◊ In 3 studies in a total of 21 patients peak plasma concentrations of tacrine hydrochloride were achieved 0.5 to 3 hours after oral doses of 25 or 50 mg and oral bioavailability ranged from less than 5% to up to 36%.[1-3] Mean elimination half-lives were 1.37 and 1.59 hours after the 25 mg dose and 2.14 and 3.2 hours after the 50 mg dose. Tacrine's elimination appears to be mainly by metabolism in the liver and less than 3% of a dose was recovered unchanged in the urine of one patient.[1] Plasma concentrations of tacrine's main metabolite 1-hydroxy-9-aminotetrahydroacridine (velnacrine) rapidly exceed those of the parent compound and elimination half-lives of 43 and 81 minutes were found for this metabolite in 2 patients studied.[2] Tacrine's pharmacokinetics have been reviewed.[4]

1. Forsyth DR, *et al.* Pharmacokinetics of tacrine hydrochloride in Alzheimer's disease. *Clin Pharmacol Ther* 1989; **46:** 634–41.
2. Hartvig P, *et al.* Clinical pharmacokinetics of intravenous and oral 9-amino-1,2,3,4-tetrahydroacridine, tacrine. *Eur J Clin Pharmacol* 1990; **38:** 259–63.
3. Sitar DS, *et al.* Bioavailability and pharmacokinetic disposition of tacrine HCl in elderly patients with Alzheimer's disease. *Clin Pharmacol Ther* 1995; **57:** 198.
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Uses and Administration

Tacrine hydrochloride is a centrally acting reversible inhibitor of acetylcholinesterase activity used in the treatment of mild to moderately severe dementia in Alzheimer's disease (below).

The initial oral dose of tacrine hydrochloride, expressed in terms of the base, is 10 mg four times a day for a minimum of 4 weeks. Dosage should not be increased during this period because the potential exists for a delay in onset of increased liver enzyme concentrations. Serum-alanine aminotransferase concentrations should be monitored regularly (see Precautions, above) and, if there is no significant increase, the daily dose may be increased by 40 mg at four-week intervals according to response and tolerance, to a maximum of 160 mg daily in four divided doses. Tacrine should be taken on an empty stomach to improve absorption, although it can be taken with food if gastrointestinal adverse effects are a problem.

Tacrine has been used intravenously to antagonise competitive neuromuscular blockers and as a postoperative respiratory stimulant.

Dementia. Tacrine is used in the symptomatic management of Alzheimer's disease (see Dementia, p.362). It may delay cognitive decline in some patients with mild or moderate Alzheimer's disease but many cannot tolerate the dosage required and have to stop treatment because of gastrointestinal effects or signs of hepatotoxicity. There have been numerous studies of the use of tacrine in Alzheimer's disease and a meta-analysis[1] found tacrine to have a small beneficial effect on both cognition and global clinical impression, although it was considered that the clinical relevance of these findings was unclear and that there were no data from long-term controlled studies. Some have considered[2-6] that a cautious trial of tacrine may be warranted in patients with mild to moderately severe Alzheimer's disease (although alternative drugs are now available) and various guidelines on its use have been issued.[5,6] The metabolite velnacrine has also been tried but does not appear to be effective, and is also associated with hepatotoxicity.[7]

1. Qizilbash N, *et al.* Cholinesterase inhibition for Alzheimer disease: a meta-analysis of the tacrine trials. *JAMA* 1998; **280:** 1777–82.
2. Crimson ML. Tacrine: first drug approved for Alzheimer's disease. *Ann Pharmacother* 1994; **28:** 744–51.
3. Davis KL, Powchik P. Tacrine. *Lancet* 1995; **345:** 625–30.
4. Samuels SC, Davis KL. A risk-benefit assessment of tacrine in the treatment of Alzheimer's disease. *Drug Safety* 1997; **16:** 66–77.
5. Lyketsos CG, *et al.* Guidelines for the use of tacrine in Alzheimer's disease: clinical application and effectiveness. *J Neuropsychiatr Clin Neurosci* 1996; **8:** 67–73.
6. Rabins PV, *et al.* APA Work Group on Alzheimer's Disease and other Dementias. Steering Committee on Practice Guidelines. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. *Am J Psychiatry* 2007; **164** (12 suppl): 5–56. Also available at: http://www.psychiatryonline.com/pracGuide/loadGuidelinePdf.aspx?file=AlzPG101007 (accessed 23/07/08)
7. Birks J, Wilcock GGW. Velnacrine for Alzheimer's disease. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2004 (accessed 14/02/06).

Preparations

USP 31: Tacrine Capsules.

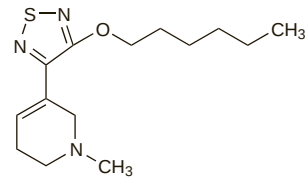
Proprietary Preparations (details are given in Part 3)
Arg.: Cognitiv†; ***Austral.:*** THA; ***Braz.:*** Tacrinal†; ***Gr.:*** Cognex†; ***Spain:*** Cognex†; ***USA:*** Cognex.

Xanomeline *(USAN, rINN)*

LY-246708; NNC-11-0232; Xanomelina; Xanoméline; Xanomelinum. 3-[4-(Hexyloxy)-1,2,5-thiadiazol-3-yl]-1,2,5,6-tetrahydro-1-methylpyridine.

Ксаномелин

$C_{14}H_{23}N_3OS$ = 281.4.
CAS — 131986-45-3.



Profile

Xanomeline is a selective muscarinic M_1 agonist. Xanomeline tartrate has been studied in the management of Alzheimer's disease but drugs of this type have not generally produced benefit.

◊ References.

1. Sramek JJ, *et al.* The safety and tolerance of xanomeline tartrate in patients with Alzheimer's disease. *J Clin Pharmacol* 1995; **35:** 800–806.
2. Bodick NC, *et al.* Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* 1997; **54:** 465–73.

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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3. Snow V, *et al.* Clinical guidelines, part 1. Pharmacologic treatment of acute major depression and dysthymia. *Ann Intern Med* 2000; **132:** 738–42.
4. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *Am J Psychiatry* 2000; **157** (suppl): 1–45. Also available at: http://www.psychiatryonline.com/pracGuide/pracGuideChapToc_7.aspx (accessed 14/08/08)
5. Fochtmann LJ, Gelenberg AJ. American Psychiatric Association. Guideline watch: practice guideline for the treatment of patients with major depressive disorder, 2nd edition. Available at: http://www.psychiatryonline.com/content.aspx?aid=148217 (accessed 14/08/08)
6. Bauer M, *et al.* World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 1: acute and continuation treatment of major depressive disorder. *World J Biol Psychiatry* 2002; **3:** 5–43. Also available at: http://www.wfsbp.org/fileadmin/pdf/guides/827MDDTreatmentBauer.pdf (accessed 14/08/08)
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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.

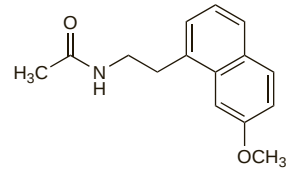
Агомелатин

$C_{15}H_{17}NO_2$ = 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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2. Ghosh A, Hellewell JSE. A review of the efficacy and tolerability of agomelatine in the treatment of major depression. *Expert Opin Invest Drugs* 2007; **16:** 1999–2004.
3. Eser D, *et al.* Evidence of agomelatine's antidepressant efficacy: the key points. *Int Clin Psychopharmacol* 2007; **22** (suppl 2): S15–S19.

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.

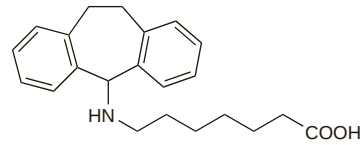
Аминептина Гидрохлорид

$C_{22}H_{27}NO_2$,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†.