is 10 mg daily, gradually increasing to 30 to 50 mg daily. In the USA, daily doses of 25 to 50 mg are recommended for initial therapy in the elderly and adolescents, increasing to a maximum of 100 mg daily as required. Since imipramine has a prolonged half-life, once-daily dosage regimens may also be suitable, usually given at night.

Imipramine, as the hydrochloride, has also been given by intramuscular injection in the treatment of depression.

Imipramine is also used for the treatment of **nocturnal enuresis** in children in whom organic pathology has been excluded. However, drug therapy for nocturnal enuresis should be reserved for those in whom other methods have failed and should preferably only be given to cover periods away from home; tricyclic antidepressants are not recommended in children under 6 years of age (the *BNF* recommends that they should not be given until 7 years of age). Suggested doses of imipramine hydrochloride are:

- 25 mg for children aged 6 to 7 years (20 to 25 kg)
- 25 to 50 mg for children aged 8 to 11 years (25 to 35 kg)
- 50 to 75 mg for children over 11 years (35 to 54 kg)

The dose should be taken just before bedtime and treatment, including a period of gradual withdrawal, should not continue for longer than 3 months. A full physical examination is recommended before a further course.

Imipramine oxide hydrochloride (imipraminoxide hydrochloride) has also been used as an antidepressant and for nocturnal enuresis.

Imipramine should be withdrawn gradually to reduce the risk of withdrawal symptoms.

Anxiety disorders. See under Clomipramine, p.387. In some countries, imipramine hydrochloride is licensed for the treatment of panic disorder in an initial oral dose of 10 mg daily; this dose may be increased as necessary to between 75 to 150 mg daily although doses of 200 mg daily may be needed in some patients.

Some references to the use of imipramine in anxiety disorders are given below.

1. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992; **160:** 191–202.
2. Lepola UM, *et al*. Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. *Int Clin Psychopharmacol* 1993; **8:** 115–18.
3. Rickels K, *et al*. Antidepressants for the treatment of generalised anxiety disorder: a placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry* 1993; **50:** 884–95.
4. Clark DM, *et al*. A comparison of cognitive therapy, applied relaxation and imipramine in the treatment of panic disorder. *Br J Psychiatry* 1994; **164:** 759–69.
5. Barlow DH, *et al*. Cognitive-behavioral therapy, imipramine, or their combination for panic disorder: a randomized controlled trial. *JAMA* 2000; **283:** 2529–36. Correction. *ibid.*; **284:** 2597.

Hyperactivity. Although not licensed in the UK for use in children with attention deficit hyperactivity disorder, the *BNFC* has suggested that imipramine hydrochloride may be given to those aged 6 years and over in an oral dose of 10 to 30 mg twice daily.

See also under Desipramine, p.388.

Pain. Antidepressants, usually amitriptyline or another tricyclic, are useful in alleviating some types of pain (see Choice of Analgesic, p.2). In some countries, imipramine hydrochloride is also available for the treatment of chronic pain; the usual recommended oral dose is 25 to 75 mg daily, although doses of up to 300 mg daily may be necessary.

Some references to the use of imipramine are given below.

1. Walsh TD. Controlled study of imipramine and morphine in chronic pain due to advanced cancer. *Proc Am Soc Clin Oncol* 1986; **5:** 237.
2. Sindrup SH, *et al*. Concentration-response relationship in imipramine treatment of diabetic neuropathy symptoms. *Clin Pharmacol Ther* 1990; **47:** 509–15.
3. Hummel T, *et al*. A comparison of the antinociceptive effects of imipramine, tramadol and anpirtoline. *Br J Clin Pharmacol* 1994; **37:** 325–33.
4. Cannon RO, *et al*. Imipramine in patients with chest pain despite normal coronary angiograms. *N Engl J Med* 1994; **330:** 1411–17.
5. Godfrey RG. A guide to the understanding and use of tricyclic antidepressants in the overall management of fibromyalgia and other chronic pain syndromes. *Arch Intern Med* 1996; **156:** 1047–52.
6. Minotti V, *et al*. Double-blind evaluation of short-term analgesic efficacy of orally administered diclofenac, diclofenac plus codeine, and diclofenac plus imipramine in chronic cancer pain. *Pain* 1998; **74:** 133–7.

Preparations

BP 2008: Imipramine Tablets;
USP 31: Imipramine Hydrochloride Injection; Imipramine Hydrochloride Tablets.

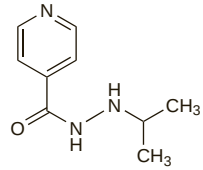
Proprietary Preparations (details are given in Part 3)
Arg.: Elepsin; Tofranil; ***Austral.:*** Melipramine; Tofranil; Tolerade; ***Austria:*** Tofranil; ***Belg.:*** Tofranil; ***Braz.:*** Depramina; Imipra; Praminan; Tofranil; Uni Imiprax; ***Canad.:*** Novo-Pramine; Tofranil; ***Cz.:*** Melipramin; ***Fr.:*** Tofranil; ***Ger.:*** Pryleugan; Tofranil; ***Hong Kong:*** Tofranil†; ***Hung.:*** Melipramin; ***India:*** Antidep; Depsonil; ***Indon.:*** Tofranil; ***Irl.:*** Tofranil; ***Israel:*** Primonil; Tofranil; ***Ital.:*** Tofranil; ***Mex.:*** Fixon; Talpramin; Tofranil; ***NZ:*** Tofranil; ***Philpp.:*** Tofranil; ***Port.:*** Tofranil; ***Rus.:*** Melipramin (Мелипрамин); ***S.Afr.:*** Ethipramine; Mipralin; Tofranil; ***Spain:*** Tofranil; ***Swed.:*** Tofranil†; ***Switz.:*** Tofranil; ***Thai.:*** Celamine; Sermonil; Topramine; ***Turk.:*** Tofranil; ***UK:*** Tofranil†; ***USA:*** Tofranil; ***Venez.:*** Tofranil.

Multi-ingredient: ***India:*** Depsonil-DZ.

Iproniazid Phosphate *(BANM, rINNM)*

Fosfato de iproniazida; Iproniazide, Phosphate d'; Iproniazidi Phosphas. 2′-Isopropylisonicotinohydrazide phosphate.

Ипрониазида Фосфат
$C_9H_{13}N_3O,H_3PO_4$ = 277.2.
CAS — 54-92-2 (iproniazid); 305-33-9 (iproniazid phosphate).
ATC — N06AF05.
ATC Vet — QN06AF05.



(iproniazid)

Profile

Iproniazid, a hydrazine derivative, is an irreversible inhibitor of both monoamine oxidase types A and B with actions and uses similar to those of phenelzine (p.419). It has been given orally in the treatment of depression.

Iproniazid is the isopropyl derivative of isoniazid (see p.288) and was developed for use in tuberculosis, but owing to its toxicity is no longer used for this purpose.

Effects on the liver. Of 91 cases of hepatitis due to antidepressant therapy, cytolytic reactions occurred in 11 treated with iproniazid.[1] Five patients died, 3 of them after involuntary rechallenge. High levels of antimitochondrial antibody were found in 5 patients.

1. Lefebure B, *et al*. Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.

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

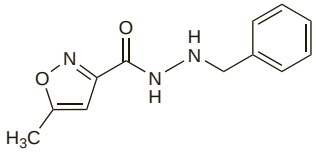
Preparations

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

Isocarboxazid *(BAN, rINN)*

Isocarboxazida; Isocarboxazide; Isocarboxazidum; Isokarboksatsidi; Isokarboxazid; Ro-50831. 2′-Benzyl-5-methylisoxazole-3-carbohydrazide.

Изокарбоксазид
$C_{12}H_{13}N_3O_2$ = 231.3.
CAS — 59-63-2.
ATC — N06AF01.
ATC Vet — QN06AF01.



Pharmacopoeias. In *Chin.*

Adverse Effects, Treatment, and Precautions

As for MAOIs in general (see Phenelzine, p.415).

Interactions

For interactions associated with MAOIs, see Phenelzine, p.417.

Pharmacokinetics

Isocarboxazid is readily absorbed from the gastrointestinal tract reaching peak plasma concentrations 3 to 5 hours after ingestion. It is metabolised by the liver, and is excreted in the urine mainly in the form of metabolites.

Uses and Administration

Isocarboxazid, a hydrazine derivative, is an irreversible inhibitor of both monoamine oxidase types A and B with actions and uses similar to those of phenelzine (p.419).

Isocarboxazid is used in the treatment of depression but because of the risks associated with irreversible non-selective MAOIs (see p.373) usually other antidepressants are preferred. It is given in an initial oral dose of 30 mg daily in single or divided doses. If no improvement occurs after 4 weeks, doses of up to 60 mg daily can be tried for up to 4 to 6 weeks. Once a response has been obtained the dosage may be gradually reduced to a maintenance dose of 10 to 20 mg daily, although doses of up to 40 mg daily may be needed in some patients. Half the normal maintenance dose may be adequate in the elderly.

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

Preparations

Proprietary Preparations (details are given in Part 3)
Chile: Marplan†; ***Denm.:*** Marplan; ***USA:*** Marplan.

Lithium Carbonate *(USAN)*

CP-15467-61; Dilithium Carbonate; Ličio karbonatas; Lithii carbonas; Lithium Carb.; Lithium, carbonate de; Litio, carbonato de; Litiumkarbonaatti; Litiumkarbonat; Lítium-karbonát; Litu węglan; Litu weglan; Lityum Karbonat; NSC-16895; Uhličitan lithný. Carbonic acid, dilithium salt.
Li_2CO_3 = 73.89.
CAS — 554-13-2.
ATC — N05AN01.
ATC Vet — QN05AN01.

NOTE. Commercially available lithium materials have atomic weights ranging from 6.939 to 6.996. The molecular weight of lithium carbonate of 73.89 given above has been calculated using the lowest atomic weight; using the highest figure would give a molecular weight of 74.00. This difference does not affect the figure of 27 mmol of lithium being provided by 1 g of lithium carbonate and is unlikely to contribute noticeably to any variations in serum concentration. Nor should it affect the outcome of assays of serum-lithium concentrations given the limits of error of the assay methods.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, and *US*.
Ph. Eur. 6.2 (Lithium Carbonate). A white or almost white powder. Slightly soluble in water; practically insoluble in alcohol.
USP 31 (Lithium Carbonate). A white odourless granular powder. Sparingly soluble in water, very slightly soluble in alcohol; dissolves, with effervescence, in dilute mineral acids.

Lithium Citrate

Citronan lithný tetrahydrát; Ličio citratas; Lithii citras; Lithii Citras Tetrahydricus; Lithium, citrate de; Litio, citrato de; Litiumcitrat; Lítium-citrát; Litiumsitraatti; Lityum Sitrat.
$C_6H_5Li_3O_7,4H_2O$ = 282.0.
CAS — 919-16-4 (anhydrous lithium citrate); 6080-58-6 (lithium citrate tetrahydrate).

NOTE. Commercially available lithium materials have atomic weights ranging from 6.939 to 6.996. The molecular weight of lithium citrate of 282.0 given above has been calculated using the lowest atomic weight; using the highest figure would give a molecular weight of 282.1. This difference does not affect the figure of 10.6 mmol of lithium being provided by 1 g of lithium citrate and is unlikely to contribute noticeably to any variations in serum concentration. Nor should it affect the outcome of assays of serum-lithium concentrations given the limits of error of the assay methods.

Pharmacopoeias. In *Eur.* (see p.vii) and *US*.
US also includes lithium hydroxide.
Ph. Eur. 6.2 (Lithium Citrate). A white or almost white fine crystalline powder. Freely soluble in water; slightly soluble in alcohol.
USP 31 (Lithium Citrate). A white odourless deliquescent powder or granules. Freely soluble in water; slightly soluble in alcohol. pH of a 5% solution in water is between 7.0 and 10.0. Store in airtight containers.

Adverse Effects

Many of the adverse effects of lithium are dose-related and the margin between the therapeutic and toxic dose is narrow.

Initial adverse effects of lithium therapy include nausea, diarrhoea, vertigo, muscle weakness, and a dazed feeling; these effects often abate with continued therapy. Fine hand tremors, polyuria, and polydipsia may, however, persist. Other adverse effects that may occur at therapeutic serum-lithium concentrations include weight gain and oedema (which should not be treated with diuretics). Hypercalcaemia, hypermagnesaemia, and hyperparathyroidism have been reported. Skin dis-

orders such as acne, psoriasis, and rashes may be exacerbated by lithium therapy. Leucocytosis is a relatively common adverse effect. Long-term adverse effects include hypothyroidism and/or goitre, rarely hyperthyroidism, and mild cognitive and memory impairment. Histological and functional changes in the kidney have been noted after long-term use of therapeutic concentrations of lithium (but see under Effects on the Kidneys, below).

Toxic effects may be expected at serum-lithium concentrations of about 1.5 mmol/litre, although they can appear at lower concentrations. They call for immediate withdrawal of treatment and should always be considered very seriously.

Signs of lithium toxicity include increasing diarrhoea, vomiting, anorexia, muscle weakness, lethargy, giddiness with ataxia, lack of coordination, tinnitus, blurred vision, coarse tremor of the extremities and lower jaw, muscle hyperirritability, choreoathetoid movements, dysarthria, and drowsiness. Symptoms of severe overdosage at serum-lithium concentrations above 2 mmol/litre include hyperreflexia and hyperextension of limbs, syncope, toxic psychosis, seizures, polyuria, renal failure, electrolyte imbalance, dehydration, circulatory failure, coma, and occasionally death.

The hazards of lithium in pregnant patients are discussed under Pregnancy in Precautions, below.

Effects on the blood. A patient developed thrombocytopenia after restarting lithium therapy after a gap of some weeks.[1] Stopping lithium led to an improvement in platelet count, but the count fell when lithium therapy was tried again. Leucocytosis is a recognised effect of lithium which this patient also experienced. Although concerns about leukaemia induction have not been verified, the author noted earlier reports of aplastic and megaloblastic anaemia and a case of fatal haemolytic anaemia reported to the UK CSM.

1. Collings S. Thrombocytopenia associated with lithium carbonate. *BMJ* 1992; **305:** 159.

Effects on the cardiovascular system. Reports of adverse effects on the heart associated with lithium have included bradycardia due to sinus node dysfunction,[1] which has persisted after stopping lithium,[2] premature ventricular contractions,[3] atrioventricular block,[4] and T-wave depression.[5] For the adverse cardiac effects associated with lithium intoxication, see under Overdosage, below.

For mention of myocarditis associated with lithium therapy, see under Effects on the Musculoskeletal System, below.

1. Montalescot G, *et al.* Serious sinus node dysfunction caused by therapeutic doses of lithium. *Int J Cardiol* 1984; **5:** 94–6.
2. Palileo EV, *et al.* Persistent sinus node dysfunction secondary to lithium therapy. *Am Heart J* 1983; **106:** 1443–4.
3. Tangedahl TN, Gau GT. Myocardial irritability associated with lithium carbonate therapy. *N Engl J Med* 1972; **287:** 867–9.
4. Martin CA, Piascik MT. First degree A-V block in patients on lithium carbonate. *Can J Psychiatry* 1985; **30:** 114–16.
5. Demers RG, Heninger GR. Electrocardiographic T-wave changes during lithium carbonate treatment. *JAMA* 1971; **218:**381–6.

Effects on the endocrine system. There is a small, but definite, risk that patients taking lithium in therapeutic doses will develop *goitre*, clinical or subclinical *hypothyroidism*, or, rarely, both.[1-3] Published prevalence figures have varied widely although most studies have found an increased risk of hypothyroidism in patients treated with lithium when compared to the general population.[2] Prevalence also appears to be higher in women taking lithium than in men;[2] in addition, the increased risk in women may be greatest during the first 2 years of lithium therapy. Other risk factors identified include a family history of thyroid disorders.[3] However, a long-term, follow-up study[4,5] suggested that the incidence of thyroid abnormalities was no greater in lithium-treated patients than in the general population.

Early goitre and lithium-induced hypothyroidism are both reversible if lithium is withdrawn; if continued treatment with lithium is desirable the patient should be treated with levothyroxine.

There have been rare reports of *hyperthyroidism* in lithium-treated patients[6] and the association may only be one of coincidence, although it is important to realise that hyperthyroidism can precipitate mania and can also be mistaken for an attack of mania.

Increases in serum concentrations of calcium and parathyroid hormone have been described in patients receiving lithium therapy. Although generally considered to be slight, some patients have experienced *parathyroid hyperplasia*.[7,8]

Cases of *diabetes mellitus* developing in patients treated with lithium have been reported but may not be attributable to lithium.[9]

1. Vincent A, *et al.* Lithium-associated hypothyroidism: a practical review. *Lithium* 1994; **5:** 73–4.
2. Johnston AM, Eagles JM. Lithium-associated clinical hypothyroidism: prevalence and risk factors. *Br J Psychiatry* 1999; **175:** 336–9.
3. Ozpoyraz N, *et al.* Thyroid abnormalities in lithium-treated patients. *Adv Therapy* 2002; **19:** 176–84.
4. Bocchetta A, *et al.* Six-year follow-up of thyroid function during lithium treatment. *Acta Psychiatr Scand* 1996; **94:** 45–8.
5. Bocchetta A, *et al.* Ten-year follow-up of thyroid function in lithium patients. *J Clin Psychopharmacol* 2001; **21:** 594–8.
6. Yamagishi S-I, Yokoyama-Ohta M. A case of lithium-associated hyperthyroidism. *Postgrad Med J* 1999; **75:** 188–9.
7. Nordenström J, *et al.* Hyperparathyroidism associated with treatment of manic-depressive disorders by lithium. *Eur J Surg* 1992; **158:** 207–11.
8. Taylor JW, Bell AJ. Lithium-induced parathyroid dysfunction: a case report and review of the literature. *Ann Pharmacother* 1993; **27:** 1040–3.
9. Pandit MK, *et al.* Drug-induced disorders of glucose tolerance. *Ann Intern Med* 1993; **118:** 529–39.

Effects on the eyes. Decrease in accommodation has been reported in up to 10% of patients taking lithium; younger patients are most affected.[1] Blurred vision can also occur, most commonly early in therapy, but this may improve with time. Lithium can affect extra-ocular muscles and produce diplopia. A reduction in dosage or withdrawal of therapy may be required. It reduces lachrymal secretions and is excreted in tears in increased concentrations. In rare cases this may result in ocular irritation but this usually causes few problems when artificial tears are used. Photophobia, which occurs rarely with lithium therapy, may also be associated with the excretion of lithium in tears. Lithium can reduce dark adaptation due to a direct neural effect but whether this can progress further to cause irreversible macular or retinal degeneration is not proven. There are some rare but poorly documented reports of deposits in the cornea or conjunctiva. It was considered unlikely that lithium increased the risk of developing senile cataracts.

Lithium can cause nystagmus, many forms of which are reversible on reducing the dose or withdrawal of the drug. However, downbeat nystagmus is a serious adverse effect and is often irreversible. Irreversible oscillopsia can occur rarely secondary to nystagmus. Oculogyric crisis has been associated with lithium therapy and may be exacerbated by haloperidol.

Some ocular effects may be secondary to the effects of lithium on other systems. Exophthalmos and other thyroid-related eye disorders may occur rarely as a secondary effect of lithium on the thyroid. Lithium can also cause pseudotumor cerebri with papilloedema (benign intracranial hypertension). Most cases have occurred a few years after starting therapy but there has been a report of this condition after only 7 months of treatment. Ptosis has been reported, mainly associated with unmasking of myasthenia gravis.

1. Fraunfelder FT, *et al.* The effects of lithium on the human visual system. *J Toxicol Cutan Ocul Toxicol* 1992; **11:** 97–169.

Effects on the kidneys. Polyuria with associated polydipsia, due to drug-induced nephrogenic diabetes insipidus, is the most common result of the effects of lithium on the kidney; an early review[1] stated that the incidence ranged from 4 to 50%. In some patients, irreversible kidney damage, associated with renal histological changes that included tubular atrophy, focal interstitial nephropathy and focal fibrosis, and impairment of glomerular filtration rate, was reported. However, although patients on long-term maintenance lithium therapy did appear to be susceptible to the development of progressive impairment of urinary concentrating ability it was most noticeable in patients with a history of acute lithium toxicity. The risk of renal damage and impaired glomerular filtration rate was thought to be extremely small in patients on stable maintenance lithium therapy with no history of acute lithium intoxication.[1]

A similar review considered that, although it was necessarily an oversimplified view, many, and perhaps all, of the renal adverse effects of lithium were induced by excessive dosage.[2] Others have also defended lithium with respect to its renal toxicity and stated that long-term therapy, if properly controlled, does not necessarily lead to chronic or irreversible renal damage.[3-5]

1. Walker RG, Kincaid-Smith P. Kidneys and the fluid regulatory system. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 206–13.
2. George CRP. Renal aspects of lithium toxicity. *Med J Aust* 1989; **150:** 291–2.
3. Schou M. Serum lithium monitoring of prophylactic treatment: critical review and updated recommendations. *Clin Pharmacokinet* 1988; **15:** 283–6.
4. Schou M. Lithium treatment of manic-depressive illness: past, present, and perspectives. *JAMA* 1988; **259:** 1834–6.
5. Gitlin M. Lithium and the kidney: an updated review. *Drug Safety* 1999; **20:** 231–43.

Effects on the musculoskeletal system. The effects of lithium on skeletal muscle are represented mainly by varying degrees of weakness and tremor (for further details see under Effects on the Nervous and Neuromuscular Systems, below). Aggravation of myasthenia gravis has been reported. Acute or subacute painful proximal myopathy causing myalgia, cramps, myokymia, or weakness has also been described. An association with myocarditis has been proposed[1] but it is unclear whether this is causal.

1. Coulter DM, *et al.* Antipsychotic drugs and heart muscle disorder in international pharmacovigilance: data mining study. *BMJ* 2001; **322:** 1207–9.

Effects on the nervous and neuromuscular systems. Neurotoxicity has long been recognised as a potential adverse effect of lithium. Minor effects of lithium on the nervous system can be minimised by reduction of lithium dose during maintenance therapy but severe effects warrant immediate and complete withdrawal of the drug.[1] Minor effects have been considered to include impaired concentration, comprehension, and short-term memory, restlessness and anxiety, depression, fine rapid tremors, and easy fatigue. Serious or severe effects might include declining cognition and mental status, gait disturbances, movement disorders such as choreoathetosis, myoclonus, and parkinsonism, seizures, cerebellar signs, pseudotumor cerebri (although this was rare), neuroleptic malignant syndrome, myopathy, axonal neuropathy, a myasthenic syndrome, and exacerbation of underlying neuromuscular disease. The cognitive effects of lithium such as mental slowing may be subtle.[2]

There are 2 types of lithium-induced tremor.[3] The first is a coarse tremor occurring with impending and actual lithium toxicity and appears to have both cerebellar and parkinsonian components. It is often associated with incoordination, facial spasms, twitching of muscles and limbs, hyperactive reflexes, and more general systemic signs of toxicity. With this type of tremor it was mandatory to stop or decrease the dose of lithium. The second type, which is more common, is a fine tremor, usually occurring within normal therapeutic concentrations, either transiently within a few days of starting treatment or later as a long-standing adverse effect. With this type of fine tremor there was evidence to show that a slight decrease in dose may be beneficial.

In addition to the effects mentioned above, impairment of taste perception (mainly involving butter and celery)[4] and speech disturbances with few other signs of toxicity[5-8] have been reported.

Neurotoxicity persisting for at least 2 months after stopping lithium therapy (SILENT; syndrome of irreversible lithium-effectuated neurotoxicity) has been described.[9] Common presentations included cerebellar dysfunction, extrapyramidal symptoms, brainstem dysfunction, and dementia with varying degrees of organic mental syndromes.

For further details of the effects of lithium on the nervous system, see under Effects on the Eyes above, Effects on the Musculoskeletal System, above, and under Epileptogenic Effect, below.

1. Sansone ME, Ziegler DK. Brain and nervous system. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 240–5.
2. Pachet AK, Wisniewski AM. The effects of lithium on cognition: an updated review. *Psychopharmacology (Berl)* 2003; **170:** 225–34.
3. Johns S, Harris B. Tremor. *BMJ* 1984; **288:** 1309.
4. Himmelhoch JM, Hanin I. Side effects of lithium carbonate. *BMJ* 1974; **4:** 233.
5. Solomon K, Vickers R. Dysarthria resulting from lithium carbonate: a case report. *JAMA* 1975; **231:** 280.
6. Worrall EP, Gillham RA. Lithium-induced constructional dyspraxia. *BMJ* 1983; **286:** 189.
7. McGovern GP. Lithium induced constructional dyspraxia. *BMJ* 1983; **286:** 646.
8. Netski AL, Piasecki M. Lithium-induced exacerbation of stutter. *Ann Pharmacother* 2001; **35:** 961.
9. Adityanjee, *et al.* The syndrome of irreversible lithium-effectuated neurotoxicity. *Clin Neuropharmacol* 2005; **28:** 38–49.

Effects on respiration. Lithium is not generally recognised as a respiratory depressant but an episode of reversible respiratory failure about 3 weeks after the start of lithium therapy has been described in a patient with stable chronic airways obstruction.[1] Recovery of consciousness and resolution of hypercapnia occurred within 24 to 36 hours of stopping lithium.

1. Weiner M, *et al.* Effect of lithium on the responses to added respiratory resistances. *N Engl J Med* 1983; **308:** 319–22.

Effects on sexual function and fertility. Lithium does not seem to interfere with sexual function in most patients, but there have been isolated reports of impotence and loss of libido attributed to lithium therapy.[1]

Studies *in vitro* have demonstrated that lithium can inhibit sperm motility in concentrations comparable with those reported to be achieved in semen,[2] but concentrations found in cervico-vaginal mucus were considered unlikely to affect motility.[3]

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Raoof NT, *et al.* Lithium inhibits human sperm motility in vitro. *Br J Clin Pharmacol* 1989; **28:** 715–17.
3. Salas IG, *et al.* Lithium carbonate concentration in cervico-vaginal mucus and serum after repeated oral dose administration. *Br J Clin Pharmacol* 1989; **28:** 751P.

Effects on the skin and hair. Patients taking lithium may develop skin disorders, though these are not necessarily serious or severe.[1-3] Male patients may be more susceptible to such effects than female, although early results suggested the reverse.[3] Onset can vary from 2 or 3 weeks to 7 or more years, but many reactions start to appear once optimal serum-lithium concentrations have been attained. Effects reported include psoriasis which may be severe and require lithium withdrawal. Seborrhoeic dermatitis and follicular keratosis also occur and can improve spontaneously or after stopping lithium. Acneform eruptions are found in areas not usually affected by acne vulgaris; in general the face is less affected or not affected at all.

Hair loss, not always severe, is more frequent than cutaneous effects. About 6% of patients may be affected and all forms of alopecias have been found. The onset occurs several weeks or months after the start of lithium therapy. The hair usually regrows despite continuing therapy but in some cases regrowth only occurs after withdrawal of lithium. In a review[4] of the ef-

fects on the ocular system, loss of eyebrows and eyelashes was noted as a rare event. Hair loss due to lithium-induced hypothyroidism can be corrected by thyroid replacement therapy.

For references to the association of lithium with lupus, see under Lupus, below.

1. Lambert D, Dalac S. Skin, hair and nails. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 232–4.
2. Gupta AK, *et al.* Lithium therapy associated with hidradenitis suppurativa: case report and a review of the dermatologic side effects of lithium. *J Am Acad Dermatol* 1995; **32:** 382–6.
3. Yeung CK, Chan HHL. Cutaneous adverse effects of lithium: epidemiology and management. *Am J Clin Dermatol* 2004; **5:** 3–8.
4. Fraunfelder FT, *et al.* The effects of lithium on the human visual system. *J Toxicol Cutan Ocul Toxicol* 1992; **11:** 97–169.

Epileptogenic effect. Seizures during lithium therapy usually indicate toxicity or impending toxicity. There have, however, been a few isolated reports describing seizures in patients with serum-lithium concentrations within the normally accepted therapeutic range.[1,2]

1. Demers R, *et al.* Convulsion during lithium therapy. *Lancet* 1970; **ii:** 315–16.
2. Massey EW, Folger WN. Seizures activated by therapeutic levels of lithium carbonate. *South Med J* 1984; **77:** 1173–5.

Lupus. Studies have found that antinuclear antibodies were more common in patients taking lithium carbonate than in controls.[1,2] The absence of anti-DNA antibodies indicated that they did not have true SLE but it was considered that patients ingesting lithium might be at risk. Dermatological manifestations of lupus with the presence of antinuclear antibodies have been reported in a patient taking lithium.[3]

1. Johnstone EC, Whaley K. Antinuclear antibodies in psychiatric illness: their relationship to diagnosis and drug treatment. *BMJ* 1975; **2:** 724–5.
2. Presley AP, *et al.* Antinuclear antibodies in patients on lithium carbonate. *BMJ* 1976; **2:** 280–1.
3. Shukla VR, Borison RL. Lithium and lupuslike syndrome. *JAMA* 1982; **248:** 921–2.

Overdosage. Nausea, vomiting, and diarrhoea are common early features of lithium toxicity, and are followed by coarse tremor, increased muscle tone, cogwheel rigidity, fasciculation, and myoclonus.[1] Coma and convulsions may occur in serious cases and cardiac effects (first-degree heart block and QRS and QT prolongation) have been described rarely. A patient may appear to be aware with open eyes but have an expressionless face and be unable to move or speak (coma vigil). Acute renal failure and nephrogenic diabetes insipidus may develop.

In **acute overdosage**[2] vomiting often occurs within an hour of ingestion due to the high concentration of lithium in the stomach, but significant amounts of lithium can still reach the systemic circulation. The typical clinical symptoms often appear after a latency period and gastrointestinal symptoms can re-appear at a later time. The symptoms of overdosage are reported to be mainly related to the gastrointestinal and nervous systems and include abdominal pain, anorexia, nausea, and vomiting, occasionally mild diarrhoea, giddiness, tremor, ataxia, slurring speech, myoclonus, twitching, asthenia, and depression; renal symptoms have also been noted by some investigators. Efficient detoxification procedures (see Treatment of Adverse Effects, below) should be instituted as rapidly as possible.

Symptoms associated with **chronic intoxication** can be more severe and neurotoxicity may be a particular feature.[3,4] One reviewer considered that the majority of lithium intoxications reported had occurred in patients with renal impairment or in patients who had been given too high a dose.[2] The patient usually experiences a prodromal period of days to a few weeks with minor 'nervous' symptoms which are signs of a manifest slight intoxication. At an unpredictable point renal function starts to deteriorate and within hours or at the most within a few days, the patient will become severely intoxicated. By this point lithium should have been stopped and efficient detoxification measures (see Treatment of Adverse Effects, below) begun if the patient is to make a complete recovery. Other risk factors[3-5] for developing chronic intoxication include use with certain medications (see Interactions, below), older age, and the presence of other conditions such as neurogenic diabetes insipidus and thyroid dysfunction (see also Precautions, below).

In a series of 28 patients with lithium self-poisoning or therapeutic intoxication many of the features and symptoms mentioned above were noted.[6] Other workers[7,8] have also reported cases which illustrate the differences between acute and chronic toxicity encountered clinically.

Serum concentrations of lithium should be measured routinely throughout treatment to ensure that values do not rise to levels associated with toxicity. However, some patients may have concentrations considered to be toxic without showing any symptoms and others may develop signs of toxicity at therapeutic serum concentrations.[9]

Other symptoms that have been noted in case reports of lithium intoxication in individual patients include photophobia,[10] acute polyarthritis involving several large joints,[11] severe hypertension,[12] deep venous thrombophlebitis,[13] reduction of central temperature,[14] and severe leucopenia.[15]

1. Proudfoot AT. Acute poisoning with antidepressants and lithium. *Prescribers' J* 1986; **26:** 97–106.
2. Amdisen A. Clinical features and management of lithium poisoning. *Med Toxicol* 1988; **3:** 18–32.
3. Oakley PW, *et al.* Lithium toxicity: an iatrogenic problem in susceptible individuals. *Aust N Z J Psychiatry* 2001; **35:** 833–40.
4. Chen K-P, *et al.* Implication of serum concentration monitoring in patients with lithium intoxication. *Psychiatry Clin Neurosci* 2004; **58:** 25–9.
5. Montagnon F, *et al.* Lithium: poisonings and suicide prevention. *Eur Psychiatry* 2002; **17:** 92–5.
6. Dyson EH, *et al.* Self-poisoning and therapeutic intoxication with lithium. *Hum Toxicol* 1987; **6:** 325–9.
7. Ananth J, *et al.* Acute and chronic lithium toxicity: case reports and a review. *Lithium* 1992; **3:** 139–45.
8. Bailey B, McGuigan M. Lithium poisoning from a poison control center perspective. *Ther Drug Monit* 2000; **22:** 650–5.
9. Stern R. Lithium in the treatment of mood disorders. *N Engl J Med* 1995; **332:** 127–8.
10. Caplan RP, Fry AH. Photophobia in lithium intoxication. *BMJ* 1982; **285:** 1314–15.
11. Black DW, Waziri R. Arthritis associated with lithium toxicity: case report. *J Clin Psychiatry* 1984; **45:** 135–6.
12. Michaeli J, *et al.* Severe hypertension and lithium intoxication. *JAMA* 1984; **251:** 1680.
13. Lyles MR. Deep venous thrombophlebitis associated with lithium toxicity. *J Natl Med Assoc* 1984; **76:** 633–4.
14. Follézou J-Y, Bleibel J-M. Reduction of temperature and lithium poisoning. *N Engl J Med* 1985; **313:** 1609.
15. Green ST, Dunn FG. Severe leucopenia in fatal lithium poisoning. *BMJ* 1985; **290:** 517.

Treatment of Adverse Effects

In recent acute overdosage with lithium, consideration should be given to emptying the stomach if ingestion has occurred within 1 hour of presentation. However gastric lavage may be of limited value after overdosage with modified-release preparations, which do not disintegrate in the stomach and may be too large to pass through a lavage tube. Activated charcoal is of no value. Whole-bowel irrigation has been suggested although there do not appear to be clinical studies to confirm efficacy.

Further measures may involve procedures to enhance the renal clearance of lithium or its active removal. Adequate hydration should be ensured and any electrolyte imbalance corrected, but forced diuresis or diuretics are contra-indicated. Appropriate supportive care may include measures to control hypotension and convulsions. Maintenance of fluid and electrolyte balance is particularly important because of the risk of hypernatraemia. The ECG should be monitored in symptomatic patients.

In severe poisoning, haemodialysis is the treatment of choice (particularly if there is renal impairment). Although effective in reducing serum-lithium concentrations, substantial rebound increases can be expected when dialysis is stopped, and prolonged or repeated treatments may be required. Peritoneal dialysis is less effective and only appropriate if haemodialysis facilities are not available. Haemofiltration has been tried to good effect.

Serum lithium concentrations should be monitored regularly throughout treatment. Once the serum and dialysis fluid are free of lithium, it has been recommended that serum-lithium concentrations should be monitored for at least another week so that allowance can be made for delayed diffusion from body tissues.

As a result of the narrow margin between therapeutic and toxic serum concentrations, lithium poisoning may also develop during the course of therapy. In some instances temporary withdrawal of lithium therapy and giving generous amounts of sodium and fluid may be all that is required while adverse effects abate. In any serious or severe case of intoxication active measures such as dialysis and supportive measures outlined above may need to be instituted.

◊ References.

1. Smith SW, *et al.* Whole-bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med* 1991; **20:** 536–9.
2. Okusa MD, *et al.* Clinical manifestations and management of acute lithium intoxication. *Am J Med* 1994; **97:** 383–9.
3. Swartz CM, Jones P. Hyperlithemia correction and persistent delirium. *J Clin Pharmacol* 1994; **34:** 865–70.
4. Tyrer SP. Lithium intoxication: appropriate treatment. *CNS Drugs* 1996; **6:** 426–39.

Precautions

The margin between the therapeutic and the toxic concentration of lithium is narrow so therapy usually requires specialist advice, and serum concentrations should be monitored regularly under controlled conditions. Patients receiving lithium therapy should be taught to recognise the symptoms of early toxicity (see Adverse Effects, above) and, should these occur, to stop therapy and request medical aid at once. They should be warned not to compensate for an omitted dose by subsequently taking a double dose. Additionally, patients should not be switched between different formulations or preparations of lithium without therapeutic monitoring, as bioavailability may be different.

Lithium should be avoided in patients with cardiac disease or renal impairment; cardiac and renal function should be monitored regularly during treatment. It should also be avoided in Addison's disease or other conditions with a sodium imbalance and in severely debilitated or dehydrated patients.

Patients receiving lithium should be examined periodically for abnormal thyroid function, since goitre and hypothyroidism may develop. Lithium should be avoided in untreated hypothyroidism. Lithium should be used with caution in patients with myasthenia gravis because exacerbation of this disorder has been reported (see Effects on the Musculoskeletal System in Adverse Effects, above).

Lithium should be used with special care in the elderly since this group may be particularly susceptible to toxicity owing to reduced renal function.

Impaired driving performance or machine operating skills may occur in patients receiving lithium (see Driving, below).

It may be necessary to temporarily reduce or stop lithium therapy in patients suffering from vomiting, diarrhoea, intercurrent infection, excessive sweating, or any other condition that causes excessive sodium loss and hence increased serum-lithium concentrations. Conversely, increased sodium levels are likely to reduce serum-lithium concentrations. Patients taking lithium should therefore maintain an adequate fluid intake and should avoid increasing or decreasing sodium intake through dietary changes or ingestion of sodium-containing medicaments. Significant changes in caffeine intake may affect serum-lithium concentrations (see Xanthines under Interactions, below).

Lithium therapy should, where possible, be withdrawn slowly over a period of weeks to allay any concerns about relapse (see Withdrawal, below).

The risks of using lithium in pregnant patients are described under Pregnancy, below. If lithium is used during pregnancy then dose adjustments will be required to compensate for the altered renal handling.

Lithium should be temporarily stopped 24 hours before major surgery to safeguard the patient from accumulation (see under Anaesthesia, below).

Anaesthesia. The *BNF* states that lithium should be stopped 24 hours before major surgery, but the normal dose can be continued for minor surgery if fluids and electrolytes are carefully monitored. Lithium may accumulate because of reduced renal clearance associated with anaesthesia;[1] treatment should be resumed as soon as possible after surgery, when kidney function and fluid-electrolyte balance have become normal. Patients are often not allowed fluids or foods by mouth the night before surgery but patients with lithium-induced polyuria should be given fluids parenterally during the night before the operation, if they vomit copiously, or if they are unconscious for several hours.

There is no clinical evidence of interaction between lithium and anaesthetics, although lithium may prolong the action of neuromuscular blockers.[1]

1. Schou M, Hippus H. Guidelines for patients receiving lithium treatment who require major surgery. *Br J Anaesth* 1987; **59:** 809–10.

Breast feeding. Lithium is distributed into breast milk. Early reports suggested that serum concentrations in breast-fed infants were about one-third to one-half of those measured in mothers.[1] However, advice regarding the decision to breast feed remains equivocal. The American Academy of Pediatrics[2] considers that lithium should be given with caution to breast-feeding women but does not contra-indicate such use, and this is supported by some authors.[3,4] Conversely, most manufacturers in the UK and other authors[5,6] suggest that mothers receiving lithium should bottle feed their infants. It has been recommended[5] that if a mother did want to breast feed this should be done at times to avoid peak blood concentrations of lithium and the infant carefully

monitored. Medication should be withheld or breast feeding stopped if the infant developed an infection or dehydration as they would be more susceptible to the adverse effects of lithium.

1. Schou M, Amdisen A. Lithium and pregnancy—III, lithium ingestion by children breast-fed by women on lithium treatment. *BMJ* 1973; **2:** 138.
2. 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 24/11/05)
3. Schou M. Lithium treatment during pregnancy, delivery, and lactation: an update. *J Clin Psychiatry* 1990; **51:** 410–13.
4. Sykes PA, *et al.* Lithium carbonate and breast-feeding. *BMJ* 1976; **2:** 1299.
5. Ananth J. Lithium during pregnancy and lactation. *Lithium* 1993; **4:** 231–7.
6. Llewellyn A, *et al.* The use of lithium and management of women with bipolar disorder during pregnancy and lactation. *J Clin Psychiatry* 1998; **59** (suppl 6): 57–64.

Cystic fibrosis. Reduced renal excretion of lithium was demonstrated in 8 patients with cystic fibrosis compared with healthy subjects.[1] The authors recommended caution when prescribing standard doses of lithium to patients with cystic fibrosis until more definitive data were available.

1. Brager NPD, *et al.* Reduced renal fractional excretion of lithium in cystic fibrosis. *Br J Clin Pharmacol* 1996; **41:** 157–9.

Driving. In the UK, the Driver and Vehicle Licensing Authority considers that patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should cease driving pending the outcome of medical enquiry.[1] Mania or hypomania is particularly dangerous and driving should cease during the acute illness. After an isolated episode, re-licensing can be reconsidered provided the patient has remained well and stable for at least 3 months, is compliant with treatment, and has regained insight; in addition, the patient should be free from any adverse effects of medication that would impair driving. If there have been 4 or more episodes of mood swing within the previous 12 months, at least 6 months of stability will be required before re-licensing can be considered.

Treatment with antidepressant drugs, including lithium, may also be hazardous,[2] although patients may be safer drivers with medication than without.[3] Lithium has been reported[2] to adversely affect the choice reaction time (a test to assess the time taken to respond correctly to some signals but not others) to a level considered dangerous for driving. Another study has found that elderly patients taking lithium may be at an increased risk of being involved in an injurious motor vehicle accident while driving when compared to a cohort of elderly, non-lithium users.[4]

1. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (updated February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)
2. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
3. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; **35:** 193–5.
4. Etminan M, *et al.* Use of lithium and the risk of injurious motor vehicle crash in elderly adults: case-control study nested within a cohort. *BMJ* 2004; **328:** 558–9.

Pregnancy. The decision whether to continue lithium treatment during pregnancy is difficult and should involve careful consideration of the risk-benefit ratio which in some cases may favour treatment. Early case reports of mothers taking lithium during pregnancy pointed to an increased risk of congenital abnormalities with the baby's heart being mainly affected.[1] Support for this increased risk also came from a study[2] of the records of 59 children born to women who had taken lithium during pregnancy. However, another study[3] which prospectively followed 138 pregnant women being treated with lithium did not identify any difference in pregnancy outcome between them and a control group. The authors considered that lithium was not a major teratogen and felt that women with major affective disorders could continue lithium treatment during pregnancy provided that adequate fetal screening tests were carried out. A subsequent review[4] considered that the teratogenic risk was lower than previously thought, but that it would still be wise for women who wished to become pregnant to stop lithium if at all possible, at least during the period of embryogenesis. If lithium is stopped, withdrawal should be slow to prevent a relapse (see below).

There is limited evidence that lithium treatment during pregnancy may increase the risk of fetal macrosomia, premature delivery, and perinatal mortality.[1,5] Polyhydramnios (an excess of amniotic fluid) in the last trimester of pregnancy has been reported and has been attributed to fetal lithium toxicity (polyuria and diabetes insipidus).[6,7]

Monitoring of serum-lithium concentrations is particularly important during pregnancy. The renal clearance of lithium by the mother is not constant during pregnancy; in the second half of the pregnancy clearance rises gradually by 30 to 50% but falls abruptly and significantly after delivery to pre-pregnancy values.[1,8] The increased doses of lithium that may be given during pregnancy to compensate for this increased clearance may result in lithium toxicity.[8] It is generally considered[1,9,10] advisable to stop lithium during the last few days of pregnancy to reduce the risk of maternal lithium toxicity due to accumulation of lithium but it should be started again a few days later after delivery at reduced dosage because of the increased postpartum risk of manic and depressive relapse.[1,10]

Reducing the dosage during the last few days of pregnancy also helps to reduce lithium concentrations in the neonate and avoid associated adverse effects.[1,9] Adverse effects that have been reported in neonates exposed *in utero* to lithium include cyanosis, lethargy, flaccidity, hypotonia, poor gag and sucking reflexes, feeding problems, bradycardia, tachycardia, goitre, hypothyroidism, nephrogenic diabetes, and jaundice;[9-12] withdrawal symptoms have also been observed.

1. Schou M. Lithium treatment during pregnancy, delivery, and lactation: an update. *J Clin Psychiatry* 1990; **51:** 410–13.
2. Källén B, Tandberg A. Lithium and pregnancy: a cohort study on manic-depressive women. *Acta Psychiatr Scand* 1983; **68:** 134–9.
3. Jacobson SJ, *et al.* Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. *Lancet* 1992; **339:** 530–3.
4. Cohen LS, *et al.* A reevaluation of risk of in utero exposure to lithium. *JAMA* 1994; **271:** 146–50.
5. Troyer WA, *et al.* Association of maternal lithium exposure and premature delivery. *J Perinatol* 1993; **XIII:** 123–7.
6. Krause S, *et al.* Polyhydramnios with maternal lithium treatment. *Obstet Gynecol* 1990; **75:** 504–6.
7. Ang MS, *et al.* Maternal lithium therapy and polyhydramnios. *Obstet Gynecol* 1990; **76:** 517–19.
8. Lemoine J-M. Pregnancy, delivery and lactation. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 139–46.
9. Ananth J. Lithium during pregnancy and lactation. *Lithium* 1993; **4:** 231–7.
10. Pinelli JM, *et al.* Case report and review of the perinatal implications of maternal lithium use. *Am J Obstet Gynecol* 2002; **187:** 245–9.
11. Frassetto F, *et al.* Goiter in a newborn exposed to lithium in utero. *Ann Pharmacother* 2002; **36:** 1745–8.
12. Kozma C. Neonatal toxicity and transient neurodevelopmental deficits following prenatal exposure to lithium: another clinical report and a review of the literature. *Am J Med Genet A* 2005; **132:** 441–4.

Surgery. For comments regarding the precautions to be observed in patients undergoing surgery, see under Anaesthesia, above.

Withdrawal. Symptoms such as anxiety, tremor, fatigue, nausea, sweating, headache, sleep disturbances, diarrhoea, or blurred vision have developed within days of sudden cessation of treatment with lithium.[1] These symptoms may simply be a recurrence of the mood disorder. Uncontrolled studies of withdrawal symptoms have raised the possibility of a lithium-withdrawal state although controlled studies have been convincingly negative. It is, however, wise to reduce lithium dosage gradually rather than stop high-dosage treatment abruptly.

A frequent worry associated with stopping lithium therapy is that of relapse. Most evidence has supported the view that any relapses occurring in the first weeks after lithium withdrawal are simply part of a pattern of recurrence of bipolar disorder in general and are not indicative of a higher rate of recurrence. Some,[2] however, have found the proportion of patients relapsing on sudden withdrawal of lithium therapy to be 50%, a figure they consider to be too high to be accounted for by the natural history of the disease process. They and others[3] advise that this risk should be considered when prescribing lithium for bipolar disorder. In patients who previously had been stable on lithium for at least 18 months, the risk of early recurrence of bipolar disorder was higher when therapy was withdrawn rapidly in less than 2 weeks than when it was withdrawn gradually over 2 to 4 weeks.[4]

1. Goodnick PJ. Terminating treatment. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 115–17.
2. Mander AJ, Loudon JB. Rapid recurrence of mania following abrupt discontinuation of lithium. *Lancet* 1988; **ii:** 15–17.
3. Goodwin GM. Recurrence of mania after lithium withdrawal. *Br J Psychiatry* 1994; **164:** 149–52.
4. Faedda GL, *et al.* Outcome after rapid vs gradual discontinuation of lithium treatment in bipolar disorders. *Arch Gen Psychiatry* 1993; **50:** 448–55.

Interactions

Some diuretics may reduce lithium excretion and result in toxicity (see below for further details). Thiazide diuretics may also show a paradoxical antidiuretic effect. Consequently, diuretics should be avoided or used with caution in those receiving lithium; if used together, a reduction in the lithium dose may be appropriate. Other drugs affecting electrolyte balance may also alter lithium excretion and should be avoided if possible or used with care.

Further interactions reported with lithium are discussed below.

◊ Reviews.

1. Amdisen A. Lithium and drug interactions. *Drugs* 1982; **24:** 133–9.
2. Beeley L. Drug interactions with lithium. *Prescribers' J* 1986; **26:** 160–2.
3. Harvey NS, Merriman S. Review of clinically important drug interactions with lithium. *Drug Safety* 1994; **10:** 455–63.
4. Finley PR, *et al.* Clinical relevance of drug interactions with lithium. *Clin Pharmacokinet* 1995; **29:** 172–91.

ACE inhibitors. Giving lithium with ACE inhibitors has been reported[1-5] to increase serum-lithium concentrations, resulting in some cases in lithium toxicity. ACE inhibitors such as *captopril*,[2] *enalapril*,[1,3,5] and *lisinopril*[4,5] have been implicated, although in a study[6] of enalapril and lithium in healthy subjects, the lithium levels remained unchanged. The mechanism is unclear but it has been suggested[7] that suppression of the renin-angiotensin-aldosterone system by ACE inhibitors may be responsible. Lithium excretion by the kidney is dependent on both glomerular filtration and sodium concentration in the proximal tubule, both of which are reduced by ACE inhibitors. It has also been suggested[5] that inhibition of angiotensin II production may lead to reduced fluid intake through lack of activation of the thirst stimulus and this would enhance the tendency to volume depletion caused by natriuresis. Patients considered[7] to be at risk from this reaction would include those whose renal function is largely dependent on the effect of angiotensin II, those with congestive heart failure, and those with volume depletion.

1. Douste-Blazy P, *et al.* Angiotensin converting enzyme inhibitors and lithium treatment. *Lancet* 1986; **i:** 1448.
2. Pulik M, Lida H. Interaction lithium-inhibiteurs de l'enzyme de conversion. *Presse Med* 1988; **17:** 755.
3. Navis GJ, *et al.* Volume homeostasis, angiotensin converting enzyme inhibition, and lithium therapy. *Am J Med* 1989; **86:** 621.
4. Baldwin CM, Safferman AZ. A case of lisinopril-induced lithium toxicity. *DICP Ann Pharmacother* 1990; **24:** 946–7.
5. Correa FJ, Eiser AR. Angiotensin-converting enzyme inhibitors and lithium toxicity. *Am J Med* 1992; **93:** 108–9.
6. DasGupta K, *et al.* The effect of enalapril on serum lithium levels in healthy men. *J Clin Psychiatry* 1992; **53:** 398–400.
7. Mignat C, Unger T. Ace inhibitors: drug interactions of clinical significance. *Drug Safety* 1995; **12:** 334–47.

Analgesics. See NSAIDs and Opioid Analgesics, below.

Angiotensin II receptor antagonists. There have been case reports of lithium intoxication occurring in patients after the addition of *candesartan*,[1] *losartan*,[2] or *valsartan*[3] to their therapy. The mechanism may be similar to that for ACE inhibitors (above).

1. Zwanzger P, *et al.*. Lithium intoxication after administration of AT blockers. *J Clin Psychiatry* 2001; **62:** 208–9.
2. Blanche P, *et al.* Lithium intoxication in an elderly patient after combined treatment with losartan. *Eur J Clin Pharmacol* 1997; **52:** 501.
3. Leung M, Remick RA. Potential drug interaction between lithium and valsartan. *J Clin Psychopharmacol* 2000; **20:** 392–3.

Antidepressants. Lithium has been used to augment the effect of other antidepressants in refractory depression. However, there have been reports of adverse reactions with some of these combinations. For further details, see Antidepressants under Interactions of Phenelzine, p.418.

Antiepileptics. Severe CNS toxicity despite 'normal' serum-lithium concentrations has been described in a patient also taking *phenytoin* and *phenobarbital*.[1] Symptoms indicative of lithium toxicity have also been reported in a patient taking lithium with phenytoin alone;[2] again concentrations were not abnormal.

For reports of neurotoxicity in patients receiving *carbamazepine* and lithium, see p.474. Carbamazepine-induced renal failure has also resulted in toxic serum-lithium concentrations.[3]

1. Speirs J, Hirsch SR. Severe lithium toxicity with "normal" serum concentrations. *BMJ* 1978; **1:** 815–16.
2. MacCallum WAG. Interaction of lithium and phenytoin. *BMJ* 1980; **280:** 610–11.
3. Mayan H, *et al.* Lithium intoxication due to carbamazepine-induced renal failure. *Ann Pharmacother* 2001; **35:** 560–2.

Antimicrobials. Lithium toxicity has been reported on isolated occasions in patients receiving *doxycycline*,[1] *metronidazole*,[2] *spectinomycin*,[3] and *tetracycline*.[4]

However, it has been noted that lithium and tetracycline have been used together without serious problems in many patients and that additionally tetracycline has been used to treat the acneform skin eruptions induced by lithium.[5] It has also been found[5] that in healthy subjects lithium concentrations were decreased, rather than increased, after the addition of tetracycline but this was probably of no clinical significance.

1. Miller SC. Doxycycline-induced lithium toxicity. *J Clin Psychopharmacol* 1997; **17:** 54–5.
2. Teicher MH, *et al.* Possible nephrotoxic interaction of lithium and metronidazole. *JAMA* 1987; **257:** 3365–6.
3. Anonymous. Possible adverse drug-drug interaction report: lithium intoxication in a spectinomycin-treated patient. *Int Drug Ther Newslett* 1978; **13:** 15.
4. McGennis AJ. Lithium carbonate and tetracycline interaction. *BMJ* 1978; **1:** 1183.
5. Fankhauser MP, *et al.* Evaluation of lithium-tetracycline interaction. *Clin Pharm* 1988; **7:** 314–17.

Antimigraine drugs. For comment on the suggestion that there may be a risk of increased CNS toxicity when *sumatriptan* and lithium are given together, see p.626.

Antineoplastics. Transient decreases in serum-lithium concentration occurred in a patient given *cisplatin*.[1] The relative contributions of cisplatin itself, or the fluid loading procedure involving intravenous fluids and mannitol, or their combined effects were unclear. The interaction, however, had no apparent clinical significance in this patient although a risk of undertreatment with lithium may occur in other patients.

1. Pietruszka LJ, *et al.* Evaluation of cisplatin-lithium interaction. *Drug Intell Clin Pharm* 1985; **19:** 31–2.

Antipsychotics and anxiolytics. In the control of acute mania lithium is often too slow in onset to be used alone and therefore additional therapy with an antipsychotic may be necessary. It should be noted, however, that such combinations should be used with care as interactions and adverse reactions have occurred.

The renal excretion of lithium is increased by *chlorpromazine* treatment,[1] which means that subsequent withdrawal of chlorpromazine can result in an abrupt rise in serum-lithium concentrations.[2] The serum concentration of chlorpromazine can also be reduced by lithium,[3] and chlorpromazine toxicity may be precipitated by the abrupt withdrawal of lithium in patients previously stabilised on both drugs. Ventricular fibrillation has been described after withdrawal of lithium in a patient also taking chlorpromazine;[4] it was suggested that the chlorpromazine dose should be reduced if lithium is to be stopped.

There have been isolated reports of neurotoxicity or brain damage, characterised by delirium, seizures, encephalopathy, or an increased incidence of extrapyramidal symptoms in patients receiving lithium with *flupentixol decanoate*,[5] *fluphenazine decanoate*,[6] or high-dose *haloperidol*,[7-9] although two earlier retrospective studies of patients taking lithium with antipsychotics had failed to detect such adverse reactions.[10,11] Neurological reactions have also been reported in patients receiving lithium with *thioridazine*,[12,13] *sulpiride*,[14] *clozapine*,[15] and *risperidone*.[16] Although a causal relationship between these events and use of lithium with antipsychotics has not been fully established, patients should be monitored for signs of neurotoxicity if receiving such combinations.

A 1987 review considered that the neurotoxicity induced by lithium and antipsychotics was a rare entity.[17] Whether the combination produced any greater risk than either drug alone, and whether the neurotoxicity was a distinct diagnostic entity or simply represented atypical cases of lithium toxicity or the neuroleptic malignant syndrome, was debatable. The interaction between lithium and haloperidol might represent a form of neuroleptic malignant syndrome and that between lithium and the phenothiazines, especially thioridazine, a form of lithium toxicity. It was concluded that the risk from combination therapy was very small but that the clinician should, nevertheless, be aware of it.

Although lithium has been reported to interact with *diazepam* resulting in hypothermic episodes,[18] this may be an idiosyncratic response rather than a true drug interaction;[17] in general it was considered safe to use lithium with benzodiazepines.

1. Sletten I, *et al.* The effect of chlorpromazine on lithium excretion in psychiatric subjects. *Curr Ther Res* 1966; **8:** 441–6.
2. Pakes GE. Lithium toxicity with phenothiazine withdrawal. *Lancet* 1979; **ii:** 701.
3. Rivera-Calimlim L, *et al.* Effect of lithium on plasma chlorpromazine levels. *Clin Pharmacol Ther* 1978; **23:** 451–5.
4. Stevenson RN, *et al.* Ventricular fibrillation due to lithium withdrawal—an interaction with chlorpromazine? *Postgrad Med J* 1989; **65:** 936–8.
5. West A. Adverse effects of lithium treatment. *BMJ* 1977; **2:** 642.
6. Singh SV. Lithium carbonate/fluphenazine decanoate producing irreversible brain damage. *Lancet* 1982; **ii:** 278.
7. Cohen WJ, Cohen NH. Lithium carbonate, haloperidol, and irreversible brain damage. *JAMA* 1974; **230:** 1283–7.
8. Loudon JB, Waring H. Toxic reactions to lithium and haloperidol. *Lancet* 1976; **ii:** 1088.
9. Thomas C, *et al.* Lithium/haloperidol combinations and brain damage. *Lancet* 1982; **i:** 626.
10. Baastrup PC, *et al.* Adverse reactions in treatment with lithium carbonate and haloperidol. *JAMA* 1976; **236:** 2645–6.
11. Prakash R. Lithium-haloperidol combination and brain damage. *Lancet* 1982; **i:** 1468–9.
12. Standish-Barry HMAS, Shelly MA. Toxic neurological reaction to lithium/thioridazine. *Lancet* 1983; **i:** 771.
13. Cantor CH. Encephalopathy with lithium and thioridazine in combination. *Med J Aust* 1986; **144:** 164–5.
14. Dinan TG, O'Keane V. Acute extrapyramidal reactions following lithium and sulpiride co-administration: two case reports. *Hum Psychopharmacol Clin Exp* 1991; **6:** 67–9.
15. Blake LM, *et al.* Reversible neurologic symptoms with clozapine and lithium. *J Clin Psychopharmacol* 1992; **12:** 297–9.
16. Swanson CL, *et al.* Effects of concomitant risperidone and lithium treatment. *Am J Psychiatry* 1995; **152:** 1096.
17. Ross DR, Coffey CE. Neuroleptics and anti-anxiety agents. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 167–71.
18. Naylor GJ, McHarg A. Profound hypothermia on combined lithium carbonate and diazepam treatment. *BMJ* 1977; **2:** 22.

Benzodiazepines. See Antipsychotics and Anxiolytics, above.

Calcium-channel blockers. Neurotoxicity has been reported in a patient receiving lithium after the addition of *verapamil*.[1] Serum-lithium concentrations were still inside the accepted therapeutic range and it was considered that the similar actions of lithium and verapamil on neurosecretory processes may have been responsible. Verapamil has also been reported to decrease serum-lithium concentrations.[2] Neurotoxicity has also been reported in a patient receiving lithium and *diltiazem*[3] as well as other drugs. Psychosis, possibly induced by the use of diltiazem and lithium together, has been reported in another patient.[4]

1. Price WA, Giannini AJ. Neurotoxicity caused by lithium-verapamil synergism. *J Clin Pharmacol* 1986; **26:** 717–19.
2. Weinrauch LA, *et al.* Decreased serum lithium during verapamil therapy. *Am Heart J* 1984; **108:** 1378–80.
3. Valdiserri EV. A possible interaction between lithium and diltiazem: case report. *J Clin Psychiatry* 1985; **46:** 540–1.
4. Binder EF, *et al.* Diltiazem-induced psychosis and a possible diltiazem-lithium interaction. *Arch Intern Med* 1991; **151:** 373–4.

Central stimulants. A woman who had been stabilised on lithium treatment for 15 months developed lithium toxicity within a few days of being given *mazindol*.[1]

There is a risk of CNS toxicity due to synergistic serotonergic actions when lithium is given with *sibutramine*.

1. Hendy MS, *et al.* Mazindol-induced lithium toxicity. *BMJ* 1980; **280:** 684–5.

Diuretics. *Thiazide diuretics* produce sodium depletion by inhibiting distal tubular sodium reabsorption. The consequent increase in proximal tubular reabsorption frequently results in an increase in serum-lithium concentrations.[1] Patients who are stabilised on lithium therapy and begin taking thiazide diuretics are at significant risk of developing lithium toxicity. Toxic lithium concentrations may be seen within 3 to 5 days of starting a diuretic. *Loop diuretics* (*furosemide*, *bumetanide*, and *etacrynic acid*) seem less likely to cause lithium retention, although caution is warranted, especially in patients whose dietary sodium is restricted.[1] *Amiloride*, and probably other potassium-sparing diuretics, have no effect on lithium excretion, but *acetazolamide* increases lithium excretion. However, the diuretic action of acetazolamide is short-lived and the interaction may therefore be transient.[1]

It has therefore been suggested that if diuretic therapy is necessary in patients stabilised on lithium, the lithium dose should be reduced by 25 to 50%,[1,2] lithium concentrations measured twice weekly until re-stabilisation occurs, and that perhaps loop diuretics such as bumetanide or furosemide would be preferable.

The topic of lithium-diuretic interaction and precautions to be observed has also been discussed.[3]

1. Beeley L. Drug interactions with lithium. *Prescribers' J* 1986; **26:** 160–3.
2. Ramsay LE. Interactions that matter: diuretics and antihypertensive drugs. *Prescribers' J* 1984; **24:** 60–5.
3. Grau E. Diuretics. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 180–3.

Gastrointestinal drugs. Giving *sodium bicarbonate* with lithium has led to reduced blood-lithium concentrations, attributed to increased renal excretion of the lithium cation in response to the extra load of bicarbonate anion to be excreted.[1] *Antacids* containing combinations of *aluminium and magnesium hydroxides* and *simeticone* had no effect on the dissolution and solubility of lithium carbonate *in vitro*[2] nor on its bioavailability *in vivo*.[3]

There has been a case report describing a possible interaction between lithium and *ispaghula* where low serum concentrations of lithium may have been due to ispaghula inhibiting intestinal absorption of lithium.[4]

There is an increased risk of extrapyramidal effects and the possibility of neurotoxicity when drugs such as *metoclopramide* are given to patients receiving lithium.

Use of *cisapride* with lithium may increase the risk of ventricular arrhythmias.

1. McSwiggan C. A significant drug interaction. *Aust J Pharm* 1978; **59:** 6.
2. Schiessler DM, *et al.* Effect of antacids on lithium carbonate dissolution and solubility in vitro. *Am J Hosp Pharm* 1983; **40:** 825–8.
3. Goode DL, *et al.* Effect of antacid on the bioavailability of lithium carbonate. *Clin Pharm* 1984; **3:** 284–7.
4. Perlman BB. Interaction between lithium salts and ispaghula husk. *Lancet* 1990; **335:** 416.

Ion-exchange resins. The cation-exchange resin *sodium polystyrene sulfonate* may decrease the absorption of lithium salts.

Methyldopa. Lithium toxicity induced by methyldopa has been described on a number of occasions.[1-3] Symptoms of toxicity may occur even though serum-lithium concentrations remain within the therapeutic range.

1. Byrd GJ. Methyldopa and lithium carbonate: suspected interaction. *JAMA* 1975; **233:** 320.
2. O'Regan JB. Adverse interaction of lithium carbonate and methyldopa. *Can Med Assoc J* 1976; **115:** 385–6.
3. Osanloo E, Deglin JH. Interaction of lithium and methyldopa. *Ann Intern Med* 1980; **92:** 433–4.

Muscle relaxants. For reports of hypothermic episodes occurring with lithium and *diazepam*, see under Antipsychotics and Anxiolytics, above.

Severe aggravation of hyperkinetic symptoms occurred in 2 patients with Huntington's chorea when *baclofen* was added to their treatment with lithium and haloperidol.[1]

1. Andén N-E, *et al.* Baclofen and lithium in Huntington's chorea. *Lancet* 1973; **ii:** 93.

Neuromuscular blockers. For reports of prolongation of neuromuscular blockade by lithium see under Atracurium, p.1904. For further comments relating to surgery and anaesthesia, see under Anaesthesia in Precautions, above.

NSAIDs. Decreased clearance and increased serum concentrations of lithium, resulting in toxicity on some occasions, have been reported after use of lithium with *celecoxib*,[1] *diclofenac*,[2] *ibuprofen*,[3,4] *indometacin*,[5,6] *ketorolac*,[7,8] *mefenamic acid*,[9,10] *naproxen*,[11] *piroxicam*,[12,13] *rofecoxib*,[14-16] and *tiaprofenic acid*;[17] secondary sources have also implicated *azapropazone*, *ketoprofen*,[18] *parecoxib*, and *phenylbutazone*.[18] However, serum-lithium concentration is not increased by *sulindac*.[11,19,20] Although serum-lithium concentrations were increased in a patient receiving *aspirin*[21] this has not been substantiated in others and an interaction is considered unlikely;[6,22] it has also been pointed out that control of sodium balance is necessary in such studies[22] and in the report purporting to demonstrate an interaction the diet had not been controlled.

It has been stated that for mild occasional aches, pains, and fever paracetamol was the preferred analgesic in patients receiving lithium, although occasional doses of aspirin were acceptable.[18] Sulindac appeared to be the safest NSAID for long-term use. Diclofenac, ibuprofen, indometacin, ketoprofen, naproxen, phenylbutazone, and piroxicam should be avoided where possible but if it was necessary to use one of these drugs the maintenance dose of lithium should be reduced. It was also considered that perhaps other NSAIDs, for which no information was available at that time, should be regarded as having the potential to cause a rise in serum-lithium concentrations.

1. Slørdal L, *et al.* A life-threatening interaction between lithium and celecoxib. *Br J Clin Pharmacol* 2003; **55:** 413–14.
2. Reimann IW, Frölich JC. Effects of diclofenac on lithium kinetics. *Clin Pharmacol Ther* 1981; **30:** 348–52.
3. Kristoff CA, *et al.* Effect of ibuprofen on lithium plasma and red blood cell concentrations. *Clin Pharm* 1986; **5:** 51–5.
4. Ragheb M. Ibuprofen can increase serum lithium level in lithium-treated patients. *J Clin Psychiatry* 1987; **48:** 161–3.
5. Frölich JC, *et al.* Indomethacin increases plasma lithium. *BMJ* 1979; **1:** 1115–16.
6. Reimann IW, *et al.* Indomethacin but not aspirin increases plasma lithium ion levels. *Arch Gen Psychiatry* 1983; **40:** 283–6.
7. Langlois R, Paquette D. Increased serum lithium levels due to ketorolac therapy. *Can Med Assoc J* 1994; **150:** 1455–6.
8. Iyer V. Ketorolac (Toradol) induced lithium toxicity. *Headache* 1994; **34:** 442–4.
9. Shelley RK. Lithium toxicity and mefenamic acid: a possible interaction and the role of prostaglandin inhibition. *Br J Psychiatry* 1987; **151:** 847–8.
10. MacDonald J, Neale TJ. Toxic interaction of lithium carbonate and mefenamic acid. *BMJ* 1988; **297:** 1339.
11. Ragheb M, Powell AL. Lithium interaction with sulindac and naproxen. *J Clin Psychopharmacol* 1986; **6:** 150–4.
12. Kerry RJ, *et al.* Possible toxic interaction between lithium and piroxicam. *Lancet* 1983; **i:** 418–19.
13. Walbridge DG, Bazire SR. An interaction between lithium carbonate and piroxicam presenting as lithium toxicity. *Br J Psychiatry* 1985; **147:** 206–7.
14. Sajbel TA, *et al.* Pharmacokinetic effects of rofecoxib therapy on lithium. *Pharmacotherapy* 2001; **21:** 380.
15. Lundmark J, *et al.* A possible interaction between lithium and rofecoxib. *J Clin Pharmacol* 2002; **53:** 403–4.
16. Rätz Bravo AE, *et al.* Lithium intoxication as a result of an interaction with rofecoxib. *Ann Pharmacother* 2004; **38:** 1189–93.
17. Alderman CP, Lindsay KSW. Increased serum lithium concentration secondary to treatment with tiaprofenic acid and fosinopril. *Ann Pharmacother* 1996; **30:** 1411–3.
18. Furnell MM. Non-steroidal anti-inflammatory drugs. In: Johnson FN, ed. *Depression & mania: modern lithium therapy.* Oxford: IRL Press, 1987: 183–6.
19. Furnell MM, Davies J. The effect of sulindac on lithium therapy. *Drug Intell Clin Pharm* 1985; **19:** 374–6.
20. Ragheb MA, Powell AL. Failure of sulindac to increase serum lithium levels. *J Clin Psychiatry* 1986; **47:** 33–4.
21. Bendz H, Feinberg M. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* 1984; **41:** 310–11.
22. Reimann I. Aspirin increases serum lithium ion levels. *Arch Gen Psychiatry* 1984; **41:** 311.

Opioid analgesics. There is a risk of CNS toxicity due to synergistic serotonergic actions when lithium is given with *tramadol*.

Parasympathomimetics. For the effect of lithium on parasympathomimetics, see Interactions of Neostigmine, p.632.

Xanthines. It has been reported[1] that *theophylline* enhances the renal clearance of lithium, thus tending to reduce serum-lithium concentrations. Lithium blood concentrations increased by 24% when *caffeine* was eliminated from the diet of 11 patients taking lithium.[2] No toxicity was observed but these patients had been maintained on low baseline lithium concentrations; toxicity might occur in patients maintained at higher concentrations.

1. Cook BL, *et al.* Theophylline-lithium interaction. *J Clin Psychiatry* 1985; **46:** 278–9.
2. Mester R, *et al.* Caffeine withdrawal increases lithium blood levels. *Biol Psychiatry* 1995; **37:** 348–50.

Pharmacokinetics

Lithium is readily and completely absorbed from the gastrointestinal tract when taken as one of its salts. Absorption can be affected by the formulation of the preparation taken. Peak serum concentrations are obtained between 0.5 and 3 hours after ingestion from conventional tablets, capsules, or liquids; with modified-release formulations peak concentrations are delayed and may occur between 2 and 12 hours after a dose. Lithium is distributed throughout the body and distribution is complete within about 6 to 10 hours; higher concentrations occur in the bones, the thyroid gland, and portions of the brain, than in the serum.

Lithium is excreted mainly in the urine; only a small amount can be detected in the faeces, saliva, and sweat. It is not bound to plasma proteins. It crosses the placenta and is distributed into breast milk. The elimination half-life in patients with normal renal function is about 12 to 24 hours, but increases with decreasing renal

function; half-lives of up to 36 hours have been reported for elderly patients and 40 to 50 hours for patients with renal impairment. Steady-state concentrations may not, therefore, be attained until 4 to 7 days after starting treatment.

There is wide intersubject variation in the serum concentrations obtained after a given dose, and also in those required for therapeutic effect. Concentrations also vary considerably according to factors such as the dosage regimen (whether given in single or divided daily doses), renal function, the dietary regimen of the patient, the patient's state of health, the time at which the blood sample is taken, and other medication, such as sodium salts or diuretics, as well as by formulation and bioavailability. Moreover, there is only a narrow margin between the therapeutic and the toxic serum concentration of lithium. Therefore, not only is individual titration of lithium dosage essential to ensure constant appropriate concentrations for the patient, but the conditions under which the blood samples are taken for monitoring must be carefully controlled. In practice, a blood sample drawn 12 hours after the last dose of lithium following a consistent dosing schedule for 4 to 7 days is used for measurement of serum-lithium concentrations. Under these conditions the distribution of the last dose of lithium is complete, and steady-state concentrations will have been attained. The usual maintenance therapeutic serum concentrations of lithium are 0.4 to 1 mmol/litre; toxic effects may be expected at concentrations exceeding 1.5 mmol/litre. For further details regarding monitoring of serum concentrations of lithium, see under Uses and Administration, below. Estimation of lithium concentrations in other body fluids such as saliva has been investigated as a less invasive method of monitoring. However, results have been equivocal and these methods have not replaced serum monitoring in general practice.

◊ References.

1. Ward ME, *et al.* Clinical pharmacokinetics of lithium. *J Clin Pharmacol* 1994; **34:** 280–5.
2. Reiss RA, *et al.* Lithium pharmacokinetics in the obese. *Clin Pharmacol Ther* 1994; **55:** 392–8.
3. Thomsen K, Schou M. Avoidance of lithium intoxication: advice based on knowledge about the renal lithium clearance under various circumstances. *Pharmacopsychiatry* 1999; **32:** 83–6.
4. Sproule BA, *et al.* Differential pharmacokinetics of lithium in elderly patients. *Drugs Aging* 2000; **16:** 165–77.

Administration. References concerning the pharmacokinetic methods of predicting lithium dosage requirements.

1. Marken PA, *et al.* Preliminary comparison of predictive and empiric lithium dosing: impact on patient outcome. *Ann Pharmacother* 1994; **28:** 1148–52.
2. Taright N, *et al.* Nonparametric estimation of population characteristics of the kinetics of lithium from observational and experimental data: individualization of chronic dosing regimen using a new Bayesian approach. *Ther Drug Monit* 1994 **16:** 258–69.
3. Sproule BA, *et al.* Fuzzy logic pharmacokinetic modeling: application to lithium concentration prediction. *Clin Pharmacol Ther* 1997; **62:** 29–40.
4. Wright R, Crimson ML. Comparison of three a priori methods and one empirical method in predicting lithium dosage requirements. *Am J Health-Syst Pharm* 2000; **57:** 1698–1702.

Cystic fibrosis. For a reference to reduced renal excretion of lithium in patients with cystic fibrosis, see under Precautions, above.

Distribution into breast milk. For references to the distribution of lithium into breast milk, see under Precautions, above.

Pregnancy. For references to changes in renal clearance of lithium during pregnancy, see under Precautions, above.

Uses and Administration

Lithium, given as one of its salts, provides a source of lithium ions, which compete with sodium ions at various sites in the body. It thus has an action and adverse effects distinct and separate from those of other antidepressants. Its mode of action is not understood, but it is effective in the management of **mania**, **bipolar disorder**, and **recurrent unipolar depression**. Since the margin between therapeutic and toxic serum concentrations is narrow the decision to give lithium is usually based on specialist advice; lithium should not be prescribed unless facilities for monitoring serum concentrations are available.

Treatment with lithium needs to be monitored by measurement of serum concentrations, which must be adjusted for each patient to give a clinical response without evidence of toxicity. There is evidence that patients are most likely to respond to concentrations of 0.8 mmol/litre or above, but individual patients may respond to concentrations as low as 0.4 mmol/litre, and it is impossible to identify these patients beforehand. Because toxic effects are associated with concentrations above 1.5 mmol/litre, and may occur with concentrations as low as 1 mmol/litre in susceptible patients such as the elderly, it is therefore recommended that doses are adjusted to provide a serum-lithium concentration of 0.4 to 1 mmol/litre (at the lower end of this range for maintenance therapy and elderly patients). Patients must be taught to recognise the symptoms of early lithium intoxication (see Adverse Effects, above) in order to omit further doses of lithium and seek medical care should it be impending.

The dose of lithium given depends on the preparation chosen since different preparations of lithium salts vary widely in bioavailability. This can be illustrated by the recommended doses for some UK preparations:

- *Camcolit* tablets (*Norgine, UK*) containing lithium carbonate; for treatment, initially 1 to 1.5 g daily; for prophylaxis, initially 300 to 400 mg daily
- *Li-Liquid* syrup (*Rosemont, UK*) containing lithium citrate; for treatment and prophylaxis, initially 1.018 to 3.054 g daily in two divided doses (elderly or patients less than 50 kg, 509 mg twice daily)
- *Liskonum* tablets (*GlaxoSmithKline, UK*) containing lithium carbonate; for treatment, initially 450 to 675 mg twice daily (elderly, 225 mg twice daily); for prophylaxis, initially 450 mg twice daily (elderly, 225 mg twice daily)
- *Priadel* tablets (*Sanofi-Aventis, UK*) containing lithium carbonate; for treatment and prophylaxis, initially 400 mg to 1.2 g daily as a single dose or in two divided doses (elderly or patients less than 50 kg, 200 to 400 mg daily)
- *Priadel* syrup (*Sanofi-Aventis, UK*) containing lithium citrate; for treatment and prophylaxis, initially 1.04 to 3.12 g daily in two divided doses (elderly or patients less than 50 kg, 520 mg to 1.04 g daily)

Doses of lithium are initially divided throughout the day; however, when serum-lithium concentrations are stabilised once-daily dosage may be preferred.

The initial dose given is adjusted after 4 to 7 days according to the results of serum-lithium estimations obtained under controlled conditions (samples being taken 12 hours after the preceding dose). Serum-lithium concentrations are then checked once a week until the dosage has remained constant for 4 weeks. The frequency of estimations can then be reduced to about once every 3 months. Should the patient's circumstances change such that the lithium pharmacokinetics or requirements might be affected, close control of serum concentrations should be reinstated until the concentrations stabilise once more. Such circumstances could involve a change of lithium preparation, an intercurrent illness (including a urinary-tract infection), a manic or depressive phase, a change in dietary regimen or body temperature, pregnancy, or use of other drugs (in particular, sodium-containing preparations and diuretics). For further details see Precautions and Interactions, above. Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Therefore, long-term treatment should only be undertaken if it is definitely indicated. Patients need to be regularly assessed and treatment should only continue after 3 to 5 years if the benefit persists.

Lithium is also used for the management of **aggressive or self-mutilating behaviour**. The doses are similar to those used in the prophylaxis of recurrent affective disorders described above.

Lithium is not licensed in the UK for use in children; however, the *BNFC* suggests that it may be considered, on the advice of a specialist, in the management of mania, bipolar disorder, recurrent depression, and aggressive or self-mutilating behaviour in those aged 12 years and over. Suggested doses are similar to those given above.

Lithium therapy should, where possible, be withdrawn slowly over a period of weeks to allay any concerns about relapse. For further details, see Withdrawal under Precautions, above.

Other lithium salts have been used in the treatment of psychiatric disorders and these include the acetate, gluconate, glutamate, and sulfate.

Homoeopathy. Lithium carbonate has been used in homoeopathic medicines under the following names: Lithium carbonicum; Lith. carb.

Lithium citrate has been used in homoeopathic medicines under the following names: Lithium citricum.

Anxiety disorders. Lithium has been tried as augmentation therapy in the treatment of obsessive-compulsive disorder (p.952).

Bipolar disorder. Lithium's main role in the management of bipolar disorder is for prophylaxis (see p.372). It is sometimes used in the control of the acute manic stage, but, because of its slow onset of action, usually with an antipsychotic.

References.

1. Aronson JK, Reynolds DJM. Lithium. *BMJ* 1992; **305:** 1273–6.
2. Price LH, Heninger GR. Lithium in the treatment of mood disorders. *N Engl J Med* 1994; **331:** 591–8.
3. Jensen HV, *et al.* Lithium prophylaxis of manic-depressive disorder: daily lithium dosing schedule versus every second day. *Acta Psychiatr Scand* 1995; **92:** 69–74.
4. Moncrieff J. Lithium revisited: a re-examination of the placebo-controlled trials of lithium prophylaxis in manic-depressive disorder. *Br J Psychiatry* 1995; **167:** 569–74.
5. Jensen HV, *et al.* Twelve-hour brain lithium concentration in lithium maintenance treatment of manic-depressive disorder: daily versus alternate-day dosing schedule. *Psychopharmacology (Berl)* 1996; **124:** 275–8.
6. Maj M, *et al.* Late non-responders to lithium prophylaxis in bipolar patients: prevalence and predictors. *J Affect Disord* 1996; **39:** 39–42.
7. Anonymous. Using lithium safely. *Drug Ther Bull* 1999; **37:** 22–4.
8. Burgess S, *et al.* Lithium for maintenance treatment of mood disorders. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 24/11/05).
9. Sproule B. Lithium in bipolar disorder: can drug concentrations predict therapeutic effect? *Clin Pharmacokinet* 2002; **41:** 639–60.
10. Geddes JR, *et al.* Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. *Am J Psychiatry* 2004; **161:** 217–22.

Depression. Lithium may be used in the treatment and prophylaxis of recurrent unipolar depression, usually when standard antidepressants have failed (p.373). Lithium is also used to augment the efficacy of other antidepressants in refractory cases.

References.

1. Heit S, Nemeroff CB. Lithium augmentation of antidepressants in treatment-refractory depression. *J Clin Psychiatry* 1998; **59** (suppl 6): 28–33.
2. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol* 1999; **19:** 427–34. Correction. *ibid.* 2000; **20:** 287.
3. Sackeim HA, *et al.* Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy; a randomized controlled trial. *JAMA* 2001; **285:** 1299–1307.

Disturbed behaviour. For mention of lithium in the management of children with disturbed behaviour see p.954.

Headache. Lithium is one of a number of drugs tried in cluster headache (p.616) to prevent headache attacks during cluster periods when ergotamine is ineffective or has had to be withdrawn. In a double-blind study[1] lithium and verapamil were found to be of similar efficacy for cluster headache prophylaxis although verapamil appeared to produce fewer adverse effects. However, in a later placebo-controlled trial[2] lithium was found to be no more effective than the placebo and the trial was stopped early.

1. Bussone G, *et al.* Double blind comparison of lithium and verapamil in cluster headache prophylaxis. *Headache* 1990; **30:** 411–17.
2. Steiner TJ, *et al.* Double-blind placebo-controlled trial of lithium in episodic cluster headache. *Cephalalgia* 1997; **17:** 673–5.

Hyperthyroidism. Lithium has been tried in hyperthyroidism (p.2165), though its practical value is a matter of debate and, rarely, it may even cause hyperthyroidism (see Effects on the Endocrine System in Adverse Effects, above). Pretreatment with lithium has also been reported to prolong the exposure of the thyroid to radioactive iodine in patients with Graves' thyrotoxicosis.[1]

1. Bogazzi F, *et al.* Treatment with lithium prevents serum thyroid hormone increase after thionamide withdrawal and radioiodine therapy in patients with Graves' disease. *J Clin Endocrinol Metab* 2002; **87:** 4490–5.

Schizophrenia. The addition of lithium to antipsychotic treatment has been tried in patients with schizophrenia (p.955) or schizoaffective disorders who fail to respond to an antipsychotic alone. The results of a meta-analysis have suggested that lithium augmentation is of some benefit, particularly in those with schizoaffective disorders, although the evidence is inconsistent.[1] However, significantly more patients with lithium augmentation left the studies early, suggesting adverse effects may be problem-

atic and the danger of an interaction between the drugs should also be borne in mind (see under Interactions, above).

1. Leucht S, *et al*. Lithium for schizophrenia revisited: a systematic review and meta-analysis of randomized controlled trials. *J Clin Psychiatry* 2004; **65:** 177–86.

Skin disorders. Some salts or derivatives of lithium (notably lithium succinate, p.1604, but also lithium gluconate) have been applied topically in preparations for seborrhoeic dermatitis.

References.

1. Dreno B, *et al*. Lithium gluconate 8% vs ketoconazole 2% in the treatment of seborrhoeic dermatitis: a multicentre, randomized study. *Br J Dermatol* 2003; **148:** 1230–6.

Preparations

BP 2008: Lithium Carbonate Tablets; Lithium Citrate Oral Solution; Prolonged-release Lithium Carbonate Tablets;
USP 31: Lithium Carbonate Capsules; Lithium Carbonate Extended-release Tablets; Lithium Carbonate Tablets; Lithium Citrate Syrup.

Proprietary Preparations (details are given in Part 3)
Arg.: Ceglution; Eskalit; Karlit; Lithiun; ***Austral.:*** Lithicarb; Quilonum; ***Austria:*** Neurolepsin; Quilonorm; ***Belg.:*** Camcolit; Maniprex; Priadel; ***Braz.:*** Carbolim; Carbolitium; Litiocar†; Neurolithium; ***Canad.:*** Carbolith; Duralith; Lithane; ***Chile:*** Cabalex†; Cade L; Carbolit; Carboron; Psicolit; ***Cz.:*** Contemnol†; ***Denm.:*** Litarex; ***Fin.:*** Lito; ***Fr.:*** Lithioderm; Neurolithium; Teralithe; ***Ger.:*** Hypnorex; leukominerase†; Li 450†; Quilonum; ***Gr.:*** Lithiofor; Milithin; ***Hong Kong:*** Camcolit; Lithicarb; Lithiofor; ***Hung.:*** Liticarb; ***India:*** Licab; Staleth; ***Indon.:*** Frimania; ***Irl.:*** Camcolit; Priadel; ***Israel:*** Licarbium; ***Ital.:*** Carbolithium; ***Jpn:*** Limas; ***Malaysia:*** Priadel†; ***Mex.:*** Carbolit; Litheum; ***Neth.:*** Camcolit; Litarex; Priadel; ***Norw.:*** Lithionit; ***NZ:*** Lithicarb; Priadel; ***Philipp.:*** Quilonium-R; ***Port.:*** Priadel; ***S.Afr.:*** Camcolit; Lentolith; Quilonum; ***Singapore:*** Camcolit; Priadel†; ***Spain:*** Plenur; ***Swed.:*** Lithionit; ***Switz.:*** Litarex; Lithiofor; Neurolithium; Priadel; Quilonorm; ***Thai.:*** Licarb; Limed; Lit-300; Phanate; ***Turk.:*** Kilonum; Lithunil; ***UK:*** Camcolit; Li-Liquid; Liskonum; Lithonate; Priadel; ***USA:*** Eskalith†; Lithobid.

Multi-ingredient: ***Austral.:*** Caprilate; ***Ger.:*** NeyDop N (Revitorgan-Dilutionen N Nr 97)†; Togal Classic; ***Spain:*** Citinoides.

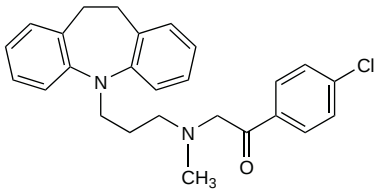
Lofepramine Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de lofepramina; Leo-640; Lofépramine, Chlorhydrate de; Lofepramini Hydrochloridum; Lopramine Hydrochloride; WHR-2908A. 5-{3-[*N*-(Chlorophenacyl)-*N*-methylamino]propyl}-10,11-5*H*-dihydrodibenz[*b,f*]azepine hydrochloride.

Лофепрамина Гидрохлорид

$C_{26}H_{27}ClN_2O,HCl$ = 455.4.

CAS — 23047-25-8 (lofepramine); 26786-32-3 (lofepramine hydrochloride).
ATC — N06AA07.
ATC Vet — QN06AA07.



(lofepramine)

Pharmacopoeias. In *Br.*
BP 2008 (Lofepramine Hydrochloride). A fine, yellowish-white to green-yellow powder with a faint characteristic odour. It exhibits polymorphism. Very slightly soluble in alcohol and in methyl alcohol; slightly soluble in acetone. Store in airtight containers. Protect from light.

Adverse Effects, Treatment, and Precautions

As for tricyclic antidepressants in general (see Amitriptyline, p.376) although it has a lower incidence of antimuscarinic adverse effects. Lofepramine should be avoided in patients with severe hepatic or severe renal impairment.

Effects on the liver. See under Amitriptyline, p.377.

Overdosage. Lofepramine may be less toxic in overdosage than earlier tricyclics.[1] An analysis of data from the Office of National Statistics in England and Wales has also shown that the risk of death after an overdose with lofepramine was not significantly different from that associated with the SSRIs which, as a group, are considered to be safer in overdose than the tricyclics.[2]

1. Reid F, Henry JA. Lofepramine overdosage. *Pharmacopsychiatry* 1990; **23:** 23–27.
2. Mason J, *et al*. Fatal toxicity associated with antidepressant use in primary care. *Br J Gen Pract* 2000; **50:** 366–70.

Interactions

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

Pharmacokinetics

Lofepramine is readily absorbed from the gastrointestinal tract; peak plasma concentrations occur within 1 hour of oral doses. Since lofepramine slows gastrointestinal transit time absorption can, however, be delayed, particularly in overdosage. It is extensively demethylated by first-pass metabolism in the liver to its active, primary metabolite, desipramine (p.387). Paths of metabolism also include *N*-oxidation and hydroxylation. The plasma half-life is about 5 hours. Lofepramine is mainly excreted in the urine, chiefly in the form of its metabolites. Up to 99% of lofepramine is bound to plasma proteins. Lofepramine is distributed into breast milk.

Uses and Administration

Lofepramine is a dibenzazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). One of its metabolites is desipramine (p.387). Lofepramine is one of the less sedating tricyclics.

In the treatment of depression (p.373) lofepramine is given orally as the hydrochloride although doses are expressed in terms of the base. Lofepramine hydrochloride 76.1 mg is equivalent to about 70 mg of lofepramine. The usual dose is the equivalent of 70 mg two or three times daily.

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

Administration in the elderly. UK licensed drug information suggests that some elderly patients may respond to lower than usual doses of lofepramine, but in a study[1] involving 46 elderly patients with various grades of depression lofepramine 70 mg once daily was no more effective than placebo at the end of 28 days of treatment.

1. Tan RSH, *et al*. The effect of low dose lofepramine in depressed elderly patients in general medical wards. *Br J Clin Pharmacol* 1994; **37:** 321–4.

Preparations

BP 2008: Lofepramine Tablets.

Proprietary Preparations (details are given in Part 3)
Cz.: Tymelyt†; ***Denm.:*** Tymelyt†; ***Ger.:*** Gamonil†; ***Irl.:*** Gamanil; ***Port.:*** Deprimil†; ***S.Afr.:*** Emdalen; ***Spain:*** Deftan†; ***Swed.:*** Tymelyt†; ***Switz.:*** Gamonil†; ***UK:*** Feprapax†; Gamanil†; Lomont.

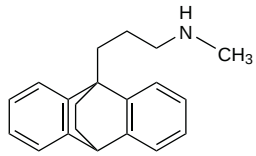
Maprotiline *(BAN, USAN, rINN)*

Maprotiliini; Maprotilin; Maprotilina; Maprotilinum. 3-(9,10-Dihydro-9,10-ethanoanthracen-9-yl)propyl(methyl)amine; *N*-Methyl-9,10-ethanoanthracene-9(10*H*)-propylamine.

Мапротилин

$C_{20}H_{23}N$ = 277.4.

CAS — 10262-69-8.
ATC — N06AA21.
ATC Vet — QN06AA21.



Maprotiline Hydrochloride *(BANM, rINNM)*

Ba-34276; Hidrocloruro de maprotilina; Maprotiliinihydrokloridi; Maprotilin Hidroklorür; Maprotiline, chlorhydrate de; Maprotilinhidroklorid; Maprotilin-hydrochlorid; Maprotilinhydroklorid; Maprotilini hydrochloridum; Maprotilino hidrochloridas.

Мапротилина Гидрохлорид

$C_{20}H_{23}N,HCl$ = 313.9.

CAS — 10347-81-6.

Pharmacopoeias. In *Chin., Eur.* (see p.vii), *Jpn,* and *US.*
Ph. Eur. 6.2 (Maprotiline Hydrochloride). A white or almost white crystalline powder. It shows polymorphism. Slightly soluble in water; soluble in alcohol; very slightly soluble in acetone; sparingly soluble in dichloromethane; freely soluble in methyl alcohol.
USP 31 (Maprotiline Hydrochloride). A fine white to off-white, practically odourless, crystalline powder. Slightly soluble in water; freely soluble in chloroform and in methyl alcohol; practically insoluble in isooctane. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

Adverse effects with maprotiline, a tetracyclic antidepressant, are broadly similar to those with tricyclic antidepressants (see Amitriptyline, p.376) but antimuscarinic effects are less frequent.

Skin rashes seem more common with maprotiline than with tricyclic antidepressants. Seizures have occurred in patients with no prior history of such disorders as well as in those with a history of epilepsy and the risk is increased if high doses of maprotiline are given. It should not be used in patients with epilepsy or a lowered seizure threshold.

Incidence of adverse effects. By March 1985 the UK CSM[1] had received reports of the following adverse reactions associated with maprotiline from a cumulative total of 2.5 million prescriptions: convulsions (124), hepatic reactions (4), and haematological reactions (8). There had also been 454 reports of skin rashes.

1. CSM. Dangers of newer antidepressants. *Current Problems 15* 1985. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024422&RevisionSelectionMethod=LatestReleased (accessed 05/08/08)

Effects on the skin. In addition to many recorded instances of skin rashes with maprotiline (see Incidence of Adverse Effects, above) cutaneous vasculitis, which resolved on stopping therapy, has also been seen.[1]

1. Oakley AMM, Hodge L. Cutaneous vasculitis from maprotiline. *Aust N Z J Med* 1985; **15:** 256–7.

Epileptogenic effect. In a retrospective review of 186 psychiatric patients with no history of seizures, 5 of 32 patients taking maprotiline developed generalised tonic-clonic seizures, compared with 1 of 45 receiving a tricyclic antidepressant.[1] There were no seizures in the remaining patients who received other medications, or no drug treatment. Two of the 5 patients having seizures with maprotiline were taking doses of 75 to 150 mg daily, 2 were taking daily doses of 200 to 300 mg, and one patient had partial complex seizures with a daily dose of 150 mg and generalised tonic-clonic seizures after increasing the daily dose to 300 mg.

1. Jabbari B, *et al*. Incidence of seizures with tricyclic and tetracyclic antidepressants. *Arch Neurol* 1985; **42:** 480–1.

Overdosage. Apart from seizures being more common with maprotiline, features of overdosage are similar to those experienced with tricyclic antidepressant poisonings (see Adverse Effects of Amitriptyline, p.376).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p.373.

References.

1. Crome P, Newman B. Poisoning with maprotiline and mianserin. *BMJ* 1977; **2:** 260.
2. Curtis RA, *et al*. Fatal maprotiline intoxication. *Drug Intell Clin Pharm* 1984; **18:** 716–20.
3. Knudsen K, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; **288:** 601–3.
4. Crome P, Ali C. Clinical features and management of self-poisoning with newer antidepressants. *Med Toxicol* 1986; **1:** 411–20.

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

Interactions

Interactions associated with maprotiline are similar to those associated with tricyclic antidepressants (see Amitriptyline, p.379).

Pharmacokinetics

Maprotiline is slowly but completely absorbed from the gastrointestinal tract. Peak plasma concentrations are reached within 8 hours of an oral dose. It is widely distributed throughout the body and plasma protein binding is about 88 to 89%.

Maprotiline is extensively demethylated in the liver to its principal active metabolite, desmethylmaprotiline; paths of metabolism of both maprotiline and desmethylmaprotiline include *N*-oxidation, aliphatic and aromatic hydroxylation, and the formation of aromatic methoxy derivatives. In addition to desmethylmaprotiline, maprotiline-*N*-oxide is also reported to be pharmacologically active. The average elimination half-life of maprotiline is reported to be about 43 hours and that of its active metabolite even longer (range 60 to 90 hours). Maprotiline is excreted in the urine, mainly in the form of its metabolites, either in free or in conjugated form; appreciable amounts are also excreted in the faeces.

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

◊ References.

1. Maguire KP, *et al*. An evaluation of maprotiline: intravenous kinetics and comparison of two oral doses. *Eur J Clin Pharmacol* 1980; **18:** 249–54.
2. Alkalay D, *et al*. Bioavailability and kinetics of maprotiline. *Clin Pharmacol Ther* 1980; **27:** 697–703.
3. Firkusny L, Gleiter H. Maprotiline metabolism appears to cosegregate with the genetically-determined CYP2D6 polymorphic hydroxylation of debrisoquine. *Br J Clin Pharmacol* 1994; **37:** 383–8.

Uses and Administration

Maprotiline is a tetracyclic antidepressant with actions and uses similar to those of tricyclic antidepressants (see Amitriptyline, p.381). It is one of the more sedating antidepressants but antimuscarinic effects are less marked. Like the tricyclics, maprotiline is an inhibitor of the reuptake of noradrenaline; it also has weak affinity for central adrenergic (α_1) receptors.

Maprotiline is usually given orally as the hydrochloride but it has also been given by injection as the mesilate and in oral drops as the resinate.

In the treatment of depression (p.373) maprotiline hydrochloride is given in oral doses of 25 to 75 mg daily in divided doses, gradually increased to 150 mg daily if necessary; up to 225 mg daily may be required in severely depressed patients in hospital. The dosage should be adjusted after 2 weeks according to response. Because of the prolonged half-life of maprotiline the total daily dose may also be given as a single dose. A suggested initial dose for elderly patients is 25 mg daily gradually increased according to response to 50 to 75 mg daily.

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