Amitriptyline *(BAN, rINN)*

Amitriptilina; Amitriptyliini; Amitriptylin; Amitriptylinum. 3-(10,11-Dihydro-5*H*-dibenzo[*a,d*]cycloheptен-5-ylidene)propyldimethylamine; 10,11-Dihydro-*N,N*-dimethyl-5*H*-dibenzo[*a,d*]cycloheptene-$\Delta^{5,}$-propylamine.

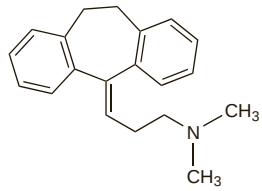
Амитриптилин

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

CAS — 50-48-6.

ATC — N06AA09.

ATC Vet — QN06AA09.



Amitriptyline Embonate *(BANM, rINNM)*

Amitriptyline, Embonate d'; Amitriptylini Embonas; Embonato de amitriptilina.

Амитриптилина Эмбонат

$(C_{20}H_{23}N)_2,C_{23}H_{16}O_6$ = 943.2.

CAS — 17086-03-2.

Pharmacopoeias. In *Br.*

BP 2008 (Amitriptyline Embonate). A pale yellow to brownish-yellow, odourless or almost odourless powder. Practically insoluble in water; slightly soluble in alcohol; freely soluble in chloroform. Protect from light.

Amitriptyline Hydrochloride *(BANM, rINNM)*

Amitriptilin Hidroklorür; Amitriptilin-hidroklorid; Amitriptilino hidrochloridas; Amitriptyliinihydrokloridi; Amitriptyline, chlorhydrate d'; Amitriptylin-hydrochlorid; Amitriptylinhydroklorid; Amitriptylini hydrochloridum; Amitryptyliny chlorowodorek; Hidrocloruro de amitriptilina.

Амитриптилина Гидрохлорид

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

CAS — 549-18-8.

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

Ph. Eur. 6.2 (Amitriptyline Hydrochloride). A white or almost white powder or colourless crystals. Freely soluble in water, in alcohol, and in dichloromethane. Protect from light.

USP 31 (Amitriptyline Hydrochloride). A white or practically white, odourless or practically odourless, crystalline powder or small crystals. Freely soluble in water, in alcohol, in chloroform, and in methyl alcohol; insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.0.

Stability. Decomposition occurred when solutions of amitriptyline hydrochloride in water or phosphate buffers were autoclaved at 115° to 116° for 30 minutes in the presence of excess oxygen.[1]

The decomposition of amitriptyline as the hydrochloride in buffered aqueous solution stored at 80° in the dark was accelerated by metal ions.[2] Disodium edetate 0.1% significantly reduced the decomposition rate of these amitriptyline solutions but propyl gallate and hydroquinone were less effective. Sodium metabisulfite produced an initial lowering of amitriptyline concentration and subsequently an acceleration of decomposition. The rate of decomposition was also much greater in amber glass ampoules than in clear glass ones (the metal ion content of amber glass is higher than that of clear glass). However, there were considerable variations between different batches of amber glass and, since amitriptyline is photolabile, its solutions are likely to be stored in amber containers.

Solutions of amitriptyline hydrochloride in water are stable for at least 8 weeks at room temperature if protected from light either by storage in a cupboard or in amber containers.[3] Decomposition to ketone and, to a lesser extent, other unidentified products was found to occur on exposure to light.

1. Enever RP, *et al.* Decomposition of amitriptyline hydrochloride in aqueous solution: identification of decomposition products. *J Pharm Sci* 1975; **64:** 1497–9.
2. Enever RP, *et al.* Factors influencing decomposition rate of amitriptyline hydrochloride in aqueous solution. *J Pharm Sci* 1977; **66:** 1087–9.
3. Buckles J, Walters V. The stability of amitriptyline hydrochloride in aqueous solution. *J Clin Pharm* 1976; **1:** 107–12.

Adverse Effects

Many adverse effects of amitriptyline and similar tricyclic antidepressants are caused by their antimuscarinic actions. Antimuscarinic effects are relatively common and occur before an antidepressant effect is obtained. They include dry mouth, constipation occasionally leading to paralytic ileus, urinary retention, blurred vision and disturbances in accommodation, increased intra-ocular pressure, and hyperthermia. Tolerance is often achieved if treatment is continued and adverse effects may be less troublesome if treatment is begun with small doses and then increased gradually, although this may delay the clinical response.

Drowsiness may also be common, although a few tricyclic antidepressants possess little or no sedative potential and may produce nervousness and insomnia. Other neurological adverse effects include headache, peripheral neuropathy, tremor, ataxia, epileptiform seizures, tinnitus, and occasional extrapyramidal symptoms including speech difficulties (dysarthria). Confusion, hallucinations, or delirium may occur, particularly in the elderly, and mania or hypomania, and behavioural disturbances (particularly in children) have been reported.

Gastrointestinal complaints include sour or metallic taste, stomatitis, and gastric irritation with nausea and vomiting.

Effects on the cardiovascular system are discussed in more detail below. Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly.

Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported and, rarely, cholestatic jaundice and blood disorders, including eosinophilia, bone-marrow depression, thrombocytopenia, leucopenia, and agranulocytosis.

Endocrine effects include testicular enlargement, gynaecomastia and breast enlargement, and galactorrhoea. Sexual dysfunction may also occur. Changes in blood sugar concentrations may also occur, and, very occasionally, hyponatraemia associated with inappropriate secretion of antidiuretic hormone.

Other adverse effects that have been reported are increased appetite with weight gain (or occasionally anorexia with weight loss). Sweating may be a problem.

Symptoms of **overdosage** may include excitement and restlessness with marked antimuscarinic effects, including dryness of the mouth, hot dry skin, dilated pupils, tachycardia, urinary retention, and intestinal stasis. Severe symptoms include unconsciousness, convulsions and myoclonus, hyperreflexia, hypothermia, hypotension, metabolic acidosis, and respiratory and cardiac depression, with life-threatening cardiac arrhythmias that may recur some days after apparent recovery. Delirium, with confusion, agitation and hallucinations, is common during recovery.

Antimuscarinic and antihistaminic properties. Studies *in vitro*[1] showed antidepressant affinities for human muscarinic acetylcholine receptors and therefore the likelihood of antimuscarinic effects to be, in descending order:

- amitriptyline
- protriptyline
- clomipramine
- trimipramine
- doxepin
- imipramine
- nortriptyline
- desipramine
- amoxapine
- maprotiline
- trazodone

The effect of affinities for other receptor sites was less certain, although those antidepressants with high affinity for histamine H_1 receptors might be expected to be more sedating. Affinities for *murine* histamine H_1 receptors in descending order were:

- doxepin
- trimipramine
- amitriptyline
- maprotiline
- amoxapine
- nortriptyline
- imipramine
- clomipramine
- protriptyline
- trazodone
- desipramine

1. Richelson E. Antimuscarinic and other receptor-blocking properties of antidepressants. *Mayo Clin Proc* 1983; **58:** 40–6.

Effects on the blood. After a case report of agranulocytosis linked with imipramine, review of the literature suggested that agranulocytosis associated with tricyclic antidepressant use was a rare idiosyncratic condition, resulting from a direct toxic effect rather than an allergic mechanism, and particularly affected the elderly from 4 to 8 weeks after beginning treatment.[1]

Between 1963 and 1993 the UK CSM received 912 reports of drug-induced agranulocytosis of which 38 were due to tricyclic antidepressants (12 fatal) and 1499 cases of neutropenia of which 46 were due to tricyclics (none fatal).[2] In a report[3] on a patient who developed aplastic anaemia associated with use of remoxipride and dosulepin it was noted that up to May 1993 the CSM had also received 11 reports of aplastic anaemia secondary to use of dosulepin.

Neutropenia reported[4] in a patient after separate exposure to imipramine and nortriptyline, indicated that there might be cross-intolerance between the tricyclic antidepressants and if neutropenia developed with one member of the group the use of others on future occasions should be avoided.

1. Albertini RS, Penders TM. Agranulocytosis associated with tricyclics. *J Clin Psychiatry* 1978; **39:** 483–5.
2. CSM/MCA. Drug-induced neutropenia and agranulocytosis. *Current Problems* 1993; **19:** 10–11. Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024456&RevisionSelectionMethod=LatestReleased (accessed 14/08/08)
3. Philpott NJ, *et al.* Aplastic anaemia and remoxipride. *Lancet* 1993; **342:** 1244–5.
4. Draper BM, Manoharan A. Neutropenia with cross-intolerance between two tricyclic antidepressant agents. *Med J Aust* 1987; **146:** 452–3.

Effects on the cardiovascular system. The cardiotoxic potential of tricyclic antidepressants after **overdosage** is widely acknowledged; symptoms include arrhythmias, conduction defects, and hypotension. This factor was, in part, responsible for the development of antidepressants with different chemical structures and pharmacological properties that are less cardiotoxic. It also led to some concern over whether tricyclic antidepressants had adverse effects on the heart or cardiovascular system when used in usual therapeutic doses.

Since the introduction of the tricyclic antidepressants, reports, often anecdotal, have been published of adverse cardiovascular effects at **therapeutic doses** and have included malignant hypertension with amitriptyline,[1] and cardiomyopathy in a patient who had received amitriptyline and imipramine.[2] QT prolongation, which in some cases progressed to torsade de pointes, has also been associated with the use of some tricyclics.[3,4] Sudden cardiac death in patients with pre-existing cardiac disease has been linked with amitriptyline[5-7] or imipramine,[6] although the Boston Collaborative Drug Surveillance Program failed to substantiate these findings.[8] In a more recent analysis, it has been suggested that the risk of sudden cardiac death may increase with high doses of tricyclic antidepressants.[9] Using patient medication records, it was found that the rate of sudden cardiac death in patients taking less than 100 mg of amitriptyline or its equivalent, [presumably as a daily dose although this is not specified], did not differ from that among non-users of antidepressants even in those with cardiovascular disease or other conditions considered to increase the risk of sudden death; however, the risk was significantly increased in those patients on doses of 100 mg or greater when compared to non-users, regardless of any predisposing conditions.

There have also been reports of sudden death in children given desipramine[10-12] or imipramine;[12-14] in at least some of these cases plasma concentrations were not elevated and the children had no cardiac abnormality. Again, however, evaluation of much of the evidence for the association suggests it is weak;[15] nonetheless, the American Heart Association recommends baseline ECG monitoring in children who are to be treated with tricyclic antidepressants, and a repeat ECG when steady-state dosage is achieved.[16]

Re-evaluations and reviews of this topic[17,18] concluded that the only significant or serious cardiovascular adverse effects, seen in *patients with no history* of cardiovascular disease given therapeutic doses of tricyclic antidepressants, are orthostatic hypotension and tachycardia, and that these effects may be particularly troublesome in elderly patients. However, a later study[19] also considered that prolongation of the QT interval might occur with therapeutic doses of tricyclics in non-risk patients.

In *patients with overt heart disease* it was considered[17] that increased risk was likely in those with intraventricular conduction abnormalities; in patients with a history of myocardial infarction or angina, but free of conduction defects, the use of tricyclics appeared to be primarily limited by how often they developed orthostatic hypotension and to what degree. In a re-evaluation of the risks and benefits of tricyclics in patients with ischaemic heart disease no consensus was reached.[20] In practice the authors used SSRIs or bupropion as first-choice therapy in patients with

ischaemic heart disease who were mildly or moderately depressed; tricyclics were reserved for unresponsive patients and were also used as first-choice therapy for patients with more severe depression despite cardiac risks. More recently an increased risk of myocardial infarction has been found in patients taking tricyclic antidepressants (but not SSRIs) with treatment for heart disease.[21] Results of a later case-control study[22] examining the risk of ischaemic heart disease for different types of antidepressants and individual antidepressants support these findings. After adjustment for confounders and use of other antidepressants the risk of ischaemic heart disease was significantly raised in patients who had ever taken tricyclics but not in those who had received other antidepressants. When the risk was calculated for the tricyclics amitriptyline, dosulepin, and lofepramine, and confounders had been adjusted for, an increased risk of ischaemic heart disease remained only for dosulepin with evidence of a dose-response relationship.

1. Dunn FG. Malignant hypertension associated with use of amitriptyline hydrochloride. *South Med J* 1982; **75:** 1124–5.
2. Howland JS, *et al.* Cardiomyopathy associated with tricyclic antidepressants. *South Med J* 1983; **76:** 1455–6.
3. Baker B, *et al.* Electrocardiographic effects of fluoxetine and doxepin in patients with major depressive disorder. *J Clin Psychopharmacol* 1997; **17:** 15–21.
4. Vieweg WVR, Wood MA. Tricyclic antidepressants, QT interval prolongation, and torsade de pointes. *Psychosomatics* 2004; **45:** 371–7.
5. Coull DC, *et al.* Amitriptyline and cardiac disease. *Lancet* 1970; **ii:** 590–1.
6. Moir DC, *et al.* Cardiotoxicity of amitriptyline. *Lancet* 1972; **ii:** 561–4.
7. Moir DC, *et al.* Medicines evaluation and monitoring group: a follow-up study of cardiac patients receiving amitriptyline. *Eur J Clin Pharmacol* 1973; **6:** 98–101.
8. Boston Collaborative Drug Surveillance Program. Adverse reactions to the tricyclic-antidepressant drugs: report from Boston Collaborative Drug Surveillance Program. *Lancet* 1972; **i:** 529–31.
9. Ray WA, *et al.* Cyclic antidepressants and the risk of sudden cardiac death. *Clin Pharmacol Ther* 2004; **75:** 234–41.
10. Anonymous. Sudden death in children treated with a tricyclic antidepressant. *Med Lett Drugs Ther* 1990; **32:** 53.
11. Riddle MA, *et al.* Another sudden death in a child treated with desipramine. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 792–7.
12. Varley CK, McClellan J. Case study: two additional sudden deaths with tricyclic antidepressants. *J Am Acad Child Adolesc Psychiatry* 1997; **36:** 390–4.
13. Swanson JR, *et al.* Death of two subjects due to imipramine and desipramine metabolite accumulation during chronic therapy: a review of the literature and possible mechanisms. *J Forensic Sci* 1997; **42:** 335–9.
14. Varley CK. Sudden death of a child treated with imipramine: case study. *J Child Adolesc Psychopharmacol* 2000; **10:** 321–5.
15. Biederman J, *et al.* Estimation of the association between desipramine and the risk for sudden death in 5- to 14-year-old children. *J Clin Psychiatry* 1995; **56:** 87–93.
16. Gutgesell H, *et al.* Cardiovascular monitoring of children and adolescents receiving psychotropic drugs: a statement for healthcare professionals from the Committee on Congenital Cardiac Defects, Council on Cardiovascular Disease in the Young, American Heart Association. *Circulation* 1999; **99:** 979–82. Also available at: http://circ.ahajournals.org/cgi/reprint/99/7/979 (accessed 24/11/05)
17. Glassman AH. Cardiovascular effects of tricyclic antidepressants. *Annu Rev Med* 1984; **35:** 503–11.
18. Mortensen SA. Cyclic antidepressants and cardiotoxicity. *Practitioner* 1984; **228:** 1180–3.
19. Reilly JG, *et al.* QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *Lancet* 2000; **355:** 1048–52.
20. Glassman AH, *et al.* The safety of tricyclic antidepressants in cardiac patients: risk-benefit reconsidered. *JAMA* 1993; **269:** 2673–5.
21. Cohen HW, *et al.* Excess risk of myocardial infarction in patients treated with antidepressant medications: association with use of tricyclic agents. *Am J Med* 2000; **108:** 2–8.
22. Hippisley-Cox J, *et al.* Antidepressants as risk factor for ischaemic heart disease: case-control study in primary care. *BMJ* 2001: **323:** 666–9.

EFFECTS ON THE PERIPHERAL CIRCULATION. Painful vasospastic episodes, characterised by cold and blue hands and feet, occurred in a woman each time she received imipramine 150 mg daily and also with amitriptyline, but only when the dose was increased to 200 mg daily.[1] This suggested that the ability of tricyclic antidepressants to induce vasospasm was not limited to imipramine and that the effect might be partly dose-dependent. Additionally, acrocyanosis of the hands and feet has been reported in a child receiving imipramine for nocturnal enuresis.[2]

1. Appelbaum PS, Kapoor W. Imipramine-induced vasospasm: a case report. *Am J Psychiatry* 1983; **140:** 913–15.
2. Anderson RP, Morris BAP. Acrocyanosis due to imipramine. *Arch Dis Child* 1988; **63:** 204–5.

Effects on the endocrine system. The *syndrome of inappropriate antidiuretic hormone secretion with hyponatraemia* has been reported in patients receiving tricyclics and other antidepressants. The UK CSM, commenting on reports it had received of hyponatraemia associated with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant and usually involved elderly patients.[1] Case reports of hyponatraemia in 24 patients treated with tricyclics and 20 patients treated with other antidepressants have been summarised.[2]

In a review covering the effects of drugs on *prolactin secretion*[3] it was stated that antidepressants could affect prolactin secretion by disturbing the balance of catecholaminergic inhibition and serotonergic stimulation of prolactin release, although any change is less than with antipsychotic therapy. Clomipramine and nortriptyline had been reported to stimulate prolactin release whereas amitriptyline, desipramine, and imipramine had been reported to be without effect. Such stimulation may account for symptoms of galactorrhoea or amenorrhoea reported with some tricyclics.

1. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; **20:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
3. Hell K, Wernze H. Drug-induced changes in prolactin secretion: clinical implications. *Med Toxicol* 1988; **3:** 463–98.

Effects on the gastrointestinal tract. Rare cases of ileus and pseudo-obstruction have apparently resulted from the antimuscarinic effects of tricyclic antidepressants.[1-4] An early report[1] from the UK CSM noted no evidence that any tricyclic was especially liable to cause ileus.

1. CSM. Tricyclic antidepressants and ileus. *Current Problems 3* 1978. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024410&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. McMahon AJ. Amitriptyline overdose complicated by intestinal pseudo-obstruction and caecal perforation. *Postgrad Med J* 1989; **65:** 948–9.
3. Sood A, Kumar R. Imipramine induced acute colonic pseudo-obstruction (Ogilvie's syndrome): a report of two cases. *Indian J Gastroenterol* 1996; **15:** 70–1.
4. Ross JP, *et al.* Imipramine overdose complicated by toxic megacolon. *Am Surg* 1998; **64:** 242–4.

Effects on the kidneys and urine. Haematuria has been seen in a patient receiving amitriptyline and carbamazepine;[1] carbamazepine had previously been taken alone for a long period without producing this effect.

Amitriptyline may have produced a blue-green colour in urine,[2] although it was considered to be a rare phenomenon.

1. Gillman MA, Sandyk R. Hematuria following tricyclic therapy. *Am J Psychiatry* 1984; **141:** 463–4.
2. Beeley L. *BMJ* 1986; **293:** 750.

Effects on the liver. In a report of 91 cases of hepatitis due to antidepressant therapy, 63 occurred in patients receiving the tricyclic antidepressant amineptine, sometimes with other psychotropic drugs; in about 50% of these amineptine cases, benzodiazepines had also been taken and it was postulated that the benzodiazepines may have increased the oxidation of amineptine to a toxic metabolite.[1] Most patients presented with abdominal pain and mixed liver damage with predominant cholestasis. One died after myocardial infarction, but all the others recovered. The mean amineptine dosage was 200 mg daily. In comparison, only a few cases were attributed to other tricyclic antidepressants—amitriptyline (4), clomipramine (3), and dibenzepin (1). Cross-hepatotoxicity between amineptine and clomipramine has also been reported in a patient.[2]

Hepatotoxicity has also been noted with lofepramine. The UK CSM had by the end of 1987 received 57 reports of abnormal liver function tests associated with lofepramine.[3] They included hepatic failure (1), jaundice (9), and hepatitis (5). All reactions occurred within the first 8 weeks of treatment and all were reversible on stopping the drug.

1. Lefebure B, *et al*. Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.
2. Larrey D, *et al*. Cross hepatotoxicity between tricyclic antidepressants. *Gut* 1986; **27:** 726–7.
3. CSM. Lofepramine (Gamanil) and abnormal blood tests of liver function. *Current Problems 23* 1988. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024430&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)

Effects on the mouth. The inhibition of salivation caused by tricyclic antidepressants (in this case clomipramine) has been implicated in dental caries formation.[1]

1. deVries MW, Peeters F. Dental caries with longterm use of antidepressants. *Lancet* 1995; **346:** 1640.

Effects on the nervous system. Effects on the nervous system attributed to tricyclic antidepressants include drowsiness (especially with those with antihistaminic activity), peripheral neuropathy, tremor, ataxia, confusion, and delirium. Of particular concern is a reduction in the seizure threshold (see Epileptogenic Effect, below). Extrapyramidal effects and neuroleptic malignant syndrome (see below) may also occasionally occur.

Effects on sexual function. Loss of libido and impotence are common in depression, often making the role of drugs in producing sexual dysfunction difficult to assess.[1]

Sedation due to tricyclic antidepressants may lead to loss of libido and many of the tricyclics have been reported to cause impotence.[1,2] Amitriptyline, clomipramine, desipramine, doxepin, nortriptyline, and trimipramine have been stated to delay or inhibit ejaculation, and amoxapine, imipramine, and protriptyline, also to cause painful ejaculation. However, some tricyclics have been used for their effect on ejaculation in the management of premature ejaculation (see Clomipramine, p.387).

In women, anorgasmia or delayed orgasm has been reported with amitriptyline, amoxapine, clomipramine, and imipramine,[1-3] although spontaneous orgasm associated with yawning has been reported with clomipramine.[4]

1. Beeley L. Drug-induced sexual dysfunction and infertility. *Adverse Drug React Acute Poisoning Rev* 1984; **3:** 23–42.
2. Anonymous. Drugs that cause sexual dysfunction. *Med Lett Drugs Ther* 1987; **29:** 65–70.
3. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med* 1983; **28:** 497–9.
4. McLean JD, *et al.* Unusual side effects of clomipramine associated with yawning. *Can J Psychiatry* 1983; **28:** 569–70.

Effects on the skin. Hypersensitivity reactions to tricyclic antidepressants are said to be uncommon.[1] Urticaria and angioedema have occurred, the urticaria occasionally clearing without drug withdrawal. Pruritus is also uncommon, but may be associated with transient erythema. Photosensitivity reactions are far less common than with phenothiazines; protriptyline has been the tricyclic most frequently implicated.[2,3] Rarely, exfoliative dermatitis has developed, and purpura, pigmentation, and lichen planus have been noted in isolated reports. In some cases pigmentation changes may be permanent.[4] Toxic epidermal necrolysis has been reported in a patient 2 weeks after starting therapy with amoxapine.[5] Hypersensitivity reactions to tricyclic antidepressants usually occur between 14 and 60 days after the start of treatment.[6]

Amitriptyline and fluoxetine have been implicated in the development of atypical cutaneous lymphoid hyperplasia in 8 patients, 7 of whom either had an underlying immunosuppressant systemic disease or were also receiving immunomodulatory drugs.[7] The lesions improved or resolved on stopping the antidepressant, although in some patients other factors may have contributed to lesional resolution.

1. Almeyda J. Drug reactions XIII: cutaneous reactions to imipramine and chlordiazepoxide. *Br J Dermatol* 1971; **84:** 298–9.
2. Smith AG. Drug-induced photosensitivity. *Adverse Drug React Bull* 1989; **136** (June): 508–11.
3. Harth Y, Rapoport M. Photosensitivity associated with antipsychotics, antidepressants and anxiolytics. *Drug Safety* 1996; **14:** 252–9.
4. Dean CE, Grund FM. Imipramine-associated hyperpigmentation. *Ann Pharmacother* 2003; **37:** 825–8.
5. Camisa C, Grines C. Amoxapine: a cause of toxic epidermal necrolysis? *Arch Dermatol* 1983; **119:** 709–10.
6. Quitkin F. Cross-tolerance of tricyclic antidepressant drugs. *JAMA* 1979; **241:** 1625.
7. Crowson AN, Magro CM. Antidepressant therapy: a possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131:** 925–9.

Epileptogenic effect. Seizures have been reported after therapeutic doses of tricyclic antidepressants as well as after overdosage, although the mechanism by which the seizures are induced is unclear.[1] Seizures usually appear within a few days of starting the drug or changing to a higher dose but in patients with no history of epilepsy or no predisposing medical condition the frequency seems[1] to be very low with an incidence of about 1 in 1000. An incidence of 0.4 per 1000 was reported[2] based on 16 cases out of an estimated group of 42 000 patients receiving tricyclics and who had no predisposing factors, but in another review[3] a reasonable estimate of the incidence was considered to be 3 to 6 per 1000. However, it is widely agreed that tricyclics should be used very cautiously in patients with epilepsy or those with a low convulsive threshold.

In a retrospective analysis of 1313 cases[4] of overdosage involving cyclic antidepressants, seizures occurred more commonly with the tricyclics amoxapine (24.5%) and desipramine (17.9%), and the tetracyclic maprotiline (12.2%). In another analysis of 302 consecutive cases of tricyclic overdosage a higher rate of seizures was seen with dosulepin in overdosage (13%) than other tricyclics.[5]

1. Zaccara G, *et al.* Clinical features, pathogenesis and management of drug-induced seizures. *Drug Safety* 1990; **5:** 109–51.
2. Jick SS, *et al.* Antidepressants and convulsions. *J Clin Psychopharmacol* 1992; **12:** 241–5.
3. Rosenstein DL, *et al.* Seizures associated with antidepressants: a review. *J Clin Psychiatry* 1993; **54:** 289–99.
4. Wedin GP, *et al.* Relative toxicity of cyclic antidepressants. *Ann Emerg Med* 1986; **15:** 797–804.
5. Buckley NA, *et al.* Greater toxicity in overdose of dothiepin than of other tricyclic antidepressants. *Lancet* 1994: **343:** 159–62.

Extrapyramidal effects. Extrapyramidal effects such as orofacial and choreoathetoid movements, and dyskinesias have been attributed to treatment with tricyclic antidepressants. Dysarthria has also been reported[1] and was said to be not uncommon in those taking higher doses of tricyclic antidepressants, but unusual at lower doses.[2]

Some patients with panic disorder may be sensitive to imipramine, developing symptoms of insomnia, jitteriness, and irritability.[3] Symptoms have also been seen in patients with panic disorder treated with low doses of desipramine although the symptoms usually subsided when the dose of the tricyclic was gradually increased. It has been suggested[4] that these symptoms may be related to akathisia and are more likely to occur with those tricyclics that have a more potent effect on inhibition of noradrenaline reuptake.

Reviews of adverse effects of drugs on the nervous system have also listed acute torsion dystonias and tremors[5] as being caused or exacerbated by tricyclic antidepressants.

1. Quader SE. Dysarthria: an unusual side effect of tricyclic antidepressants. *BMJ* 1977; **2:** 97.
2. Saunders M. Dysarthria with tricyclic antidepressants. *BMJ* 1977; **2:** 317.
3. Yeragani VK, *et al.* Tricyclic induced jitteriness—a form of akathisia? *BMJ* 1986; **292:** 1529.
4. Cole JO, Bodkin JA. Antidepressant drug side effects. *J Clin Psychiatry* 1990; **51** (suppl): 21–6.
5. Llau M-E, *et al.* Mouvements anormaux d'origine médicamenteuse: l'expérience d'un centre de pharmacovigilance sur cinq ans. *Therapie* 1995; **50:** 425–7.

Hypersensitivity. A hypersensitivity syndrome developed in a 24-year-old woman 3 weeks after starting amitriptyline 50 mg daily for the treatment of depression;[1] symptoms included generalised erythroderma with mild scaling, sinus tachycardia, haematological abnormalities such as eosinophilia, and raised liver enzyme values. The patient recovered after drug withdrawal and treatment with intravenous prednisolone.

See also under Effects on the Skin, above.

1. Milionis HJ, *et al.* Hypersensitivity syndrome caused by amitriptyline administration. *Postgrad Med J* 2000; **76:** 361–3.

Hyponatraemia. See Effects on the Endocrine System, above.

Neuroleptic malignant syndrome. Of 16 cases of neuroleptic malignant syndrome reported to the UK CSM by July 1986, 3 cases occurred in patients receiving a tricyclic antidepressant; amitriptyline with perphenazine had been taken by one patient and dosulepin or clomipramine alone by 2 other patients. The clomipramine case was fatal.[1] Other reports have been associated with amoxapine,[2] clomipramine alone,[3] clomipramine with triazolam,[4] and nortriptyline.[5]

1. CSM. Neuroleptic malignant syndrome—an underdiagnosed condition? *Current Problems 18* 1986. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024425&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Madakasira S. Amoxapine-induced neuroleptic malignant syndrome. *DICP Ann Pharmacother* 1989; **23:** 50–1.
3. Haddow AM, *et al.* Clomipramine induced neuroleptic malignant syndrome and pyrexia of unknown origin. *BMJ* 2004; **329:** 1333–5.
4. Domingo P, *et al.* Benign type of malignant syndrome. *Lancet* 1989; **i:** 50.
5. June R, *et al.* Neuroleptic malignant syndrome associated with nortriptyline. *Am J Emerg Med* 1999; **17:** 736–7.

Overdosage. In a 1993 report[1] tricyclic antidepressants were associated with a higher risk of fatality after suicide attempts by drug overdose compared with the non-tricyclics available at the time. Some reports[2] have considered desipramine to be associated more frequently than other tricyclic antidepressants with fatal overdosage, although others[3] assign this status to dosulepin. The *BNF* considers amitriptyline and dosulepin to be particularly dangerous in overdosage.

Later reviews continue to cite tricyclic antidepressants as one of the most commonly ingested substances in fatal cases of self-poisoning.[3,4]

1. Anonymous. Antidepressant drugs and the risk of suicide. *WHO Drug Inf* 1993; **7:** 18–20.
2. Amitai Y, Frischer H. The toxicity and dose of desipramine hydrochloride. *JAMA* 1994; **272:** 1719–20.
3. Kerr GW, *et al.* Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001; **18:** 236–41.
4. Glauser J. Tricyclic antidepressant poisoning. *Cleve Clin J Med* 2000; **67:** 704–19.

Treatment of Adverse Effects

The basis of the management of tricyclic antidepressant poisoning is intensive supportive care and symptomatic therapy.

Since tricyclic antidepressants slow gastrointestinal transit time, absorption may be delayed in overdosage. Activated charcoal may be given by mouth or nasogastric tube if more than 4 mg/kg of a tricyclic antidepressant has been ingested and the patient presents within 1 hour; a second dose may be considered after 2 hours in patients with central features of toxicity. Gastric lavage is rarely used but may be considered in life-threatening overdoses. Multiple doses of charcoal may be appropriate in patients who have ingested modified-release preparations.

The patient should be monitored for cardiac arrhythmias. UK authorities consider that although cardiac arrhythmias are of concern they are best treated by correction of hypoxia and acidosis with intravenous sodium bicarbonate; the use of antiarrhythmic drugs is best avoided. Intravenous sodium bicarbonate should also be given to treat arrhythmias or significant ECG abnormalities even in the absence of acidosis.

Convulsions can be managed by giving diazepam or lorazepam intravenously. Phenytoin should be avoided because it may increase the risk

of arrhythmias. Diazepam by mouth is usually adequate to sedate delirious patients, although large doses may be needed.

Peritoneal dialysis, haemodialysis, and measures to increase urine production are not of value in tricyclic antidepressant poisoning, and charcoal haemoperfusion is of doubtful benefit.

Precautions

The antimuscarinic effects of tricyclic antidepressants warrant care in patients with urinary retention, prostatic hyperplasia, or chronic constipation; caution has also been advised in untreated angle-closure glaucoma and in phaeochromocytoma.

The epileptogenic potential of tricyclic antidepressants requires care in patients with a history of epilepsy. In addition, because of their potential cardiotoxicity, tricyclics should be used with caution in patients with cardiovascular disease and avoided in those with heart block, cardiac arrhythmias, or in the immediate recovery period after myocardial infarction. Caution has also been recommended in patients with hyperthyroidism as tricyclics may increase the risk of developing cardiac arrhythmias.

Blood-sugar concentrations may be altered in diabetic patients.

Because tricyclic antidepressants are metabolised and inactivated in the liver they should be used with caution in patients with hepatic impairment and avoided in severe liver disease.

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

If tricyclic antidepressants are used for the depressive component of bipolar disorder, mania may be precipitated; similarly, psychotic symptoms may be aggravated if tricyclics are used for a depressive component of schizophrenia.

Drowsiness often occurs, particularly at the start of therapy, and patients, if affected, should not drive or operate machinery.

Tricyclic antidepressants may inhibit salivation and regular dental check-ups are recommended for patients on long-term therapy, particularly when taking those with marked antimuscarinic actions.

Elderly patients can be particularly sensitive to the adverse effects of tricyclic antidepressants and a reduced dose, especially initially, should be used.

Tricyclic antidepressants are not recommended for depression in children. If they are used for nocturnal enuresis in children they should be limited to short courses with a full physical examination before subsequent courses.

Tricyclic antidepressants should be withdrawn gradually to reduce the risk of withdrawal symptoms (see below).

Licensed drug information recommends that, where possible, tricyclic antidepressants should be stopped several days before elective surgery, and that they should be used with caution in patients requiring ECT; however, see also under Anaesthesia, below.

Anaesthesia. Patients receiving tricyclic antidepressants are at an increased risk of developing hypotension or cardiac arrhythmias during anaesthesia. Tricyclics may also dangerously potentiate the cardiovascular effects of vasopressor drugs such as sympathomimetics that may be required during anaesthesia. Although some licensed drug information recommends stopping tricyclics several days before elective surgery where possible, the *BNF* advises that this is unnecessary as long as the anaesthetist is informed.

Commenting on the anaesthetic considerations relevant to ECT,[1] it was considered that therapy with tricyclic antidepressants should not be a contra-indication to anaesthesia for ECT. A major consideration, though, was said to be the interaction of tricyclics with barbiturates resulting in increased sleep time and duration of anaesthesia. This meant that lower doses of barbiturate anaesthetics should be used.

Antidepressants with significant serotonergic effects such as the tricyclic clomipramine may increase the risk of bleeding during surgery; for further details see under Precautions in Fluoxetine, p.396.

1. Gaines GY, Rees DI. Electroconvulsive therapy and anesthetic considerations. *Anesth Analg* 1986; **65:** 1345–56.

Breast feeding. In general, only small amounts of tricyclic antidepressants are distributed into breast milk. Nevertheless, the American Academy of Pediatrics[1] considers that all antidepressants, including tricyclics, are drugs whose effect on nursing infants is unknown but may be of concern. In addition, most manufacturers advise that tricyclics should be avoided by the mother during breast feeding.

Case reports indicate that amitriptyline and its metabolite (nortriptyline),[2,3] clomipramine,[4] desipramine and its metabolite (2-hydroxydesipramine),[5] dosulepin and its primary metabolites (nordothiepin, dothiepin-*S*-oxide, and nordothiepin-*S*-oxide),[6] doxepin and its metabolite (*N*-desmethyldoxepin),[7-9] imipramine and its metabolite (desipramine),[10] and maprotiline[11] are all present in breast milk in concentrations similar to those in maternal blood; amoxapine and its metabolite (8-hydroxyamoxapine)[12] have also been detected in breast milk but in concentrations lower than in maternal blood. In all but two of the above cases the infants were breast fed without experiencing adverse effects and tricyclics were undetectable in the infant's blood or present only in minute amounts. In one of the affected infants,[8] adverse effects included sedation and shallow respiration. The infant's mother had received doxepin and, although doxepin was almost undetectable in the infant's serum, the desmethyl metabolite appeared to have accumulated. In the other infant, drowsiness, poor suckling, and difficulty in swallowing were noted.[9] In this case the levels of both doxepin and its desmethyl metabolite were below the lower level of quantification; however, it was considered that the infant may have been at a greater risk for adverse effects because he had also developed hyperbilirubinaemia. There were no data for the effects of amoxapine on breast-fed infants because the case reported[12] involved samples of milk taken from a woman who had galactorrhoea as an adverse effect of tricyclic use. No adverse effects were seen during a 27-month follow-up of 14 breast-fed infants whose mothers had received imipramine 100 to 225 mg daily for 4 to 24 weeks.[13]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Bader TF, Newman K. Amitriptyline in human breast milk and the nursing infant's serum. *Am J Psychiatry* 1980; **137:** 855–6.
3. Brixen-Rasmussen L, *et al.* Amitriptyline and nortriptyline excretion in human breast milk. *Psychopharmacology (Berl)* 1982; **76:** 94–5.
4. Schimmell MS, *et al.* Toxic neonatal effects following maternal clomipramine therapy. *Clin Toxicol* 1991; **29:** 479–84.
5. Stancer HC, Reed KL. Desipramine and 2-hydroxydesipramine in human breast milk and the nursing infant's serum. *Am J Psychiatry* 1986; **143:** 1597–1600.
6. Ilett KF, *et al.* The excretion of dothiepin and its primary metabolites in breast milk. *Br J Clin Pharmacol* 1992; **33:** 635–9.
7. Kemp J, *et al.* Excretion of doxepin and N-desmethyldoxepin in human milk. *Br J Clin Pharmacol* 1985; **20:** 497–9.
8. Matheson I, *et al.* Respiratory depression caused by N-desmethyldoxepin in breast milk. *Lancet* 1985; **ii:** 1124.
9. Frey OR, *et al.* Adverse effects in a newborn infant breast-fed by a mother treated with doxepin. *Ann Pharmacother* 1999; **33:** 690–3.
10. Sovner R, Orsulak PJ. Excretion of imipramine and desipramine in human breast milk. *Am J Psychiatry* 1979; **136:** 451–2.
11. Lloyd AH. Practical considerations in the use of maprotiline (Ludiomil) in general practice. *J Int Med Res* 1977; **5** (suppl 4): 122–38.
12. Gelenberg AJ. Amoxapine, a new antidepressant, appears in human milk. *J Nerv Ment Dis* 1979; **167:** 635–6.
13. Misri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. *Int J Psychiatry Med* 1991; **21:** 157–71.

Cardiovascular disease. For comments on the potential cardiotoxicity of tricyclic antidepressants and precautions to be observed in patients with pre-existing cardiovascular disorders, see under Effects on the Cardiovascular System in Adverse Effects, above.

Contact lenses. Based on reports involving amitriptyline[1] and maprotiline[2] it has been considered that the antimuscarinic action of tricyclic antidepressants may decrease tear flow enough to cause corneal drying and staining of contact lenses.[3]

1. Litovitz GL. Amitriptyline and contact lenses. *J Clin Psychiatry* 1984; **45:** 188.
2. Troiano G. Amitriptyline and contact lenses. *J Clin Psychiatry* 1985; **46:** 199.
3. Anonymous. Drugs interfering with contact lenses. *Aust J Hosp Pharm* 1987; **17:** 55–6.

Diabetes mellitus. The fact that tricyclic antidepressants may cause alterations in blood-glucose concentrations has led to the recommendation that these drugs should be used with caution in

diabetic patients. Amitriptyline has also been reported[1] to cause hypoglycaemic unawareness; a patient did not experience the usual adrenergic symptoms that preceded or accompanied her hypoglycaemic episodes.

1. Sherman KE, Bornemann M. Amitriptyline and asymptomatic hypoglycemia. *Ann Intern Med* 1988; **109:** 683–4.

Driving. While affective disorders probably adversely affect driving skill,[1,2] treatment with antidepressant drugs may also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative and antimuscarinic effects both of which are more pronounced at the start of treatment; sedative tricyclics, such as amitriptyline and doxepin, are likely to cause greater psychomotor impairment than less sedative tricyclics such as imipramine and nortriptyline.[1] However, an epidemiological study[3] was unable to confirm any increased risk of road-traffic accidents in those drivers receiving tricyclic antidepressants or SSRIs. In healthy subjects fluoxetine (an SSRI) and dosulepin appeared to have a similar but apparently small potential for impairing psychomotor and driving performance.[4]

In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that drugs such as the older tricyclic antidepressants may have pronounced antimuscarinic and antihistaminic effects which may impair driving.[5] In addition, all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. 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. Ashton H. Drugs and driving. *Adverse Drug React Bull* 1983; **98:** 360–3.
2. Cremona A. Mad drivers: psychiatric illness and driving performance. *Br J Hosp Med* 1986; **35:** 193–5.
3. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; **352:** 1331–6.
4. Ramaekers JG, *et al.* A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 1995; **39:** 397–404.
5. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (issued February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

ECT. For comments concerning the precautions to be observed in patients receiving ECT, see under Anaesthesia, above.

Epilepsy. For comments on the epileptogenic effect of tricyclic antidepressants and the need for caution in patients with a history of epilepsy or other risk factors for development of seizures, see under Epileptogenic Effect in Adverse Effects, above.

Food. A high-fibre diet reduced or abolished the effectiveness of tricyclic antidepressant therapy in 3 patients;[1] the tricyclics involved were doxepin in two patients and desipramine in one.

1. Stewart DE. High-fiber diet and serum tricyclic antidepressant levels. *J Clin Psychopharmacol* 1992; **12:** 438–40.

Gastro-oesophageal reflux disease. The antimuscarinic action of tricyclic antidepressants may cause relaxation of the lower oesophageal sphincter and could aggravate nocturnal symptoms of gastro-oesophageal reflux if given in the late evening.[1]

1. Atkinson M. Use and misuse of drugs in the treatment of gastro-oesophageal reflux. *Prescribers' J* 1982; **22:** 129–36.

Glaucoma. It has been considered by the manufacturers that tricyclic antidepressants, because of their antimuscarinic actions, should be used with caution in patients with angle-closure glaucoma or raised intra-ocular pressure. There have been few reports of glaucoma associated with tricyclics, although acute angle-closure glaucoma was reported in 4 patients with narrow angles while taking imipramine in usual doses,[1] and in another patient taking clomipramine.[2] In the latter case, the presenting sign was amaurosis fugax, caused by the combination of raised intra-ocular pressure and an abnormally large drop in blood pressure on standing.

1. Ritch R, *et al.* Oral imipramine and acute angle closure glaucoma. *Arch Ophthalmol* 1994; **112:** 67–8.
2. Schlingemann RO, *et al.* Amaurosis fugax on standing and angle-closure glaucoma with clomipramine. *Lancet* 1996; **347:** 465.

Phaeochromocytoma. Use of imipramine[1,2] or desipramine[3] has caused adverse effects such as seizures and cardiovascular abnormalities (tachycardia and hypertension or hypotension) in patients with previously undiagnosed phaeochromocytoma. It has been suggested[3] that imipramine and its metabolite, desipramine, may be particularly effective in unmasking phaeochromocytoma and that this may be a reflection of their relative potency in inhibiting the noradrenaline reuptake mechanism.

1. Kaufmann JS. Pheochromocytoma and tricyclic antidepressants. *JAMA* 1974; **229:** 1282.
2. Mok J, Swann I. Diagnosis of phaeochromocytoma after ingestion of imipramine. *Arch Dis Child* 1978; **53:** 676–7.
3. Achong MR, Keane PM. Pheochromocytoma unmasked by desipramine therapy. *Ann Intern Med* 1981; **94:** 358–9.

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

Pregnancy. Management of depression during pregnancy can be difficult, and one report[1] on experience in 8 pregnant women being treated with a tricyclic antidepressant suggested that the dose might need to be increased during the second half of pregnancy to achieve a response. There are obvious concerns about such treatment (see also Depression, p.373). However, although there have been isolated reports[2] attributing *congenital malformations* to the use of tricyclic antidepressants during pregnancy, large-scale studies and case-control data[3,4] have failed to substantiate any association.

The effects of tricyclics on *fetal neurodevelopment* were studied[5] in 80 pregnant women by later assessing global IQ of the children; no differences were seen in those exposed to tricyclics *in utero* in the first trimester compared with those exposed to fluoxetine or no adverse developmental influences. A subsequent study indicated that exposure to tricyclic antidepressants or fluoxetine throughout gestation did not appear to adversely affect cognition.[6]

Fetal tachyarrhythmia detected at 37 weeks of gestation was attributed to maternal use of dosulepin during pregnancy. When this was stopped, no abnormalities in fetal heart rate were found and an uneventful labour led to a healthy infant being delivered. However, the authors expressed concern that fetal tachycardias might result in *in-utero* cardiac failure and considered that tricyclic antidepressants should be used during pregnancy only if there were compelling reasons.[7]

Withdrawal syndromes manifesting as hypothermia and jitteriness,[8] convulsions,[9,10] or myoclonus[11] have been reported in neonates whose mothers took clomipramine during pregnancy. Management has been with phenobarbital or clomipramine. Licensed product information advises that if it is justifiable to do so, clomipramine should be withdrawn at least 7 weeks before the calculated date of delivery.

1. Wisner KL, *et al.* Tricyclic dose requirements across pregnancy. *Am J Psychiatry* 1993; **150:** 1541–2.
2. Barson AJ. Malformed infant. *BMJ* 1972; **2:** 45.
3. Greenberg G, *et al.* Maternal drug histories and congenital abnormalities. *BMJ* 1977; **2:** 853–6.
4. Winship KA, *et al.* Maternal drug histories and central nervous system anomalies. *Arch Dis Child* 1984; **59:** 1052–60.
5. Nulman I, *et al.* Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; **336:** 258–62.
6. Nulman I, *et al.* Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002; **159:** 1889–95.
7. Prentice A, Brown R. Fetal tachyarrhythmia and maternal antidepressant treatment. *BMJ* 1989; **298:** 190.
8. Musa AB, Smith CS. Neonatal effects of maternal clomipramine therapy. *Arch Dis Child* 1979; **54:** 405.
9. Cowe L, *et al.* Neonatal convulsions caused by withdrawal from maternal clomipramine. *BMJ* 1982; **284:** 1837–8.
10. Bromiker R, Kaplan M. Apparent intrauterine fetal withdrawal from clomipramine hydrochloride. *JAMA* 1994; **272:** 1722–3.
11. Bloem BR, *et al.* Clomipramine withdrawal in newborns. *Arch Dis Child Fetal Neonatal Ed* 1999; **81:** F77–F79.

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

Withdrawal. Suddenly stopping antidepressant therapy after regular use for 8 weeks or more may precipitate withdrawal symptoms. The symptoms associated with withdrawal of tricyclic antidepressants appear to form four distinct syndromes:[1]

- gastrointestinal disturbances and generalised somatic symptoms such as malaise, chills, headache, and increased perspiration, which may also be accompanied by anxiety and agitation
- sleep disturbances characterised by insomnia followed by excessive and vivid dreams
- parkinsonism or akathisia
- hypomania or mania

Tricyclic withdrawal has also resulted in cardiac arrhythmias in some patients. Withdrawal symptoms seem to be more common and more severe in children.[2]

Many of the symptoms associated with stopping tricyclics may be produced by cholinergic rebound[1] and can be minimised by a gradual reduction in dosage. The *BNF* recommends that any antidepressant, including a tricyclic, that has been given regularly for 8 weeks or more should be stopped gradually over a period of at least 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy. If withdrawal symptoms do occur, they can be managed by restarting at a dose sufficient to eliminate them, and then stopping gradually.[1,2] On the occasions that it may be necessary to stop a tricyclic abruptly, the withdrawal symptoms can be treated with a centrally active antimuscarinic such as atropine or benzatropine,[1] or alternatively, if withdrawal symptoms are just gastrointestinal, an antimuscarinic that does not cross the blood-brain barrier such as propantheline.[1] Awareness of the possibility of withdrawal syndromes helps to avoid misinterpreting new symptoms after withdrawal as evidence of relapse.

Tricyclic antidepressants have been included in some classifications as drugs of dependence because of their potential to produce withdrawal syndromes, but a review[3] of several substance abuse studies challenged this on finding no evidence of abuse or dependence of the barbiturate type developing with the tricyclics.

For reports of withdrawal symptoms in neonates born to mothers who took tricyclic antidepressants during pregnancy, and their management, see under Pregnancy, above.

1. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10:** 103–14.
2. Anonymous. Problems when withdrawing antidepressives. *Drug Ther Bull* 1986; **24:** 29–30.
3. Lichtigfeld FJ, Gillman MA. The possible abuse of and dependence on major tranquillisers and tricyclic antidepressants. *S Afr Med J* 1994; **84:** 5–6.

Interactions

Interactions involving tricyclic antidepressants often result from additive toxicity or from altered metabolism of one drug by the other. Drugs that inhibit or induce the cytochrome P450 isoenzyme CYP2D6 may affect tricyclic metabolism and produce marked alterations in plasma concentrations.

Adverse effects may be enhanced by antimuscarinic drugs or CNS depressants, including alcohol. Barbiturates and other enzyme inducers such as rifampicin and some antiepileptics can increase the metabolism of tricyclic antidepressants and may lower plasma concentrations and reduce antidepressant response. Cimetidine, methylphenidate, antipsychotics, and calcium-channel blockers can reduce the metabolism of the tricyclics, leading to the possibility of increased plasma concentrations and accompanying toxicity.

Patients taking thyroid preparations may show an accelerated response to tricyclic antidepressants and occasionally liothyronine has been used to produce this effect in patients with refractory depression. However, the use of tricyclics with thyroid hormones may precipitate cardiac arrhythmias.

The antihypertensive effects of debrisoquine, guanethidine, and clonidine may be reduced by tricyclic antidepressants. The pressor effects of sympathomimetics, especially those of the direct-acting drugs adrenaline and noradrenaline, can be enhanced by tricyclic antidepressants; however, there is no clinical evidence of dangerous interactions between adrenaline-containing local anaesthetics and tricyclic antidepressants. Great care should, however, be taken to avoid inadvertent intravenous injection of the local anaesthetic preparation.

Drugs that prolong the QT interval, including antiarrhythmics such as amiodarone or quinidine, the antihistamines astemizole and terfenadine, some antipsychotics (notably pimozide, sertindole, and thioridazine), cisapride, halofantrine, and sotalol, may increase the likelihood of ventricular arrhythmias when taken with tricyclic antidepressants. This may be exacerbated where the interacting drug (such as quinidine or some antipsychotics) also reduces tricyclic metabolism.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions including the serotonin syndrome (see p.416) may occur. For this reason an appropriate drug-free interval should elapse between stopping some types of antidepressant and starting another. Tricyclic antidepressants should not generally be given to patients receiving MAOIs or for at least 2 weeks (3 weeks if starting clomipramine or imipramine) after their withdrawal. No treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting a tricyclic. At least 1 to 2 weeks (3 weeks in the case of clomipramine or imipramine) should elapse between withdrawing a tricyclic antidepressant and starting any drug liable to provoke a serious reaction (e.g. phenelzine).

Further details concerning some of the above interactions, and others, are given below.

Alcohol. For reference to the effect of alcohol on amitriptyline, see under CNS depressants, below.

Analgesics. Doubling of plasma-doxepin concentrations with associated lethargy has been reported in a patient after the addition of *dextropropoxyphene* to the tricyclic.[1] This was consistent with previous studies indicating that dextropropoxyphene can impair the hepatic metabolism of other drugs.

For general reference to the effect of tricyclic antidepressants, notably amitriptyline and clomipramine, on *opioid analgesics*, see under Morphine, p.88.

1. Abernethy DR, *et al.* Impairment of hepatic drug oxidation by propoxyphene. *Ann Intern Med* 1982; **97:** 223–4.

Antiarrhythmics. Antiarrhythmics that prolong the QT interval may increase the likelihood of ventricular arrhythmias when given with tricyclic antidepressants. This includes various class I antiarrhythmics such as *disopyramide*, *flecainide*, *procainamide*, *propafenone*, and *quinidine*, and the class III antiarrhythmic *amiodarone*.

Raised serum-desipramine concentrations and signs of toxicity were noted[1] in a patient taking desipramine after starting treatment with digoxin and propafenone for paroxysmal atrial fibrillation. It was considered that propafenone probably reduced the metabolism and clearance of desipramine.

1. Katz MR. Raised serum levels of desipramine with the antiarrhythmic propafenone. *J Clin Psychiatry* 1991; **52:** 432–3.

Anticoagulants. For the effect of tricyclic antidepressants on anticoagulants, see under Warfarin, p.1428.

Antidepressants. Combination therapy with differing classes of antidepressants has been used successfully in the treatment of drug-resistant depression. It should be emphasised, however, that such combinations may result in interactions or enhanced adverse reactions, and should be used only under expert supervision. This practice is considered unsuitable or controversial by some authorities. For further details of the interactions between different antidepressants when used together, see Phenelzine, p.418. For details of the serotonin syndrome that can arise when two serotonergic drugs with different mechanisms of action are given, see under Adverse Effects of Phenelzine, p.416.

Antidiabetics. For the effect of tricyclic antidepressants on *sulfonylureas* and *insulin*, see Interactions, p.461 and p.449, respectively.

Antiepileptics. Antidepressants may antagonise the activity of antiepileptics by lowering the convulsive threshold.

A review[1] of drug interactions with *phenytoin* noted that although there had been reports of interactions between antiepileptics and tricyclic or related antidepressants, most involved enzyme-inducing antiepileptics other than phenytoin or phenytoin with other drugs. In the only report where phenytoin could be identified as the sole antiepileptic used, 2 patients required high doses of desipramine to achieve an antidepressant effect and to maintain plasma-desipramine concentrations in the range usually associated with therapeutic efficacy.

Carbamazepine has been reported to induce the metabolism of a number of tricyclic antidepressants (amitriptyline, desipramine, doxepin, imipramine, and nortriptyline) and to reduce their plasma concentrations. The clinical importance of the interaction is unclear. Use of nortriptyline with carbamazepine in a patient led to a decrease in serum-nortriptyline concentration requiring an increase in nortriptyline dose.[2] In another patient a prolonged QT interval was noted after use of desipramine with carbamazepine;[3] the authors hypothesised that the accelerated metabolism of desipramine had resulted in high levels of a cardiotoxic metabolite.

Valproate has been reported to increase plasma concentrations of amitriptyline,[4] clomipramine,[5] and nortriptyline.[4,6]

For the effect of the cyclic antidepressants desipramine and viloxazine on carbamazepine, see p.474. For the effects of tricyclic antidepressants on phenytoin, see p.498.

1. Nation RL, *et al.* Pharmacokinetic drug interactions with phenytoin (part II). *Clin Pharmacokinet* 1990; **18:** 131–50.
2. Brøsen K, Kragh-Sørensen P. Concomitant intake of nortriptyline and carbamazepine. *Ther Drug Monit* 1993; **15:** 258–60.
3. Baldessarini RJ, *et al.* Anticonvulsant cotreatment may increase toxic metabolites of antidepressants and other psychotropic drugs. *J Clin Psychopharmacol* 1988; **8:** 381–2.
4. Wong SL, *et al.* Effects of divalproex sodium on amitriptyline and nortriptyline pharmacokinetics. *Clin Pharmacol Ther* 1996; **60:** 48–53.
5. Fehr C, *et al.* Increase in serum clomipramine concentrations caused by valproate. *J Clin Psychopharmacol* 2000; **20:** 493–4.
6. Fu C, *et al.* Valproate/nortriptyline interaction. *J Clin Psychopharmacol* 1994; **14:** 205–6.

Antifungals. Increased serum concentrations of nortriptyline[1] or amitriptyline[2,3] have occurred in patients also taking *fluconazole*. In some patients the use of amitriptyline with fluconazole has led to syncope[3] or torsade de pointes.[4] Raised serum concentrations of nortriptyline and associated symptoms of intoxication have been reported in 2 patients during treatment with *terbinafine*;[5,6] the interaction was confirmed on rechallenge. In another case, dizziness, dry mouth, and muscle twitching were reported in a patient on long-term imipramine treatment after starting terbinafine;[7] serum imipramine concentrations were found to be elevated and symptoms subsided after the dose of imipramine was reduced. A study in healthy subjects also indicated that terbinafine similarly inhibited the metabolism of desipramine.[8]

1. Gannon RH. Fluconazole-nortriptyline drug interaction. *Ann Pharmacother* 1992; **26:** 1456.
2. Newberry DL, *et al.* A fluconazole/amitriptyline drug interaction in three male adults. *Clin Infect Dis* 1997; **24:** 270–1.
3. Robinson RF, *et al.* Syncope associated with concurrent amitriptyline and fluconazole therapy. *Ann Pharmacother* 2000; **34:** 1406–1409.
4. Dorsey ST, Biblo LA. Prolonged QT interval and torsades de pointes caused by the combination of fluconazole and amitriptyline. *Am J Emerg Med* 2000; **18:** 227–9.
5. van der Kuy P-HM, *et al.* Nortriptyline intoxication induced by terbinafine. *BMJ* 1998; **316:** 441.
6. van der Kuy P-HM, *et al.* Pharmacokinetic interaction between nortriptyline and terbinafine. *Ann Pharmacother* 2002; **36:** 1712–14.
7. Teitelbaum ML, Pearson VE. Imipramine toxicity and terbinafine. *Am J Psychiatry* 2001; **158:** 2086.
8. Madani S, *et al.* Effect of terbinafine on the pharmacokinetics and pharmacodynamics of desipramine in healthy volunteers identified as cytochrome P450 2D6 (CYP2D6) extensive metabolizers. *J Clin Pharmacol* 2002; **42:** 1211–18.

Antihypertensives. In general, the hypotensive effect of antihypertensives is enhanced by tricyclic antidepressants, but there may be antagonism of the effect of *adrenergic neurone blockers* and of *clonidine*.

Antimigraine drugs. For the effects when some tricyclics are used with *dihydroergotamine*, see p.621.

Antineoplastics. For the effects when tricyclic antidepressants are used with *altretamine*, see p.678.

Antiprotozoals. Toxic psychosis developed in a patient on amitriptyline after starting *furazolidone*, an antiprotozoal with monoamine oxidase inhibiting activity.[1]

1. Aderhold RM, Muniz CE. Acute psychosis with amitriptyline and furazolidone. *JAMA* 1970; **213:** 2080.

Antipsychotics. For a discussion of interactions between antipsychotics and tricyclic antidepressants, see *Chlorpromazine* (p.974). For details of a possible interaction between clomipramine and *clozapine*, see p.984.

Antivirals. HIV-protease inhibitors may increase the plasma concentrations of tricyclic antidepressants whose metabolism is mediated through common cytochrome P450 isoenzymes. *Ritonavir* has produced moderate increases in the plasma concentrations of desipramine and a lower initial dose of desipramine may be appropriate. Licensed product information for ritonavir has warned that a similar increase may occur for other tricyclics; monitoring of therapeutic and adverse effects is recommended when tricyclics are used with ritonavir.

Anxiolytics. For a suggestion that *benzodiazepines* may increase the oxidation of amineptine to a toxic metabolite, see under Effects on the Liver in Adverse Effects, above. For a possible interaction of desipramine and other antidepressants with *zolpidem* see p.1038.

Barbiturates. Antidepressants may antagonise the antiepileptic activity of some barbiturates by lowering the convulsive threshold.

Barbiturates can increase the metabolism of tricyclic antidepressants and thereby produce lower plasma concentrations.

For details of the interaction of tricyclic antidepressants with barbiturate anaesthetics, see under Anaesthesia in Precautions, above.

Beta blockers. Raised imipramine plasma concentrations were noted in two 9-year-old children also given *propranolol*;[1] in both cases, no significant adverse effects were reported. *Labetalol* has also increased the bioavailability of imipramine in healthy subjects and inhibited its metabolism.[2]

The risk of ventricular arrhythmias may be increased when tricyclic antidepressants are taken with *sotalol*.

1. Gillette DW, Tannery LP. Beta blocker inhibits tricyclic metabolism. *J Am Acad Child Adolesc Psychiatry* 1994; **33:** 223–4.
2. Hermann DJ, *et al.* Comparison of verapamil, diltiazem, and labetalol on the bioavailability and metabolism of imipramine. *J Clin Pharmacol* 1992; **32:** 176–83.

Calcium-channel blockers. *Diltiazem* and *verapamil* each increased the bioavailability of imipramine in healthy subjects; second-degree heart block developed in 2 subjects.[1] Diltiazem also increased the bioavailability of nortriptyline in one patient,[2] probably by reducing the first-pass metabolism of nortriptyline. Increased serum concentrations of trimipramine have been reported when taken with diltiazem,[3] although there was no evidence of toxicity.

1. Hermann DJ, *et al.* Comparison of verapamil, diltiazem, and labetalol on the bioavailability and metabolism of imipramine. *J Clin Pharmacol* 1992; **32:** 176–83.
2. Krähenbühl S, *et al.* Pharmacokinetic interaction between diltiazem and nortriptyline. *Eur J Clin Pharmacol* 1996; **49:** 417–19.
3. Cotter PA, *et al.* Asymptomatic tricyclic toxicity associated with diltiazem. *Ir J Psychol Med* 1996; **13:** 168–9.

CNS depressants. Drugs with depressant actions on the CNS may be expected to enhance the drowsiness and related effects produced by the sedating type of tricyclic antidepressants. Such an interaction may occur between *alcohol* and tricyclic antidepressants and a study has shown that alcohol decreases the hepatic first-pass extraction of amitriptyline resulting in increased free plasma-amitriptyline concentrations, especially during the period of drug absorption.[1]

The problems that may be encountered with *barbiturate anaesthetics* are discussed under Anaesthesia in Precautions, above.

1. Dorian P, *et al.* Amitriptyline and ethanol: pharmacokinetic and pharmacodynamic interaction. *Eur J Clin Pharmacol* 1983; **25:** 325–31.

Disulfiram. Acute organic brain syndrome has been reported in 2 patients receiving disulfiram after the addition of amitriptyline to their treatment.[1] It was suspected that the syndrome was potentiated by the combined action of the drugs and the synergistic elevation in dopamine concentration.

For a report of the enhancement of the disulfiram-alcohol reaction by amitriptyline, see p.2297.

1. Maany I, *et al.* Possible toxic interaction between disulfiram and amitriptyline. *Arch Gen Psychiatry* 1982; **39:** 743–4.

Dopaminergics. Serious adverse effects have been reported[1] when *selegiline*, an irreversible selective inhibitor of monoamine oxidase type B, was used with tricyclic antidepressants. In some instances effects resembled the potentially fatal serotonin syndromes reported when tricyclics are given with non-selective MAOIs (see under Phenelzine, p.416).

Some manufacturers of selegiline advise that tricyclic antidepressants should not generally be given at the same time, or for at least 2 weeks after it has been discontinued. Similarly, at least one week should elapse between withdrawing a tricyclic antidepressant and starting selegiline.

For reference to the effect of tricyclic antidepressants on *levodopa*, see p.807.

1. Anonymous. Selegiline and antidepressants: risk of serious interactions. *WHO Drug Inf* 1995; **9:** 160–1.

General anaesthetics. For the effect of amitriptyline on *enflurane*, see p.1783. For the effects of using tricyclic antidepressants with *barbiturates* see under Anaesthesia in Precautions, above.

Histamine H_2-antagonists. *Cimetidine* is a known inhibitor of hepatic metabolism of drugs and symptoms of tricyclic toxicity have been reported in patients receiving cimetidine with desipramine,[1] doxepin,[2] and imipramine;[1] there has been a report of psychosis developing in a patient given imipramine and cimetidine.[3] Elevated tricyclic concentrations during combined therapy or reductions in tricyclic concentrations after withdrawal of cimetidine have been reported for imipramine[4] and nortriptyline.[5] Studies in healthy subjects have also indicated increased bioavailability and/or impaired hepatic metabolism of amitriptyline,[6] doxepin,[7,8] and imipramine[9] during cimetidine therapy. Adjustment of tricyclic antidepressant dosage may therefore be required if cimetidine therapy is begun or stopped.

Ranitidine has been reported not to alter the pharmacokinetics of amitriptyline,[10] doxepin,[8] or imipramine.[9]

1. Miller DD, Macklin M. Cimetidine-imipramine interaction: a case report. *Am J Psychiatry* 1983; **140:** 351–2.
2. Brown BA, *et al.* Cimetidine-doxepin interaction. *J Clin Psychopharmacol* 1985; **5:** 245–7.
3. Miller ME, *et al.* Psychosis in association with combined cimetidine and imipramine treatment. *Psychosomatics* 1987; **28:** 217–19.
4. Shapiro PA. Cimetidine-imipramine interaction: case report and comments. *Am J Psychiatry* 1984; **141:** 152.
5. Miller DD, *et al.* Cimetidine's effect on steady-state serum nortriptyline concentrations. *Drug Intell Clin Pharm* 1983; **17:** 904–5.
6. Curry SH, *et al.* Cimetidine interaction with amitriptyline. *Eur J Clin Pharmacol* 1985; **29:** 429–33.
7. Abernethy DR, Todd EL. Doxepin-cimetidine interaction: increased doxepin bioavailability during cimetidine treatment. *J Clin Psychopharmacol* 1986; **6:** 8–12.
8. Sutherland DL, *et al.* The influence of cimetidine versus ranitidine on doxepin pharmacokinetics. *Eur J Clin Pharmacol* 1987; **32:** 159–64.
9. Wells BG, *et al.* The effect of ranitidine and cimetidine on imipramine disposition. *Eur J Clin Pharmacol* 1986; **31:** 285–90.
10. Curry SH, *et al.* Lack of interaction of ranitidine with amitriptyline. *Eur J Clin Pharmacol* 1987; **32:** 317–20.

Muscle relaxants. There has been an isolated report[1] of a patient taking *baclofen* for spasticity who experienced leg weakness and was unable to stand after starting treatment with nortriptyline. Symptoms improved on stopping nortriptyline but recurred when imipramine was given.

1. Silverglat MJ. Baclofen and tricyclic antidepressants: possible interaction. *JAMA* 1981; **246:** 1659.

Sex hormones. There have been anecdotal reports of interactions between tricyclic antidepressants and *oestrogens*[1-3] resulting in a lack of antidepressant response and/or tricyclic toxicity; the significance of these interactions is not, however, established.

1. Prange AJ, *et al.* Estrogen may well affect response to antidepressant. *JAMA* 1972; **219:** 143–4.
2. Khurana RC. Estrogen-imipramine interaction. *JAMA* 1972; **222:** 702–3.
3. Somani SM, Khurana RC. Mechanism of estrogen-imipramine interaction. *JAMA* 1973; **223:** 560.

Smoking. Tobacco smoke has been reported to reduce the plasma levels of tricyclic antidepressants.[1-3] The clinical significance is not, however, fully established as the plasma concentration of unbound drug may not be affected.[3] The mechanism is probably by stimulation of hepatic drug metabolism by components present in cigarette smoke.

1. Perel JM, *et al.* Pharmacodynamics of imipramine in depressed patients. *Psychopharmacol Bull* 1975; **11:** 16–18.
2. John VA, *et al.* Effects of age, cigarette smoking and the oral contraceptive on the pharmacokinetics of clomipramine and its desmethyl metabolite during chronic dosing. *J Int Med Res* 1980; **8** (suppl 3): 88–95.
3. Perry PJ, *et al.* Effects of smoking on nortriptyline plasma concentrations in depressed patients. *Ther Drug Monit* 1986; **8:** 279–84.

Sympathomimetics. The pressor effects of sympathomimetics can be enhanced by tricyclic antidepressants.

For precautions to be observed in patients on tricyclic therapy who may require sympathomimetics during anaesthesia, see under Anaesthesia in Precautions, above.

Thyroid hormones. An increase in receptor sensitivity to catecholamines produced by thyroid hormones has been proposed as the reason for an increase in response to tricyclic antidepressants given with *liothyronine*.[1,2]

1. Banki CM. Cerebrospinal fluid amine metabolites after combined amitriptyline-triiodothyronine treatment of depressed women. *Eur J Clin Pharmacol* 1977; **11:** 311–15.
2. Goodwin FK, *et al.* Potentiation of antidepressant effects by -triiodothyronine in tricyclic nonresponders. *Am J Psychiatry* 1982; **139:** 34–8.

Pharmacokinetics

Amitriptyline is readily absorbed from the gastrointestinal tract, peak plasma concentrations occurring within about 6 hours after oral doses.

Amitriptyline undergoes extensive first-pass metabolism and is demethylated in the liver by the cytochrome P450 isoenzymes CYP3A4, CYP2C9, and CYP2D6 to its primary active metabolite, nortriptyline. Other paths of metabolism of amitriptyline include hydroxylation (possibly to active metabolites) by CYP2D6 and *N*-oxidation; nortriptyline follows similar paths. Amitriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Amitriptyline and nortriptyline are widely distributed throughout the body and are extensively bound to plasma and tissue protein. Amitriptyline has been estimated to have an elimination half-life ranging from about 9 to 25 hours, which may be considerably extended in overdosage. Plasma concentrations of amitriptyline and nortriptyline vary very widely between individuals and no simple correlation with therapeutic response has been established.

Amitriptyline and nortriptyline cross the placenta and are distributed into breast milk (see Breast Feeding under Precautions, above).

◊ References.

1. Schulz P, *et al.* Discrepancies between pharmacokinetic studies of amitriptyline. *Clin Pharmacokinet* 1985; **10:** 257–68.
2. Brøsen K, Gram LF. Clinical significance of the sparteine/debrisoquine oxidation polymorphism. *Eur J Clin Pharmacol* 1989; **36:** 537–47.
3. Caccia S, Garattini S. Formation of active metabolites of psychotropic drugs: an updated review of their significance. *Clin Pharmacokinet* 1990; **18:** 434–59.
4. Wood AJJ, Zhou HH. Ethnic differences in drug disposition and responsiveness. *Clin Pharmacokinet* 1991; **20**: 350–73.
5. Llerena A, *et al.* Debrisoquin and mephenytoin hydroxylation phenotypes and CYP2D6 genotype in patients treated with neuroleptic and antidepressant agents. *Clin Pharmacol Ther* 1993; **54:** 606–11.
6. Ghahramani P, *et al.* Cytochromes P450 mediating the N-demethylation of amitriptyline. *Br J Clin Pharmacol* 1997; **43:** 137–44.

Uses and Administration

Tricyclic antidepressants such as amitriptyline were developed from phenothiazine compounds related to chlorpromazine and, as the name suggests, possess a 3-ring molecular structure. They inhibit the neuronal reuptake of noradrenaline in the CNS; some, in addition, inhibit the reuptake of serotonin (5-HT). Prevention of the reuptake of these monoamine neurotransmitters, which potentiates their action in the brain, appears to be associated with antidepressant activity. Tricyclic antidepressants also possess affinity for muscarinic and histamine H_1 receptors to varying degrees, see under Adverse Effects, above. Amitriptyline is one of the more sedating tricyclics. Antidepressants with one, two, or four rings have also been developed, and these share only some of the properties of the tricyclics.

While the sedative action and other adverse effects of amitriptyline and other tricyclics are soon apparent, it may be several weeks before any antidepressant effect is seen. After a response has been obtained, maintenance therapy should be continued at the optimum dose for at least 4 to 6 months (12 months in the elderly) to avoid relapse on stopping therapy. Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 5 years and possibly indefinitely. It is important to use doses that are sufficiently high for effective treatment, but not so high as to cause toxic effects.

Amitriptyline, a dibenzocycloheptadiene, is usually given orally as the hydrochloride and doses are expressed in terms of this salt. Amitriptyline hydrochloride is also given by intramuscular or slow intravenous injection; doses may be expressed in terms of the base or the hydrochloride. Amitriptyline hydrochloride 75 mg is equivalent to about 66.3 mg of the base. Amitriptyline has also been given orally as the embonate and as the oxide (amitriptylinoxide).

In the treatment of **depression**, amitriptyline hydrochloride is given initially in a daily dose of 50 to 75 mg orally in divided doses (or as a single dose at night). Thereafter, the dose may be gradually increased, if necessary, to 150 mg daily, the additional doses being given in the late afternoon or evening. Doses of up to 200 mg daily and, occasionally, up to 300 mg daily have been used in severely depressed patients in hospital.

Adolescent and elderly patients often have reduced tolerance to tricyclic antidepressants and UK licensed drug information states that initial doses of amitriptyline hydrochloride as low as 25 mg daily may be used in these groups, given either in divided doses or as a single dose, preferably at bedtime. The *BNF* suggests a minimum initial dose of 30 mg daily. In the UK, the use of amitriptyline in children under 16 years for the treatment of depression is not recommended.

In the initial stages of treatment, if dosage by mouth is impracticable or inadvisable, amitriptyline hydrochloride may be given by intramuscular injection, but the oral route should be substituted as soon as possible. Doses are similar to those usually given orally. The intravenous route has also been used.

Amitriptyline 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 when 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). Oral doses of amitriptyline hydrochloride that may be used are:

- 10 to 20 mg for children aged 6 to 10 years
- 25 to 50 mg for children 11 years and over

The dose should be given 30 minutes 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.

Tricyclic antidepressants, including amitriptyline, may be helpful in some **anxiety disorders** such as panic disorder, and in the management of **neuropathic pain** (see below).

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

Anxiety disorders. For the use of tricyclic antidepressants in anxiety disorders, see under Clomipramine, p.387.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment for bulimia nervosa. Antidepressants can help to reduce the frequency of overeating and some other symptoms of bulimia but relapse tends to occur when stopped. Many antidepressants have been tried, but the tricyclic desipramine and the SSRI fluoxetine have been the most commonly used and are considered to be well tolerated.

References.

1. Bacaltchuk J, *et al.* Antidepressants versus psychological treatments and their combination for bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 24/11/05).
2. Bacaltchuk J, Hay P. Antidepressants versus placebo for people with bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/11/05).

Ciguatera poisoning. Amitriptyline has relieved some of the neurological symptoms associated with ciguatera poisoning (see Mannitol, p.1331).

Cocaine dependence. For the use of tricyclic antidepressants in cocaine dependence, see under Desipramine, p.387.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs, and choice is often made on the basis of adverse effect profile. Although less well tolerated than the newer antidepressants, tricyclic antidepressants may still be chosen because of wide experience with their use and familiarity with their pharmacological actions. The more sedating tricyclics such as amitriptyline, clomipramine, dosulepin, doxepin, and trimipramine may be of value in depression with associated agitation or anxiety. The less sedating tricyclics such as amoxapine, desipramine, imipramine, lofepramine, nortriptyline, and protriptyline may be of value for withdrawn or apathetic depressed patients.

Combination therapy with differing classes of antidepressants, including the tricyclics, has been used in the treatment of refractory or drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and requires expert supervision; it is considered unsuitable or controversial by some. For further details, see Antidepressants under Interactions of Phenelzine, p.418.

References.

1. Deisenhammer EA, *et al.* Intravenous versus oral administration of amitriptyline in patients with major depression. *J Clin Psychopharmacol* 2000; **20:** 417–22.
2. Guaiana G, *et al.* Amitriptyline for depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 07/05/08).

Headache. Tricyclic antidepressants can be effective in the management of some types of headache and, although they are especially useful when the headache is accompanied by depression, their beneficial effects appear to be independent of their antidepressant action. They are used for the prophylaxis of migraine (p.616) when drugs such as propranolol have proved ineffective. Amitriptyline is the tricyclic usually used but others have been tried. It has also been investigated in children. The *BNF* suggests an adult dosage for amitriptyline in the prophylaxis of migraine of 10 mg at night, increased to a maintenance dose of 50 to 75 mg at night; the need for continuing prophylaxis should be reviewed at intervals of about 6 months. Tricyclics are also used prophylactically in the control of chronic tension-type headache (p.617) although benefit is rarely complete. Improvement is generally seen with low doses, but full antidepressant doses are necessary in the presence of underlying depression.

References.

1. Mathew NT. Prophylaxis of migraine and mixed headache: a randomized controlled study. *Headache* 1981; **21:** 105–9.
2. Pfaffenrath V, *et al.* Combination headache: practical experience with a combination of a β-blocker and an antidepressive. *Cephalalgia* 1986; **6** (suppl 5): 25–32.
3. Wörz R, Scherhag R. Treatment of chronic tension headache with doxepin or amitriptyline—results of a double-blind study. *Headache Q* 1990; **1:** 216–23.
4. Ziegler DK, *et al.* Propranolol and amitriptyline in prophylaxis of migraine: pharmacokinetic and therapeutic effects. *Arch Neurol* 1993; **50:** 825–30.
5. Pfaffenrath V, *et al.* Efficacy and tolerability of amitriptylinoxide in the treatment of chronic tension-type headache: a multi-centre controlled study. *Cephalalgia* 1994; **14:** 149–55.
6. Hershey AD, *et al.* Effectiveness of amitriptyline in the prophylactic management of childhood headaches. *Headache* 2000; **40:** 539–49.
7. Holroyd KA, *et al.* Management of chronic tension-type headache with tricyclic antidepressant medication, stress management therapy, and their combination: a randomized controlled trial. *JAMA* 2001; **285:** 2208–15.

Hiccup. Amitriptyline is one of many drugs for which there are anecdotal reports[1] of success in the treatment of intractable hiccup (p.976).

1. Stalnikowicz R, *et al.* Amitriptyline for intractable hiccups. *N Engl J Med* 1986; **315:** 64–5.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p.2148), initial treatment is usually with a central stimulant. Tricyclic antidepressants such as imipramine or desipramine are reserved for patients who fail to respond to or who are intolerant of stimulants. They may also be of use for selected patients with certain co-existing disorders.

Interstitial cystitis. Tricyclic antidepressants have been found to be of benefit in the treatment of interstitial cystitis (p.2179). In a placebo-controlled trial in 48 patients with interstitial cystitis, amitriptyline treatment (in doses ranging from 25 to 100 mg daily) significantly reduced the symptom score and improved pain and urgency when compared to placebo;[1] however, in some patients the antimuscarinic adverse effects of amitriptyline were troublesome. Amitriptyline or imipramine have also been given at night, together with methenamine hippurate during the day, in the treatment of interstitial cystitis.[2]

1. van Ophoven A, *et al.* A prospective, randomized, placebo controlled, double-blind study of amitriptyline for the treatment of interstitial cystitis. *J Urol (Baltimore)* 2004; **172:** 533–6.
2. Cardozo L. Postmenopausal cystitis. *BMJ* 1996; **313:** 129.

Irritable bowel syndrome. A tricyclic antidepressant may be tried in irritable bowel syndrome (p.1699), particularly where diarrhoea and abdominal pain are presenting symptoms.

Micturition disorders. Tricyclic antidepressants are among the drugs used as an alternative or adjunct to nonpharmacological methods for the treatment of **nocturnal enuresis** in children

(p.2180) in whom organic pathology has been excluded. However, because of their potentially fatal toxicity in overdosage, there has been concern over the safety of using tricyclics in households with children. Most experience in nocturnal enuresis has been with imipramine, but other tricyclics such as amitriptyline, nortriptyline, and clomipramine have also been used. Their mechanism of action in nocturnal enuresis is unclear. It may be the result of their antimuscarinic and antispasmodic actions as well as their effect on sleep patterns and possible stimulation of antidiuretic hormone secretion. Imipramine appears to be most effective in older children, but many patients develop tolerance and increasingly higher doses are required.

Tricyclic antidepressants are also sometimes used in the management of **urinary incontinence** (p.2180).

References.

1. Glazener CMA, *et al.* Tricyclic and related drugs for nocturnal enuresis in children. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2003 (accessed 24/11/05).

Narcoleptic syndrome. Tricyclic antidepressants are the primary treatment for cataplexy and sleep paralysis associated with narcolepsy (p.2148). Imipramine has been widely used for these symptoms although some consider clomipramine more effective. The onset of action is quicker than when used for depression and doses required appear to be lower (typically 10 to 75 mg of imipramine daily) although tolerance may develop. Doses should be titrated to provide maximal protection for the time of day when symptoms usually occur.

Pain. Tricyclic antidepressants, usually amitriptyline, are useful in alleviating some types of pain when given in subantidepressant doses. An initial oral dose of amitriptyline hydrochloride 10 to 25 mg at night increased gradually if necessary to about 75 mg daily has been suggested by the *BNF* for the management of neuropathic pain in adults. Similar doses of amitriptyline hydrochloride are also suggested by the *BNFC* for the treatment of neuropathic pain in palliative care in children aged 12 years and over; in addition, younger children aged 2 years and above may receive an initial dose of 200 to 500 micrograms/kg (to a maximum of 25 mg) once daily at night, increased if necessary to a maximum of 1 mg/kg twice daily. See also Choice of Analgesic on p.2. Chronic neuropathic pain as seen in cancer (p.5), central post-stroke pain (p.6), diabetic neuropathy (p.6), phantom limb pain (p.9), and postherpetic neuralgia (p.9) responds to therapy with tricyclics. Tricyclics are also often of benefit in the treatment of idiopathic orofacial pain (p.8), and may be of value for patients with complex regional pain syndrome (p.6). Pain and sleep quality may be improved by tricyclics in patients with fibromyalgia (see Soft-tissue Rheumatism, p.13), a condition that responds poorly to analgesics and anti-inflammatory drugs. Patients with migraine or chronic tension-type headache may also benefit from tricyclics (see Headache, above). There is little evidence for an analgesic effect of tricyclics in acute or arthritic pain.

References.

1. Onghena P, Van Houdenhove, B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. *Pain* 1992; **49:** 205–19.
2. McQuay HJ, *et al.* A systematic review of antidepressants in neuropathic pain. *Pain* 1996; **68:** 217–27.
3. 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.
4. McQuay HJ, Moore RA. Antidepressants and chronic pain. *BMJ* 1997; **314:** 763–4.
5. Joss JD. Tricyclic antidepressant use in diabetic neuropathy. *Ann Pharmacother* 1999; **33:** 996–1000.
6. Arnold LM, *et al.* Antidepressant treatment of fibromyalgia: a meta-analysis and review. *Psychosomatics* 2000; **41:** 104–13.
7. Lynch ME. Antidepressants as analgesics: a review of randomized controlled trials. *J Psychiatry Neurosci* 2001; **26:** 30–6.
8. Reisner L. Antidepressants for chronic neuropathic pain. *Curr Pain Headache Rep* 2003; **7:** 24–33.

Pathological crying or laughing. Pathological crying or laughing can result from lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressants and favourable results have been reported in double-blind studies with amitriptyline[1] and nortriptyline.[2]

1. Schiffer RB, *et al.* Treatment of pathologic laughing and weeping with amitriptyline. *N Engl J Med* 1985; **312:** 1480–2.
2. Robinson RG, *et al.* Pathological laughing and crying following stroke: validation of a measurement scale and a double-blind treatment study. *Am J Psychiatry* 1993; **150:** 286–93.

Premenstrual syndrome. For reference to the tricyclic antidepressant, clomipramine, in premenstrual syndrome, see p.387.

Schizophrenia. Antidepressants such as the tricyclics are considered worth trying as an adjunct in the treatment of patients with schizophrenia (p.955) who develop depression during the recovery phase after an acute episode of psychosis. There is, however, no clear evidence that they are effective during acute psychotic episodes or for depression during periods of remission in patients with chronic schizophrenia.[1]

1. Anonymous. The drug treatment of patients with schizophrenia. *Drug Ther Bull* 1995; **33:** 81–6.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of tricyclic antidepressants (see Effects on Sexual Function in Adverse Effects, above). Such properties have been studied as a potential form of treatment for men with premature ejaculation (see Clomipramine, p.387).

Skin disorders. See under Doxepin, p.389, for use of tricyclic antidepressants in skin disorders.

Smoking cessation. Tricyclic antidepressants are among the drugs that have been tried with varying degrees of success as alternatives to nicotine replacement therapy (NRT) to alleviate the withdrawal syndrome associated with smoking cessation (p.2354). Nortriptyline is recommended by some as a second-line treatment in those patients who cannot tolerate or relapse after NRT.

References.

1. Hughes JR, *et al.* Antidepressants for smoking cessation. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2007 (accessed 14/08/08).

Preparations

BP 2008: Amitriptyline Tablets;
USP 31: Amitriptyline Hydrochloride Injection; Amitriptyline Hydrochloride Tablets; Chlordiazepoxide and Amitriptyline Hydrochloride Tablets; Perphenazine and Amitriptyline Hydrochloride Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Tryptanol; Uxen; ***Austral.:*** Endep; Tryptanol; ***Austria:*** Saroten; Tryptizol; ***Belg.:*** Redomex; Tryptizol; ***Braz.:*** Amytril; Neurotrypt; Protanol; Tripsol; Tryptanol; ***Canad.:*** Elavil†; Novo-Triptyn; ***Denm.:*** Saroten; Tryptizol†; ***Fin.:*** Saroten†; Triptyl; ***Fr.:*** Elavil; Laroxyl; ***Ger.:*** Amineurin; Amioxid; Equilibrin; Novoprotect; Saroten; Syneudon; ***Gr.:*** Maxivalet; Saroten; Stelminal; ***Hong Kong:*** Qualitriptine; Tryptanol†; ***Hung.:*** Teperin; ***India:*** Sarotena; Tryptomer; ***Irl.:*** Lentizol†; ***Israel:*** Elatrol; Elatrolet; Tryptal; ***Ital.:*** Adepril; Laroxyl; Triptizol; ***Malaysia:*** Endep†; Tripta; Tryptanol; ***Mex.:*** Anapsique; Tryptanol; ***Neth.:*** Sarotex; Tryptizol; ***Norw.:*** Sarotex; Tryptizol†; ***NZ:*** Amitrip; ***Port.:*** ADT; Tryptizol; ***Rus.:*** Amyzol (Амизол); Eliwel (Элливел); Saroten (Саротен); ***S.Afr.:*** Noriline; Saroten; Trepiline; Tryptanol; ***Singapore:*** Tripta; ***Spain:*** Deprelio; Tryptizol; ***Swed.:*** Saroten; Tryptizol; ***Switz.:*** Saroten; Tryptizol; ***Thai.:*** Polytanol; Tripsyline†; Tripta; Triptyline; Tryptanol; ***Turk.:*** Laroxyl; Triptilin; ***UK:*** Elavil; ***USA:*** Elavil†; ***Venez.:*** Tryptanol.

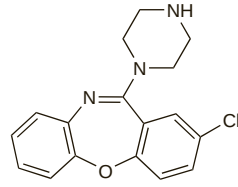
Multi-ingredient: ***Arg.:*** Mutabon D†; ***Austria:*** Limbitrol; ***Braz.:*** Limbitrol; ***Canad.:*** PMS-Levazine; Triavil†; ***Chile:*** Antalin; Limbatrilin; Morelin; Mutabon D†; Tiperin; ***Fin.:*** Klotriptyl; Limbitrol; Pertriptyl; ***Gr.:*** Minitran; ***India:*** Emotrip; ***Indon.:*** Limbritol; Mutabon-D; Mutabon-M; ***Ital.:*** Diapatol; Limbitryl; Mutabon; Sedans; ***Mex.:*** Adepsique; ***Port.:*** Mutabon; ***Rus.:*** Amixide (Амиксид); ***S.Afr.:*** Etrafon†; Limbitrol; ***Spain:*** Mutabase; Nobritol; ***Switz.:*** Limbitrol; ***Thai.:*** Anxipress-D†; Neuragon; Polybon; ***UK:*** Triptafen; ***USA:*** Etrafon; Limbitrol; Triavil†.

Amoxapine *(BAN, USAN, rINN)*

Amoksapiini; Amoksapin; Amoxapin; Amoxapina; Amoxapinum; CL-67772. 2-Chloro-11-(piperazin-1-yl)dibenz[*b,f*][1,4]oxazepine.

Амоксапин

$C_{17}H_{16}ClN_3O$ = 313.8.
CAS — 14028-44-5.
ATC — N06AA17.
ATC Vet — QN06AA17.



Pharmacopoeias. In *Jpn* and *US*.
USP 31 (Amoxapine). A white to yellowish crystalline powder. Practically insoluble in water; slightly soluble in acetone; freely soluble in chloroform; sparingly soluble in methyl alcohol and in toluene; soluble in tetrahydrofuran. Store in airtight containers.

Adverse Effects, Treatment, and Precautions

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

Rare cases of tardive dyskinesias and the neuroleptic malignant syndrome have been reported with amoxapine.

Antidopaminergic effects. Amoxapine is a derivative of the antipsychotic loxapine (p.1005) and possesses some antipsychotic activity. It also has dopamine-receptor blocking properties as do its hydroxylated metabolites. Adverse effects that are symptoms of such blockade have been reported and reviewed[1,2] and include akinesia, akathisia, withdrawal dyskinesia, reversible tardive dyskinesia, persistent dyskinesia, elevated serum concentration of prolactin, and galactorrhoea. Chorea[3] and oculogyric crisis[4] have also been reported.

1. Tao GK, *et al.* Amoxapine-induced tardive dyskinesia. *Drug Intell Clin Pharm* 1985; **19:** 548–9.
2. Devarajan S. Safety of amoxapine. *Lancet* 1989; **ii:** 1455.
3. Patterson JF. Amoxapine-induced chorea. *South Med J* 1983; **76:** 1077.
4. Hunt-Fugate AK, *et al.* Adverse reactions due to dopamine blockade by amoxapine. *Pharmacotherapy* 1984; **4:** 35–9.

Antimuscarinic effects. Amoxapine therapy has been reported to produce adverse effects associated with antimuscarinic activity (such as constipation, blurred vision, and dry mouth), but such reports did not reflect *in-vitro* findings that amoxapine had considerably less affinity for muscarinic binding sites than amitriptyline;[1] this was supported by results in healthy subjects. The adverse effects described as antimuscarinic could possibly be explained by amoxapine affecting noradrenergic mechanisms.

1. Bourne M, *et al.* A comparison of the effects of single doses of amoxapine and amitriptyline on autonomic functions in healthy volunteers. *Eur J Clin Pharmacol* 1993; **44:** 57–62.

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

Effects on the endocrine system. Reversible nonketotic hyperglycaemia developed in a 49-year-old woman with no history of diabetes mellitus within 5 days of oral therapy with amoxapine 50 mg three times daily.[1] She had previously had nonketotic hyperglycaemic coma after loxapine 150 mg daily. 7-Hydroxyamoxapine, a metabolite common to both amoxapine and loxapine, was implicated.

See also Antidopaminergic Effects, above, for mention of galactorrhoea and hyperprolactinaemia.

1. Tollefson G, Lesar T. Nonketotic hyperglycemia associated with loxapine and amoxapine: case report. *J Clin Psychiatry* 1983; **44:** 347–8.

Overdosage. In overdosage, amoxapine is reported to cause acute renal failure with rhabdomyolysis,[1,2] coma, and seizures.[3-5] Although there has been some debate as to whether the incidence of seizures and death is higher with overdosage of amoxapine than with other tricyclic antidepressants, some[6] consider that evidence does seem to favour increased neurological consequences.

It has been reported that amoxapine is not cardiotoxic in overdosage[3] but later evidence would suggest that there is cardiotoxic potential.[6,7]

1. Pumariega AJ, *et al.* Acute renal failure secondary to amoxapine overdose. *JAMA* 1982; **248:** 3141–2.
2. Jennings AE, *et al.* Amoxapine-associated acute renal failure. *Arch Intern Med* 1983; **143:** 1525–7.
3. Kulig K, *et al.* Amoxapine overdose: coma and seizures without cardiotoxic effects. *JAMA* 1982; **248:** 1092–4.
4. Litovitz TL, Troutman WG. Amoxapine overdose: seizures and fatalities. *JAMA* 1983; **250:** 1069–71.
5. Jefferson JW. Convulsions associated with amoxapine. *JAMA* 1984; **251:** 603–4.
6. Leonard BE. Safety of amoxapine. *Lancet* 1989; **ii:** 808.
7. Sørensen MR. Acute myocardial failure following amoxapine intoxication. *J Clin Psychopharmacol* 1988; **8:** 75.

Interactions

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

Pharmacokinetics

Amoxapine is readily absorbed from the gastrointestinal tract. It bears a close chemical relationship to loxapine (p.1005) and is similarly metabolised by hydroxylation. It is excreted in the urine, mainly as its metabolites in conjugated form as glucuronides.

Amoxapine has been reported to have a plasma half-life of 8 hours and its major metabolite, 8-hydroxyamoxapine, has been reported to have a biological half-life of 30 hours; 7-hydroxyamoxapine has been identified as another metabolite. Both metabolites are pharmacologically active. Amoxapine is about 90% bound to plasma proteins.

Amoxapine and its metabolite 8-hydroxyamoxapine are distributed into breast milk.

Uses and Administration

Amoxapine, the *N*-desmethyl derivative of loxapine (p.1005), is a dibenzoxazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). Amoxapine is one of the less sedating tricyclics and its antimuscarinic effects are mild; it also inhibits the reuptake of dopamine.

In the treatment of depression (p.373) amoxapine is given in oral doses of 50 mg two or three times daily initially, gradually increased up to 100 mg three times daily as necessary. In the USA, higher doses of up to 600 mg daily may also be given, if required, in severely depressed patients in hospital. A suggested dose for the elderly is 25 mg two or three times daily initially, increased after 5 to 7 days to up to 150 mg daily as necessary; in the USA further increases to a maximum of 300 mg daily are permitted, if required.

Once-daily dosage regimens, usually given at night, are suitable for amoxapine up to 300 mg daily; divided-dosage regimens are recommended for doses above 300 mg daily.

It has been claimed that, in the treatment of depression, amoxapine has a more rapid onset of action than amitriptyline or imipramine with a clinical effect possibly appearing 4 to 7 days after starting therapy, although this has been disputed.

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

Amoxapine has also been investigated for its potential as an antipsychotic.

◊ References.

1. Jue SG, *et al.* Amoxapine: a review of its pharmacology and efficacy in depressed states. *Drugs* 1982; **24:** 1–23.