15.

Cocaine. The risk of antipsychotic-induced dystonic reactions may be increased in cocaine abusers. Dystonia occurred in 6 of 7 cocaine abusers treated with haloperidol.[1]

1. Kumor K, *et al.* Haloperidol-induced dystonia in cocaine addicts. *Lancet* 1986; **ii:** 1341–2.

Desferrioxamine. Loss of consciousness lasting 48 to 72 hours occurred in 2 patients given prochlorperazine during desferrioxamine therapy.[1] Prochlorperazine may enhance the removal of transition metals from brain cells by desferrioxamine.

1. Blake DR, *et al.* Cerebral and ocular toxicity induced by desferrioxamine. *Q J Med* 1985; **56:** 345–55.

Disulfiram. A psychotic patient, previously maintained with plasma-perphenazine concentrations of 2 to 3 nanomol/mL on a dose of 8 mg twice daily by mouth, was readmitted with subtherapeutic plasma-perphenazine concentrations of less than 1 nanomol/mL, despite unchanged dosage, after disulfiram therapy.[1] The concentration of the sulfoxide metabolite of perphena-

zine was much increased. After a change from oral to intramuscular perphenazine therapy there was a substantial clinical improvement associated with a return to therapeutic plasma concentrations of perphenazine and a fall in concentration of the metabolite. Disulfiram appears to greatly enhance biotransformation of oral perphenazine to inactive metabolites, but parenteral administration avoids the 'first-pass' effect in the liver.

1. Hansen LB, Larsen N-E. Metabolic interaction between perphenazine and disulfiram. *Lancet* 1982; **ii:** 1472.

General anaesthetics. A schizophrenic patient without a history of epilepsy who was receiving oral chlorpromazine and flupentixol depot injection had a convulsive seizure when given *enflurane* anaesthesia.[1]

1. Vohra SB. Convulsions after enflurane in a schizophrenic patient receiving neuroleptics. *Can J Anaesth* 1994; **41:** 420–2.

Naltrexone. Two patients maintained on thioridazine experienced intense sleepiness and lethargy after receiving 2 doses of naltrexone.[1]

1. Maany I, *et al.* Interaction between thioridazine and naltrexone. *Am J Psychiatry* 1987; **144:** 966.

NSAIDs. A report of severe drowsiness and confusion in patients given haloperidol with *indometacin*.[1]

1. Bird HA, *et al.* Drowsiness due to haloperidol/indomethacin in combination. *Lancet* 1983; **i:** 830–1.

Opioid analgesics. For reference to the effects of phenothiazines on *pethidine*, see p.114.

Piperazine. There has been an isolated report[1] of convulsions associated with the use of chlorpromazine in a child who had received piperazine several days earlier. Subsequent *animal*[1-3] studies produced conflicting evidence for an interaction and it was suggested[3] that an interaction would only be clinically significant when high concentrations of piperazine were reached in the body.

1. Boulos BM, Davis LE. Hazard of simultaneous administration of phenothiazine and piperazine. *N Engl J Med* 1969; **280:** 1245–6.
2. Armbrecht BH. Reaction between piperazine and chlorpromazine. *N Engl J Med* 1970; **282:** 1490–1.
3. Sturman G. Interaction between piperazine and chlorpromazine. *Br J Pharmacol* 1974; **50:** 153–5.

Sympathomimetics. For reference to the possible interaction between phenothiazines and *adrenaline*, see Treatment of Adverse Effects, above.

A 27-year-old woman with schizophrenia and T-wave abnormality of the heart,[1] receiving thioridazine 100 mg daily with procyclidine 2.5 mg twice daily, died from ventricular fibrillation within 2 hours of also taking a single dose of a preparation reported to contain chlorphenamine maleate 4 mg with *phenylpropanolamine hydrochloride* 50 mg (*Contac C*).

1. Chouinard G, *et al.* Death attributed to ventricular arrhythmia induced by thioridazine in combination with a single Contac C capsule. *Can Med Assoc J* 1978; **119:** 729–31.

Tobacco smoking. Smoking has been shown to decrease the incidence of chlorpromazine-induced sedation[1,2] and orthostatic hypotension.[2] Studies indicate that the clearance of chlorpromazine,[3] fluphenazine,[4] tiotixene,[5] haloperidol,[6] and thioridazine[7] may be increased in patients who smoke. It has been suggested that some of the components of smoke may act as liver-enzyme inducers. The clinical significance of this effect is unclear but the possible need to use increased doses in smokers should be borne in mind.

1. Swett C. Drowsiness due to chlorpromazine in relation to cigarette smoking: a report from the Boston Collaborative Drug Surveillance Program. *Arch Gen Psychiatry* 1974; **31:** 211–13.
2. Pantuck EJ, *et al.* Cigarette smoking and chlorpromazine disposition and actions. *Clin Pharmacol Ther* 1982; **31:** 533–8.
3. Chetty M, *et al.* Smoking and body weight influence the clearance of chlorpromazine. *Eur J Clin Pharmacol* 1994; **46:** 523–6.
4. Ereshefsky L, *et al.* Effects of smoking on fluphenazine clearance in psychiatric inpatients. *Biol Psychiatry* 1985; **20:** 329–32.
5. Ereshefsky L, *et al.* Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991; **11:** 296–301.
6. Jann MW, *et al.* Effects of smoking on haloperidol and reduced haloperidol plasma concentrations and haloperidol clearance. *Psychopharmacology (Berl)* 1986; **90:** 468–70.
7. Berecz R, *et al.* Thioridazine steady-state plasma concentrations are influenced by tobacco smoking and CYP2D6, but not by the CYP2C9 genotype. *Eur J Clin Pharmacol* 2003; **59:** 45–50.

Vitamins. Giving *ascorbic acid*, for vitamin C deficiency, to a patient receiving fluphenazine for bipolar disorder was associated with a fall in serum concentrations of fluphenazine and a deterioration of behaviour.[1]

1. Dysken MW, *et al.* Drug interaction between ascorbic acid and fluphenazine. *JAMA* 1979; **241:** 2008.

Xanthine-containing beverages. Studies *in vitro* have shown precipitation of some antipsychotics from solution by addition of coffee and tea.[1,2] However, in a study of 16 patients taking antipsychotics no correlation could be found between plasma-antipsychotic concentrations or behaviour and tea or coffee consumption.[3]

1. Kulhanek F, *et al.* Precipitation of antipsychotic drugs in interaction with coffee or tea. *Lancet* 1979; **ii:** 1130.
2. Lasswell WL, *et al.* In vitro interaction of neuroleptics and tricyclic antidepressants with coffee, tea, and gallotannic acid. *J Pharm Sci* 1984; **73:** 1056–8.
3. Bowen S, *et al.* Effect of coffee and tea on blood levels and efficacy of antipsychotic drugs. *Lancet* 1981; **i:** 1217–18.

Pharmacokinetics

Chlorpromazine is readily, although sometimes erratically, absorbed from the gastrointestinal tract; peak plasma concentrations are attained 2 to 4 hours after ingestion. It is subject to considerable first-pass metabolism in the gut wall and is also extensively metabolised in the liver and is excreted in the urine and bile in the form of numerous active and inactive metabolites; there is some evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations after oral doses are much lower than those after intramuscular doses. Moreover, there is very wide intersubject variation in plasma concentrations of chlorpromazine; no simple correlation has been found between plasma concentrations of chlorpromazine and its metabolites, and their therapeutic effect (see Administration under Uses and Administration, below). Paths of metabolism of chlorpromazine include hydroxylation and conjugation with glucuronic acid, *N*-oxidation, oxidation of a sulfur atom, and dealkylation. Although the plasma half-life of chlorpromazine itself has been reported to be about 30 hours, elimination of the metabolites may be very prolonged. There is limited evidence that chlorpromazine induces its own metabolism.

Chlorpromazine is about 95 to 98% bound to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Chlorpromazine and its metabolites also cross the placenta and are distributed into breast milk.

Uses and Administration

Chlorpromazine is a phenothiazine antipsychotic. It has a wide range of activity arising from its depressant actions on the CNS and its alpha-adrenergic blocking and antimuscarinic activities. Chlorpromazine is a dopamine inhibitor; the turnover of dopamine in the brain is also increased. There is some evidence that the antagonism of central dopaminergic function, especially at the D_2-dopaminergic receptor, is related to therapeutic effect in psychotic conditions. Chlorpromazine possesses sedative properties but patients usually develop tolerance rapidly to the sedation. It has antiemetic, serotonin-blocking, and weak antihistaminic properties and slight ganglion-blocking activity. It inhibits the heat-regulating centre so that the patient tends to acquire the temperature of the surroundings (poikilothermy). Chlorpromazine can relax skeletal muscle.

Chlorpromazine is widely used in the management of psychotic conditions as well as in some non-psychotic disorders, such as:

- acute and chronic schizophrenia (p.955) in adults and children
- to reduce acute mania, as in bipolar disorder (p.372)
- control of severely disturbed, agitated, or violent behaviour in adults and children (p.954) and sometimes other psychiatric conditions
- in autistic children
- as an adjunct for the short-term treatment of severe anxiety (but see also p.952), and to reduce pre-operative anxiety in adults and children
- as an antiemetic in some forms of nausea and vomiting (p.1700) in adults and children; it is ineffective in motion sickness
- in the alleviation of intractable hiccup (below)
- as an adjunct in the treatment of tetanus in adults and children (p.196 and p.1901) and to control symptoms in acute intermittent porphyria (p.1448)
- for induction of hypothermia

Chlorpromazine is given orally as the hydrochloride and the embonate. For both salts, the doses are expressed as the hydrochloride; chlorpromazine embonate 144 mg is equivalent to about 100 mg of chlorpromazine hydrochloride. Chlorpromazine is also given by injection as the hydrochloride and doses are expressed in terms of this salt. The base is given rectally as suppositories; doses are in terms of the base.

Dosage varies both with the individual and with the purpose for which the drug is being used. In most patients with **psychiatric conditions** *oral treatment* may be used from the start, typically commencing with a dosage of 25 mg of the hydrochloride, or its equivalent as the embonate, three times daily and increasing as necessary; daily doses of 75 mg may be given as a single dose at night. In some patients doses of 10 mg three times daily may be adequate. Maintenance doses, when required, usually range from 25 to 100 mg three times daily, although psychotic patients may require daily doses of up to 1 g or more.

For *parenteral use*, deep intramuscular injection is preferable, but diluted solutions have sometimes been given by slow intravenous infusion for indications such as tetanus, severe intractable hiccup, or nausea and vomiting associated with surgery. Subcutaneous injection is contra-indicated. After injection of chlorpromazine, patients should remain in the supine position for at least 30 minutes; blood pressure should be monitored. The usual dose by intramuscular injection is 25 to 50 mg repeated every 6 to 8 hours if required, although oral therapy should be substituted as soon as possible.

If the oral and parenteral routes are not suitable chlorpromazine may be given *rectally* as suppositories containing 100 mg of chlorpromazine base; this is stated to have an effect comparable with 40 to 50 mg of the hydrochloride orally or 20 to 25 mg intramuscularly. The usual rectal dose is 100 mg every 6 to 8 hours.

Initial oral doses of chlorpromazine of one-third to one-half the usual adult dose have been recommended for *elderly* or *debilitated patients*; doses should be increased more gradually. Intramuscular doses in the elderly may need to be reduced to up to one-quarter of the usual dose.

Chlorpromazine hydrochloride may be given to *children* aged 1 to 12 years in a dose of 500 micrograms/kg every 4 to 6 hours orally or every 6 to 8 hours by intramuscular injection. However, for psychiatric indications the oral dose for children aged over 5 years is usually one-third to one-half the adult dose; alternatively, the *BNFC* suggests a dose of 10 mg 3 times daily. Daily doses should not normally exceed 40 mg of chlorpromazine hydrochloride for children aged 1 to 5 years or 75 mg for children over 5 years of age. Chlorpromazine may be given to infants under 1 year of age if considered to be life-saving. Suppositories containing 25 mg of chlorpromazine base are available in some countries for use in children.

Doses of 10 to 25 mg every 4 to 6 hours orally are recommended for control of **nausea and vomiting**. If necessary, an initial dose of 25 mg may be given by intramuscular injection, followed by 25 to 50 mg every 3 to 4 hours until vomiting stops.

If **intractable hiccup** does not respond to an oral dose of 25 to 50 mg three or four times daily for 2 to 3 days then 25 to 50 mg may be given intramuscularly; if this fails 25 to 50 mg in 500 to 1000 mL of 0.9% sodium chloride should be given by slow intravenous infusion, with the patient supine, and careful monitoring of the blood pressure.

Action. The therapeutic effects of antipsychotics appear to be mediated, at least in part, by interference with dopamine transmission in the brain. Chlorpromazine, thioridazine, and thioxanthene derivatives have relatively equal affinity for D_1 or D_2 receptors, although their metabolites tend to be more potent as D_2 blockers.[1] Butyrophenones (such as haloperidol) and diphenylbutylpiperidines (such as pimozide) are relatively selective for D_2 receptors, and the substituted benzamides (such as sulpiride) are highly D_2-specific. Clozapine has complex actions: it is a relatively weak inhibitor of D_2 receptors but has a high affinity for a number of other receptors including D_1, D_4, and serotonin$_2$ (5-HT_2) receptors.[2] Other atypicals mostly share this profile of greater 5-HT_2 than D_2 antagonism.[2]

The traditional hypothesis of the action of antipsychotics has been that blockade of D_2 receptors in the limbic and cortical regions is responsible for the antipsychotic effects, and that adverse extrapyramidal motor effects result from blockade of D_2 receptors in the striatum (a typical motor region of the basal ganglia).[3] Modification of prolactin secretion results from blockade of D_2

receptors in the anterior pituitary. However, this hypothesis cannot satisfactorily account for the pharmacological profiles of atypical antipsychotics and the debate concerning their mechanism of action continues. It has been suggested that the balance between 5-HT_2 and D_2 antagonism is important in determining 'atypicality' (but the atypical antipsychotic amisulpride lacks marked 5-HT_2 antagonism), or that rapid dissociation from the D_2 receptor may be the determining factor (but it is not clear that some atypicals such as risperidone meet this criterion).[2] Other systems, such as glutamate, may play a role in modulating effectiveness against negative versus positive symptoms;[2] it has been suggested that the calcium antagonist actions of the diphenylbutylpiperidines may also be important in this respect.[4]

Division of antipsychotics into low- and high-potency drugs is discussed in Administration, below. For reference to the actions of antipsychotics on neuroendocrine function, see Effects on Endocrine Function under Adverse Effects, above.

1. Ereshefsky L, *et al.* Pathophysiologic basis for schizophrenia and the efficacy of antipsychotics. *Clin Pharm* 1990; **9:** 682–707.
2. Remington G. Understanding antipsychotic 'atypicality': a clinical and pharmacological moving target. *J Psychiatry Neurosci* 2003; **28:** 275–84.
3. Anonymous. Now we understand antipsychotics? *Lancet* 1990; **336:** 1222–3.
4. Snyder SH. Drug and neurotransmitter receptors: new perspectives with clinical relevance. *JAMA* 1989; **261:** 3126–9.

Administration. The classical antipsychotics are often divided into:

- **low-potency** drugs (phenothiazines with an aliphatic or piperidine side-chain or thioxanthenes with an aliphatic side-chain)
- **high-potency** drugs (butyrophenones, diphenylbutylpiperidines, and phenothiazines or thioxanthenes with a piperazine side-chain)

At doses with equipotent antipsychotic activity, the low-potency drugs are more prone to cause sedation and antimuscarinic or α-adrenergic-blocking effects than the high-potency drugs. However, they are associated with a lower incidence of extrapyramidal effects, with the exception of tardive dyskinesia which is likely to occur to the same extent with all classical antipsychotics.

Equivalent doses of antipsychotics quoted in the literature have varied considerably. In the UK the following daily doses of oral antipsychotics have been suggested to have approximately equipotent antipsychotic activity for doses up to the maximum licensed doses:

- chlorpromazine hydrochloride 100 mg
- clozapine 50 mg
- haloperidol 2 to 3 mg
- pimozide 2 mg
- risperidone 0.5 to 1 mg
- sulpiride 200 mg
- thioridazine 100 mg
- trifluoperazine 5 mg

It should be noted that all patients receiving pimozide require an annual ECG and all those receiving more than 16 mg of pimozide daily require periodic ECGs (see p.1018). Thioridazine also requires specialist supervision (p.1032).

Suggested equipotent doses of intramuscular depot antipsychotics are:

- flupentixol decanoate 40 mg every 2 weeks
- fluphenazine decanoate 25 mg every 2 weeks
- haloperidol (as the decanoate) 100 mg every 4 weeks
- pipotiazine palmitate 50 mg every 4 weeks
- zuclopenthixol decanoate 200 mg every 2 weeks

It has been noted[1] that *high doses* of antipsychotics (greater than the equivalent of 600 mg of chlorpromazine daily) are generally not necessary for the treatment (both initial and maintenance) of psychotic disorders, and may be associated with an increased risk of adverse effects as well as with a diminished clinical response. However, if high doses of antipsychotics have to be used, then doses should be increased gradually with caution and under the supervision of a specialist with facilities for emergency resuscitation available. The Royal College of Psychiatrists in the UK (which defines high-dose therapy as that involving a total daily dose greater than the upper limit recommended in the *BNF*) has issued recommendations concerning the use of high-dose antipsychotic medication.[2] It considers:

- current evidence does not justify the routine use of high-dose therapy with antipsychotics
- if high-dose therapy is used, this should only be after evidence-based strategies have failed, and as a carefully-monitored therapeutic trial
- the decision to use high-dose therapy, and the expected outcome, should be fully documented, after expert assessment of the patient
- the possible contra-indications to therapy, and the risk of drug interactions, should be assessed beforehand
- an ECG should be carried out before starting high-dose therapy and should be repeated after a few days, and then every 1 to 3 months in the early stages of treatment, or as clinically indicated
- doses should be increased in relatively small increments, with time to assess response before a further increase
- the use of 'as-required' antipsychotic medication, and of drug combinations, should be carefully monitored to avoid the inadvertent increase of total doses above high-dose thresholds

The existence of a *therapeutic range* (or therapeutic window) has not been demonstrated for most antipsychotics (with the possible exception of haloperidol[3]), and plasma concentrations of these drugs must be interpreted with caution.[1,3] Many factors make it difficult to establish a meaningful correlation between dose, plasma concentrations, and clinical improvement. These include incomplete absorption, first-pass effect, enzyme induction, the presence of active and inactive metabolites, ethnicity, smoking, and factors occurring at the receptor level.[3]

1. Baldessarini RJ, *et al.* Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch Gen Psychiatry* 1988; **45:** 77–91.
2. The Royal College of Psychiatrists. Consensus statement on high-dose antipsychotic medication. *Council Report CR138*; London: Royal College of Psychiatrists, May 2006. Available at: http://www.rcpsych.ac.uk/files/pdfversion/CR138.pdf (accessed 30/05/06)
3. Sramek JJ, *et al.* Neuroleptic plasma concentrations and clinical response: in search of a therapeutic window. *Drug Intell Clin Pharm* 1988; **22:** 373–80.

Administration in children. For reference to the use of lytic cocktails containing chlorpromazine, promethazine, and pethidine, and the view that alternatives should be considered in children, see Lytic Cocktails, under Sedation, p.115.

Bipolar disorder. Patients with bipolar disorder (p.372) suffering from acute mania with coexisting psychotic features, agitation, or disruptive behaviour are usually treated with antipsychotics as they produce rapid control of symptoms. Classical antipsychotics such as chlorpromazine or haloperidol have been widely used, although use of atypical antipsychotics, such as clozapine or olanzapine, is growing.

Chorea. For a discussion of the management of various choreas, including mention of the use of phenothiazines such as chlorpromazine, see p.953.

Dyspnoea. It has been shown that in healthy subjects an oral dose of 25 mg of chlorpromazine hydrochloride can reduce exercise-induced breathlessness without affecting ventilation or causing sedation.[1] Although other drugs may be preferred in patients with advanced cancer and dyspnoea (p.104), chlorpromazine may relieve air hunger unresponsive to usual measures,[2] and, if required, can be used to sedate dying patients who have unrelieved distress. It is recommended that initial doses should be small: 12.5 mg by slow intravenous injection or 25 mg by suppository may be given.

1. O'Neill PA, *et al.* Chlorpromazine—a specific effect on breathlessness? *Br J Clin Pharmacol* 1985; **19:** 793–7.
2. Walsh D. Dyspnoea in advanced cancer. *Lancet* 1993; **342:** 450–1.

Dystonia. Antipsychotics such as phenothiazines, haloperidol, or pimozide are sometimes useful in the treatment of idiopathic dystonia (p.809) in patients who have failed to respond to other drugs.[1] However, they often act non-specifically, damping down excessive movements by causing a degree of drug-induced parkinsonism and there is the risk of adding drug-induced extrapyramidal disorders to the dystonia being treated (see Extrapyramidal Disorders under Adverse Effects, above).

1. Marsden CD, Quinn NP. The dystonias. *BMJ* 1990; **300:** 139–44.

Eclampsia and pre-eclampsia. Drug combinations known as lytic cocktails have been used in many countries for the management of pre-eclampsia and imminent eclampsia. The cocktail has usually consisted of a combination of chlorpromazine, pethidine, and/or promethazine. In general, however, phenothiazines are not recommended in late pregnancy, and other treatments are preferred for hypertension (see Hypertension in Pregnancy, under Hypertension, p.1171); the management of eclampsia, which is the convulsive phase, is discussed on p.470.

Headache. Some phenothiazines such as chlorpromazine, levomepromazine, and prochlorperazine have been used in migraine to control severe nausea and vomiting unresponsive to antiemetics such as metoclopramide and domperidone (see p.616), and to relieve the pain of severe migraine attacks unresponsive to parenteral dihydroergotamine or sumatriptan.

References.

1. Stiell IG, *et al.* Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. *Ann Emerg Med* 1991; **20:** 1201–5.
2. Jones EB, *et al.* Safety and efficacy of rectal prochlorperazine for the treatment of migraine in the emergency department. *Ann Emerg Med* 1994; **24:** 237–41.
3. Coppola M, *et al.* Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. *Ann Emerg Med* 1995; **26:** 541–6.
4. Jones J, *et al.* Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. *Am J Emerg Med* 1996; **14:** 262–4.
5. Kelly AM, *et al.* Intravenous chlorpromazine versus intramuscular sumatriptan for acute migraine. *J Accid Emerg Med* 1997; **14:** 209–11.
6. Bigal ME, *et al.* Intravenous chlorpromazine in the emergency department treatment of migraines: a randomized controlled trial. *J Emerg Med* 2002; **23:** 141–8.

Hiccup. A hiccup is an involuntary spasmodic contraction of the diaphragm that causes a sudden inspiration of air which is then checked abruptly by closure of the glottis. Hiccups often have a simple cause such as gastric distension and usually resolve spontaneously or respond to simple measures. Intractable hiccups may stem from a serious underlying cause such as brain disorders, metabolic or endocrine disturbances, CNS infections, and oesophageal or other gastrointestinal disorders. Other precipitants include anaesthesia or drug therapy.

Treatment of intractable hiccups should initially be aimed at controlling or removing the underlying cause including the relief of gastric distension or oesophageal obstruction.[1-5] Measures that raise carbon dioxide pressure such as breath holding, rebreathing, or alteration of normal respiratory rhythm can be effective. Stimulation of the pharynx can also interrupt hiccups and may explain the action of a host of remedies such as sipping iced water, gargling, and swallowing granulated sugar. Many drugs have been tried in the treatment of hiccups but evidence of efficacy is largely from anecdotal reports or uncontrolled studies. An early treatment protocol[6] for intractable hiccups (based on a review of the literature and the authors' experience) suggested stepwise management until an effective measure was found, as follows:

- correction of any metabolic abnormality
- swallowing dry granulated sugar
- decompressing the stomach via nasogastric tube, then irritation of the pharynx
- intravenous chlorpromazine 25 to 50 mg, repeated up to 3 times if necessary; if parenteral therapy is effective maintain on chlorpromazine by mouth for 10 days (licensed information recommends the use of oral therapy first —see Uses and Administration, above)
- metoclopramide 10 mg intravenously; if successful maintain on metoclopramide by mouth for 10 days
- quinidine 200 mg by mouth 4 times daily
- if this fails, consider left phrenic nerve block and crush

In later discussions,[1,3] chlorpromazine still emerged as the most consistently effective drug treatment; metoclopramide appeared to be an acceptable second choice and nifedipine an appropriate third choice,[3] although haloperidol was also considered to be of value.[1,4] Other phenothiazines that have been used for intractable hiccup include perphenazine and promazine. It was also considered that clonazepam, carbamazepine, phenytoin, and valproic acid might be of value, especially in neuropathic hiccups.[1] Some beneficial results have been reported with amitriptyline and amantadine; other drugs being tried in the treatment of hiccups include baclofen and gabapentin. The *BNF* recommends that in palliative care patients, a preparation combining an antacid with an antiflatulent be given for hiccups due to gastric distension. If this fails, metoclopramide (orally or by subcutaneous or intramuscular injection) should be added; baclofen, nifedipine, or chlorpromazine should be reserved for those patients in whom metoclopramide is also ineffective.

1. Howard RS. Persistent hiccups: if excluding or treating any underlying pathology fails try chlorpromazine. *BMJ* 1992; **305:** 1237–8.
2. Rousseau P. Hiccups. *South Med J* 1995; **88:** 175–81.
3. Friedman NL. Hiccups: a treatment review. *Pharmacotherapy* 1996; **16:** 986–95.
4. WHO. Hiccup. In: *Symptom relief in terminal illness*. Geneva: WHO, 1998.
5. Smith HS, Busracamwongs A. Management of hiccups in the palliative care population. *Am J Hosp Palliat Care* 2003; **20:** 149–54.
6. Williamson BWA, Macintyre IMC. Management of intractable hiccup. *BMJ* 1977; **2:** 501–3.

Lesch-Nyhan syndrome. The Lesch-Nyhan syndrome is an inherited disorder caused by a complete deficiency of hypoxanthine-guanine phosphoribosyl transferase, an enzyme involved in purine metabolism. It is characterised by hyperuricaemia, spasticity, choreoathetosis, self-mutilation, and mental retardation. The hyperuricaemia (see p.552) can be controlled by drugs such as allopurinol but there appears to be no effective treatment for the neurological deficits. It has been suggested that the behavioural problems might be associated with alterations in the brain's dopamine system. There have been rare reports of improvement in self-mutilation in patients given antipsychotics or antiepileptics such as carbamazepine and gabapentin.

References.

1. Nyhan WL, Wong DF. New approaches to understanding Lesch-Nyhan disease. *N Engl J Med* 1996; **334:** 1602–4.

Migraine. See under Headache, above.

Nausea and vomiting. Many antipsychotics, with the notable exception of thioridazine, have antiemetic properties and have been used in the prevention and treatment of nausea and vomiting (p.1700) arising from a variety of causes such as radiation sickness, malignancy, and emesis caused by drugs, including antineoplastics and opioid analgesics. Reference to the risk to the fetus of therapy with phenothiazines during pregnancy can be found under Precautions, above and on p.563.

Schizophrenia. Classical antipsychotics such as chlorpromazine, haloperidol, and thioridazine have been the traditional drug treatment of choice for patients with schizophrenia (p.955); however, atypical antipsychotics may now be preferred as first-line therapy. There is little difference in efficacy between the

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.

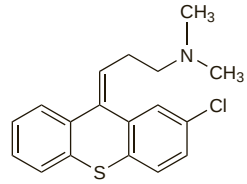
Хлорпротиксен

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

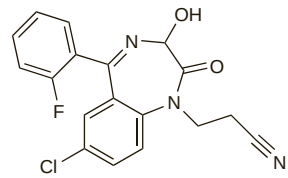
Цинолазепам

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

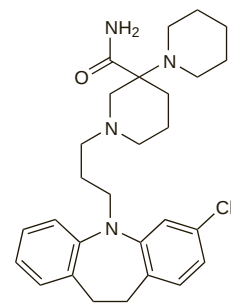
Clocapramine Hydrochloride *(rINNM)*

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.