A suggested maximum daily dose in elderly or debilitated patients is 40 mg; US licensed product information also recommends a starting dose of 10 mg daily in such patients. Reduced doses should be given to patients with hepatic or renal impairment, see below.

A modified-release preparation (as the hydrochloride) is also available in the USA for the treatment of depression, panic disorder, and social anxiety disorder; the maximum doses with this preparation may be slightly greater than those recommended with the immediate-release preparation. The modified-release preparation may also be used in the treatment of **premenstrual dysphoric disorder**. The initial dose is 12.5 mg once daily, usually in the morning, which may be increased to 25 mg once daily, if necessary, after an interval of at least one week. Treatment may be given throughout the menstrual cycle or limited to the luteal phase.

Paroxetine should be withdrawn gradually to reduce the risk of withdrawal symptoms. For further details, see Withdrawal under Precautions of Fluoxetine, p.396.

◊ Reviews.

1. Wagstaff AJ, *et al.* Paroxetine: an update of its use in psychiatric disorders in adults. *Drugs* 2002; **62:** 655–703. Correction. *ibid.*; 1461.

Administration. Although paroxetine is licensed in the UK at higher doses the UK CSM considers that there is a lack of evidence from clinical trials of additional efficacy with paroxetine when given above the following daily doses:

- depression, generalised anxiety disorder, social anxiety disorder, post-traumatic stress disorder: 20 mg
- obsessive-compulsive disorder, panic disorder: 40 mg

1. CSM/MCA Paroxetine prescribing advice. *Current Problems* 2004; **30:** 3. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007448&RevisionSelectionMethod= LatestReleased (accessed 14/08/08)

Administration in hepatic or renal impairment. In the USA the recommended initial oral dose of paroxetine in patients with severe renal or hepatic impairment is the equivalent of 10 mg daily, increased to a maximum of 40 mg daily as necessary. UK licensed drug information recommends that doses in such patients are limited to the lower end of the range.

Anxiety disorders. Paroxetine is used in anxiety disorders including generalised anxiety disorder (p.952), obsessive-compulsive disorder (p.952), panic disorder (p.952), post-traumatic stress disorder (p.953), and social anxiety disorder (see under Phobic Disorders, p.953). It has also been tried for adult night terrors (see under Sleep-associated Movement Disorders, p.958).

References.

1. Oehrberg S, *et al.* Paroxetine in the treatment of panic disorder: a randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 1995; **167:** 374–9.
2. Zohar J, *et al.* Paroxetine versus clomipramine in the treatment of obsessive-compulsive disorder. *Br J Psychiatry* 1996; **169:** 468–74.
3. Lecrubier Y, *et al.* Long-term evaluation of paroxetine, clomipramine and placebo in panic disorder. *Acta Psychiatr Scand* 1997; **95:** 153–60.
4. Wilson SJ, *et al.* Adult night terrors and paroxetine. *Lancet* 1997; **350:** 185.
5. Stein MB, *et al.* Paroxetine treatment of generalized social phobia (social anxiety disorder). *JAMA* 1998; **280:** 708–13.
6. Baldwin D, *et al.* Paroxetine in social phobia/social anxiety disorder: randomised, double-blind, placebo-controlled study. *Br J Psychiatry* 1999; **175:** 120–6.
7. Baldwin DS. Clinical experience with paroxetine in social anxiety disorder. *Int Clin Psychopharmacol* 2000; **15** (suppl): S19–24.
8. Marshall RD, *et al.* Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. *Am J Psychiatry* 2001; **158:** 1982–8.
9. Tucker P, *et al.* Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 2001; **62:** 860–8.
10. Liebowitz MR, *et al.* A randomized, double-blind, fixed-dose comparison of paroxetine and placebo in the treatment of generalized social anxiety disorder. *J Clin Psychiatry* 2002; **63:** 66–74.
11. Stein DJ, *et al.* Efficacy of paroxetine for relapse prevention in social anxiety disorder: a 24-week study. *Arch Gen Psychiatry* 2002; **59:** 1111–18.
12. Stocchi F, *et al.* Efficacy and tolerability of paroxetine for the long-term treatment of generalized anxiety disorder. *J Clin Psychiatry* 2003; **64:** 250–8.
13. Hollander E, *et al.* Acute and long-term treatment and prevention of relapse of obsessive-compulsive disorder with paroxetine. *J Clin Psychiatry* 2003; **64:** 1113–21.
14. Lepola U, *et al.* Controlled-release paroxetine in the treatment of patients with social anxiety disorder. *J Clin Psychiatry* 2004; **65:** 222–9.
15. Sheehan DV, *et al.* Efficacy and tolerability of controlled-release paroxetine in the treatment of panic disorder. *J Clin Psychiatry* 2005; **66:** 34–40.
16. Rickels K, *et al.* Remission of generalized anxiety disorder: a review of the paroxetine clinical trials database. *J Clin Psychiatry* 2006; **67:** 41–7.

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. SSRIs such as paroxetine are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Leyman S, *et al.* Paroxetine: post-marketing experience on 4024 depressed patients in Belgium. *Eur J Clin Res* 1995; **7:** 287–96.
2. Rodríguez-Ramos P, *et al.* Effects of paroxetine in depressed adolescents. *Eur J Clin Res* 1996; **8:** 49–61.
3. Franchini L, *et al.* Dose-response efficacy of paroxetine in preventing depressive recurrences: a randomized, double-blind study. *J Clin Psychiatry* 1998; **59:** 229–32.
4. Williams JW, *et al.* Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. *JAMA* 2000; **284:** 1519–26.
5. Golden RN, *et al.* Efficacy and tolerability of controlled-release and immediate-release paroxetine in the treatment of depression. *J Clin Psychiatry* 2002; **63:** 577–84.
6. Rapaport MH, *et al.* Efficacy of controlled-release paroxetine in the treatment of late-life depression. *J Clin Psychiatry* 2003; **64:** 1065–74.
7. Misri S, *et al.* The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry* 2004; **65:** 1236–41.
8. Trivedi MH, *et al.* Effectiveness of low doses of paroxetine controlled release in the treatment of major depressive disorder. *J Clin Psychiatry* 2004; **65:** 1356–64.
9. Dunner DL, *et al.* Efficacy and tolerability of controlled-release paroxetine in the treatment of severe depression: post hoc analysis of pooled data from a subset of subjects in four double-blind clinical trials. *Clin Ther* 2005; **27:** 1901–11.

Hot flushes. Some SSRIs, including paroxetine, have been tried in the treatment of hot flushes; for further details see under Fluoxetine, p.398.

Hypochondriasis. For mention of the use of SSRIs, including paroxetine, in hypochondriasis, see under Fluoxetine, p.398.

Premenstrual syndrome. Paroxetine (as a modified-release preparation) is used to control both the psychological and somatic symptoms of premenstrual syndrome (p.2099).

References.

1. Cohen LS, *et al.* Paroxetine controlled release for premenstrual dysphoric disorder: a double-blind, placebo-controlled trial. *Psychosom Med* 2004; **66:** 707–13.

Pruritus. Paroxetine has produced some benefit in the relief of non-dermatological pruritus.[1]

1. Zylicz Z, *et al.* Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. *J Pain Symptom Manage* 2003; **26:** 1105–12.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs; for the potential use of these effects in the management of premature ejaculation see Fluoxetine, p.399.

Preparations

BP 2008: Paroxetine Tablets;
USP 31: Paroxetine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Afenexil; Aropax; Datevan; Meplar; Neurotrox; Olane; Pamoxet; Paxil; Psicoasten; Sicopax; Sicotral; Sostel; Tiarix; Xilanic; ***Austral.:*** Aropax; Extine; Oxetine; Paxtine; ***Austria:*** Allenopar; Aparo†; Ennos; Glaxopar; Paluxetil†; Parocetan; Paroglax; Paroxat; Seroxat; ***Belg.:*** Aropax; Seroxat; ***Braz.:*** Aropax; Benepax; Cebrilin; Parox; Paxtrat; Pondera; Roxetin; ***Canad.:*** Paxil; ***Chile:*** Aroxat; Bectam; Pamax; Posivyl; Seretran; Traviata; ***Cz.:*** Apo-Parox; Arketis; Parolex; Remood; Seroxat; ***Denm.:*** Oxetine†; Serodur; Seroxat; ***Fin.:*** Optipar; Seroxat; ***Fr.:*** Deroxat; Divarius; ***Ger.:*** Euplix; Oxet†; ParoLich; Paroxat; Paroxedura; Seroxat; Tagonis; ***Gr.:*** Noprilex; Seroxat; Taberil; ***Hong Kong:*** Seroxat; ***Hung.:*** Apodepi; Paretin; Parogen; Paroxat; Rexetin; Seroxat; ***India:*** Pari; Parotin; Xet; ***Indon.:*** Seroxat; ***Irl.:*** Meloxat; Paroser; Parox; Paxt; Seroxat; ***Israel:*** Paxxet; Seroxat; ***Ital.:*** Daparox; Dropaxin; Eutimil; Serestill; Sereupin; Seroxat; Stiliden; ***Jpn:*** Paxil; ***Malaysia:*** Seroxat; ***Mex.:*** Apo-Oxpar; Aropax; Paxil; ***Neth.:*** Seroxat; ***Norw.:*** Seroxat; ***NZ:*** Aropax; Loxamine; ***Philipp.:*** Seroxat; ***Pol.:*** Deprozel; Paromerck; Paxeratio; Paxtin; Rexetin; Seroxat; Xetanor; ***Port.:*** Denerval; Oxepar†; Paxetil; Seroxat; ***Rus.:*** Paxil (Паксил); Rexetin (Рексетин); ***S.Afr.:*** Aropax; Deparoc; Parax; Paxil; Sedarin; Serrapress; Xet; ***Singapore:*** Seroxat; ***Spain:*** Casbol; Frosinor; Motivan; Paratonina; Paroturt; Seroxat; Xetin; ***Swed.:*** Euplix†; Paroxiflex; Seroxat; ***Switz.:*** Deroxat; Dexantol; Parexat; Paronex; Paroxetop; ***Thai.:*** Seroxat; ***Turk.:*** Paxil; Seroxat; ***UK:*** Seroxat; ***USA:*** Paxil; Pexeva; ***Venez.:*** Paxil.

Phenelzine Sulfate *(pINNM)*

Phénelzine, Sulfate de; Phenelzine Sulphate *(BANM)*; Phenelzini Sulfas; Sulfato de fenelzina. Phenethylhydrazine hydrogen sulphate.

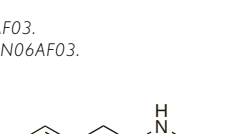
Фенельзина Сульфат

$C_8H_{12}N_2,H_2SO_4$ = 234.3.

CAS — 51-71-8 (phenelzine); 156-51-4 (phenelzine sulfate).

ATC — N06AF03.

ATC Vet — QN06AF03.



(phenelzine)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Phenelzine Sulphate). A white powder or pearly platelets with a pungent odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. Protect from light.

USP 31 (Phenelzine Sulfate). A white to yellowish-white powder having a characteristic odour. Freely soluble in water; practically insoluble in alcohol, in chloroform, and in ether. pH of a 1% solution in water is between 1.4 and 1.9. Store in airtight containers. Protect from heat and light.

Adverse Effects

Adverse effects commonly associated with phenelzine and other MAOIs include orthostatic hypotension and attacks of dizziness. Other common adverse effects include headache, dry mouth, constipation and other gastrointestinal disturbances (including nausea and vomiting), and oedema. Drowsiness, weakness, and fatigue are reported frequently although CNS stimulation may also occur and symptoms include agitation, nervousness, euphoria, restlessness, insomnia, and convulsions. Psychotic episodes, with hypomania or mania, confusion, hallucinations, or toxic delirium, may be induced in susceptible persons.

Sweating and muscle tremors, twitching, or hyperreflexia may occur, which in overdosage may present as extreme hyperpyrexia and neuromuscular irritability. Other reported reactions include blurred vision, nystagmus, urinary retention or difficulty in micturition, arrhythmias, skin rashes, leucopenia, sexual disturbances, and weight gain with inappropriate appetite. Jaundice has been reported with hydrazine MAOIs and, on rare occasions, fatal progressive hepatocellular necrosis. Peripheral neuropathies associated with the hydrazine derivatives may be caused by pyridoxine deficiency. Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly.

Symptoms of **overdosage** may be minor at first and progress over the ensuing 24 to 48 hours. After mild overdosage and symptomatic and supportive therapy, recovery may occur in 3 to 4 days, but after massive overdosage symptoms may persist for up to 2 weeks. CNS depression and drowsiness have been observed with overdosage, but CNS stimulation is more common, with irritability, hyperactivity, agitation, hallucinations, or convulsions. Respiratory depression and coma may ultimately occur. Cardiovascular effects include hypertension, sometimes with severe headache, although hypotension is more frequently observed; cardiac arrhythmias and peripheral collapse can also develop. Profuse sweating, hyperpyrexia, and neuromuscular excitation with hyperreflexia are also prominent features of overdosage.

MAOIs have been the most commonly implicated drugs in the serotonin syndrome (see below). A severe hypertensive crisis, sometimes fatal, may occur if an MAOI is taken with some other drugs or certain foods (see Interactions, below). These reactions are characterised by severe headache and a rapid and sometimes prolonged rise in blood pressure followed by intracranial haemorrhage or acute cardiac failure.

For the adverse effects of reversible inhibitors of monoamine oxidase type A (RIMAs), see Moclobemide, p.411.

Incidence of adverse effects. A suspicion that the reported adverse effects of MAOIs were both exaggerated and overemphasised prompted a comparative study in patients receiving phenelzine or imipramine.[1] The report noted that the dosages of phenelzine used were at the upper end of the usual therapeutic range (mean 77 mg daily) while those of imipramine were in the middle of the usual therapeutic range (mean 139 mg daily). A very similar profile of adverse effects in the two groups was observed. With the exception of significantly increased incidence of drowsiness in the phenelzine-treated group, the 2 groups did not differ in the frequency of autonomic, CNS, cardiovascular, or psychological adverse effects. However, a significantly greater number of phenelzine-treated patients had to stop their treatment because of the severity of the adverse effects. Nonetheless it was considered that phenelzine was reasonably well-tolerated when compared with imipramine.

Others have also studied the adverse effect profile of phenelzine and made comparisons with tranylcypromine and imipramine.[2,3] A retrospective review involving 198 patients concluded that although phenelzine was more likely than the other two drugs to induce adverse effects, drug withdrawal because of adverse effects was less likely to occur. This was probably because phenelzine showed clear-cut clinical efficacy resulting in prescribers being reluctant to stop therapy.

1. Evans DL, *et al.* Early and late side effects of phenelzine. *J Clin Psychopharmacol* 1982; **2:** 208–10.
2. Rabkin J, *et al.* Adverse reactions to monoamine oxidase inhibitors. Part I: a comparative study. *J Clin Psychopharmacol* 1984; **4:** 270–8.
3. Rabkin JG, *et al.* Adverse reactions to monoamine oxidase inhibitors. Part II: treatment correlates and clinical management. *J Clin Psychopharmacol* 1985; **5:** 2–9.

Effects on the cardiovascular system. MAOIs are generally considered to be relatively free of adverse cardiovascular effects. The hypertensive reaction that may follow interactions of MAOIs with foods or other drugs is well known (see Interactions, below) but orthostatic hypotension may also occur when these drugs are used on their own.

In a study[1] involving 14 patients it was found that phenelzine produced both a significant decrease in systolic blood pressure while lying down, and significant orthostatic hypotension; in 2 patients these effects on blood pressure meant treatment had to be altered. Differences between the effects of phenelzine and those reported for the tricyclic antidepressants were noted. Tricyclics were not known to affect lying systolic blood pressure and although both tricyclics and phenelzine could cause orthostatic hypotension, with the tricyclics it typically reaches a maximum within the first week of treatment whereas with phenelzine the maximum effect was noted after 4 weeks. Additionally, the study provided some indication that the blood pressure effects of phenelzine may attenuate with time, a phenomenon that is not known to occur with the tricyclics.

1. Kronig MH, *et al.* Blood pressure effects of phenelzine. *J Clin Psychopharmacol* 1983; **3:** 307–10.

Effects on the endocrine system. MAOIs may induce *hyperprolactinaemia*[1] and this has led to galactorrhoea in women.[2] Occasionally, MAOIs may cause *dilutional hyponatraemia* due to a reduction in the renal excretion of free water mediated by both enhanced vasopressin release and increased antidiuretic action on the renal tubule.[3] The UK CSM, commenting on reports[4] it had received of hyponatraemia with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant and usually involved elderly patients.

1. Slater SL, *et al.* Elevation of plasma-prolactin by monoamine-oxidase inhibitors. *Lancet* 1977; **ii:** 275–6.
2. Segal M, Heys RF. Inappropriate lactation. *BMJ* 1969; **4:** 236.
3. Baylis PH. Drug-induced endocrine disorders. *Adverse Drug React Bull* 1986; No 116: 432–5.
4. 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 05/08/08)

Effects on the liver. Published case reports of hepatotoxic reactions to MAOIs have included jaundice in 4 patients[1] and hepatic failure progressing to encephalopathy in 2 patients;[2] this latter reaction was attributed to a hypersensitivity reaction.

Of 91 cases of hepatitis associated with antidepressants reported to French pharmacovigilance centres from 1977 to 1983, an MAOI (iproniazid) was implicated in 11. These 11 cases were associated with cytolytic reactions and 5 patients died.[3]

Two cases of fulminant hepatic failure have been reported[4] after use of phenelzine for 4 months; all other causes of acute liver damage were ruled out. Both patients recovered after emergency liver transplantation.

1. Holdsworth CD, *et al.* Hepatitis caused by the newer amine-oxidase-inhibiting drugs. *Lancet* 1961; **ii:** 621–3.
2. Wilkinson SP, *et al.* Frequency and type of renal and electrolyte disorders in fulminant hepatic failure. *BMJ* 1974; **1:** 186–9.
3. Lefebure B, *et al.* Hépatites aux antidépresseurs. *Therapie* 1984; **39:** 509–16.
4. Gómez-Gil E, *et al.* Phenelzine-induced fulminant hepatic failure. *Ann Intern Med* 1996; **124:** 692–3.

Effects on the nervous system. MAOIs produce a variety of effects on the nervous system. Drowsiness is frequently reported but symptoms of CNS stimulation, including agitation, nervousness, and euphoria may also occur; psychotic episodes may be induced in susceptible individuals. Further adverse neurological reactions are described under Epileptogenic Effect and Extrapyramidal Effects, below.

Peripheral neuropathies, sometimes associated with a documented pyridoxine deficiency, have been reported in patients receiving phenelzine.[1,2] In most of the patients the neuropathies developed 6 weeks to 4 months after starting phenelzine,[2] although in one case symptoms did not occur for 11 years.[1] The symptoms also generally disappeared when pyridoxine was given with continued phenelzine therapy.[2] The possibility that the dietary restrictions imposed on persons taking phenelzine might have contributed to a low pyridoxine intake was considered unlikely. The most probable mechanism for the induced pyridoxine deficiency was combination of the hydrazine moiety with the pyridoxal form of the vitamin to form an inactive compound.

Many drugs can inhibit transmission at the myoneural junction under experimental conditions and it has been said that phenelzine may cause postoperative respiratory depression, possibly through a combined action with neuromuscular blockers.[3] For further details, see Anaesthesia under Precautions, below.

1. Heller CA, Friedman PA. Pyridoxine deficiency and peripheral neuropathy associated with long-term phenelzine therapy. *Am J Med* 1983; **75:** 887–8.
2. Stewart JW, *et al.* Phenelzine-induced pyridoxine deficiency. *J Clin Psychopharmacol* 1984; **4:** 225–6.
3. Lane RJM, Routledge PA. Drug-induced neurological disorders. *Drugs* 1983; **26:** 124–47.

Effects on sexual function. MAOIs such as phenelzine and tranylcypromine have been implicated in producing both impotence and failure of ejaculation.[1,2] Priapism has been reported with phenelzine.[3] There have also been several reports of female anorgasmia attributed to MAOIs, an effect which appears to be dose-related.[4] Loss of libido and impotence are common symptoms of depression, often making the role of drugs in producing sexual dysfunction difficult to assess.

1. Simpson GM, *et al.* Effects of anti-depressants on genito-urinary function. *Dis Nerv Syst* 1965; **26:** 787–9.
2. Wyatt RJ, *et al.* Treatment of intractable narcolepsy with a monoamine oxidase inhibitor. *N Engl J Med* 1971; **285:** 987–91.
3. Yeragani VK, Gershon S. Priapism related to phenelzine therapy. *N Engl J Med* 1987; **317:** 117–18.
4. Shen WW, Sata LS. Inhibited female orgasm resulting from psychotropic drugs: a clinical review. *J Reprod Med* 1983; **28:** 497–9.

Epileptogenic effect. Licensed product information indicates that convulsions represent one of the less common adverse effects of MAOIs; they may be a feature of overdosage.

A typical grand-mal seizure with tonic-clonic convulsions has been reported in a patient with no history of epilepsy or predisposing factors shortly after the start of phenelzine therapy.[1] The point was made that phenelzine-induced seizures had rarely been observed.

1. Bhugra DK, Kaye N. Phenelzine induced grand mal seizure. *Br J Clin Pract* 1986; **40:** 173–4.

Extrapyramidal effects. A parkinsonian syndrome developed in a patient about 5 weeks after the start of therapy with phenelzine. Symptoms gradually resolved over 10 days after the withdrawal of phenelzine. The mechanisms by which phenelzine could have induced these effects were discussed.[1]

1. Gillman MA, Sandyk R. Parkinsonism induced by a monoamine oxidase inhibitor. *Postgrad Med J* 1986; **62:** 235–6.

Hyponatraemia. See Effects on the Endocrine System, above.

Lupus. A reversible lupus-like reaction has been reported in a patient who had been taking phenelzine sulfate for 8 months.[1]

1. Swartz C. Lupus-like reaction to phenelzine. *JAMA* 1978; **239:** 2693.

Overdosage. MAOIs in overdose rarely produce severe hypertension; the blood pressure may be high or low, or may alternate between the two. More commonly the patient gradually develops widespread muscle spasms, trismus, and opisthotonus with widely dilated pupils and a hot and sweating skin. About 16 to 24 hours after ingestion potentially fatal hyperthermia may develop; temperatures of 42.1 to 43.8° have been recorded immediately before death. Disseminated intravascular coagulation, rhabdomyolysis, and acute tubular necrosis can also occur.[1]

1. Henry JA. Specific problems of drug intoxication. *Br J Anaesth* 1986; **58:** 223–33.

Serotonin syndrome. The serotonin syndrome is a drug-induced excess in serotonergic activity at central receptors.[1-10] It is characterised by the development of *at least three* of the following clinical features after a recent change in a treatment regimen involving serotonergic drugs:[1]

- agitation
- ataxia
- diaphoresis
- diarrhoea
- fever
- hyperreflexia
- myoclonus
- shivering
- changes in mental status

Strict application of these criteria may not identify early, mild, or subacute cases of serotonin syndrome and a simpler diagnostic approach focusing on neuromuscular features has also been suggested.[10] The syndrome should be distinguished from the hypertensive crises produced by the interaction between MAOIs and tyramine (see Interactions of MAOIs with Foods, below), and from the neuroleptic malignant syndrome (see p.972).[3,8-10]

The onset of the syndrome is often within minutes of altering the regimen,[10] although some cases have occurred as much as several weeks later.[2] The occurrence and severity of the syndrome do not appear to be dose-related,[2] but to depend on the extent and duration of the rise in intrasynaptic serotonin.[5]

The serotonin syndrome is relatively uncommon and symptoms are usually mild. However, severe complications, including disseminated intravascular coagulation, severe hyperthermia, respiratory failure, and seizures have been reported; there have also been fatalities.

The serotonin syndrome may follow exposure to a single serotonergic drug or, more commonly, a combination of such drugs.[2,8-10] In the past, **MAOIs** have been the most commonly implicated drugs in this syndrome, particularly when taken with other antidepressants such as the tricyclics, SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs) including venlafaxine, trazodone, lithium, and tryptophan. (The use of combination therapy with serotonergic antidepressant drugs is discussed under Interactions of MAOIs with other Drugs, below.) MAOIs combined with the opioids dextromethorphan and pethidine have also produced the serotonin syndrome. The interaction can occur with both irreversible and reversible MAOIs, and with those selective for monoamine oxidase type A such as moclobemide as well as with non-selective MAOIs.[11] The selective inhibitor of monoamine oxidase type B, selegiline, may also pose problems at high doses as its selectivity starts to diminish.

As usage of the **SSRIs** has increased, so too has the number of reports of adverse reactions when these drugs have been combined with other serotonergic drugs, including the herbal preparation St John's wort.

Other drugs that may potentially cause serotonin syndrome in certain circumstances include antiemetics such as ondansetron, buspirone, carbamazepine, dihydroergotamine, methylenedioxyamfetamine, sibutramine, selective serotonin (5-HT_1) agonists such as sumatriptan, and tramadol.[5,8-10]

Serotonergic potentiation may also occur if one serotonergic drug is used after another without allowing a sufficient **drug-free interval** after stopping the first. This is a particular problem when the first drug is an irreversible MAOI or a drug with a long half-life such as the SSRI fluoxetine.

Most cases of serotonin syndrome resolve within 24 hours after withdrawal of the offending drugs and giving supportive **therapy**,[1-4,8-10] including appropriate management of fever and hyperthermia (p.10). Benzodiazepines may be of value to control agitation, myoclonus, and seizures. The non-specific serotonin antagonist cyproheptadine may be useful in more severe cases although its efficacy has not been established;[8,10] methysergide has also been used with some success.[2,3,6] Other drugs that have been tried include propranolol, chlorpromazine, and dantrolene[2,3,6,8-10] although adverse effects may limit their usefulness.

1. Sternbach H. The serotonin syndrome. *Am J Psychiatry* 1991; **148:** 705–13.
2. Sporer KA. The serotonin syndrome: implicated drugs, pathophysiology and management. *Drug Safety* 1995; **13:** 94–104.
3. Corkeron MA. Serotonin syndrome—a potentially fatal complication of antidepressant therapy. *Med J Aust* 1995; **163:** 481–2.
4. Brown TM, *et al.* Pathophysiology and management of the serotonin syndrome. *Ann Pharmacother* 1996; **30:** 527–33.
5. Gillman PK. Serotonin syndrome: history and risk. *Fundam Clin Pharmacol* 1998; **12:** 482–91.
6. Gillman PK. The serotonin syndrome and its treatment. *J Psychopharmacol* 1999; **13:** 100–109.
7. Mason PJ, *et al.* Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine (Baltimore)* 2000; **79:** 201–9.
8. Birmes P, *et al.* Serotonin syndrome: a brief review. *Can Med Assoc J* 2003; **168:** 1439–42.
9. Bilj D. The serotonin syndrome. *Neth J Med* 2004; **62:** 309–13.
10. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med* 2005; **352:** 1112–20.
11. Livingston MG. Interactions with selective MAOIs. *Lancet* 1995; **345:** 533–4. Correction. *ibid.* 2007; **356:** 2437.

Treatment of Adverse Effects

In cases of overdosage with MAOIs the benefit of gastric decontamination is uncertain; however, in patients who present within 1 hour activated charcoal may be given by mouth, or, in potentially life-threatening cases, the stomach may be emptied by lavage. Management then largely involves intensive symptomatic and supportive therapy with particular attention being given to CNS effects, raised body temperature (which may develop into malignant hyperthermia), and cardiovascular effects. Delayed effects may develop some time after the overdose even in patients who are initially asymptomatic, and therefore prolonged monitoring is warranted. Other drugs taken with an overdose of MAOIs may complicate the features and result in the need for an even longer period of monitoring. Special care should be observed with any drug therapy used in the management of MAOI overdosage in view of the many known interactions which occur with this class of drugs.

Muscle spasm, agitation, and convulsions should be treated with diazepam. Severe neuromuscular irritability may call for the use of a competitive neuromuscular blocker such as pancuronium and intubation with assisted ventilation. Hyperthermia may be a particular problem; if simple antipyretics such as paracetamol and external cooling measures fail a competitive neu-

romuscular blocker has often been advocated; dantrolene has also been suggested.

Hypotension, which is a fairly common feature, should be managed by intravenous fluid therapy and volume expansion; vasopressors should be avoided. Conversely, a hypertensive crisis may occasionally occur after an overdose with MAOIs and can be managed with phentolamine given by slow intravenous injection. A short-acting beta blocker such as esmolol or metoprolol has also been advocated for persistent tachycardia and hypertension.

Precautions

Phenelzine and other MAOIs should not be given to patients with liver disease or a history of abnormal liver function tests, or, because of their effects on blood pressure, to patients with congestive heart failure, cerebrovascular disease, or phaeochromocytoma. (Blood pressure should be monitored in all patients.) MAOIs should be avoided or only used with great caution in patients with blood disorders or cardiovascular disease, and in elderly or agitated patients who may be particularly susceptible to their adverse effects. They should be given with caution to epileptic patients. Caution has also been advised in diabetic patients because of conflicting evidence whether glucose metabolism is altered or requirements for hypoglycaemics changed. MAOIs should be used with caution in patients with hyperthyroidism because of increased sensitivity to pressor amines.

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 observed when treating patients with other disorders.

Mania may be precipitated if MAOIs are used for the depressive component of bipolar disorder, and they are not usually indicated; similarly psychotic symptoms may be aggravated if they are used for a depressive component of schizophrenia.

MAOIs have a prolonged action so patients should not take any of the foods or drugs known to cause reactions (see Interactions, below) for at least 14 days after stopping treatment. A similar drug-free period has been advised before any patient undergoes surgery since it may involve the use of drugs that can interact with MAOIs, although not all agree that this is necessary; caution has been advised in patients requiring MAOIs with ECT; for further details see under Anaesthesia, below. Patients should carry cards giving details of their MAOI therapy; they and their relatives should be fully conversant with the implications of food and drug interactions and the precautions to be taken.

Patients liable to take charge of vehicles or other machinery should be warned that MAOIs may modify behaviour and state of alertness. Patients affected by drowsiness should not drive or operate machinery.

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

For the precautions to be observed with reversible inhibitors of monoamine oxidase A (RIMAs), see Moclobemide, p.411.

Anaesthesia. The considerations given to patients receiving tricyclic antidepressants before receiving anaesthesia for ECT or surgery (see Amitriptyline, p.378) are also generally applicable to patients being treated with MAOIs; licensed drug information for phenelzine also warns that transient respiratory and cardiovascular depression following ECT have been reported. The interactions of other drugs with MAOIs may be more numerous or more severe than those with tricyclics and the interaction with pethidine should not be forgotten.

A review[1] of the potential problems of anaesthesia in patients receiving MAOIs considered that stopping MAOIs about 2 weeks before anaesthesia was unreasonable, as there was a wide range of safe and suitable anaesthetics available, although the dangers of sympathetic overactivity must always be remembered. This view, that it is safe to continue MAOIs throughout the period of anaesthesia, ECT, and surgery, is also held by others[2-4] although some disagree.[5]

Regardless of any decision, the anaesthetist should be informed of all drugs that the patient is or has been taking; this is particularly important when emergency surgery is required in a patient receiving MAOI therapy.

- It has been stated[1] that the interaction between MAOIs and *opioid analgesics* has two distinct forms: an excitatory form [serotonin syndrome—see above]; and a depressive form consisting of respiratory depression, hypotension, and coma as a result of the inhibition of hepatic microsomal enzymes by the MAOI leading to accumulation of free opioid analgesic. *Pethidine* use during anaesthesia has elicited the excitatory response, which has frequently been severe and often fatal. For this reason, pethidine should never be given to patients receiving MAOIs. *Morphine* does not block neuronal serotonin uptake but its narcotic effects may be potentiated in the presence of MAOIs and a single case report of the depressive type of reaction has been described. Thus, morphine is the opioid analgesic of choice but must be given in reduced dosage and the dosage carefully titrated against clinical response. *Papaveretum* would appear to have no advantage over morphine. Although interactions of MAOIs with *pentazocine* have occurred in *animals*, it is not clear if this occurs in man. *Methadone* has been used in a patient without mishap and there is also anecdotal evidence to support the safety of *fentanyl*. A case report[6] described the successful use of *alfentanil* (with propofol and atracurium) mentioning that this was the first report of such use in patients receiving MAOIs. A further case report[7] has also described the safe use of alfentanil (with propofol and suxamethonium) for anaesthesia during ECT in 2 patients taking phenelzine. *Remifentanil* has also been used safely as part of an anaesthetic regimen (with sevoflurane, vecuronium, and isoflurane) in a patient also taking phenelzine.[8] In another case[9] a patient underwent successful anaesthesia with *sufentanil* (with thiopental, lidocaine, and vecuronium) while continuing to take an MAOI (tranylcypromine) as well as a tricyclic antidepressant (imipramine) and lorazepam.
- With regard to induction agents,[1] the use of *ketamine* in patients receiving MAOIs should be avoided on theoretical grounds, although no interactions have been reported. Potentiation of *barbiturates* may be expected.
- With neuromuscular blockers, phenelzine has been shown to decrease plasma cholinesterase concentrations and there have been case reports of a prolonged effect with *suxamethonium*; additionally this prolongation of the effect of suxamethonium may lead to apnoea and modification of the convulsion during ECT. However, a small case series of 4 patients taking tranylcypromine while undergoing ECT treatment (with suxamethonium as the neuromuscular blocker) found no difference in seizure length when compared to previous ECT courses when the patients were not taking an MAOI.[4] There may be a theoretical hazard with *pancuronium* since it releases stored adrenaline (although its use has been advocated in the treatment of symptoms of overdosage with MAOIs, see above), but *alcuronium*, *atracurium*, or *vecuronium* would all appear to be suitable alternatives.[1]
- *Enflurane*, *halothane*, *isoflurane*, and *nitrous oxide* are all safe in the presence of MAOIs, although there is a theoretical possibility of an increased risk of hepatic damage with halothane.
- *Indirect-acting sympathomimetics* pose the risk of a serious and possibly lethal hypertensive interaction but *direct-acting sympathomimetics*, such as *adrenaline*, *isoprenaline*, and *noradrenaline*, are reliable vasopressors in the presence of MAOIs although great care should be taken with their use because of enhanced receptor sensitivity.

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7. Beresford BJ, *et al.* Combination propofol-alfentanil anesthesia for electroconvulsive therapy in patients receiving monoamine oxidase inhibitors. *J ECT* 2004; **20:** 120–2.
8. Ure DS, *et al.* Safe use of remifentanil in a patient treated with the monoamine oxidase inhibitor phenelzine. *Br J Anaesth* 2000; **84:** 414–16.
9. O'Hara JF, *et al.* Sufentanil-isoflurane-nitrous oxide anesthesia for a patient treated with monoamine oxidase inhibitor and tricyclic antidepressant. *J Clin Anesth* 1995; **7:** 148–50.

Children. Phenelzine is not recommended for the treatment of depression in children and adolescents less than 16 years of age. In addition, other antidepressants have been shown to increase the risk of suicidal thoughts and behaviour in such patients (see Effects on Mental State, under Fluoxetine, p.392).

Driving. While affective disorders probably impair 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 properties and some MAOIs can adversely affect psychomotor performance.[1,2]

In the UK, the Driver and Vehicle Licensing Authority (DVLA) considers that 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;[3] 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. Driver and Vehicle Licensing Agency. For medical practitioners: at a glance guide to the current medical standards of fitness to drive (updated February 2008). Available at: http://www.dvla.gov.uk/media/pdf/medical/aagv1.pdf (accessed 14/08/08)

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

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

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 can precipitate withdrawal symptoms which may be very severe.

Symptoms associated with withdrawal of MAOIs[1,2] include gastrointestinal disturbances and generalised somatic symptoms such as nausea and vomiting, anorexia, chills, headache, and giddiness; sleep disturbances characterised by insomnia, severe nightmares, and somnolence; and a range of CNS symptoms including panic, anxiety, restlessness, agitation, cognitive impairment, mood swings, depression and suicidal ideation, hypomania, delusions, and hallucinations. Some of the above may be controlled by restarting the MAOI in low doses, but the best management is considered to be prevention by gradually stopping the drug.[2] The *BNF* recommends reducing the dose over a period of 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

The pathophysiology of the MAOI withdrawal syndrome is not fully known, although it has been hypothesised that some of the symptoms represent adrenergic hyperactivity[1] produced by the release of excessive amounts of dopamine and noradrenaline.[2]

With the exception of tranylcypromine, the withdrawal syndrome of MAOIs is not a consequence of drug dependence.[1] Tranylcypromine has been reported to produce dependence and tolerance in patients receiving high doses irrespective of whether or not they had a history of substance abuse. Tranylcypromine is similar in structure to amfetamine, which may be responsible for its addictive properties.[1]

1. Anonymous. Problems when withdrawing antidepressives. *Drug Ther Bull* 1986; **24:** 29–30.
2. Dilsaver SC. Withdrawal phenomena associated with antidepressant and antipsychotic agents. *Drug Safety* 1994; **10:** 103–14.

Interactions of MAOIs with Foods

A major disadvantage of MAOIs such as phenelzine is that by inhibiting monoamine oxidase they cause an accumulation of amine neurotransmitters. This means that the pressor effects of *tyramine*, which occurs in a number of common foods and is also metabolised by monoamine oxidase, can be dangerously enhanced. Reactions to foods rich in pressor amines such as tyramine can therefore occur in patients being treated with MAOIs, producing hypertensive crises. Cheese, especially aged or matured cheeses, meat or yeast extracts, pickled herrings, sauerkraut, dry sausage, smoked foods, and broad bean pods have caused such reactions. Patients should be warned not to eat any of these foods while being treated with an MAOI and for at least 14 days after its discontinuation. Some foods will only cause a reaction if large amounts are eaten, and foods may vary in tyramine content depending upon methods of manufacture and storage. Any protein-containing food such as meat, fish, or game subject to hydrolysis, fermentation, pickling, smoking, or spoilage could contain tyramine derived from tyrosine as a result of these processes or of deterioration. Patients taking MAOIs should therefore be advised to eat protein-containing foods only if fresh.

Alcoholic beverages, including wines, beers, and drinks that are de-alcoholised or are low in alcohol,

contain variable amounts of tyramine and are best avoided.

The above dietary restrictions that need to be observed with MAOIs may be less stringent for reversible inhibitors of monoamine oxidase type A (RIMAs) such as moclobemide (see p.411), although licensed drug information recommends that since some patients may be especially sensitive to tyramine, consumption of large amounts of tyramine-rich food should be avoided.

◊ MAOIs can, when taken with certain foodstuffs, cause a potentially fatal hypertensive reaction. This effect is accepted and well documented and has led to the publication of many lists of prohibited foods and drinks. Some workers consider that the dangers of the interaction may have been slightly overemphasised or exaggerated and that the published lists may have been overinclusive;[1-3] this may have led to reduced compliance in a number of patients.

A review and discussion[1] of the MAOI interaction with tyramine made the following observations and recommendations:

- the hyperadrenergic state resulting from this interaction consisted of three syndromes although significant overlap between them existed: paroxysmal headache of great severity; cardiovascular symptoms with paroxysmal hypertension; and intracerebral haemorrhage and death
- the most common offending drug reported had been tranylcypromine at doses of 20 to 50 mg daily although a few reports had involved phenelzine
- only 4 foodstuffs clearly warranted total prohibition: aged cheese, pickled herring or fish, concentrated yeast extracts, and broad bean pods
- the ingestion of cheese was said to have been associated with 80% of all case reports and with virtually all fatalities. It was agreed that aged cheese should not be permitted, although cottage and cream cheese required no restriction. There was less agreement concerning dairy products such as yogurt and sour cream and it was suggested that limited amounts were permissible
- pickled herring or smoked fish were to be avoided because of several well-documented cases of hypertensive crisis as well as detection of high levels of tyramine. Any meat may become dangerous unless consumed while fresh as tyramine is formed from bacterial protein degradation
- concentrated yeast extracts have a significant tyramine content and yeast vitamin supplements may also constitute a hazard; baker's yeast was considered to be safe
- broad bean pods contain dopamine although the beans themselves were stated to have little pressor activity and carried no prohibition
- other foods which had been reported to have caused a hypertensive reaction but for which these authors considered that there was insufficient evidence to warrant dietary restriction were chocolate and caffeine-containing beverages, soy sauce, fresh fish, wild game, and fruits although caution was necessary with avocados and bananas.

Other reviews of foods[2,4,5] give broadly similar recommendations.

The consumption of alcoholic beverages, and in particular Chianti wine, has frequently been advised against. However, sources have differed on whether particular types of drink (white wine, red wine, spirits, or beer) are safe or not. A study[6] demonstrated no significant differences in mean free tyramine concentration between white wine, red wine, Chianti, and beer although within each category of wine there could be up to a fiftyfold variation even if from the same grape stock. Mention has also been made[7,8] that alcohol-free or low-alcohol beers are likely to contain similar amounts of tyramine to alcoholic beers. The consumption of alcoholic drinks with MAOIs still appears to be controversial with some advocating total abstinence while others permit a modest intake.

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5. Gardner DM, *et al.* The making of a user friendly MAOI diet. *J Clin Psychiatry* 1996; **57:** 99–104.
6. Hannah P, *et al.* Tyramine in wine and beer. *Lancet* 1988; **i:** 879.
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Interactions of MAOIs with other Drugs

MAOIs inhibit the metabolism of some *amine drugs* (notably indirect-acting sympathomimetics), which can lead to dangerous enhancement of their pressor effects. MAOIs also inhibit other drug-metabolising enzymes and are therefore responsible for a large number of *other drug interactions*. Moreover, they have an additive effect with serotonergic drugs which may result in the *serotonin syndrome* (see under Adverse Effects, above). As in the case of foods, the danger of an interaction persists for at least 14 days after treatment with an MAOI has been stopped.

Severe hypertensive reactions due to enhancement of pressor activity have followed the use of sympathomimetics such as *amfetamines, dopamine, ephedrine, levodopa, phenylephrine, phenylpropanolamine,* and *pseudoephedrine*. Reactions may also follow the use of anorectics and stimulants with sympathomimetic activity such as *fenfluramine, methylphenidate, pemoline,* and *phentermine*. There have been case reports of fatalities in patients who took cough preparations containing *dextromethorphan*. There is no clinical evidence of dangerous interactions between *local anaesthetic preparations containing adrenaline* and MAOIs although they could occur if the preparation was accidentally given into a vein. Significant rises in blood pressure have been reported after the use of *buspirone* with MAOIs.

Inhibition of drug-metabolising enzymes by MAOIs may enhance the effects of *barbiturates* and possibly other *hypnotics, hypoglycaemics*, and possibly *antimuscarinics*. *Alcohol* metabolism may be altered and its effects enhanced; see also under Interactions of MAOIs with Foods, above. Licensed drug information suggests that the effects of various classes of *antihypertensives* may be enhanced by MAOIs, including *ACE inhibitors, beta blockers, calcium-channel blockers* and *thiazides*, with the potential for hypotension, although published evidence for most of these seems to be scanty. Some antihypertensives with direct actions on the sympathetic nervous system, such as *guanethidine, indoramin, methyldopa,* and, historically, *reserpine*, are suggested to be contra-indicated or used with great caution; both hypotensive and hypertensive reactions have been suggested.

Giving *pethidine* and possibly other *opioid analgesics* to patients taking an MAOI has also been associated with very severe and sometimes fatal reactions. When it is considered essential to use an opioid analgesic a test dose of morphine should be given. It has been suggested that the test dose should be one-tenth to one-fifth of the normal dose and if this produces no untoward reaction, the dose of morphine can be gradually and carefully increased over a period of 2 to 3 hours. The use of opioid analgesics and other drugs used during general anaesthesia in patients continuing to take MAOIs is discussed in Anaesthesia under Precautions, above.

Clozapine may enhance the CNS effects of MAOIs.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions may occur. MAOIs should not generally be given to patients receiving *tricyclic antidepressants, SSRIs, serotonin and noradrenaline reuptake inhibitors (SNRIs), bupropion, mirtazapine, nefazodone, reboxetine,* or *trazodone*. An appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. An MAOI should not be started until at least 1 or 2 weeks after stopping a tricyclic antidepressant. For the tricyclic antidepressants clomipramine and imipramine a drug-free interval of 3 weeks should be allowed. For an SSRI, an SNRI, reboxetine, nefazodone, trazodone, or any related antidepressant the drug-free interval should be at least one week; in the case of bupropion, mirtazapine, and the SSRI sertraline, the interval is extended to 2 weeks, and for fluoxetine, at least 5 weeks because of their longer half-lives. Conversely, 2 weeks should elapse between stopping MAOI therapy and starting patients on a tricyclic antidepressant (3 weeks in the case of clomipramine or imipramine), an SSRI, an SNRI, bupropion, mirtazapine, reboxetine, or any related antidepressant. For further warnings on the combined use of antidepressants, see below. Interactions can also occur between MAOIs themselves.

For details of the less severe interactions associated with reversible inhibitors of monoamine oxidase A (RIMAs), see Interactions of Moclobemide, p.411.

◊ References.

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Antidepressants. Combination therapy with differing classes of antidepressants may result in interactions or enhanced adverse reactions such as the serotonin syndrome (see under Adverse Effects, above), and is therefore considered unsuitable or controversial by some authorities. Despite these drawbacks certain combinations of drugs have been found to be beneficial in the treatment of drug-resistant depression, although others are considered unsuitable; absence of information documenting unsuitability or hazard does not necessarily imply that the two drugs may be used safely together but may merely reflect an untried combination. Because combination therapy poses increased risks it should be used only under expert supervision.

- MAOIs have been used fairly frequently under expert supervision with tricyclics in refractory depression and it has been stated[1] that the risk of serious problems in combining *tricyclic antidepressant and MAOI* antidepressant therapy is almost exclusively limited to sequential prescribing, in particular the addition of a tricyclic to established treatment with an MAOI. The recommended procedure was said to be to allow a drug-free interval of at least one week and then to start both drugs together at a low dosage. The dosage of both drugs is then gradually increased to around half that normally prescribed for the drugs when given on their own. The dietary restrictions for MAOIs alone apply equally to the combined antidepressant regimen.

  Amitriptyline and trimipramine were considered to be the tricyclics least likely to produce adverse effects with MAOIs, while phenelzine and isocarboxazid were the safest MAOIs. In contrast, clomipramine (a tricyclic with serotonin reuptake inhibiting activity) and imipramine are unsuitable for such use.[2,3] The combination of clomipramine with tranylcypromine is particularly dangerous. Symptoms suggestive of the serotonin syndrome occurred in an elderly patient due to an interaction between clomipramine and moclobemide, a reversible inhibitor of monoamine oxidase type A (RIMA).[4] Two fatalities due to serotonin syndrome have been reported after overdosage with clomipramine and moclobemide.[5] The syndrome has also developed when a patient was switched from clomipramine to moclobemide with no suitable drug-free interval.[6] A 39-year-old woman developed the serotonin syndrome while taking imipramine with moclobemide, although it was suggested that an excessive dose of the tricyclic may have been ingested accidentally.[7]
- The UK CSM has warned[8] that enhanced serotonergic effects may result from using *SSRIs with MAOIs* or other antidepressants. Although such an enhancement may be beneficial in some instances it can produce a life-threatening serotonin syndrome. Such reactions were later reported in patients taking sertraline with MAOIs.[9-11] Three fatalities due to serotonin syndrome have been reported after overdosage with citalopram and moclobemide.[5] A case of serotonin syndrome has been reported after switching from fluoxetine to moclobemide with no suitable drug-free interval.[6] Some authors[12] have reported good efficacy and tolerability with combinations of moclobemide and SSRIs. However, others[13] reported a high rate of adverse events although, as significant improvement in depressive symptoms was observed in some patients, it was suggested that giving moclobemide with SSRIs deserved consideration as an option for the treatment of refractory depression.
- Combination therapy with a *tricyclic antidepressant and an SSRI* has sometimes been used to treat resistant depression. Fluvoxamine[14] and fluoxetine[15] have been reported to increase plasma concentrations of the tricyclic, although to varying degrees. Fluoxetine has been reported to produce three- to fourfold increases in plasma concentrations of desipramine and imipramine. Fluvoxamine has a minimal effect on desipramine plasma levels but produces a three- to fourfold increase in concentrations of imipramine.[16] Plasma-desipramine concentrations are elevated threefold by paroxetine but increases of only 30% are produced by sertraline.[16] However, an inadequate interval of one day between stopping desipramine and starting paroxetine resulted in a case of serotonin syndrome.[6] Serotonin syndrome has also been reported[17] in a patient who received paroxetine and imipramine and in another given sertraline and amitriptyline.[18] A threefold increase in concentrations of trimipramine resulting in sedation and orthostatic hypotension has been reported[19] in 2 patients also given paroxetine. Additionally, norfluoxetine, the active metabolite of fluoxetine, has a long half-life and is responsible for the continuing interaction with tricyclics for

several days or weeks after fluoxetine has been withdrawn. Citalopram was reported to have no effect on plasma-tricyclic concentrations in a patient although antidepressant effects were augmented.[20]

- *Lithium* and *tryptophan* have been used to augment the effect of other antidepressants in refractory depression. Phenelzine has been used successfully with lithium and tryptophan[21] in patients with treatment-resistant chronic depression although such a regimen has probably been used less since the reports of the eosinophilia-myalgia syndrome associated with tryptophan (see p.427). There have, however, been several case reports of reactions similar to the serotonin syndrome in patients receiving MAOIs with tryptophan.[22,23]

  Although lithium is often added to tricyclic antidepressant therapy in patients with refractory depression, epileptic seizures have been reported in a patient receiving amitriptyline when lithium was added.[24] Serotonin syndrome has been reported[25] in a patient given clomipramine and lithium. Severe neurotoxicity has been reported[26,27] in some patients receiving lithium and tricyclic or tetracyclic antidepressants; adverse effects included tremor, memory impairment, disorganised thinking, and auditory hallucinations. One manufacturer of lithium preparations also reports symptoms of nephrogenic diabetes in patients receiving these combinations.

  By 1989 the CSM had received 19 reports of adverse reactions in patients treated with fluvoxamine and lithium; 5 reports concerned convulsions and 1 hyperthermia.[8] Tremor has been reported when lithium was given with paroxetine,[28] and in general the risk of CNS toxicity is increased when lithium is given with fluoxetine, fluvoxamine, paroxetine, or sertraline. There has been a report[29] of a fatality when fluoxetine was replaced by tranylcypromine and tryptophan with no drug-free period; the patient was also receiving other drugs concurrently.
- Use of the serotonin and noradrenaline reuptake inhibitor (SNRI) *venlafaxine with tricyclic antidepressants* has been associated with increased antimuscarinic adverse effects.[30,31] Seizures have also been reported with venlafaxine and trimipramine[32] and serotonin syndrome developed in a patient given amitriptyline, venlafaxine, and pethidine.[33] Similar antimuscarinic adverse effects have occurred in patients given *venlafaxine and the SSRI* fluoxetine;[31] serotonin syndrome has been reported in a patient who received venlafaxine and paroxetine.[6] The use of *venlafaxine with MAOIs* is contra-indicated by the manufacturers of venlafaxine because of the risk of life-threatening adverse reactions. Serious adverse reactions have been reported when venlafaxine was combined with isocarboxazid,[34] moclobemide,[6] phenelzine,[35] or tranylcypromine.[36]
- *Trazodone* is chemically unrelated to other antidepressants but does have serotonergic actions. Serotonin syndrome has been reported when trazodone was combined with the SSRI *paroxetine*.[37]
- Serotonin syndrome has been reported[38] in a patient who took *nefazodone* with *fluoxetine*. There has been a similar report[39] in a patient who received *paroxetine* 2 days after finishing gradual withdrawal from over 6 months of treatment with nefazodone.
- Symptoms resembling serotonin syndrome have occurred in a patient taking the noradrenergic and specific serotonergic antidepressant, *mirtazapine* with *fluvoxamine*;[40] another report[41] suggests that the plasma concentrations of mirtazapine may be increased as much as fourfold by fluvoxamine.
- Raised *nortriptyline* levels were noted in a patient also taking *bupropion*; the effect recurred on rechallenge.[42]
- In a report[43] of an interaction between *St John's wort* and *paroxetine*, a 50-year-old woman was found incoherent, groggy, and slow-moving after self-administering a single dose of paroxetine while taking St John's wort; recovery was uneventful. Use of St John's wort with the SSRIs may potentiate their serotonergic effects and increase the incidence of adverse reactions. The CSM has advised that patients should stop taking St John's wort if treatment with an SSRI is necessary.[44] Symptoms of serotonin syndrome have also been reported when St John's wort and *nefazodone* were taken.[45]

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

Licensed UK drug product information states that *carbamazepine* should be avoided with or within 2 weeks of a MAOI because of structural similarities with the tricyclic antidepressants; however, published evidence of adverse interactions is lacking. There is also a theoretical possibility of a similar interaction with *oxcarbazepine*.

Antimigraine drugs. For the effect of MAOIs on *serotonin (5-HT_1) agonists*, see under Sumatriptan, p.626.

Antineoplastics. For the effect when MAOIs are used with *altretamine*, see p.678.

Dopaminergics. For the effect of MAOIs with *amantadine*, see p.793, with *levodopa*, see p.807, and with *selegiline*, see p.817.

General anaesthetics. The problems that may occur when patients receiving MAOIs are also given general anaesthetics are discussed under Anaesthesia in Precautions, above.

Ginseng. There have been 2 reports[1,2] of adverse effects, including headaches, insomnia, tremulousness, and irritability when ginseng was taken with phenelzine.

1. Shader RI, Greenblatt DJ. Phenelzine and the dream machine—ramblings and reflections. *J Clin Psychopharmacol* 1985; **5:** 65.
2. Jones BD, Runikis AM. Interaction of ginseng with phenelzine. *J Clin Psychopharmacol* 1987; **7:** 201–2.

Insulin. For the effect of MAOIs on insulin, see p.449.

Neuromuscular blockers. For the effects of MAOIs on *suxamethonium*, see p.1912. Problems that may be encountered with MAOIs and neuromuscular blockers used during anaesthesia are discussed under Anaesthesia in Precautions, above.

Opioid analgesics. The problems that may occur with MAOIs and opioid analgesics used during anaesthesia are discussed under Anaesthesia in Precautions, above.

Respiratory stimulants. For the effect of MAOIs on *doxapram*, see p.2155.

Pharmacokinetics

Phenelzine is readily absorbed from the gastrointestinal tract reaching peak plasma concentrations 2 to 4 hours after ingestion. It is metabolised in the liver and is excreted in the urine almost entirely in the form of metabolites.

Uses and Administration

Monoamine oxidase inhibitors (MAOIs) inhibit the action of monoamine oxidase, the enzyme responsible for the metabolism of several biogenic amines. Monoamine oxidase exists in two forms, type A and type B. Monoamine oxidase type A preferentially deaminates adrenaline, noradrenaline, and serotonin whereas monoamine oxidase type B preferentially metabolises benzylamine and phenylethylamine; dopamine and tyramine are de-aminated by both forms of the enzyme.

- The traditional MAOIs such as phenelzine, iproniazid, isocarboxazid, and tranylcypromine are inhibitors of both types; apart from tranylcypromine, which produces a less prolonged inhibition of the enzyme than phenelzine, all are hydrazine derivatives and bind irreversibly.
- Selective inhibitors include selegiline (p.817), an irreversible inhibitor of monoamine oxidase type B used in the treatment of Parkinson's disease and depression. Clorgiline, an irreversible selective type A inhibitor, was investigated for use as an antidepressant.
- Reversible inhibitors of monoamine oxidase type A (RIMAs) include brofaromine and moclobemide.

Antidepressant activity appears to reside mainly with inhibition of monoamine oxidase type A although the mode of action of these drugs in depression is not fully understood. Selective inhibitors are claimed to have fewer or less severe adverse effects than non-selective inhibitors. As tyramine is de-aminated by both monoamine oxidase types A and B, inhibiting only one of the enzymes allows for continued, albeit reduced, de-amination. Thus the dietary precautions that need to be observed with non-selective inhibitors are less stringent with the selective inhibitors.

Phenelzine and other antidepressant MAOIs are used in the treatment of atypical depression, particularly where phobic features or associated anxiety are present, or in patients who have not responded to other antidepressants. However, the risks associated with irreversible non-selective MAOIs usually mean that other antidepressants are preferred. Up to a month may elapse before an antidepressant response is obtained with MAOIs. After a response has been obtained maintenance therapy may need to be continued 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. Care should be taken in elderly patients because of an increased susceptibility to adverse effects. Moreover,

therapy with the non-selective inhibitors is particularly unsuitable for patients considered unable to adhere to the strict dietary requirements necessary for safe usage. (For contra-indication in children, see under Precautions, above).

Phenelzine is given orally as the sulfate although doses are expressed in terms of the base. Phenelzine sulfate 25.8 mg is equivalent to about 15 mg of phenelzine. The usual initial dose is equivalent to phenelzine 15 mg three times daily; if no response has been obtained after 2 weeks the dosage may be increased to 15 mg four times daily; severely depressed patients in hospital may be given up to 30 mg three times daily. Once a response has been obtained the dosage may be gradually reduced for maintenance therapy; some patients may continue to respond to 15 mg on alternate days.

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

Anxiety disorders. MAOIs have been used in the treatment of anxiety disorders. MAOIs appear to be effective in *panic disorder* (p.952). They also appear to be effective in *social anxiety disorder* (see under Phobic Disorders, p.953) and can improve anticipatory anxiety and functional disability. The main treatment for *post-traumatic stress disorder* (p.953) is psychotherapy but MAOIs are one of the alternatives that can help to reduce traumatic recollections and nightmares, and to repress flashbacks.

References.

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3. Heimberg RG, *et al.* Cognitive behavioural group therapy vs phenelzine therapy for social phobia: 12 week outcome. *Arch Gen Psychiatry* 1998; **55:** 1133–41.
4. Aarre TF. Phenelzine efficacy in refractory social anxiety disorder: a case series. *Nord J Psychiatry* 2003; **57:** 313–15.

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 effects. MAOIs are rarely used as first-choice antidepressants because of the dangers of dietary and drug interactions. Even in depressed patients with atypical, hypochondriacal, hysterical, or phobic features, for which MAOIs are particularly effective, it is often recommended that another antidepressant type should be tried first. Reversible inhibitors of monoamine oxidase type A (RIMAs) offer an alternative to the MAOIs and less strict dietary restrictions are necessary. They may be effective in a wide range of depressive disorders, although their relative efficacy in atypical depression remains to be established.

Combination therapy with differing classes of antidepressants, including the MAOIs, has been used in the treatment of drug-resistant depression. However, such therapy may result in enhanced adverse reactions or interactions and is considered unsuitable or controversial by some. For further details, see Antidepressants under Interactions, above.

Hyperactivity. When drug therapy is required for attention deficit hyperactivity disorder (p.2148), initial treatment is usually with a central stimulant. MAOIs have been used successfully but problems with dietary restriction and potential drug interactions have limited their use.

Migraine. A number of drugs have been used for the prophylaxis of migraine (p.616), although propranolol is generally preferred. Antidepressants such as the tricyclics can be useful alternatives when these drugs are ineffective or unsuitable. MAOIs are best reserved for severe cases refractory to other forms of prophylactic treatment.

Preparations

BP 2008: Phenelzine Tablets;
USP 31: Phenelzine Sulfate Tablets.

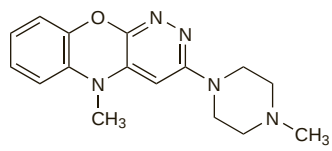
Proprietary Preparations (details are given in Part 3)
Austral.: Nardil; ***Belg.:*** Nardelzine; ***Canad.:*** Nardil; ***Irl.:*** Nardil; ***NZ:*** Nardil; ***UK:*** Nardil; ***USA:*** Nardil.

Pipofezine Hydrochloride *(rINNM)*

Hidrocloruro de pipofezina; Pipofézine, Chlorhydrate de; Pipofezine Dihydrochloride; Pipofezini Hydrochloridum. 5-Methyl-3-(4-methyl-1-piperazinyl)-5*H*-pyridazino[3,4-*b*][1,4]benzoxazine dihydrochloride.

Пипофезина Гидрохлорид

$C_{16}H_{19}N_5O,2HCl$ = 370.3.
CAS — 24886-52-0 (pipofezine); 24853-80-3 (pipofezine hydrochloride).



(pipofezine)

Profile

Pipofezine is a tricyclic antidepressant (see Amitriptyline, p.376).

In the treatment of depression (p.373) pipofezine is usually given orally as the hydrochloride although doses are expressed in terms of the base; pipofezine hydrochloride 31.1 mg is equivalent to about 25 mg of pipofezine. An initial dose is 25 mg given four times daily, increased to an optimum total daily dose of 150 to 200 mg; if necessary up to a maximum of 500 mg may be given daily in divided doses. For maintenance a modified-release preparation providing pipofezine 150 mg may be given once or twice daily.

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

Preparations

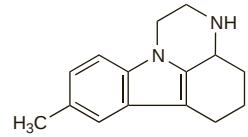
Proprietary Preparations (details are given in Part 3)
Rus.: Azaphen (Азафен).

Pirlindole *(rINN)*

Pirlindol; Pirlindolum. 2,3,3a,4,5,6-Hexahydro-8-methyl-1*H*-pyrazino[3,2,1-*jk*]carbazole.

Пирлиндол

$C_{15}H_{18}N_2$ = 226.3.
CAS — 60762-57-4.



Profile

Pirlindole has been given by mouth in the treatment of depression.

Preparations

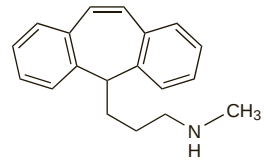
Proprietary Preparations (details are given in Part 3)
Port.: Implementor; ***Rus.:*** Pyrazidol (Пиразидол).

Protriptyline Hydrochloride *(BANM, USAN, rINNM)*

Hidrocloruro de protriptilina; MK-240; Protriptyline, chlorhydrate de; Protriptylini hydrochloridum. 3-(5*H*-Dibenzo[*a,d*]cyclohept-5-enyl)propyl(methyl)amine hydrochloride.

Протриптилина Гидрохлорид

$C_{19}H_{21}N,HCl$ = 299.8.
CAS — 438-60-8 (protriptyline); 1225-55-4 (protriptyline hydrochloride).
ATC — N06AA11.
ATC Vet — QN06AA11.



(protriptyline)

Pharmacopoeias. In *Br.* and *US.*

BP 2008 (Protriptyline Hydrochloride). A white to yellowish-white, odourless or almost odourless, powder. Freely soluble in water, in alcohol, and in chloroform; practically insoluble in ether. A 1% solution in water has a pH of 5.0 to 6.5.

USP 31 (Protriptyline Hydrochloride). A white to yellowish powder. Is odourless or has not more than a slight odour. Soluble 1 in 2 of water, 1 in 3.5 of alcohol, and 1 in 2.5 of chloroform; practically insoluble in ether. pH of a 1% solution in water is between 5.0 and 6.5.

Adverse Effects, Treatment, and Precautions

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

Since protriptyline may have some stimulant properties anxiety and agitation can occur more frequently; cardiovascular effects such as tachycardia and orthostatic hypotension may also be more frequent than with other tricyclics. Photosensitivity rashes have been noted more often with protriptyline than with other tricyclic antidepressants and patients taking it should avoid direct sunlight.

Interactions

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

Pharmacokinetics

Protriptyline is well but slowly absorbed after oral doses: licensed drug information states that peak plasma concentrations are achieved only after 8 to 12 hours.

Paths of metabolism of protriptyline include *N*-oxidation and hydroxylation. Protriptyline is excreted in the urine, mainly in the form of its metabolites, either free or in conjugated form.

Protriptyline is widely distributed throughout the body and extensively bound to plasma and tissue protein. Protriptyline has been estimated to have a very prolonged elimination half-life ranging from 55 to 198 hours, which may be further prolonged in overdosage.

Uses and Administration

Protriptyline is a dibenzocycloheptatriene tricyclic antidepressant with actions and uses similar to those of amitriptyline (p.381). It is considerably less sedative than other tricyclics and may have a stimulant effect, thus making it particularly suitable for apathetic and withdrawn patients; its antimuscarinic effects are moderate.

In the treatment of depression, protriptyline hydrochloride is given in oral doses of 5 to 10 mg three or four times daily. It has been suggested that, because of its potential stimulant activity, any dosage increases should be added to the morning dose first and if insomnia occurs the last dose should be given no later than mid-afternoon. Higher doses of up to 60 mg daily may be required in severely depressed patients. A suitable initial dose for adolescents and the elderly is 5 mg three times daily; close monitoring of the cardiovascular system has been recommended if the dose exceeds a total of 20 mg daily in elderly subjects.

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

Preparations

BP 2008: Protriptyline Tablets;
USP 31: Protriptyline Hydrochloride Tablets.

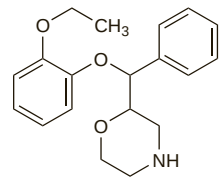
Proprietary Preparations (details are given in Part 3)
USA: Vivactil.

Reboxetine Mesilate *(BANM, rINNM)*

FCE-20124 (reboxetine or reboxetine mesilate); Mesilato de reboxetina; PNU-155950E; Réboxétine, Mésilate de; Reboxetine Mesylate *(USAN)*; Reboxetini Mesilas. (±)-(2*RS*)-2-[(α*RS*)-α-(2-Ethoxyphenoxy)benzyl]morpholine methanesulphonate.

Ребоксетина Мезилат

$C_{19}H_{23}NO_3,CH_4O_3S$ = 409.5.
CAS — 71620-89-8; 98769-81-4 (both reboxetine); 98769-82-5; 98769-84-7 (both reboxetine mesilate).
ATC — N06AX18.
ATC Vet — QN06AX18.



(reboxetine)

Adverse Effects

Adverse effects most commonly seen with reboxetine include insomnia, dry mouth, constipation, and increased sweating. Disturbance of visual accommodation, loss of appetite, vertigo, tachycardia, palpitations, vasodilatation, orthostatic hypotension, urinary hesitancy or retention (mainly in men), and erectile dysfunction including ejaculatory delay are also reported as being common adverse reactions. There have been reports of allergic dermatitis, convulsions, aggressive behaviour, cold extremities, and nausea and vomiting. Reduced plasma-potassium concentrations have been seen in elderly patients after prolonged use.