Symptoms of **anxiety and depression** often coexist, and although it may be difficult to distinguish which is the predominant disorder, especially in milder forms, patients usually require an antidepressant. Anxiolytics and antipsychotics can be useful adjuncts in agitated depression, but a sedative antidepressant might be preferable. Combination preparations of antidepressants with antipsychotics or anxiolytics should not be used because the dosage of the individual components should be adjusted separately. Also, anxiolytics should only be prescribed on a short-term basis whereas antidepressants are given for longer periods.

The efficacy of antidepressants in **chronic fatigue syndrome** in clinical studies have been equivocal although it has been suggested that antidepressant therapy should be tried in patients with co-existing depression.[62] Cognitive therapy may also be useful.

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Mania

Although isolated episodes of mania (see p.372) may occur, mania is usually followed by depression when it is considered to be part of bipolar disorder. It is accepted practice to include mania without depression within the bipolar category. The treatment and prophylaxis of acute mania are therefore described under Bipolar Disorder, above.

Agomelatine *(rINN)*

Agomelatina; Agomélatine; Agomelatinum; S-20098. *N*-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide.

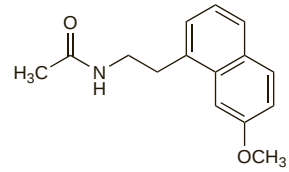
Агомелатин

$C_{15}H_{17}NO_2$ = 243.3.

CAS — 138112-76-2.

ATC — N06AX22.

ATC Vet — QN06AX22.



Profile

Agomelatine is an agonist at melatonergic MT_1 and MT_2 receptors and an antagonist at $5\text{-}HT_{2C}$ receptors. It has antidepressant actions and is used orally in the treatment of depression (p.373) in doses of 25 to 50 mg given daily at bedtime.

◊ References.

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Amineptine Hydrochloride *(rINNM)*

Amineptine, Chlorhydrate d'; Amineptini Hydrochloridum; Hidrocloruro de amineptina; S-1694. 7-[(10,11-Dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)amino]heptanoic acid hydrochloride.

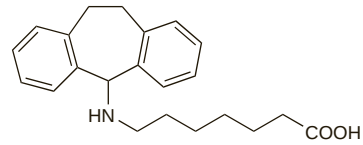
Аминептина Гидрохлорид

$C_{22}H_{27}NO_2$,HCl = 373.9.

CAS — 57574-09-1 (amineptine); 30272-08-3 (amineptine hydrochloride).

ATC — N06AA19.

ATC Vet — QN06AA19.



(amineptine)

Profile

Amineptine hydrochloride is a tricyclic antidepressant (see Amitriptyline, below). It has been given orally in the treatment of depression.

Hepatic adverse effects seem to be more common than with most other tricyclic antidepressants (see Effects on the Liver, p.377). Also amineptine has been subject to abuse and withdrawal has been both prolonged and difficult; for these reasons, it is no longer marketed in many countries.

Adverse effects. In 5 patients very severe acne-type lesions were associated with the chronic self-increased use of high doses of amineptine (200 to 1000 mg daily).[1] Unusual lactam metabolites were detected in all patients and in 2 these metabolites were still present, along with the lesions, 3 months after therapy had been withdrawn. In another case, a 48-year-old woman developed acne-like eruptions after long-term treatment with amineptine at a dose of 400 mg daily.[2] There was no clinical improvement 6 months after amineptine withdrawal.

1. Vexiau P, *et al.* Severe acne-like lesions caused by amineptine overdose. *Lancet* 1988; **i:** 585.
2. De Gálvez Aranda MV, *et al.* Acneiform eruption caused by amineptine: a case report and review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15:** 337–9.

Porphyria. Amineptine is considered to be unsafe in patients with porphyria because it has been shown to be porphyrinogenic in *in-vitro* systems.

Preparations

Proprietary Preparations (details are given in Part 3)
Braz.: Survector†; ***Port.:*** Directim†; Survector†.

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.

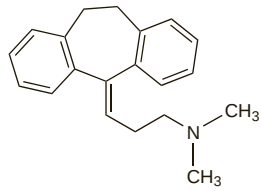
Амитриптилин

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