

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.<sup>62</sup> Cognitive therapy may also be useful.

- Anderson IM, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 1993 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2000; **14**: 3–20. Also available at: <http://www.bap.org.uk/consensus/antidepressant.pdf> (accessed 24/11/05)
- NICE. Depression: management of depression in primary and secondary care (issued December 2004). Available at: <http://www.nice.org.uk/nicemedia/pdf/CG023NICEguideline.pdf> (accessed 14/08/08)
- Snow V, et al. Clinical guidelines, part 1. Pharmacologic treatment of acute major depression and dysthymia. *Ann Intern Med* 2000; **132**: 738–42.
- 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](http://www.psychiatryonline.com/pracGuide/pracGuideChapToc_7.aspx) (accessed 14/08/08)
- 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)
- 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)
- Bauer M, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, part 2: maintenance treatment of major depressive disorder and treatment of chronic depressive disorders and subthreshold depressions. *World J Biol Psychiatry* 2002; **3**: 69–86. Also available at: <http://www.wfsbp.org/fileadmin/pdf/guides/depression2.pdf> (accessed 14/08/08)
- The UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 2003; **361**: 799–808.
- NICE. Guidance on the use of electroconvulsive therapy: Technology Appraisal 59 (issued April 2003). Available at: <http://www.nice.org.uk/nicemedia/pdf/59ectfullguidance.pdf> (accessed 14/08/08)
- Partonen T, Lonnqvist J. Seasonal affective disorder. *Lancet* 1998; **352**: 1369–74.
- Golden RN, et al. The efficacy of light therapy in the treatment of mood disorders: a review and meta-analysis of the evidence. *Am J Psychiatry* 2005; **162**: 656–62.
- Kent JM. SNARIs, NaSSAa, and NaRIs: new agents for the treatment of depression. *Lancet* 2000; **355**: 911–8. Correction. *ibid.*; 2000.
- Anderson IM. Meta-analytical studies on new antidepressants. *Br Med Bull* 2001; **57**: 161–78.
- Mulrow CD, et al. Efficacy of newer medications for treating depression in primary care patients. *Am J Med* 2000; **108**: 54–64.
- Henry JA. Epidemiology and relative toxicity of antidepressant drugs in overdose. *Drug Safety* 1997; **16**: 374–90.
- Beaumont G. The toxicity of antidepressants. *Br J Psychiatry* 1989; **154**: 454–8.
- Kapur S, et al. Antidepressant medications and the relative risk of suicide attempt and suicide. *JAMA* 1992; **268**: 3441–5.
- de Jonghe F, Swinkels JA. The safety of antidepressants. *Drugs* 1992; **43** (suppl 2): 40–7.
- Mason J, et al. Fatal toxicity associated with antidepressant use in primary care. *Br J Gen Pract* 2000; **50**: 366–70.
- Knudsen KAI, Heath A. Effects of self poisoning with maprotiline. *BMJ* 1984; **288**: 601–3.
- Inman WHW. Blood disorders and suicide in patients taking mianserin or amitriptyline. *Lancet* 1988; **ii**: 90–2.
- Buckley NA, McManus PR. Fatal toxicity of serotonergic and other antidepressant drugs: analysis of United Kingdom mortality data. *BMJ* 2002; **325**: 1332–3.
- Cassidy S, Henry J. Fatal toxicity of antidepressant drugs in overdose. *BMJ* 1987; **295**: 1021–4.
- Kerr GW, et al. Tricyclic antidepressant overdose: a review. *Emerg Med J* 2001; **18**: 236–41.
- Malmvik J, et al. Antidepressants in suicide: differences in fatality and drug utilisation. *Eur J Clin Pharmacol* 1994; **46**: 291–4.
- Henry JA, et al. Relative mortality from overdose of antidepressants. *BMJ* 1995; **310**: 221–4. Correction. *ibid.*; 911.
- Freemantle N, et al. Prescribing selective serotonin reuptake inhibitors as strategy for prevention of suicide. *BMJ* 1994; **309**: 249–53.
- Trindade E, Menon D. Selective serotonin reuptake inhibitors (SSRIs) for major depression. Part 1: evaluation of the clinical literature. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 1997. Available at: [http://cadth.ca/media/pdf/ssris1\\_tr\\_e.pdf](http://cadth.ca/media/pdf/ssris1_tr_e.pdf) (accessed 14/08/08)
- Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998; **7** (suppl 1): 11–17.

- MacGillivray S, et al. Efficacy and tolerability of selective serotonin reuptake inhibitors compared with tricyclic antidepressants in depression treated in primary care: systematic review and meta-analysis. *BMJ* 2003; **326**: 1014–17.
- Guiana G, et al. Amitriptyline for depression. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2007 (accessed 30/05/08).
- Spigset O, Mårtensson B. Drug treatment of depression. *BMJ* 1999; **318**: 188–91.
- Richelson E. Pharmacology of antidepressants—characteristics of the ideal drug. *Mayo Clin Proc* 1994; **69**: 1069–81.
- Soares JC, Gershon S. Prospects for the development of new treatments with a rapid onset of action in affective disorders. *Drugs* 1996; **52**: 477–82.
- Kendrick T. Prescribing antidepressants in general practice. *BMJ* 1996; **313**: 829–30.
- Schweitzer I, Tuckwell V. Risk of adverse events with the use of augmentation therapy for the treatment of resistant depression. *Drug Safety* 1998; **19**: 45–64.
- Angst J. A regular review of the long term follow up of depression. *BMJ* 1997; **315**: 1143–6.
- Paykel ES. Continuation and maintenance therapy in depression. *Br Med Bull* 2001; **57**: 145–59.
- Geddes JR, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. *Lancet* 2003; **361**: 653–61. Correction. *ibid.* 2004; **363**: 662.
- Edwards JG. Long term pharmacotherapy of depression. *BMJ* 1998; **316**: 1180–1.
- Montgomery SA. Prophylactic treatment of depression. *Br J Hosp Med* 1994; **52**: 5–7.
- Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10**: 103–114.
- Haddad P, et al. Antidepressant discontinuation reactions. *BMJ* 1998; **316**: 1105–6.
- Anonymous. Withdrawing patients from antidepressants. *Drug Ther Bull* 1999; **37**: 49–52.
- Haddad PM. Antidepressant discontinuation syndromes: clinical relevance, prevention and management. *Drug Safety* 2001; **24**: 183–97.
- NICE. Depression in children and young people: identification and management in primary, community and secondary care (issued September 2005). Available at: <http://www.nice.org.uk/nicemedia/pdf/CG028NICEguideline.pdf> (accessed 14/08/08)
- Royal Australian and New Zealand College of Psychiatrists, Royal Australian College of General Practitioners, and Royal Australasian College of Physicians. Clinical guidance on the use of antidepressant medications in children and adolescents March 2005. Available at: [http://www.ranzcp.org/images/stories/ranzcp-attachments/Resources/College\\_Statements/Practice\\_Guidelines/Clinical\\_Guidance\\_on\\_the\\_use\\_of\\_Antidepressant\\_medications\\_in\\_Children\\_and\\_Adolescents.pdf](http://www.ranzcp.org/images/stories/ranzcp-attachments/Resources/College_Statements/Practice_Guidelines/Clinical_Guidance_on_the_use_of_Antidepressant_medications_in_Children_and_Adolescents.pdf) (accessed 14/08/08)
- Leslie LK, et al. The Food and Drug Administration's deliberations on antidepressant use in pediatric patients. *Pediatrics* 2005; **116**: 195–204.
- Ryan ND. Treatment of depression in children and adolescents. *Lancet* 2005; **366**: 933–40.
- Dopheide JA. Recognizing and treating depression in children and adolescents. *Am J Health-Syst Pharm* 2006; **63**: 233–43.
- Treatment for Adolescents with Depression Study (TADS) Team. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA* 2004; **292**: 807–20.
- Committee for Medicinal Products for Human Use, European Medicines Agency. European Medicines Agency adopts a positive opinion for the use of Prozac in the treatment of children and adolescents suffering from depression (issued 6th June, 2006). Available at: <http://www.emea.europa.eu/pdfs/human/press/pr/20255406en.pdf> (accessed 14/08/08)
- Hazell P, et al. Tricyclic drugs for depression in children and adolescents. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2002 (accessed 24/11/05).
- Harrington R. Depressive disorder in adolescence. *Arch Dis Child* 1995; **72**: 193–5.
- Friedman RA, Leon AC. Expanding the black box — depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007; **356**: 2343–6.
- Weller IVD. Report of the CSM Expert Working Group on the safety of selective serotonin reuptake inhibitor antidepressants. London: The Stationery Office, 2005. Also available at: [http://www.mhra.gov.uk/home/idcplg?IdcService=GET\\_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased](http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019472&RevisionSelectionMethod=LatestReleased) (accessed 14/08/08)
- Alexopoulos GS. Depression in the elderly. *Lancet* 2005; **365**: 1961–70.
- Lotrich FE, Pollock BG. Aging and clinical pharmacology: implications for antidepressants. *J Clin Pharmacol* 2005; **45**: 1106–22.
- Scottish Intercollegiate Guidelines Network. Postnatal depression and puerperal psychosis: a national clinical guideline (issued June 2002). Available at: <http://www.sign.ac.uk/pdf/sign60.pdf> (accessed 24/11/05)
- Hoffbrand S, et al. Antidepressant treatment for post-natal depression. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2001 (accessed 24/11/05).
- American Academy of Pediatrics Committee on Drugs. 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)
- The Royal Colleges of Physicians, General Practitioners and Psychiatrists. Chronic fatigue syndrome. *Council Report CR54*; London: Royal Colleges of Physicians, General Practitioners and Psychiatrists, 1997.

## 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 bi-

polar category. The treatment and prophylaxis of acute mania are therefore described under Bipolar Disorder, above.

## Agomelatine (rINN)

Agomelatine; Agomelatine; Agomelatium; S-20098. N-[2-(7-Methoxy-1-naphthyl)ethyl]acetamide.

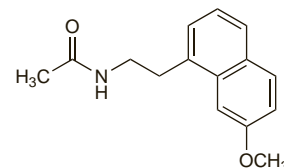
АГОМЕЛАТИН

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

CAS — 138112-76-2.

ATC — N06AX22.

ATC Vet — QN06AX22.



## Profile

Agomelatine is an agonist at melatonergic MT<sub>1</sub> and MT<sub>2</sub> receptors and an antagonist at 5-HT<sub>2C</sub> 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

- Zupancic M, Guilleminault C. Agomelatine: a preliminary review of a new antidepressant. *CNS Drugs* 2006; **20**: 981–92.
- 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.
- Eser D, et al. Evidence of agomelatine's antidepressant efficacy: the key points. *Int Clin Psychopharmacol* 2007; **22** (suppl 2): S15–S19.

## Amineptine Hydrochloride (rINN)

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

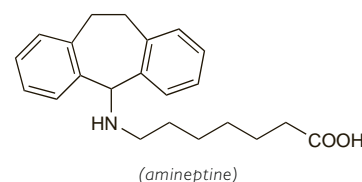
АМИНЕПТИНА ГИДРОХЛОРИД

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

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).<sup>1</sup> 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.<sup>2</sup> 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 Venerol* 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†.