Escitalopram Oxalate

(BANM, USAN, rINNM)

S-Citalopram Oxalate; Escitalopram, Oxalate d'; Escitalopramі Oxalas; Lu-26-054/0; Oxalato de escitalopram. (+)-(*S*)-1-[3-(dimethylamino)propyl]-1-(*p*-fluorophenyl)-5-phthalancarbonitrile oxalate.

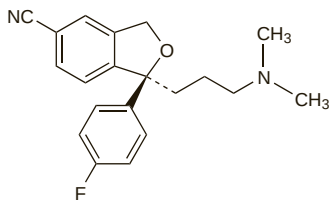
Эсциталопрама Оксалат

$C_{20}H_{21}FN_2O,C_2H_2O_4$ = 414.4.

CAS — 128196-01-0 (escitalopram); 219861-08-2 (escitalopram oxalate).

ATC — N06AB10.

ATC Vet — QN06AB10.



(escitalopram)

Adverse Effects and Precautions

As for Citalopram, p.385.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State in Fluoxetine, p.392.

Pharmacokinetics

Escitalopram has similar pharmacokinetics to those of racemic citalopram (p.385).

◊ References.

1. Søgaard B, *et al.* The pharmacokinetics of escitalopram after oral and intravenous administration of single and multiple doses to healthy subjects. *J Clin Pharmacol* 2005; **45:** 1400–6.
2. Rao N. The clinical pharmacokinetics of escitalopram. *Clin Pharmacokinet* 2007; **46:** 281–90.

Uses and Administration

Escitalopram, the *S*-enantiomer of citalopram (p.385), is an SSRI with actions and uses similar to those of fluoxetine (p.391). It is given orally as the oxalate although doses are expressed in terms of the base; escitalopram oxalate 12.8 mg is equivalent to about 10 mg of escitalopram.

In the treatment of **depression**, the usual dose is 10 mg once daily increased, after at least a week, to a maximum of 20 mg once daily if necessary.

Escitalopram is also used in the treatment of **panic disorder** with or without agoraphobia. Initial doses are 5 mg once daily, increased after a week to 10 mg once daily; further increases up to a maximum of 20 mg daily may be necessary in some patients.

Doses of escitalopram used in the treatment of **generalised anxiety disorder**, **social anxiety disorder**, and **obsessive-compulsive disorder** are similar to those used in depression.

Initial treatment with half the usual recommended dose and a lower maximum dose should be considered in elderly patients. Patients with hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 may also require lower doses (see below).

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

Administration in hepatic impairment. Increases of 51% and 69% in the area under the concentration-time curve occurred in a single-dose study of escitalopram in patients with mild and moderate hepatic impairment (Child-Pugh score 5 or 6, and 7 to 9, respectively).[1] This study also reported that activity of the cytochrome P450 isoenzyme CYP2C19 was a better predictor of escitalopram clearance than the Child-Pugh classification.

UK licensed product information for escitalopram suggests that patients with mild to moderate hepatic impairment or those who are poor metabolisers with respect to the cytochrome P450 isoenzyme CYP2C19 should receive an initial oral dose of 5 mg daily, increased to 10 mg daily after 2 weeks depending on response; more careful dose titration is advised in those with severe impairment. US licensed product information recommends 10 mg daily as a suitable dose for most patients with hepatic impairment.

1. Areberg J, *et al.* The pharmacokinetics of escitalopram in patients with hepatic impairment. *AAPS J* 2006; **8:** E14–E19.

Anxiety disorders. Escitalopram has been given in anxiety disorders (p.952) including panic disorder (p.952), obsessive-compulsive disorder (p.952), and social anxiety disorder (see under Phobic Disorders, p.953).

References.

1. Stahl SM, *et al.* Escitalopram in the treatment of panic disorder: a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry* 2003; **64:** 1322–7.
2. Davidson JR, *et al.* Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety* 2004; **19:** 234–40.
3. Lader M, *et al.* Efficacy and tolerability of escitalopram in 12- and 24-week treatment of social anxiety disorder: randomised, double-blind, placebo-controlled, fixed-dose study. *Depress Anxiety* 2004; **19:** 241–8.
4. Kasper S, *et al.* Escitalopram in the treatment of social anxiety disorder: randomised, placebo-controlled, flexible-dosage study. *Br J Psychiatry* 2005; **186:** 222–6.
5. Stein DJ, *et al.* Escitalopram in obsessive-compulsive disorder: a randomized, placebo-controlled, paroxetine-referenced, fixed-dose, 24-week study. *Curr Med Res Opin* 2007; **23:** 701–11.

Depression. As discussed on p.373, there is very little difference in efficacy between the different groups of antidepressant drugs. SSRIs such as escitalopram are widely used as an alternative to the older tricyclics as they have fewer adverse effects and are safer in overdosage.

References.

1. Burke WJ, *et al.* Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry* 2002; **63:** 331–6.
2. Wade A, *et al.* Escitalopram 10mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2002; **17:** 95–102.
3. Lepola UM, *et al.* Escitalopram (10-20 mg/day) is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol* 2003; **18:** 211–17.
4. Rapaport MH, *et al.* Escitalopram continuation treatment prevents relapse of depressive episodes. *J Clin Psychiatry* 2004; **65:** 44–9.
5. Montgomery SA, *et al.* A randomised study comparing escitalopram with venlafaxine XR in primary care patients with major depressive disorder. *Neuropsychobiology* 2004; **50:** 57–64.
6. Murdoch D, Keam SJ. Escitalopram: a review of its use in the management of major depressive disorder. *Drugs* 2005; **65:** 2379–2404.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Aramix; Citalax; Lexapro; Lextor; Meridian; ***Austral.:*** Esipram; Lexapro; ***Austria:*** Cipralex; ***Belg.:*** Sipralexa; ***Braz.:*** Lexapro; ***Canad.:*** Cipralex; ***Chile:*** Celtium; Ectiban; Ipran; Lexapro; Neozentius; Zepaz; ***Cz.:*** Cipralex; ***Denm.:*** Cipralex; ***Fin.:*** Cipralex; ***Fr.:*** Seroplex; ***Ger.:*** Cipralex; ***Gr.:*** Cipralex; Entact; ***Hong Kong:*** Lexapro; ***Hung.:*** Cipralex; ***India:*** Cipralex; Recita; S-Citadep; ***Indon.:*** Cipralex; ***Irl.:*** Lexapro; ***Israel:*** Cipralex; ***Ital.:*** Cipralex; Entact; ***Malaysia:*** Lexapro; ***Mex.:*** Lexapro; ***Neth.:*** Cipralex; Lexapro; ***Norw.:*** Cipralex; ***NZ:*** Lexapro; ***Philipp.:*** Lexapro; ***Pol.:*** Lexapro; ***Port.:*** Cipralex; ***Rus.:*** Cipralex (Ципралекс); ***S.Afr.:*** Cipralex; ***Singapore:*** Lexapro; ***Spain:*** Cipralex; Entact; Esertia; ***Swed.:*** Cipralex; ***Switz.:*** Cipralex; ***Thai.:*** Lexapro; ***Turk.:*** Cipralex; ***UK:*** Cipralex; ***USA:*** Lexapro; ***Venez.:*** Lexapro.

Fluoxetine Hydrochloride

(BANM, USAN, rINNM)

Fluoksetiinihydrokloridi; Fluoksetin Hidroklorür; Fluoksetino hidrochloridas; Fluoksetyny chlorowodorek; Fluoxétine, chlorhydrate de; Fluoxetin-hidroklorid; Fluoxetin-hydrochlorid; Fluoxetinhydroklorid; Fluoxetini hydrochloridum; Hidrocloruro de fluoxetina; Lilly-103472; LY-110140. (±)-*N*-Methyl-3-phenyl-3-(α,α,α-trifluoro-*p*-tolyloxy)propylamine hydrochloride.

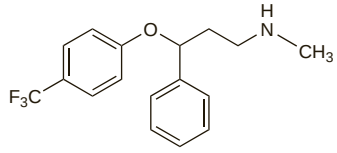
Флуоксетина Гидрохлорид

$C_{17}H_{18}F_3NO,HCl$ = 345.8.

CAS — 54910-89-3 (fluoxetine); 59333-67-4 (fluoxetine hydrochloride).

ATC — N06AB03.

ATC Vet — QN06AB03.



(fluoxetine)

NOTE. The following terms have been used as 'street names' (see p.vi) or slang names for various forms of fluoxetine:
Distas; Green and whites; Greens; Limes; Pros; Zacs.

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fluoxetine Hydrochloride). A white or almost white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in methyl alcohol. A 1% solution in water has a pH of 4.5 to 6.5.

USP 31 (Fluoxetine Hydrochloride). A white to off-white crystalline powder. Sparingly soluble in water and in dichloromethane; freely soluble in alcohol and in methyl alcohol; practically insoluble in ether. Store in airtight containers.

Adverse Effects

SSRIs such as fluoxetine are less sedating than tricyclic antidepressants and have fewer antimuscarinic and cardiotoxic effects. Adverse effects reported with SSRIs include dry mouth and gastrointestinal disturbances such as nausea, vomiting, dyspepsia, constipation, and diarrhoea. Anorexia and weight loss may also occur. Neurological adverse effects have included either anxiety, restlessness, nervousness, and insomnia, or drowsiness and fatigue; headache, tremor, dizziness, seizures, hallucinations, confusion, agitation, extrapyramidal effects, depersonalisation, mania, panic attacks, sexual dysfunction, and symptoms suggestive of a serotonin syndrome (p.416) have also occurred. The concern that SSRIs may be associated with increased suicidal ideation is discussed under Effects on Mental State, below.

Excessive sweating, pruritus, skin rashes, alopecia, photosensitivity, and urticaria have also been reported. Angioedema and anaphylactoid reactions have occurred. In some patients who have developed rashes while taking fluoxetine, systemic hypersensitivity reactions involving the lungs, kidneys, or liver, and possibly related to vasculitis, have developed; it has therefore been advised that fluoxetine therapy should be stopped in any patient who develops a skin rash.

Hyponatraemia, possibly due to inappropriate secretion of antidiuretic hormone, has been associated with the use of antidepressants, particularly in the elderly. Hyperprolactinaemia and galactorrhoea have occurred, as have changes in blood sugar, in patients receiving SSRIs.

Arthralgia and myalgia have been reported and there have also been cases of orthostatic hypotension, yawning, urinary retention, and abnormal vision including blurred vision and mydriasis. Abnormal liver function tests have been reported rarely. SSRIs have occasionally been associated with bleeding disorders such as ecchymosis and purpura and other effects on the blood.

In overdosage nausea, vomiting, and excitation of the CNS are considered to be prominent features; death has been reported.

Incidence of adverse effects. In June 1992 the UK CSM had received 1236 reports of adverse effects with fluvoxamine (from about 280 000 prescriptions) compared with 2422 for fluoxetine (from about 480 000 prescriptions).[1] The overall patterns of adverse effects were similar but dermatological reactions were more likely with fluoxetine and gastrointestinal reactions with fluvoxamine. Reports of attempted suicide increased after adverse publicity about SSRIs in 1990, and the number of reports per million prescriptions were similar for the 2 drugs (25 for fluoxetine and 20 for fluvoxamine); at that time such figures were not considered disconcerting given that features of depression, including attempted suicide, can worsen after the introduction of any antidepressant (see also Effects on Mental State, below). A later review[2] by the CSM of the 5 SSRIs available in the UK (citalopram, fluoxetine, fluvoxamine, paroxetine, and sertraline) found that the SSRIs were broadly similar with respect to their safety profile. A list of adverse reactions common to all SSRIs was provided.

A review[3] of 1861 adverse reactions to citalopram, fluoxetine, fluvoxamine, paroxetine, or sertraline reported to the Swedish Adverse Drug Reactions Advisory Committee found that the most commonly reported reactions were neurological (22.4% of all reports), psychiatric (19.5%), and gastrointestinal (18.0%). Compared with other SSRIs, gastrointestinal symptoms were more common with fluvoxamine, psychiatric symptoms with sertraline, and dermatological symptoms with fluoxetine.

A more recent meta-analysis[4] has compared the adverse effect profile of fluoxetine with other antidepressants including the tricyclics and other SSRIs. The overall risk of any adverse effect with fluoxetine was less than that for the tricyclic antidepressants; however, there was no difference in risk when fluoxetine was compared with other SSRIs. When considering individual adverse reactions, fluoxetine was more likely to cause activating

effects such as insomnia, agitation, tremor, and anxiety, and gastrointestinal disturbances such as nausea, vomiting, diarrhoea, weight loss, and anorexia than other antidepressants. In contrast, the tricyclics were associated with a greater risk of sedation, antimuscarinic effects (such as dry mouth, dizziness, and blurred vision), constipation, and weight gain, than fluoxetine.

1. CSM. Safety of fluoxetine (Prozac): comparison with fluvoxamine (Faverin). *Current Problems 34* 1992. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024452&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. CSM/MCA. Selective serotonin reuptake inhibitors (SSRIs). *Current Problems* 2000; **26:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 27/11/05)
3. Spigset O. Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. *Drug Safety* 1999; **20:** 277–87.
4. Brambilla P, *et al.* Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. *Pharmacopsychiatry* 2005; **38:** 69–77.

Effects on the blood. Abnormalities in platelet aggregation were associated with fluoxetine given to a severely underweight patient.[1] Platelet activity returned to normal when fluoxetine was stopped. Fluoxetine was also suspected of being the cause of bruising in a patient whose blood clotting parameters were within normal limits.[2] Purpura and bruising have been reported to be the commonest adverse blood effects associated with fluoxetine, paroxetine, or sertraline although cases of thrombocytopenia have been recorded for all three antidepressants.[3] The suggested mechanism was inhibition of uptake of serotonin into platelets, thereby disrupting platelet aggregation; caution was recommended when treating patients with a history of bleeding disorders with SSRIs. However, a subsequent cohort study based on prescription-event monitoring provided only weak evidence of a link between the use of SSRIs and the development of bleeding disorders.[4] A similar study[5] found no evidence of a major increased risk of intracranial haemorrhage with the use of SSRIs, although smaller increases in risk could not be ruled out.

For mention of a possibly increased risk of gastrointestinal bleeding, see Effects on the Gastrointestinal Tract, below.

1. Alderman CP, *et al.* Abnormal platelet aggregation associated with fluoxetine therapy. *Ann Pharmacother* 1992; **26:** 1517–19.
2. Pai VB, Kelly MW. Bruising associated with the use of fluoxetine. *Ann Pharmacother* 1996; **30:** 786–8.
3. Anonymous. Bruising and bleeding with SSRIs. *Aust Adverse Drug React Bull* 1998; **17:** 10. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9808.pdf (accessed 14/08/08)
4. Layton D, *et al.* Is there an association between selective serotonin reuptake inhibitors and risk of abnormal bleeding? Results from a cohort study based on prescription event monitoring in England. *Eur J Clin Pharmacol* 2001; **57:** 167–76.
5. de Abajo FJ, *et al.* Intracranial haemorrhage and use of selective serotonin reuptake inhibitors. *Br J Clin Pharmacol* 2000; **50:** 43–7.

Effects on the cardiovascular system. SSRIs are not associated with the same degree of cardiotoxicity as the tricyclic antidepressants (see p.376), although orthostatic hypotension has been reported in some patients. A decrease in heart rate with ECG changes has been noted with fluvoxamine. However, a study[1] on long-term fluvoxamine treatment in 311 patients followed for 1 year revealed no significant effect on ECG findings compared with patients given placebo.

Concern over the use of sertraline in patients with coronary heart disease was raised after a report[2] of a 53-year-old man with a history of coronary heart disease who experienced attacks of sudden precordial chest pain on starting treatment with sertraline. The pain responded to glyceryl trinitrate. The manufacturers[3] pointed out that there had been no ECG changes confirming an ischaemic origin of the disorder in this patient and that in studies sertraline had had no demonstrable clinical effects on intraventricular conduction or ECG intervals. Furthermore, no significant changes in cardiovascular indices had been recorded in patients who had taken overdoses of up to 6 g of sertraline. It was suggested that this might have been an effect on the gastrointestinal tract possibly at the oesophageal level.

1. Hochberg HM, *et al.* Electrocardiographic findings during extended clinical trials of fluvoxamine in depression: one years experience. *Pharmacopsychiatry* 1995; **28:** 253–6.
2. Iruela LM. Sudden chest pain with sertraline. *Lancet* 1994; **343:** 1106.
3. Berti CA, Doogan DP. Sudden chest pain with sertraline. *Lancet* 1994; **343:** 1510–11.

Effects on the cerebrovascular system. There have been rare reports of cerebral ischaemic events associated with the use of SSRIs. In one case[1] a 57-year-old man receiving long-term treatment for atrial fibrillation and hypercholesterolaemia presented with a facial droop and slurred speech 3 days after starting paroxetine 20 mg twice daily. Symptoms resolved after anticoagulant therapy and stopping paroxetine but recurred when paroxetine was reintroduced at a dose of 10 mg twice daily. Paroxetine was stopped and no further episodes had occurred within 4 months at follow-up.

For a report that there is no major increased risk of intracranial haemorrhage associated with the SSRIs, see Effects on the Blood, above.

1. Manos GH, Wechsler SM. Transient ischemic attack reported with paroxetine use. *Ann Pharmacother* 2004; **38:** 617–20.

Effects on the endocrine system. The *syndrome of inappropriate antidiuretic hormone secretion (SIADH)* with *hyponatraemia* has been reported in patients receiving antidepressants. The UK CSM, commenting on reports it had received of hyponatraemia associated with antidepressants (fluoxetine, paroxetine, lofepramine, clomipramine, and imipramine), considered that it was likely to occur with any antidepressant, and usually involved elderly patients.[1] However, the results of a later study[2] have suggested that cases are more likely to occur with serotonergic antidepressants such as the SSRIs, clomipramine, and venlafaxine. Case reports of hyponatraemia in 16 patients treated with SSRIs have been summarised.[3] A further review[4] of reports on 15 patients with hyponatraemia with SIADH induced by fluoxetine (12 cases), fluvoxamine (2 cases), and paroxetine (1 case) showed that the risk was greatest during the early treatment phase. This is borne out by single-case reports[5-12] of hyponatraemia with SIADH in elderly patients receiving either citalopram, paroxetine, or sertraline. A retrospective study[13] of hyponatraemia associated with either fluoxetine or paroxetine use also showed the early onset of the condition and identified low bodyweight as being another risk factor for developing hyponatraemia. Not unexpectedly, replacing one SSRI with another has resulted in a recurrence of hyponatraemia; however, in one report,[14] the symptoms of hyponatraemia did not recur until about 16 months after switching SSRIs.

SSRI-associated *hyperprolactinaemia* has been reported.[15] Lactation and raised prolactin levels occurred in a teenager 3 days after fluoxetine was added to her existing therapy which included pimozide. Stopping fluoxetine had no effect on lactation, which only ceased after withdrawing pimozide. In another report,[16] hyperprolactinaemia and galactorrhoea in an elderly woman receiving fluoxetine resolved on stopping the drug.

Gynaecomastia, unrelated to prolactin concentrations, was associated with the start of fluoxetine therapy in a 49-year-old man. Symptoms subsided 10 months after withdrawing fluoxetine.[17]

Although SSRIs may be favoured for the management of depression in patients with diabetes, there is some evidence that sertraline and fluoxetine can induce *hypoglycaemia*.[18,19] Licensed product information for other SSRIs also warns of similar risks with these products.

1. CSM/MCA. Antidepressant-induced hyponatraemia. *Current Problems* 1994; **20:** 5–6. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2015616&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Movig KLL, *et al.* Serotonergic antidepressants associated with an increased risk for hyponatraemia in the elderly. *Eur J Clin Pharmacol* 2002; **58:** 143–8.
3. Spigset O, Hedenmalm K. Hyponatraemia and the syndrome of inappropriate antidiuretic hormone secretion (SIADH) induced by psychotropic drugs. *Drug Safety* 1995; **12:** 209–25.
4. Canadian Medical Association. Hyponatraemia and selective serotonin reuptake inhibitors. *Can Med Assoc J* 1996; **154:** 63.
5. Bluff DD. SIADH in a patient receiving sertraline. *Ann Intern Med* 1995; **123:** 811.
6. Adverse Drug Reactions Advisory Committee. Selective serotonin reuptake inhibitors and SIADH. *Med J Aust* 1996; **164:** 562.
7. Kessler J, Samuels SC. Sertraline and hyponatremia. *N Engl J Med* 1996; **335:** 524.
8. Robinson D, *et al.* SIADH—compulsive drinking or SSRI influence? *Ann Pharmacother* 1996; **30:** 885.
9. Monmany J, *et al.* Syndrome of inappropriate secretion of antidiuretic hormone induced by paroxetine. *Arch Intern Med* 1999; **159:** 2089–90.
10. Odeh M, *et al.* Severe life-threatening hyponatremia during paroxetine therapy. *J Clin Pharmacol* 1999; **39:** 1290–1.
11. Barclay TS, Lee AJ. Citalopram-associated SIADH. *Ann Pharmacother* 2002; **36:** 1558–63.
12. Flores G, *et al.* Severe symptomatic hyponatremia during citalopram therapy–a case report. *BMC Nephrol* 2004; **5:** 2.
13. Wilkinson TJ, *et al.* Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol* 1999; **47:** 211–17.
14. Arinzon ZH, *et al.* Delayed recurrent SIADH associated with SSRIs. *Ann Pharmacother* 2002; **36:** 1175–7.
15. Arya DK, *et al.* Lactation associated with fluoxetine treatment. *Aust N Z J Psychiatry* 1995; **29:** 697.
16. Peterson MC. Reversible galactorrhea and prolactin elevation related to fluoxetine use. *Mayo Clin Proc* 2001; **76:** 215–16.
17. Sahin M, *et al.* A possible case of gynecomastia with fluoxetine. *Ann Pharmacother* 2005; **39:** 1369.
18. Deeg MA, Lipkin EW. Hypoglycemia associated with the use of fluoxetine. *West J Med* 1996; **164:** 262–3.
19. Pollak PT, *et al.* Sertraline-induced hypoglycemia. *Ann Pharmacother* 2001; **35:** 1371–4.

Effects on the eyes. Symptoms of glaucoma that developed in a patient receiving fluoxetine subsided within 2 days of drug withdrawal.[1] Similar symptoms have been reported with citalopram,[2] fluvoxamine,[3] paroxetine,[2,4] and sertraline.[2] In some cases, the SSRI may have aggravated pre-existing glaucoma.[2,3] Intra-ocular pressure after doses of fluoxetine was recorded in 20 patients in a placebo-controlled crossover double-blind study.[5] Significant increases were found in all patients 2 hours after receiving fluoxetine by mouth; some patients still had raised intraocular pressure after 8 hours. A review of case reports documenting SSRI-associated changes in intra-ocular pressure concluded that such changes were difficult to predict;[6] however, it was recommended that those with risk factors for glaucoma, such as elderly patients with a family history, should be considered for ophthalmic consultations before starting an SSRI and regularly throughout treatment.

Anisocoria (uneven pupillary dilatation) has been reported[7] in a patient taking paroxetine and in another taking sertraline. It was noted that the UK CSM had received 21 reports of mydriasis associated with paroxetine but it appeared that noticeably asymmetrical mydriasis as seen in these 2 patients had not previously been reported.

1. Ahmad S. Fluoxetine and glaucoma. *DICP Ann Pharmacother* 1991; **25:** 436.
2. Anonymous. SSRIs and increased intraocular pressure. *Aust Adverse Drug React Bull* 2001; **20:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr0102.pdf (accessed 14/08/08)
3. Jiménez-Jiménez FJ, *et al.* Aggravation of glaucoma with fluvoxamine. *Ann Pharmacother* 2001; **35:** 1565–6.
4. Eke T, Carr S. Acute glaucoma, chronic glaucoma, and serotoninergic drugs. *Br J Ophthalmol* 1998; **82:** 976–7.
5. Costagliola C, *et al.* Fluoxetine oral administration increases intraocular pressure. *Br J Ophthalmol* 1996; **80:** 678.
6. Costagliola C, *et al.* SSRIs and intraocular pressure modifications: evidence, therapeutic implications and possible mechanisms. *CNS Drugs* 2004; **18:** 475–84.
7. Barrett J. Anisocoria associated with selective serotonin reuptake inhibitors. *BMJ* 1994; **309:** 1620.

Effects on the gastrointestinal tract. A case-control study[1] suggested that treatment with SSRIs produced a moderately increased risk of upper gastrointestinal bleeding (adjusted relative risk 3.0). The risk was greatly increased if SSRIs were given with NSAIDs (relative risk 15.6). Treatment with SSRIs did not appear to increase the risk of ulcer perforation. The absolute risk of bleeding was estimated at one case per 8000 prescriptions, a risk similar to that of low-dose ibuprofen. A more recent cohort study[2] found a similar increase in risk. However, others have questioned whether such an association exists.[3]

A retrospective cohort study[4] in *elderly* patients found that there was an increasing risk of upper gastrointestinal bleeding as the extent of inhibition of serotonin reuptake by the antidepressant used increased. The effect was considered to be clinically important for patients with a high risk of such bleeding, namely the very elderly and those with a history of previous upper gastrointestinal bleeding.

Some[5] consider that gastroprotection is unlikely to be justified in those given SSRIs alone and furthermore there are no studies to suggest that gastroprotective drugs reduce the risk of SSRI-associated haemorrhage. However, it has been recommended[5] that such protection should be considered when SSRIs and NSAIDs are used together because of the increased risk.

1. de Abajo FJ, *et al.* Association between selective serotonin reuptake inhibitors and upper gastrointestinal bleeding: population based case-control study. *BMJ* 1999; **319:** 1106–9.
2. Dalton SO, *et al.* Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med* 2003; **163:** 59–64.
3. Dunn NR, *et al.* Association between SSRIs and upper gastrointestinal bleeding. *BMJ* 2000; **320:** 1405–6.
4. van Walraven C, *et al.* Inhibition of serotonin reuptake by antidepressants and upper gastrointestinal bleeding in elderly patients: retrospective cohort study. *BMJ* 2001; **323:** 655–8.
5. Paton C, Ferrier IN. SSRIs and gastrointestinal bleeding. *BMJ* 2005; **331:** 529–30.

Effects on the hair. A report[1] on 2 patients who had hair loss associated with the use of fluoxetine noted 4 other published cases and stated that, up to the end of 1991, the US manufacturers had received 498 reports of fluoxetine-associated alopecia.

1. Ogilvie AD. Hair loss during fluoxetine treatment. *Lancet* 1993; **342:** 1423.

Effects on the liver. Acute hepatitis occurred in 2 patients after several months of fluoxetine treatment;[1] it was noted that 5 other cases of acute hepatitis with fluoxetine had been reported.

Abnormal liver function tests were seen in a patient after a suicide attempt with sertraline and cefalexin.[2] The patient was then started on venlafaxine but, again abnormal liver function tests were noted. When these abnormal values had decreased, sertraline was restarted at therapeutic doses, with a subsequent increase in liver function tests. Values returned to normal once all medications were stopped. Auto-immune hepatitis has been reported after therapeutic doses of sertraline;[3] rechallenge in this case was also positive.

Hepatotoxicity has also been rarely associated with citalopram[4] and with paroxetine use.[5]

1. Cai Q, *et al.* Acute hepatitis due to fluoxetine therapy. *Mayo Clin Proc* 1999; **74:** 692–4.
2. Kim KY, *et al.* Acute liver damage possibly related to sertraline and venlafaxine ingestion. *Ann Pharmacother* 1999; **33:** 381–2.
3. Persky S, Reinus JF. Sertraline hepatotoxicity: a case report and review of the literature on selective serotonin reuptake inhibitor hepatotoxicity. *Dig Dis Sci* 2003; **48:** 939–44.
4. López-Torres E, *et al.* Hepatotoxicity related to citalopram. *Am J Psychiatry* 2004; **161:** 923–4.
5. Azaz-Livshits T, *et al.* Paroxetine associated hepatotoxicity: a report of 3 cases and a review of the literature. *Pharmacopsychiatry* 2002; **35:** 112–15.

Effects on mental state. As early as 1990 there was concern that the SSRIs increased the risk of *suicidal ideation* after the publication of a case series of such events with fluoxetine.[1] Meta-analyses[2,3] performed around that time (criticism of statistical power notwithstanding[4]) did not confirm an increased risk

and this was supported by the results of prescription-event monitoring.[5] Nevertheless, reports of suicidal ideation as well as suicide and self-harm have continued to be published for the SSRIs and the issue remains controversial. A subsequent meta-analysis[6] of 702 randomised controlled studies found an increased risk for attempted suicide in those taking SSRIs when compared with placebo but not when compared with tricyclic antidepressants.

Risk analysis of suicidal behaviour with any antidepressant is confounded by the rarity of suicide even in patients with depression, and by the possibility that such behaviour is a manifestation of the underlying depression. Furthermore, the more favourable safety profile of the SSRIs, particularly in overdosage (see Depression, p.373), when compared to the older MAOIs and tricyclic antidepressants may have resulted in the SSRIs being prescribed to those patients at greater risk of suicidal behaviour.

In 2003, the UK CSM established an Expert Working Group to address increasing public concerns regarding the safety of the SSRIs. The serotonergic antidepressants venlafaxine and mirtazapine were also included and the conclusions given below also apply to these drugs. In its final report[7] issued in December 2004, the Working Group concluded that the risk of suicide may increase in the early stages of treatment for depression in **adults** and consequently careful and frequent monitoring is important, particularly if a patient has worsening of symptoms or new symptoms after starting therapy. However, the Working Group noted that increases in the prescribing of SSRIs have not been associated with an increase in suicide rates, although they acknowledged that the interpretation of these findings was difficult. They could not rule out that there might be a modest increase in the risk of suicidal ideation and self-harm with the SSRIs when compared with placebo. However, there was insufficient evidence from clinical trials to determine any differences between the SSRIs as a group, or between the SSRIs and other antidepressants regarding the risk of suicidal behaviour; evidence from the General Practice Research database has suggested that there is no increased risk of such behaviour with the SSRIs when compared with the tricyclic antidepressants. The Working Group also concluded that the evidence for a relationship between suicidal behaviour and a change in dose was not robust; however, patients should be monitored for any new symptoms or worsening of disease around the time of any dose change.

The Expert Working Group of the CSM has also commented[7] on the use of SSRIs in **young adults**. They concluded that although there was no clear evidence of an increased risk of self-harm or suicidal thoughts in young adults of 18 years or over, such patients have a higher background risk of suicidal behaviour than older adults and consequently those treated with SSRIs should be closely monitored. Furthermore, the results of a meta-analysis undertaken by the FDA found that although the overall risk of suicide was not increased in adult patients receiving antidepressants, there was a non-significant trend toward increased risk with younger age. The FDA considered the trend sufficiently convincing to warn that, like children and adolescents, young adults aged between 18 and 24 years treated with antidepressants of any type may be at increased risk of suicidal thinking and behaviour.[8]

In 2003 the CSM recommended (on the basis of their Expert Working Group's finding) that paroxetine should not be used to treat depressive illness in **children under 18 years old**. Data from studies received by CSM in May 2003 failed to show that paroxetine was effective in depressive illness in this age group and indicated that the risk of harmful outcome, including self-harm and potentially suicidal behaviour, was 1.5 to 3.2 times greater in those who received paroxetine when compared with placebo.[9] Following a further review,[10] the CSM extended their recommendation to include the SSRIs citalopram, escitalopram, and sertraline; subsequent analysis had also associated these antidepressants with an unfavourable risk to benefit ratio in the treatment of depression in children under 18. The CSM also included fluvoxamine in their recommendation as its risk to benefit ratio was unassessable. Fluoxetine was not included and the CSM acknowledged that clinical trials had shown a favourable risk to benefit ratio for fluoxetine in the treatment of depression in young patients. The European Medicines Agency (EMEA) has also recommended that serotonergic antidepressants, including the SSRIs, should not be used in children and adolescents except within their approved indications,[11] but considered[12] that studies with fluoxetine in children and adolescents have shown a positive effect that outweighs any potential risks, and recommended that it should be licensed for use where needed, as an adjunct to psychological therapies in children from 8 years of age.

The FDA have not issued advice contra-indicating the use of these antidepressants in those under 18 years old in the USA, although they have stressed that all patients, including adolescents and children, should be closely monitored for worsening depression or suicidal behaviour, especially at the beginning of treatment.[13] They also comment that, apart from fluoxetine, the SSRIs are not licensed in the USA for the treatment of depression in young patients.

The use of SSRIs has been associated with the development of *akathisia*, *restlessness*, and *psychomotor agitation* such as an inability to sit or stand still, particularly in the first few weeks of treatment.[14] In some patients these symptoms have precipitated suicidal behaviour. However, the Expert Working Group of the CSM considered that it was not possible to draw any conclusions on the link between the development of these symptoms and the risk of suicidal behaviour, as such data were not included in the majority of cases.[7]

There have been suggested links between the use of fluoxetine and *irritability, hostility, and aggression*.[15] However, one review[16] noted that an unpublished analysis had indicated that patients taking fluoxetine for a variety of disorders were not more likely to be aggressive than those taking placebo. Prescription-event monitoring has also found no evidence to suggest that fluoxetine increases the frequency of aggression.[5]

Initiation of antidepressant therapy with paroxetine or sertraline has been associated with either worsening or a new onset of *flashback syndrome* in 2 patients with a history of lysergide abuse.[17]

There have been isolated reports of *memory loss* associated with the use of SSRIs.[18]

For further effects on mental function, see also under Withdrawal and under Mania in Precautions, below.

1. Teicher MH, *et al.* Emergence of intense suicidal preoccupation during fluoxetine treatment. *Am J Psychiatry* 1990; **147:** 207–10.
2. Beasley CM, *et al.* Fluoxetine and suicide: a meta-analysis of controlled trials of treatment for depression. *BMJ* 1991; **303:** 685–92. Correction. *ibid.*; 968.
3. Goldstein DJ, *et al.* Analyses of suicidality in double-blind, placebo-controlled trials of pharmacotherapy for weight reduction. *J Clin Psychiatry* 1993; **54:** 309–16.
4. Li Wan Po A. Fluoxetine and suicide: meta-analysis and Monte-Carlo simulations. *Pharmacoepidemiol Drug Safety* 1993; **2:** 79–84.
5. Nakielny J. Fluoxetine and suicide. *Lancet* 1994; **343:** 1359.
6. Fergusson D, *et al.* Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. *BMJ* 2005; **330:**396. Correction. *ibid.*; 653.
7. 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 (accessed 14/08/08)
8. Friedman RA, Leon AC. Expanding the black box — depression, antidepressants, and the risk of suicide. *N Engl J Med* 2007; **356:** 2343–6.
9. MHRA. Safety of Seroxat (paroxetine) in children and adolescents under 18 years - contraindication in the treatment of depressive illness. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 10th June, 2003). Available at: http://www.mhra.gov.uk/home/groups/pl-p/documents/websiteresources/con019507.pdf (accessed 14/08/08)
10. MHRA. Selective Serotonin Reuptake Inhibitors - use in children and adolescents with major depressive disorder. Epinet message from Professor G Duff, Chairman of Committee on Safety of Medicines (issued 10th December, 2003). Available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=2024&noSaveAs=1&Rendition=WEB (accessed 20/09/05)
11. European Medicines Agency. European Medicines Agency finalises review of antidepressants in children and adolescents (issued 25th April, 2005). Available at: http://www.emea.europa.eu/pdfs/human/press/pr/12891805en.pdf (accessed 14/08/08)
12. 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)
13. The FDA Public Health Advisory. Worsening depression and suicidality in patients being treated with antidepressant medications (issued 22nd March, 2004). Available at: http://www.fda.gov/cder/drug/antidepressants/AntidepressanstPHA.htm (accessed 24/11/05)
14. Lane RM. SSRI-induced extrapyramidal side-effects and akathisia: implications for treatment. *J Psychopharmacol* 1998; **12:** 192–214.
15. Anonymous. Fluoxetine, suicide and aggression. *Drug Ther Bull* 1992; **30**: 5–6.
16. Power AC, Cowen PJ. Fluoxetine and suicidal behaviour; some clinical and theoretical aspects of a controversy. *Br J Psychiatry* 1992; **161:** 735–41.
17. Markel H, *et al.* LSD flashback syndrome exacerbated by selective serotonin reuptake inhibitor antidepressants in adolescents. *J Pediatr* 1994; **125:** 817–19.
18. Joss JD, *et al.* Memory loss in a patient treated with fluoxetine. *Ann Pharmacother* 2003; **37:** 1800–3.

Effects on sexual function. Sexual dysfunction is often noted in patients with depression and may be due to their antidepressant medication or to the disease itself. Complaints include a decrease in or loss of libido, delayed ejaculation, erectile difficulty, or anorgasmia in men;[1] loss of libido, delayed orgasm, or anorgasmia have been reported in women.[1,2] Early identification is important since drug-induced sexual dysfunction is a common cause of non-compliance; in addition, it may adversely affect the quality of life of patients and hamper their recovery.[3,4]

It has been considered that sexual dysfunction occurs in up to 1.9% of patients taking fluoxetine, with impotence or ejaculatory problems occurring in less than 1% of patients.[5] However, these figures, which were based on information supplied by the US manufacturer, have been disputed[6,7] and the incidence of sexual dysfunction may be higher than the manufacturer's data suggest. Earlier studies and anecdotal reports quoted rates of 7.8 to 75% for sexual dysfunction with fluoxetine but it appears that only small numbers of men were studied.[8] A later review[9] also estimated the incidence of SSRI-induced sexual dysfunction at between 10 and 75%.

The incidence of sexual dysfunction may differ between types of antidepressants. A large, observational study[3] found the rate of sexual dysfunction to be higher with the SSRIs (citalopram, fluoxetine, paroxetine, and sertraline) and the SNRI venlafaxine than with bupropion or nefazodone. However, no significant difference in rate was found among the SSRIs as a group. The study also identified other risk factors for developing sexual dysfunction which included increasing age, the use of high doses, and use with other medications. Gender, race, and length of treatment were not associated with an increased risk.

Suggested[1,4,10] strategies for managing SSRI-induced sexual dysfunction include reducing the dosage of the SSRI or altering the timing of doses, or changing to another antidepressant. In some cases tolerance may develop, particularly if the dysfunction occurred early in treatment. One small study[11] has indicated that spontaneous improvement may occur even up to 6 months after the start of therapy.[11] Evidence of efficacy for drug treatments is mainly anecdotal. Cyproheptadine seems to have been tried most often, but the SSRI may become less effective (see Antihistamines, under Interactions, below) and patients should be monitored for worsening symptoms of depression.

The effects of the SSRIs on sexual function have been studied as a potential form of treatment for men with premature ejaculation (see Sexual Dysfunction in Uses, below).

1. Frye CB, Berger JE. Treatment of sexual dysfunction induced by selective serotonin-reuptake inhibitors. *Am J Health-Syst Pharm* 1998; **55:** 1167–9.
2. Feiger A, *et al.* Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. *J Clin Psychiatry* 1996; **57** (suppl 2): 53–62.
3. Clayton AH, *et al.* Prevalence of sexual dysfunction among newer antidepressants. *J Clin Psychiatry* 2002; **63:** 357–66.
4. Hirschfeld RMA. Long-term side effects of SSRIs: sexual dysfunction and weight gain. *J Clin Psychiatry* 2003; **64** (suppl 18): 20–4.
5. Hollander JB. Fluoxetine and sexual dysfunction. *JAMA* 1994; **272:** 242.
6. Balon R. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1489.
7. Hopkins HS, Gelenberg AJ. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1489–90.
8. Hollander JB. Fluoxetine and sexual dysfunction. *JAMA* 1995; **273:** 1490.
9. Gregorian RS, *et al.* Antidepressant-induced sexual dysfunction. *Ann Pharmacother* 2002; **36:** 1577–89.
10. Woodrum ST, Brown CS. Management of SSRI-induced sexual dysfunction. *Ann Pharmacother* 1998; **32:** 1209–15.
11. Haberfellner EM, Rittmannsberger H. Spontaneous remission of SSRI-induced orgasm delay. *Pharmacopsychiatry* 2004; **37:** 127–30.

Effects on the skin. *Toxic epidermal necrolysis* developed in a 16-year-old girl 8 days after beginning fluvoxamine therapy.[1] Other drugs, which included metoclopramide, clorazepate, and clomipramine were discounted as possible causes.

Amitriptyline and fluoxetine have been implicated in the development of *atypical cutaneous lymphoid hyperplasia* in 8 patients, 7 of whom either had an underlying immunosuppressant systemic disease or were also receiving immunomodulatory drugs.[2] The lesions improved or resolved on stopping the antidepressant, although in some patients other factors may have contributed to the improvement.

Bullous pemphigoid induced by fluoxetine has been reported in a 75-year-old woman.[3] Spontaneous resolution followed within 3 weeks of stopping the drug.

Paroxetine treatment has been associated with the development of *cutaneous vasculitis*, which involved several fingers, in a 20-year-old woman;[4] rechallenge was positive. On both occasions the patient recovered when paroxetine was withdrawn.

A severe *bullous reaction with full-thickness skin necrosis* has been reported in a 48-year-old woman after 6 months of treatment with sertraline.[5] The lesions required extensive skin grafts and recovery was prolonged, with drug-induced scleroderma developing in the affected area.

1. Wolkenstein P, *et al.* Toxic epidermal necrolysis after fluvoxamine. *Lancet* 1993; **342:** 304–5.
2. Crowson AN, Magro CM. Antidepressant therapy: a possible cause of atypical cutaneous lymphoid hyperplasia. *Arch Dermatol* 1995; **131:** 925–9.
3. Rault S, *et al.* Bullous pemphigoid induced by fluoxetine. *Br J Dermatol* 1999; **141:** 755–6.
4. Margolese HC, *et al.* Cutaneous vasculitis induced by paroxetine. *Am J Psychiatry* 2001; **158:** 497.
5. Kirkup ME, *et al.* Delayed onset of bullous reaction with severe deep skin necrosis in association with sertraline. *Br J Dermatol* 2004; **150:** 164–6.

Epileptogenic effect. Generalised seizures have been reported in 2 patients with no history of seizures after starting fluoxetine therapy.[1,2] Although convulsions have been noted in patients taking fluvoxamine (see Incidence of Adverse Effects, p.399), a small clinical study involving 35 depressed epileptic patients[3] found no change in the number of seizures or in their nature when fluvoxamine was given in doses of up to 200 mg daily.

1. Weber JJ. Seizure activity associated with fluoxetine therapy. *Clin Pharm* 1989; **8:** 296–8.
2. Ware MR, Stewart RB. Seizures associated with fluoxetine therapy. *DICP Ann Pharmacother* 1989; **23:** 428.
3. Harmant J, *et al.* Fluvoxamine: an antidepressant with low (or no) epileptogenic effect. *Lancet* 1990; **336:** 386.

Extrapyramidal effects. Extrapyramidal effects, such as tics[1] and akathisia,[2,3] have been reported with fluoxetine. By 1993, the

UK CSM had received 39 reports of extrapyramidal reactions with paroxetine including 15 of dystonia of the face and mouth.[4] Although extrapyramidal effects might occur with other SSRIs, orofacial dystonias appeared to be more common with paroxetine. However, evidence from monitoring prescriptions within the UK showed that the overall incidence of extrapyramidal effects was the same for paroxetine as for other SSRIs.[5] Orofacial dystonias (teeth clenching) or dyskinesias (teeth grinding), resulting in severe damage to teeth and gums in many cases, have been reported[6] in 6 patients receiving fluoxetine, fluvoxamine, paroxetine, or sertraline. The authors concluded that these adverse effects were not specific for any particular SSRI. Analysis of spontaneous adverse reaction reports received by the national pharmacovigilance centre in The Netherlands found that there had been 41 reports of extrapyramidal effects associated with the SSRIs over a period of nearly 15 years;[7] parkinsonism and dystonia were the most frequently reported effects. Over the same time period, 14 reports had been received in total for other antidepressants. The authors commented that the results might be biased by the selective reporting of adverse reactions to the SSRIs.

Dyskinesia associated with withdrawal of citalopram and risperidone has been reported in a patient.[8]

The onset of akathisia may be linked to suicidal ideation; for further details, see Effects on Mental State, above.

1. Eisenhauer G, Jermain DM. Fluoxetine and tics in an adolescent. *Ann Pharmacother* 1993; **27:** 725–6.
2. Lipinski JF, *et al.* Fluoxetine-induced akathisia: clinical and theoretical implications. *J Clin Psychiatry* 1989; **50:** 339–42.
3. Rothschild AJ, Locke CA. Reexposure to fluoxetine after serious suicide attempts by three patients: the role of akathisia. *J Clin Psychiatry* 1991; **52:** 491–3.
4. CSM/MCA. Dystonia and withdrawal symptoms with paroxetine (Seroxat). *Current Problems* 1993; **19:** 1. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024454&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
5. Choo V. Paroxetine and extrapyramidal reactions. *Lancet* 1993; **341:** 624.
6. Fitzgerald K, Healy D. Dystonias and dyskinesias of the jaw associated with the use of SSRIs. *Hum Psychopharmacol Clin Exp* 1995; **10:** 215–19.
7. Schillevoort I, *et al.* Extrapyramidal syndromes associated with selective serotonin reuptake inhibitors: a case-control study using spontaneous reports. *Int Clin Psychopharmacol* 2002; **17:** 75–9.
8. Miller LJ. Withdrawal-emergent dyskinesia in a patient taking risperidone/citalopram. *Ann Pharmacother* 2000; **34:** 269.

Hypersensitivity. Hypersensitivity reactions to SSRIs are well documented. Interestingly, despite structural dissimilarities, there have been a few reports of cross-sensitivity between SSRIs. A young man who had previously developed a maculopapular rash while taking paroxetine suffered a similar reaction after starting sertraline;[1] both episodes resolved after the SSRI was withdrawn.

1. Warnock CA, Azadian AG. Cross-sensitivity between paroxetine and sertraline. *Ann Pharmacother* 2002; **36:** 631–3.

Hyponatraemia. See Effects on the Endocrine System, above.

Overdosage. SSRIs are generally regarded as being less toxic in overdosage than tricyclic antidepressants or MAOIs. A review[1] of SSRI overdosage, covering the period 1985 to 1997, noted that there had been remarkably few fatal overdoses when taken alone. Moderate overdoses (up to about 30 times the usual daily dose) were generally associated with minor symptoms at most; only at very high doses (more than 75 times the usual daily dose) did more serious effects such as seizures, ECG abnormalities, and decreased consciousness tend to occur. Toxicity was greatly increased, however, when overdoses of SSRIs were taken with alcohol or other drugs. There was no evidence of a difference in the various SSRIs with respect to safety in overdosage. The results of a more recent cohort study[2] have also confirmed the relative safety of the SSRIs in overdosage. However, the study also found that citalopram was potentially more cardiotoxic than other SSRIs in overdose, causing significant prolongation of the QT interval (see below). In addition, serotonin syndrome was noted as being a common feature of SSRI overdosage although in most cases symptoms were not severe or life-threatening.

- Fatal overdose was reported with *citalopram* in 6 patients,[3] although the suggested cause of death as cardiac dysfunction rather than seizures was disputed.[4] Nonetheless, cases[2,5] of cardiac abnormalities (including prolongation of the QT interval) associated with citalopram overdose have continued to be reported, and routine ECG monitoring may be necessary in the management of overdosage. Some authors consider that a metabolite, didemethylcitalopram, rather than citalopram itself, may be responsible for the cardiotoxicity seen with citalopram overdose.[5] At therapeutic doses, concentrations of didemethylcitalopram are much lower than those of citalopram and, in general, significant cardiotoxicity is not seen; however, in overdosage the amount of didemethylcitalopram may be sufficient to induce cardiac conduction abnormalities.
- A report involving 87 cases in which *fluoxetine* was taken in overdosage without other drugs found that the main symptoms were tachycardia, drowsiness, tremor, and nausea and vomiting.[6] These were considered relatively minor, and were of short duration, and supportive care was considered to be the only intervention necessary.
- Of 41 cases of self-poisoning with *fluvoxamine*, only one patient died and even here fluvoxamine was not implicated.[7] Prolonged cerebral depression occurred in a patient after fluvoxamine overdose,[7] but this may have been due to an interaction with temazepam which the patient also took in overdose.
- One hour after taking 2 g of *sertraline* in a suicide attempt a 42-year-old woman was flushed, angry, emotionally labile, and easily distracted but not psychotic.[8] Apart from watery bowel movements recovery was mainly uneventful after treatment with gastric lavage, oral activated charcoal with sorbitol, and intravenous hydration. In another case,[9] symptoms resembling serotonin syndrome developed in a 51-year-old woman after an overdose attempt with sertraline; it was believed that the patient may have taken as much as 8 g of sertraline. She recovered with supportive treatment. Abnormal liver function tests have also been noted after a suicide attempt with sertraline (see Effects on the Liver, above).

For a discussion of choice of antidepressant with respect to toxicity in overdosage, see under Depression, p.373.

1. Barbey JT, Roose SP. SSRI safety in overdose. *J Clin Psychiatry* 1998; **59** (suppl 15): 42–8.
2. Isbister GK, *et al.* Relative toxicity of selective serotonin reuptake inhibitors (SSRIs) in overdose. *J Toxicol Clin Toxicol* 2004; **42:** 277–85.
3. Öström M, *et al.* Fatal overdose with citalopram. *Lancet* 1996; **348:** 339–40.
4. Brion F, *et al.* Fatal overdose with citalopram? *Lancet* 1996; **348:** 1380.
5. Catalano G, *et al.* QTc interval prolongation associated with citalopram overdose: a case report and literature review. *Clin Neuropharmacol* 2001; **24:** 158–62.
6. Borys DJ, *et al.* Acute fluoxetine overdose: a report of 234 cases. *Am J Emerg Med* 1992; **10:** 115–20.
7. Banerjee AK. Recovery from prolonged cerebral depression after fluvoxamine overdose. *BMJ* 1988; **296:** 1774.
8. Brown DF, Kerr HD. Sertraline overdose. *Ann Pharmacother* 1994; **28:** 1307.
9. Brendel DH, *et al.* Massive sertraline overdose. *Ann Emerg Med* 2000; **36:** 524–6.

Treatment of Adverse Effects

Treatment of overdosage with an SSRI involves appropriate symptomatic and supportive therapy. Activated charcoal may be given by mouth if the amount ingested was large (see below) and treatment is within an hour of ingestion. Dialysis, haemoperfusion, exchange transfusion, and measures to increase urine production are considered unlikely to be of benefit.

Activated charcoal. The UK Poisons Information Service considers the benefit of gastric decontamination in the management of overdosage with SSRIs to be uncertain. However, it is suggested that oral activated charcoal may be considered if this is given within 1 hour of ingestion and the quantity of SSRI exceeds the following amount:

- citalopram: 5 mg/kg (adult); 5 mg/kg (child)
- escitalopram: 2.5 mg/kg (adult); 2.5 mg/kg (child)
- fluoxetine: 500 mg (adult); 5 mg/kg (child)
- fluvoxamine: 1 g (adult); 100 mg (child)
- paroxetine: 600 mg (adult); 5 mg/kg (child)
- sertraline: 1 g (adult); 10 mg/kg (child)

Precautions

Because of their epileptogenic effect SSRIs should be used with caution in patients with epilepsy or a history of such disorders (and should be avoided if the epilepsy is poorly controlled). Treatment should be stopped if seizures develop or when there is an increase in seizure frequency. Care is advised in patients receiving ECT as prolonged seizures have occurred rarely. SSRIs should also be used with caution in patients with cardiac disease or a history of bleeding disorders. Although SSRIs are preferred to tricyclics for the treatment of depression in patients with diabetes, they may alter glycaemic control and therefore caution is also warranted in diabetic subjects. SSRIs should be used with caution in patients with angle-closure glaucoma.

Fluoxetine should be stopped in patients who develop a rash since systemic effects, possibly related to vasculitis, have occurred in such patients. Fluoxetine undergoes hepatic metabolism and should be used with caution and in reduced doses in patients with impaired hepatic function.

Patients should be closely monitored during early 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. For a discussion of the concern that SSRIs may increase suicidal ideation, and concerns about their use for depression in children and adolescents, see Effects on Mental State in Adverse Effects, above. 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. If SSRIs are given for the depressive component of bipolar disorder, mania may be precipitated. Symptoms may also worsen during the initial treatment of panic disorder with SSRIs.

SSRIs may impair performance of skilled tasks and, if affected, patients should not drive or operate machinery.

Some licensed product information recommends reduced or less frequent dosage of SSRIs for elderly patients.

SSRIs should generally be withdrawn gradually to reduce the risk of withdrawal symptoms although this may be unnecessary for fluoxetine because of its long half-life.

Abuse. There have been occasional reports of individuals abusing fluoxetine.[1,2]

1. Pagliaro LA, Pagliaro AM. Fluoxetine abuse by an intravenous drug user. *Am J Psychiatry* 1993; **150:** 1898.
2. Tinsley JA, *et al.* Fluoxetine abuse. *Mayo Clin Proc* 1994; **69:** 166–8.

Blood disorders. For a reference recommending cautious use of SSRIs in patients with a history of bleeding disorders, see Effects on the Blood in Adverse Effects, above.

Breast feeding. The American Academy of Pediatrics[1] considers that all antidepressants, including SSRIs (fluoxetine, fluvoxamine, paroxetine, and sertraline) are drugs whose effect on nursing infants is unknown but may be of concern. In addition, most licensed drug information advises that SSRIs should be avoided by the mother during breast feeding.

- *Citalopram* and its metabolites have been detected in breast milk; however, in one study, the plasma concentrations in exposed infants were either very low or undetectable and no adverse effects were reported.[2] In another study, 3 out of 31 breast-fed infants whose mothers were taking citalopram had adverse effects, specifically one case each of colic, decreased feeding, and irritability.[3] However, there was no significant increase in the risk of adverse events in this group of infants when compared with either infants of depressed mothers not taking citalopram, or infants of healthy controls.
- Symptoms of colic were reported[4] in a 6-week-old infant whose mother was taking *fluoxetine* 20 mg daily. The concentrations of fluoxetine and its active metabolite norfluoxetine were 69 nanograms/mL and 90 nanograms/mL respectively in breast milk, and 340 nanograms/mL and 208 nanograms/mL respectively in the infant's plasma. The infant's symptoms resolved when he was formula fed. Postnatal weight gain has been reduced in infants exposed to fluoxetine during breast feeding, although in all cases the reduction was less than 2 standard deviations below the norm.[5] In another report,[6] several seizure-like episodes occurred in a breast-fed infant whose mother was taking fluoxetine in addition to carbamazepine and buspirone; however, plasma drug concentrations in the infant were significant only for fluoxetine and norfluoxetine. In a study[7] of 10 women taking fluoxetine while breast feeding 11 infants, breast milk concentrations of fluoxetine ranged from 17.4 to 293 nanograms/mL and of norfluoxetine from 23.4 to 379.1 nanograms/mL. No adverse effects were noted in the infants. Similar levels have occurred in other breast-fed infants without any apparent drug-induced adverse effects.[8-10] Fluoxetine and norfluoxetine were detected in the milk of 14 nursing women.[11] Blood samples were taken from 9 of the infants in the study, and of these, fluoxetine was detected in the plasma of 5 and norfluoxetine in 7. Although it was felt that many infants would tolerate the mean combined dose of fluoxetine and norfluoxetine transmitted via breast milk in this study, there was considerable interpatient variability in estimated infant dose and caution should be exercised; neonates in particular exhibited higher concentrations of norfluoxetine than older infants. Moreover, since both fluoxetine and norfluoxetine have long half-lives, neonates already exposed *in utero* may have an additional risk of adverse effects during breast feeding.
- The excretion of *fluvoxamine* into breast milk was studied[12] in a woman who had been receiving fluvoxamine maleate 100 mg twice daily for 2 weeks. The concentration of fluvoxamine base 4.75 hours after a dose was 310 nanograms/mL in maternal plasma and 90 nanograms/mL in breast milk. It was estimated that an infant would ingest only 0.5% of the daily maternal intake. It was considered that these data supported the notion that the use of fluvoxamine by nursing mothers posed little risk to the infant. A subsequent study[13] found no detectable drug levels in the plasma of breast-fed infants

exposed to fluvoxamine; the authors suggested that fluvoxamine was a reasonable choice for nursing mothers requiring treatment for depression.

- Although *paroxetine* was detected in measurable concentrations in the breast milk of a group of 10 nursing mothers receiving paroxetine no adverse effects were reported in any of their breast-fed infants.[14] Paroxetine could not be detected in the plasma of 7 of the 8 infants from whom samples were obtained and in the other infant, concentrations were not quantifiable. Another study involving 7 women suggested that the dose of paroxetine to suckling infants would be 0.7 to 2.9% of the weight-adjusted maternal dose.[15] A later study[13] also found no detectable drug levels in the plasma of breast-fed infants exposed to paroxetine; the authors suggested that paroxetine was a reasonable choice for nursing mothers requiring treatment for depression. In a prospective cohort study, weight gain at 6 and 12 months of age in infants whose mothers took paroxetine during breast feeding was not adversely affected when compared with the infants of mothers who either did not breast feed or breast fed without taking any drugs during lactation;[16] in addition, there was no difference in reaching the usual developmental milestones between the infants of the 3 groups.
- Plasma concentrations of *sertraline* were undetectable in a breast-fed infant despite the presence of concentrations in the mother's breast milk ranging from 8.8 to 43 nanograms/mL over a 24-hour period.[17] However, the authors pointed out that metabolite levels were not measured and that sertraline may have been present in the infant at a concentration below the level of sensitivity of the assay. Other studies[13,18-21] have detected desmethylsertraline in breast milk, which was also detected in the plasma of some of the infants in a number of the studies[13,18,20,21] but not all.[19] The authors of at least one study[13] suggested that sertraline was a reasonable choice for nursing mothers requiring treatment for depression. In addition, some authors recommend expressing and discarding breast milk 8 to 9 hours after a maternal dose, when levels of desmethylsertraline and sertraline are maximal, in order to significantly reduce infant exposure to sertraline.[21]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 24/11/05)
2. Heikkinen T, *et al.* Citalopram in pregnancy and lactation. *Clin Pharmacol Ther* 2002; **72:** 184–91.
3. Lee A, *et al.* Frequency of infant adverse events that are associated with citalopram use during breast-feeding. *Am J Obstet Gynecol* 2004; **190:** 218–21.
4. Lester BM, *et al.* Possible association between fluoxetine hydrochloride and colic in an infant. *J Am Acad Child Adolesc Psychiatry* 1993; **32:** 1253–5.
5. Chambers CD, *et al.* Weight gain in infants breastfed by mothers who take fluoxetine. *Pediatrics* 1999; **104:** 1120–1.
6. Brent NB, Wisner KL. Fluoxetine and carbamazepine concentrations in a nursing mother/infant pair. *Clin Pediatr (Phila)* 1998; **37:** 41–4.
7. Taddio A, *et al.* Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. *J Clin Pharmacol* 1996; **36:** 42–7.
8. Isenberg KE. Excretion of fluoxetine in human breast milk. *J Clin Psychiatry* 1990; **51:** 169.
9. Burch KJ, Wells BG. Fluoxetine/norfluoxetine concentrations in human milk. *Pediatrics* 1992; **89:** 676–7.
10. Yoshida K, *et al.* Fluoxetine in breast-milk and developmental outcome of breast-fed infants. *Br J Psychiatry* 1998; **172:** 175–9.
11. Kristensen JH, *et al.* Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br J Clin Pharmacol* 1999; **48:** 521–7.
12. Wright S, *et al.* Excretion of fluvoxamine in breast milk. *Br J Clin Pharmacol* 1991; **31:** 209.
13. Hendrick V, *et al.* Use of sertraline, paroxetine and fluvoxamine by nursing women. *Br J Psychiatry* 2001; **179:** 163–6.
14. Begg EJ, *et al.* Paroxetine in human milk. *Br J Clin Pharmacol* 1999; **48:** 142–7.
15. Öhman R, *et al.* Excretion of paroxetine into breast milk. *J Clin Psychiatry* 1999; **60:** 519–23.
16. Merlob P, *et al.* Paroxetine during breast-feeding: infant weight gain and maternal adherence to counsel. *Eur J Pediatr* 2004; **163:** 135–9.
17. Altshuler LL, *et al.* Breastfeeding and sertraline: a 24-hour analysis. *J Clin Psychiatry* 1995; **56:** 243–5.
18. Stowe ZN, *et al.* Sertraline and desmethylsertraline in human breast milk and nursing infants. *Am J Psychiatry* 1997; **154:** 1255–60.
19. Kristensen JH, *et al.* Distribution and excretion of sertraline and N-desmethylsertraline in human milk. *Br J Clin Pharmacol* 1998; **45:** 453–7.
20. Epperson N, *et al.* Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. *Am J Psychiatry* 2001; **158:** 1631–7.
21. Stowe ZN, *et al.* The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. *J Clin Psychiatry* 2003; **64:** 73–80.

Children. SSRIs are associated with an increased risk of potentially suicidal behaviour when used for the treatment of depression in children and adolescents under 18 years old; for further details, see under Effects on Mental State, above.

Diabetes mellitus. A patient with type 1 diabetes mellitus experienced a loss of hypoglycaemic awareness following the start of treatment with fluoxetine.[1] Awareness returned on tapered withdrawal of fluoxetine. Changes in blood sugar concentrations may occur in patients with diabetes treated for depression with SSRIs (see also Effects on the Endocrine System, above); however, these may represent an improvement in glycaemic control.[2]

1. Sawka AM, *et al.* Loss of hypoglycemia awareness in an adolescent with type 1 diabetes mellitus during treatment with fluoxetine hydrochloride. *J Pediatr* 2000; **136:** 394–6.
2. Lustman PJ, *et al.* Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. *Diabetes Care* 2000; **23:** 618–23.

Driving. While affective disorders probably adversely affect driving skill,[1,2] treatment with antidepressants can also be hazardous,[1] although patients may be safer drivers with medication than without.[2] Impairment of performance is largely related to sedative and antimuscarinic effects. These are more pronounced with older antidepressants such as the tricyclic antidepressants than with the SSRIs, but a comparative study[3] of fluoxetine (an SSRI) and dosulepin (a tricyclic) in healthy subjects showed a similar but apparently small potential for impairing psychomotor and driving performance. A later epidemiological study[4] was unable to confirm any increased risk of road-traffic accidents in those drivers receiving tricyclic antidepressants or SSRIs.

In the UK, the Driver and Vehicle Licensing Authority[5] considers that drugs such as SSRIs may have fewer adverse effects on drivers than antidepressants with pronounced antimuscarinic or antihistaminic adverse effects, such as tricyclic antidepressants. However, all drugs acting on the CNS can impair alertness, concentration, and driving performance, particularly at the start of treatment or when the dose is increased; driving must cease if patients are adversely affected. Patients with severe depressive illnesses complicated by significant memory or concentration problems, agitation, behavioural disturbances, or suicidal thoughts should also 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. Ramaekers JG, *et al.* A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. *Br J Clin Pharmacol* 1995; **39:** 397–404.
4. Barbone F, *et al.* Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998; **352:** 1331–6.
5. 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)

Gastrointestinal disorders. For the opinion that the SSRIs may produce a clinically important increase in the risk of upper gastrointestinal bleeding in patients with a high risk of such bleeding, see under Effects on the Gastrointestinal Tract, above.

Glaucoma. For reference to SSRIs precipitating or exacerbating symptoms of glaucoma, see Effects on the Eyes, above.

Mania. Hypomania or mania have been reported with the SSRIs; consequently, UK licensed drug information recommends that SSRIs should be withdrawn in any patient entering a manic phase.

Fluvoxamine was associated with manic behaviour in 8 patients who were being treated for major depression;[1] 3 also had obsessive-compulsive disorder. Daily doses of fluvoxamine ranged from 75 to 300 mg and duration of therapy to development of manic behaviour from 2 to 6 weeks. The authors were unable to determine whether fluvoxamine had induced mania or unmasked latent bipolar disorder in these patients. However, they recommended that fluvoxamine-treated patients should be monitored for manic behaviour.

Symptoms of manic behaviour also developed in a 7-year-old girl after taking *sertraline* for about 2 weeks for the treatment of major depression.[2] She recovered within a few weeks of stopping sertraline.

1. Dorevitch A, *et al.* Fluvoxamine-associated manic behavior: a case series. *Ann Pharmacother* 1993; **27:** 1455–7.
2. Ghaziuddin M. Mania induced by sertraline in a prepubertal child. *Am J Psychiatry* 1994; **151:** 944.

Pregnancy. In an early prospective study[1] comparing 128 pregnant women exposed to a mean daily dose of about 26 mg of fluoxetine during their first trimester with control groups receiving tricyclic antidepressants or non-teratogens, the incidence of **neonatal malformations** was similar in all groups and did not exceed that in the general population. However, there was a tendency to a higher incidence of **miscarriages** in the groups receiving fluoxetine or tricyclics. A more recent prospective study[2] comparing 228 pregnant women taking fluoxetine with a control group taking non-teratogens also failed to find a significant increased incidence in major fetal abnormalities in the fluoxetine group; it also did not reveal an increased risk of miscarriage. There was an increase in the incidence of minor fetal abnormalities in infants exposed to fluoxetine during the first trimester. Also, infants exposed to fluoxetine during the third trimester experienced more perinatal complications such as prematurity, low full-term birth-weight and length, and poor neonatal adaptation compared with infants exposed only during the first and second trimesters. However, the design of this study was criticised[3] because of several methodological problems such as unmatched controls and a higher maternal age in the fluoxetine group, which may partly explain the excess of poor perinatal outcomes.

The manufacturer evaluated the outcome of 796 pregnancies in which the mother received fluoxetine during the first trimester and considered that it was unlikely that fluoxetine increased the risk of miscarriage or fetal malformation.[4] A prospective controlled study[5] on pregnancy outcome in women exposed to fluvoxamine, paroxetine, or sertraline also found that, when used in recommended doses, there appeared to be no increase in the risk of major congenital malformations, miscarriages, or still-births when compared with women exposed to non-teratogens. Nonetheless, the results from a more recent meta-analysis which included some of the above studies have suggested that maternal exposure to antidepressant treatment (specifically SSRIs, tricyclics, nefazodone, trazodone, or venlafaxine) may significantly increase the risk of miscarriage in comparison to women not exposed to antidepressants.[6] However, the authors acknowledged that the underlying depression itself might be a contributing factor to the increased risk.

There is some evidence that paroxetine may be more teratogenic than other antidepressants. The manufacturer *GlaxoSmithKline* has reported[7] that overall the data from a retrospective US epidemiological study and a study using the Swedish national birth registry have indicated that there was a twofold increase in cardiovascular malformations, particularly ventricular septal defects, in infants born to mothers who had taken paroxetine during pregnancy compared with the general population. However, whereas the US study also showed an overall risk of major congenital malformations (inclusive of the cardiovascular defects), the Swedish study found no such increase.

Maternal use of SSRIs has been associated with **neonatal complications**. CNS toxicity and an increased heart rate were reported in a neonate whose mother had received 20 mg of fluoxetine daily throughout most of her pregnancy.[8] The neonate's symptoms resolved 96 hours after delivery. In another neonate whose mother took up to 30 mg daily of fluoxetine throughout the third trimester cardiac arrhythmias were noted.[9] In a matched-control study[10] the rate of complications after delivery in 55 infants exposed to paroxetine during the third trimester was higher than in a control group who had been exposed to paroxetine or non-teratogenic agents during the first or second timesters. Complications that occurred in the infants exposed in the third trimester included respiratory distress (9), hypoglycaemia (2), bradycardia (1), jaundice (1), and suckling problems (1). More recently, another matched-control study[11] has suggested that exposure to SSRIs (in this case fluoxetine, paroxetine, and sertraline) after the 20th week of gestation may increase the risk of persistent pulmonary hypertension of the newborn (PPHN). Of 377 infants with a confirmed diagnosis of PPHN, the mothers of 14 (3.7%) had taken an SSRI after the 20th week of gestation, compared with only 6 out of 836 infants (0.7%) in the matched-control group. Although these figures represent about a sixfold increase in the risk of PPHN in infants exposed to SSRIs *in utero*, the absolute risk remains relatively low (about 6 to 12 per 1000 women).

A number of reports[2,12-16] have described symptoms such as jitteriness, irritability, sleep disturbances, and altered muscle tone in neonates who had been exposed to SSRIs *in utero*, especially during the third trimester; in the majority of cases the symptoms are mild and self-limiting. Although withdrawal symptoms have been reported with most SSRIs, they have been more commonly reported in those neonates exposed to paroxetine.[17] More recently, some authors have used the term neonatal behavioural syndrome to refer to such symptoms.[15] It is unclear whether the symptoms represent a withdrawal syndrome or direct serotonin toxicity;[14,16,18] however, it has been suggested by some that *in-utero* exposure to SSRIs with a short half-life such as paroxetine may lead to a neonatal withdrawal syndrome whereas exposure to an SSRI with a long half-life, particularly fluoxetine, may manifest as neonatal serotonin toxicity.[15] There have been case reports of intraventricular haemorrhage in neonates whose mothers took SSRIs during late pregnancy but there is currently not enough data to determine whether the frequency of such bleeds in infants exposed to SSRIs is higher than normal.[16]

The effects of fluoxetine on fetal **neurodevelopment** were studied[19] in 55 pregnant women by later assessing global IQ of the children; no differences were seen in those exposed to fluoxetine *in utero* during the first trimester compared with those exposed to tricyclic antidepressants or adverse developmental influences. A subsequent study indicated that exposure to fluoxetine or tricyclic antidepressants throughout gestation did not appear to affect cognition adversely.[20] In another follow-up study, subtle differences in motor development and control, in particular tremulousness and inappropriate fine motor movements, were noted in the infants and children of depressed mothers who had taken SSRIs during pregnancy when compared with the infants of depressed mothers who had not taken any medication.[21] However, in other measures of mental development there were no observed differences between the two groups.

1. Pastuszak A, *et al.* Pregnancy outcome following first-trimester exposure to fluoxetine (Prozac). *JAMA* 1993; **269:** 2246–8.
2. Chambers CD, *et al.* Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med* 1996; **335:** 1010–15.
3. Robert E. Treating depression in pregnancy. *N Engl J Med* 1996; **335:** 1056–8.
4. Goldstein DJ, *et al.* Effects of first-trimester fluoxetine exposure on the newborn. *Obstet Gynecol* 1997; **89:** 713–18.
5. Kulin NA, *et al.* Pregnancy outcome following maternal use of the new selective serotonin reuptake inhibitors: a prospective controlled multicenter study. *JAMA* 1998; **279:** 609–10.

6. Hemels MEH, *et al.* Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. *Ann Pharmacother* 2005; **39:** 803–9.
7. GlaxoSmithKline USA. Important prescribing information (issued December 2005). Available at: http://www.fda.gov/medwatch/safety/2005/Paxil_DHCP%20Letter_Dec%202005.pdf (accessed 17/01/06)
8. Spencer MJ. Fluoxetine hydrochloride (Prozac) toxicity in a neonate. *Pediatrics* 1993; **92:** 721–2.
9. Abebe-Campino G, *et al.*. Cardiac arrhythmia in a newborn infant associated with fluoxetine use during pregnancy. *Ann Pharmacother* 2002; **36:** 533–4.
10. Costei AM, *et al.* Perinatal outcome following third trimester exposure to paroxetine. *Arch Pediatr Adolesc Med* 2002; **156:** 1129–32.
11. Chambers CD, *et al.* Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006; **354:** 579–87.
12. Nijhuis IJM, *et al.* Withdrawal reactions of a premature neonate after maternal use of paroxetine. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F77.
13. Stiskal JA, *et al.* Neonatal paroxetine withdrawal syndrome. *Arch Dis Child Fetal Neonatal Ed* 2001; **84:** F134–F135.
14. Zeskind PS, Stephens LE. Maternal selective serotonin reuptake inhibitor use during pregnancy and newborn neurobehavior. *Pediatrics* 2004; **113:** 368–75.
15. Moses-Kolko EL, *et al.* Neonatal signs after late in utero exposure to serotonin reuptake inhibitors: literature review and implications for clinical applications. *JAMA* 2005; **293:** 2372–83.
16. Nordeng H, Spigset O. Treatment with selective serotonin reuptake inhibitors in the third trimester of pregnancy: effects on the infant. *Drug Safety* 2005; **28:** 565–81.
17. Sanz EJ, *et al.* Selective serotonin reuptake inhibitors in pregnant women and neonatal withdrawal syndrome: a database analysis. *Lancet* 2005; **365:** 482–7.
18. Isbister GK, *et al.* Neonatal paroxetine withdrawal syndrome or actually serotonin syndrome? *Arch Dis Child Fetal Neonatal Ed* 2001; **85:** F147–F148.
19. Nulman I, *et al.* Neurodevelopment of children exposed in utero to antidepressant drugs. *N Engl J Med* 1997; **336:** 258–62.
20. Nulman I, *et al.* Child development following exposure to tricyclic antidepressants or fluoxetine throughout fetal life: a prospective, controlled study. *Am J Psychiatry* 2002; **159:** 1889–95.
21. Casper RC, *et al.* Follow-up of children of depressed mothers exposed or not exposed to antidepressant drugs during pregnancy. *J Pediatr* 2003; **142:** 402–8.

Surgery. In patients undergoing orthopaedic surgery, the risk of perioperative blood loss was significantly increased in those taking serotonergic antidepressants (specifically clomipramine, fluoxetine, fluvoxamine, paroxetine, sertraline, and venlafaxine) when compared with those on non-serotonergic antidepressants.[1] In addition, there was a significant increase in the need for blood transfusion during surgery in those on serotonergic antidepressants compared with those not receiving antidepressant medication.

1. Movig KLL, *et al.* Relationship of serotonergic antidepressants and need for blood transfusion in orthopedic surgical patients. *Arch Intern Med* 2003; **163:** 2354–8.

Withdrawal. Withdrawal reactions have been reported for all SSRIs and the related antidepressants mirtazapine and venlafaxine on dosage reduction or stopping treatment, although the frequency of such reactions may vary.[1-5] Paroxetine and venlafaxine have been associated with withdrawal reactions more often than other serotonergic antidepressants; in the case of paroxetine this may be due, in part, to its short half-life. Fluvoxamine also has a short half-life and has been shown in some studies to have a high risk of withdrawal reactions. The apparent lower risk of withdrawal reactions with fluoxetine may be due to its long half-life. Other factors that increase the risk of withdrawal reactions include abrupt withdrawal, the use of high doses, and prolonged therapy.[5]

In general, withdrawal reactions tend to occur within 3 days of stopping an SSRI or related antidepressant,[1,4,5] although a delay of up to 2 weeks may be noted with fluoxetine.[5] Common symptoms include dizziness, numbness and tingling, gastrointestinal disturbances (particularly nausea and vomiting), headache, sweating, anxiety, and sleep disorders. In some cases withdrawal symptoms may be severe and disabling. There has also been a report[6] of 2 patients without a history of major psychiatric disorder who developed severe behavioural symptoms when paroxetine was withdrawn. Withdrawal was abrupt in one patient and more gradual, over a 12-day period, in the other. Symptoms were mainly hypomanic over the first few days, followed by a period of escalated ego-dystonic aggression, behavioural dyscontrol, and suicidal ideation.

Antidepressant dose tapering appears to reduce the frequency and severity of withdrawal reactions.[5] The *BNF* recommends that any antidepressant, including an SSRI, that has been taken regularly for 8 weeks or more should be stopped gradually over a period of about 4 weeks, or as much as 6 months in patients who have been receiving long-term maintenance therapy.

The withdrawal syndrome of the SSRIs is not considered to be a consequence of dependence.[4,5]

See also Extrapyramidal Effects under Adverse Effects, above. For debate about whether a withdrawal syndrome exists in neonates whose mothers have received SSRIs see Pregnancy, above.

1. Price JS, *et al.* A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 1996; **42:** 757–63.
2. Adverse Drug Reactions Advisory Committee (ADRAC). SSRI's and withdrawal syndrome. *Aust Adverse Drug React Bull* 1996; **15:** 3. Also available at: http://www.tga.gov.au/adr/aadrb/aadr9602.htm (accessed 14/08/08)
3. Coupland NJ, *et al.* Serotonin reuptake inhibitor withdrawal. *J Clin Psychopharmacol* 1996; **16:** 356–62.
4. CSM/MCA. Selective serotonin reuptake inhibitors (SSRIs). *Current Problems* 2000; **26:** 11–12. Also available at: http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON007460&RevisionSelectionMethod=LatestReleased (accessed 24/11/05)
5. 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 (accessed 14/08/08)
6. Bloch M, *et al.* Severe psychiatric symptoms associated with paroxetine withdrawal. *Lancet* 1995; **346:** 57.

Interactions

SSRIs interact with other drugs mainly as a result of their inhibitory activity on hepatic cytochrome P450 isoenzymes. Individual SSRIs do not all exhibit the same degree of inhibition nor do they react with the same isoenzymes. The drugs inhibited by specific SSRIs depends on the isoenzyme affected.

As SSRIs have occasionally been associated with bleeding disorders and other effects on the blood, caution is advised when they are given with drugs known to affect platelet function.

Although different antidepressants have been used together under expert supervision in refractory cases of depression, severe adverse reactions including the *serotonin syndrome* (see p.416) may occur. Sequential prescribing of different types of antidepressant may also produce adverse reactions, and an appropriate drug-free interval should elapse between stopping one type of antidepressant and starting another. SSRIs should not generally be given to patients receiving MAOIs or for at least 2 weeks after their use. No treatment-free period is necessary after stopping a reversible inhibitor of monoamine oxidase type A (RIMA) and starting an SSRI. At least one week should elapse between withdrawing an SSRI and starting any drug liable to provoke a serious reaction (e.g. phenelzine); in the case of the SSRI sertraline the drug-free interval is extended to 2 weeks, and for fluoxetine 5 weeks, because of their longer half-lives. (For fluoxetine, the interval may need to be further extended if therapy has been prolonged or if high doses have been given.) Adverse effects such as the serotonin syndrome may also occur when the SSRIs are given with other drugs known to act on the same neurotransmitter, a consequence of synergistic interaction.

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

◊ References.

1. Mitchell PB. Drug interactions of clinical significance with selective serotonin reuptake inhibitors. *Drug Safety* 1997; **17:** 390–406.
2. Sproule BA, *et al.* Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997; **33:** 454–71.
3. Hemeryck A, Belpaire FM. Selective serotonin reuptake inhibitors and cytochrome P-450 mediated drug-drug interactions: an update. *Curr Drug Metab* 2002; **3:** 13–37.

Antibacterials. Rapid development of delirium was reported[1] in a patient when *clarithromycin* was added to his existing regimen of fluoxetine and nitrazepam. It was suggested that his delirium was a result of increased plasma-fluoxetine concentrations produced by the inhibition of cytochrome P450 enzymes by clarithromycin. Serotonin syndrome developed in a patient given *erythromycin* in addition to sertraline;[2] this was attributed to inhibition of CYP3A4 by the antibacterial, resulting in accumulation of the SSRI. There have also been reports of serotonin syndrome when *linezolid* was given with fluoxetine,[3] sertraline,[4] paroxetine,[5] and citalopram[6]; in the latter case the patient developed complications including metabolic acidosis and ultimately fatal cardiac arrest.[6] Reviews of serotonin syndrome associated with the use of linezolid suggest that SSRIs are the interacting drug most often implicated.[7,8] However, it has been suggested that if warranted, linezolid may be given to patients receiving SSRIs provided the patient is carefully monitored for signs and symptoms of serotonin syndrome.[8]

1. Pollak PT, *et al.* Delirium probably induced by clarithromycin in a patient receiving fluoxetine. *Ann Pharmacother* 1995; **29:** 486–8.
2. Lee DO, Lee CD. Serotonin syndrome in a child associated with erythromycin and sertraline. *Pharmacotherapy* 1999; **19:** 894–6.
3. Steinberg M, Morin AK. Mild serotonin syndrome associated with concurrent linezolid and fluoxetine. *Am J Health-Syst Pharm* 2007; **64:** 59–62.
4. Lavery S, *et al.* Linezolid and serotonin syndrome. *Psychosomatics* 2001; **42:** 432–4.
5. Wigen CL, Goetz MB. Serotonin syndrome and linezolid. *Clin Infect Dis* 2002; **34:** 1651–2.
6. Bernard L, *et al.* Serotonin syndrome after concomitant treatment with linezolid and citalopram. *Clin Infect Dis* 2003; **36:** 1197.
7. Lawrence KR, *et al.* Serotonin toxicity associated with the use of linezolid: a review of postmarketing data. *Clin Infect Dis* 2006; **42:** 1578–83.
8. Taylor JJ, *et al.* Linezolid and serotonergic drug interactions: a retrospective survey. *Clin Infect Dis* 2006; **43:** 180–7.

Anticoagulants. SSRIs may increase the anticoagulant activity of some anticoagulants including *acenocoumarol* and *warfarin* (see p.1428).

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

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

There has been a report of the serotonin syndrome (see p.416) developing in a patient 14 days after fluoxetine had been added to *carbamazepine* therapy.[1]

Phenobarbital has been reported to reduce serum concentrations of paroxetine.[2] Steady-state serum concentrations of paroxetine were found to be lower in patients taking *phenytoin* than in those taking carbamazepine or valproate.[3]

Low serum concentrations of citalopram have been reported in 2 patients also taking carbamazepine.[4] Serum concentrations increased when carbamazepine was changed to oxcarbazepine.

Some SSRIs have been reported to increase plasma concentrations of carbamazepine (see p.474) and phenytoin (see p.498). For conflicting reports of the effect of fluoxetine on serum-*valproate* concentrations, see p.511.

1. Dursun SM, *et al.* Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342:** 442–3.
2. Greb WH, *et al.* The effect of liver enzyme inhibition by cimetidine and enzyme induction by phenobarbitone on the pharmacokinetics of paroxetine. *Acta Psychiatr Scand* 1989; **80** (suppl 350): 95–8.
3. Andersen BB, *et al.* No influence of the antidepressant paroxetine on carbamazepine, valproate and phenytoin. *Epilepsy Res* 1991; **10:** 201–4.
4. Leinonen E, *et al.* Substituting carbamazepine with oxcarbazepine increases citalopram levels. A report on two cases. *Pharmacopsychiatry* 1996; **29:** 156–8.

Antihistamines. *Cyproheptadine* given to male and female patients as treatment for sexual dysfunction induced by fluoxetine or paroxetine has produced re-emergence of previously controlled depressive symptoms[1,2] or bulimia nervosa[3] in some patients.

Citalopram, fluoxetine, and fluvoxamine may increase plasma concentrations of *astemizole* or *terfenadine* by inhibition of their hepatic cytochrome P450 metabolism, increasing the risk of ventricular arrhythmias; use together should be avoided.

1. Feder R. Reversal of antidepressant activity of fluoxetine by cyproheptadine in three patients. *J Clin Psychiatry* 1991; **52:** 163–4.
2. Christensen RC. Adverse interaction of paroxetine and cyproheptadine. *J Clin Psychiatry* 1995; **56:** 433–4.
3. Goldbloom DS, Kennedy SH. Adverse interaction of fluoxetine and cyproheptadine in two patients with bulimia nervosa. *J Clin Psychiatry* 1991; **52:** 261–2.

Antimalarials. For mention of the effect of the SSRI fluvoxamine on the metabolism of *proguanil*, see p.609.

Antimigraine drugs. There have been rare reports of serotonin syndrome associated with the use of SSRIs with serotonin (5-HT_1) agonists such as *sumatriptan* (see p.626). Fluvoxamine may inhibit the metabolism of *frovatriptan* and *zolmitriptan* (see p.622 and p.628, respectively). For the effects when some SSRIs are used with *dihydroergotamine*, see p.621.

Antimuscarinics. For the effect of SSRIs on *benzatropine*, see p.797. For the effect of paroxetine on *procyclidine*, see p.815.

Antineoplastics. Paroxetine may inhibit the metabolism of *tamoxifen*; for further details, see p.774.

Antipsychotics. For reports of adverse effects in patients treated with SSRIs and antipsychotics, see under *Chlorpromazine*, p.974. Interactions between SSRIs and atypical antipsychotics are also mentioned under *clozapine*, p.984, *olanzapine*, p.1013, *risperidone*, p.1025, *sertindole*, p.1028, and *zotepine*, p.1040.

Antivirals. Plasma concentrations of fluoxetine and other SSRIs are possibly increased by HIV-protease inhibitors, such as *ritonavir*, which may inhibit metabolism of the SSRI. Unexpectedly, however, total exposure to paroxetine was approximately halved by a *ritonavir-boosted fosamprenavir* combination in a study in healthy subjects.[1] Although the free fraction of paroxet-

ine in plasma was increased, suggesting that it had been displaced from protein binding, the maximum concentration of free paroxetine was reduced.

The serotonin syndrome has been described[2] in a few patients given regimens that included fluoxetine and antiretroviral-dose ritonavir. The reaction also occurred in another patient given fluoxetine and *efavirenz*.

1. van der Lee MJ, *et al.* Interaction study of the combined use of paroxetine and fosamprenavir-ritonavir in healthy subjects. *Antimicrob Agents Chemother* 2007; **51:** 4098–4104.
2. DeSilva KE, *et al.* Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. *AIDS* 2001; **15:** 1281–5.

Anxiolytics. Fluoxetine and fluvoxamine increase plasma concentrations of some *benzodiazepines* (see under Diazepam, p.990). There is a report of hyponatraemia and serotonin syndrome developing in a patient who received high doses of citalopram and *buspirone*.[1]

1. Spigset O, Adielsson G. Combined serotonin syndrome and hyponatraemia caused by a citalopram-buspirone interaction. *Int Clin Psychopharmacol* 1997; **12:** 61–3.

Beta blockers. For the effect of fluoxetine and fluvoxamine on beta blockers, see p.1228.

Ciclosporin. For the effect of fluoxetine and fluvoxamine on ciclosporin, see p.1826.

Cough suppressants. For the effects when using fluoxetine or paroxetine with *dextromethorphan*, see p.1556.

Dopaminergics. *Selegiline* is an irreversible selective inhibitor of monoamine oxidase type B. Serious adverse effects have been reported when selegiline and SSRIs have been used together (see p.817). In some instances, these reactions resemble the potentially fatal serotonin syndromes reported when SSRIs are given with non-selective MAOIs (see p.416).

SSRIs should not generally be given to patients receiving selegiline, or for at least 2 weeks after it has been stopped. Similarly, at least one week should elapse between withdrawing an SSRI and starting selegiline; this interval should be increased to 2 weeks for sertraline, and to 5 weeks for fluoxetine because of their longer half-lives.

Gastrointestinal drugs. Acute dystonia has been noted in a patient given fluvoxamine and *metoclopramide*.[1] Similar reports have been published for other SSRIs (fluoxetine[2] or sertraline[3]) and metoclopramide. Involuntary twitching, tremor, and stiffness of the jaw and tongue occurred on both occasions after the use of intravenous metoclopramide in a patient also taking sertraline.[4] The authors considered the adverse effects to be features of the serotonin syndrome.

For the effect of fluvoxamine on *alosetron*, and a recommendation that the combination be avoided, see p.1706.

For the effect of fluvoxamine on proton pump inhibitors, including *omeprazole*, see p.1755.

1. Palop V, *et al.* Acute dystonia associated with fluvoxamine-metoclopramide. *Ann Pharmacother* 1999; **33:** 382.
2. Coulter DM, Pillans PI. Fluoxetine and extrapyramidal side effects. *Am J Psychiatry* 1995; **152:** 122–5.
3. Christensen RC, Byerly MJ. Mandibular dystonia associated with the combination of sertraline and metoclopramide. *J Clin Psychiatry* 1996; **57:** 596.
4. Fisher AA, Davis MW. Serotonin syndrome caused by selective serotonin reuptake-inhibitors–metoclopramide interaction. *Ann Pharmacother* 2002; **36:** 67–71.

General anaesthetics. For a report of a generalised tonic-clonic seizure in a patient receiving paroxetine and *methohexital sodium*, see p.1789.

Hypnotics. For reference to visual hallucinations in patients receiving an SSRI concomitantly with *zolpidem*, see p.1038.

Levothyroxine. For mention of a decreased effect of levothyroxine in patients given sertraline concomitantly, see p.2172.

Local anaesthetics. For the effect of fluvoxamine on *ropivacaine*, see p.1871.

Muscle relaxants. For a report of QT prolongation in a patient taking fluoxetine and *cyclobenzaprine*, see p.1895.

For the effect of fluvoxamine on *tizanidine*, see p.1898.

NSAIDs. For reference to an increased risk of upper gastrointestinal bleeding in patients taking SSRIs and NSAIDs together, see under Effects on the Gastrointestinal Tract, above.

Opioid analgesics. A possible case of serotonin syndrome (p.416) has been reported with *tramadol* and sertraline,[1] and another when sertraline was given with high doses of *oxycodone*.[2] There have also been occasional reports of the syndrome in patients given tramadol with citalopram,[3] fluoxetine,[4] or paroxetine.[5,6] Other reports of serotonin syndrome were associated with use of oxycodone and fluvoxamine,[7] *pethidine* and fluoxetine,[8] and citalopram with *fentanyl*[9] or pethidine.[10] For reference to SSRIs enhancing the effects and toxicity of *methadone*, see p.84.

1. Mason BJ, Blackburn KH. Possible serotonin syndrome associated with tramadol and sertraline coadministration. *Ann Pharmacother* 1997; **31:** 175–7.
2. Rosebraugh CJ, *et al.* Visual hallucination and tremor induced by sertraline and oxycodone in a bone marrow transplant patient. *J Clin Pharmacol* 2001; **41:** 224–7.
3. Mahlberg R, *et al.* Serotonin syndrome with tramadol and citalopram. *Am J Psychiatry* 2004; **161:** 1129.
4. Kesavan S, Sobala GM. Serotonin syndrome with fluoxetine plus tramadol. *J R Soc Med* 1999; **92:** 474–5.
5. Egberts ACG, *et al.* Serotonin syndrome attributed to tramadol addition to paroxetine therapy. *Int Clin Psychopharmacol* 1997; **12:** 181–2.
6. Lantz MS, *et al.* Serotonin syndrome following the administration of tramadol with paroxetine. *Int J Geriatr Psychiatry* 1998; **13:** 343–5.
7. Karunatilake H, Buckley NA. Serotonin syndrome induced by fluvoxamine and oxycodone. *Ann Pharmacother* 2006; **40:** 155–7.
8. Tissot TA. Probable meperidine-induced serotonin syndrome in a patient with a history of fluoxetine use. *Anesthesiology* 2003; **98:** 1511–12.
9. Ailawadhi S, *et al.* Serotonin syndrome caused by interaction between citalopram and fentanyl. *J Clin Pharm Ther* 2007; **32:** 199–202.
10. Altman EM, Manos GH. Serotonin syndrome associated with citalopram and meperidine. *Psychosomatics* 2007; **48:** 361–3.

Parasympathomimetics. For the effect of fluvoxamine on *tacrine*, see p.370. For the effect of some SSRIs on *galantamine*, see p.366.

Sibutramine. There is a risk of CNS toxicity due to synergistic serotonergic actions when an SSRI is given with sibutramine.

Smoking. Serum concentrations of fluvoxamine were lower in smokers than non-smokers in a single-dose study.[1] It was proposed that the polycyclic hydrocarbons present in cigarette smoke stimulated hepatic metabolism of fluvoxamine by cytochrome P450 isoenzymes.

1. Spigset O, *et al.* Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther* 1995; **58:** 399–403.

Stimulants. For the effect of paroxetine on the metabolism of *atomoxetine*, see p.2151.

Theophylline. For the effect of fluvoxamine on theophylline, see p.1143.

Pharmacokinetics

Fluoxetine is readily absorbed from the gastrointestinal tract with peak plasma concentrations appearing about 6 to 8 hours after oral doses. Systemic bioavailability does not appear to be affected by food. Fluoxetine is extensively metabolised, by demethylation, in the liver to its primary active metabolite norfluoxetine. Excretion is mainly via the urine. Protein binding is reported to be about 95%.

Fluoxetine used clinically is a racemic mixture consisting of *R*- and *S*-enantiomers in equal amounts. Both enantiomers are active according to *animal* studies, but *S*-fluoxetine is eliminated more slowly. Metabolism is believed to be mediated by cytochrome P450 isoenzyme CYP2D6 (but see below), and leads to *R*- and *S*-enantiomers of norfluoxetine, with the *S*-enantiomer being considered as active as the parent drug; the *R*-enantiomer is considered to be much less active. This metabolism is subject to genetic polymorphism. While the small proportion of the population known as slow metabolisers do show a different spectrum of parent drug and metabolite, the overall activity does not appear to be altered.

Fluoxetine is widely distributed throughout the body.

Fluoxetine has a relatively long elimination half-life of about 1 to 3 days after acute use and 4 to 6 days after long-term use; that of its metabolite, norfluoxetine, is even longer, being about 4 to 16 days. These long half-lives have clinical implications. Steady-state plasma concentrations will only be attained after several weeks. Additionally, fluoxetine and its metabolites may persist for a considerable time after treatment, and this has led to precautions concerning the subsequent use of other serotonergic drugs (see Interactions, above).

Fluoxetine and norfluoxetine are distributed into breast milk (see Breast Feeding under Precautions, above).

◊ References.

1. Altamura AC, *et al.* Clinical pharmacokinetics of fluoxetine. *Clin Pharmacokinet* 1994; **26:** 201–14.
2. Baumann P. Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. *Clin Pharmacokinet* 1996; **31:** 444–69.
3. Greenblatt DJ, *et al.* Inhibition of human cytochrome P450-3A isoforms by fluoxetine and norfluoxetine: in vitro and in vivo studies. *J Clin Pharmacol* 1996; **36:** 792–8.
4. Hamelin BA, *et al.* The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 1996; **60:** 512–21.
5. Preskorn SH. Clinically relevant pharmacology of selective serotonin reuptake inhibitors: an overview with emphasis on pharmacokinetics and effects on oxidative drug metabolism. *Clin Pharmacokinet* 1997; **32** (suppl 1): 1–21.
6. Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.

Metabolism. Although fluoxetine is stated by the manufacturers to be metabolised by the cytochrome P450 isoenzyme CYP2D6, which is supported by studies[1] indicating that its disposition is altered in poor metabolisers of debrisoquine (a substrate for this enzyme), others have suggested that CYP2C19, and perhaps CYP2C9, play an important role.[2]

1. Hamelin BA, *et al.* The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 1996; **60:** 512–21.
2. Liu Z-Q, *et al.* Effect of the CYP2C19 oxidation polymorphism on fluoxetine metabolism in Chinese healthy subjects. *Br J Clin Pharmacol* 2001; **52:** 96–9.

Uses and Administration

Prevention of the reuptake of monoamine transmitters such as serotonin, which potentiates their action in the brain, appears to be associated with antidepressant activity. SSRIs such as fluoxetine preferentially inhibit the reuptake of serotonin compared with noradrenaline, and have limited direct action at other neurotransmitter sites, including muscarinic receptors. They therefore cause fewer antimuscarinic or sedative adverse effects than the tricyclic antidepressants and are less cardiotoxic. Citalopram is the most selective of the SSRIs currently available, whereas paroxetine is the most potent.

SSRIs provide an alternative to the tricyclics for the treatment of depression. As with the tricyclics, it may be several weeks before an antidepressant effect is seen. Once depression has then resolved, maintenance therapy should 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.

Some SSRIs are also used as part of the management of generalised anxiety disorder, obsessive-compulsive disorder, panic disorders with or without agoraphobia, social phobia, and post-traumatic stress disorder, and as part of the management of bulimia nervosa. Fluoxetine is also used in the treatment of premenstrual dysphoric disorder.

Fluoxetine, a phenylpropylamine derivative, is given orally as the hydrochloride; doses are expressed in terms of the base. Fluoxetine hydrochloride 22.4 mg is equivalent to about 20 mg of fluoxetine.

In the treatment of **depression** the usual initial dose of fluoxetine is 20 mg once daily; US product information recommends giving this dose in the morning. If no clinical response is seen after several weeks, the daily dose may be gradually increased, up to a maximum of 80 mg daily (60 mg in the elderly). Doses above 20 mg daily may be given in 2 divided doses, for example in the morning and at noon, or as a once daily dose. A once-weekly, modified-release preparation equivalent to 90 mg of fluoxetine is available in the USA for use in patients whose depressive symptoms have stabilised, and who require long-term treatment; it is recommended that weekly dosing is started 7 days after the last daily dose of fluoxetine.

Fluoxetine is also used for the treatment of depression in children aged 8 years and over. Initial doses of 10 mg should be increased to 20 mg daily after 1 week (except in low-weight children when such increases should not be made for several weeks, and then only if the clinical response is insufficient). Because of concerns about the use of SSRIs in children (see Effects on Mental State, above) its use is licensed in the European Union only as an adjunct to psychological therapy in children and adolescents with moderate to severe depression who have not responded to psychological therapy alone.

Fluoxetine is used in recommended doses of 60 mg once daily in the management of **bulimia nervosa**.

In the management of **obsessive-compulsive disorder** the initial dose of fluoxetine is 20 mg once daily in-

creased after several weeks if there is no response to up to 60 mg daily. Up to 80 mg daily has been used, sometimes divided into 2 doses. Fluoxetine is also licensed in the USA for use in children aged 7 years and over for obsessive-compulsive disorder. The starting dose is 10 mg daily; in low-weight children this is increased after several weeks to 20 to 30 mg daily, if required. Adolescents and heavier children may be increased to 20 mg daily after 2 weeks; further increases to 60 mg daily may be made after several weeks, as necessary.

Fluoxetine may be used in the treatment of **panic disorder** in initial doses of 10 mg once daily. After a week the dose should be increased to 20 mg daily; further increases to 60 mg daily may be considered after several weeks if no improvement is seen.

A dose of 20 mg daily is used in the treatment of **premenstrual dysphoric disorder**. Intermittent dosing is also permitted: for each new cycle, fluoxetine should be started 14 days before the onset of menstruation and continued until the first full day of menstruation. Treatment may be continued for 6 months; benefit should then be reassessed before continuing further.

A lower or less frequent dosage is recommended in elderly patients. For dosage in hepatic or renal impairment see below.

It should be noted that because fluoxetine and norfluoxetine have prolonged half-lives several weeks of therapy are required before steady-state concentrations are attained; similarly after dosage adjustments a time lag will occur before steady-state concentrations are again achieved. Although SSRIs should generally be withdrawn gradually to reduce the risk of withdrawal symptoms, the long half-life may reduce the need for dose tapering with fluoxetine.

Administration in hepatic or renal impairment. Fluoxetine is subject to hepatic metabolism, and, therefore, lower doses, such as alternate-day dosing, have been recommended in patients with significant hepatic impairment.

It is also excreted by the kidneys and licensed information for some UK products recommends a similar dose reduction in patients with mild to moderate renal impairment and that fluoxetine should be avoided in those with severe impairment. However, other UK and US product information states that plasma concentrations of fluoxetine or its metabolite norfluoxetine in patients with severe impairment requiring dialysis did not differ from those in controls with normal renal function when given fluoxetine 20 mg daily for 2 months.

Anorexia nervosa. Counselling and psychotherapy form the major part of treatment of anorexia nervosa and there is little or no role for specific drug therapy. Antidepressants may be indicated when there is co-existing depression or obsessive-compulsive disorder but malnourished anorexic patients may be more susceptible to adverse effects and less responsive than other patients with depression. Fluoxetine has been tried with some success particularly when used to prevent relapse once weight gain has been achieved.

References.

1. Bergh C, *et al.* Selective serotonin reuptake inhibitors in anorexia. *Lancet* 1996; **348:** 1459–60.
2. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
3. Kaye WH, *et al.* Double-blind placebo-controlled administration of fluoxetine in restricting- and restricting-purging-type anorexia nervosa. *Biol Psychiatry* 2001; **49:** 644–52.
4. Kim SS. Role of fluoxetine in anorexia nervosa. *Ann Pharmacother* 2003; **37:** 890–2.

Anxiety disorders. SSRIs have been given in a variety of anxiety disorders but their role in these disorders is most well established in the treatment of *obsessive-compulsive disorder* (p.952). Efficacy in obsessive-compulsive disorder appears to have been best demonstrated for fluvoxamine and fluoxetine but other SSRIs are also effective and patients unresponsive to one SSRI may respond to another. SSRIs are also of use in the treatment of *generalised anxiety disorder* (p.952), *panic disorder* (p.952), and *post-traumatic stress disorder* (p.953). SSRIs are considered to be the first choice for the treatment of *social anxiety disorder* (see under Phobic Disorders, p.953). Fluoxetine is one of the SSRIs that has been tried in the treatment of *trichotillomania*.

References.

1. Tollefson GD, *et al.* A multicenter investigation of fixed-dose fluoxetine in the treatment of obsessive-compulsive disorder. *Arch Gen Psychiatry* 1994; **51:** 559–67.
2. Yanchick JK, *et al.* Efficacy of fluoxetine in trichotillomania. *Ann Pharmacother* 1994; **28:** 1245–6.
3. Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: a meta-analysis. *Int Clin Psychopharmacol* 1995; **10:** 45–9.
4. Michelson D, *et al.* Continuing treatment of panic disorder after acute response: randomised, placebo-controlled trial with fluoxetine. *Br J Psychiatry* 1999; **174:** 213–18.
5. Connor KM, *et al.* Fluoxetine in post-traumatic stress disorder: randomised, double-blind study. *Br J Psychiatry* 1999; **175:** 17–22.
6. Meltzer-Brody S, *et al.* Symptom-specific effects of fluoxetine in post-traumatic stress disorder. *Int Clin Psychopharmacol* 2000; **15:** 227–31.
7. Geller DA, *et al.* Fluoxetine treatment for obsessive-compulsive disorder in children and adolescents: a placebo-controlled clinical trial. *J Am Acad Child Adolesc Psychiatry* 2001; **40:** 773–9.
8. Romano S, *et al.* Long-term treatment of obsessive-compulsive disorder after an acute response: a comparison of fluoxetine versus placebo. *J Clin Psychopharmacol* 2001; **21:** 46–52.
9. Barnett SD, *et al.* Tolerability of fluoxetine in posttraumatic stress disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2002; **26:** 363–7.
10. Liebowitz MR, *et al.* Fluoxetine in children and adolescents with OCD: a placebo-controlled trial. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1431–8.
11. Birmaher B, *et al.* Fluoxetine for the treatment of childhood anxiety disorders. *J Am Acad Child Adolesc Psychiatry* 2003; **42:** 415–23.
12. Davidson JR, *et al.* Fluoxetine, comprehensive cognitive behavioral therapy, and placebo in generalized social phobia. *Arch Gen Psychiatry* 2004; **61:** 1005–13.

Bipolar disorder. Treatment of the depressive phase of bipolar disorder (p.372) with antidepressants needs caution since these drugs may precipitate mania or hypomania. SSRIs such as fluoxetine have nonetheless been used in bipolar disorder with some success. In some countries, fluoxetine is also available as a fixed-dose combination with the atypical antipsychotic olanzapine for use in the depressive phase of bipolar disorder.

References.

1. Amsterdam JD, *et al.* Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. *J Clin Psychopharmacol* 1998; **18:** 435–40.
2. Megna JL, Devitt PJ. Treatment of bipolar depression with twice-weekly fluoxetine: management of antidepressant-induced mania. *Ann Pharmacother* 2001; **35:** 45–7.
3. Tohen M, *et al.* Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 2003; **60:** 1079–88. Correction. *ibid.* 2004; **61:** 176.
4. Amsterdam JD, *et al.* Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression - low manic switch rate. *Bipolar Disord* 2004; **6:** 75–81.

Bulimia nervosa. A combination of counselling, support, psychotherapy, and antidepressants is the usual treatment for bulimia nervosa. Fluoxetine and the tricyclic desipramine have been suggested as the antidepressants of choice because they have been used extensively and are considered to be well tolerated. Other SSRIs that have been tried include sertraline, fluvoxamine, and paroxetine. Antidepressants in general do not appear to alter the patient's disturbed self-image, although disturbed attitudes might improve during short-term therapy with fluoxetine.

References.

1. Goldbloom DS, Olmsted MP. Pharmacotherapy of bulimia nervosa with fluoxetine: assessment of clinically significant attitudinal change. *Am J Psychiatry* 1993; **150:** 770–4.
2. Mayer LES, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
3. Bacaltchuk J, *et al.* Antidepressants versus psychological treatments and their combination for bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 24/11/05).
4. Bacaltchuk J, Hay P. Antidepressants versus placebo for people with bulimia nervosa. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2003 (accessed 24/11/05).

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

Combination therapy with differing classes of antidepressants, including the SSRIs, 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 workers. For further details see Antidepressants, under Interactions of Phenelzine, p.418.

References to the use of SSRIs in general and to the use of fluoxetine are given below.

1. Anderson IM, Tomenson BM. Treatment discontinuation with selective serotonin reuptake inhibitors compared with tricyclic antidepressants: a meta-analysis. *BMJ* 1995; **310:** 1433–8.
2. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J Clin Psychiatry* 1995; **56:** 30–4.
3. Fava M, *et al.* Relapse in patients on long-term fluoxetine treatment: response to increased fluoxetine dose. *J Clin Psychiatry* 1995; **56:** 52–5.
4. Mourilhe P, Stokes PE. Risks and benefits of selective serotonin reuptake inhibitors in the treatment of depression. *Drug Safety* 1998; **18:** 57–82.
5. Anderson IM. SSRIs versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety* 1998; **7** (suppl 1): 11–17.
6. Cheer SM, Goa KL. Fluoxetine: a review of its therapeutic potential in the treatment of depression associated with physical illness. *Drugs* 2001; **61:** 81–110.
7. Sampson SM. Treating depression with selective serotonin reuptake inhibitors: a practical approach. *Mayo Clin Proc* 2001; **76:** 739–44.
8. Wagstaff AJ, Goa KL. Once-weekly fluoxetine. *Drugs* 2001; **61:** 2221–8.
9. Bull SA, *et al.* Discontinuing or switching selective serotonin-reuptake inhibitors. *Ann Pharmacother* 2002 **36:** 578–84.
10. Emslie GJ, *et al.* Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. *J Am Acad Child Adolesc Psychiatry* 2002; **41:** 1205–15.
11. March J, *et al.* 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.
12. Devanand DP, *et al.* Randomized, double-blind, placebo-controlled trial of fluoxetine treatment for elderly patients with dysthymic disorder. *Am J Geriatr Psychiatry* 2005; **13:** 59–68.

Disturbed behaviour. SSRIs appear to have been of some benefit in controlling symptoms such as impulsiveness and aggression[1-3] when tried in various disorders for the management of disturbed behaviour (see p.954). There have been several case reports of fluoxetine being used with some success in the control of fantasies associated with various paraphilias.[4]

1. Cornelius JR, *et al.* Fluoxetine trial in borderline personality disorder. *Psychopharmacol Bull* 1990; **26:** 151–4.
2. Vartiainen H, *et al.* Citalopram, a selective serotonin reuptake inhibitor, in the treatment of aggression in schizophrenia. *Acta Psychiatr Scand* 1995; **91:** 348–51.
3. Coccaro EF, Kavoussi RJ. Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Arch Gen Psychiatry* 1997; **54:** 1081–8.
4. Richer M, Crismon ML. Pharmacotherapy of sexual offenders. *Ann Pharmacother* 1993; **27:** 316–19.

Headache. The results of several studies have suggested that SSRIs may be of benefit in the treatment of chronic tension-type headache (p.617); however, results in the prophylaxis of migraine (p.616) have been conflicting.

References.

1. Sosin D. Clinical efficacy of fluoxetine vs sertraline in a headache clinic population. *Headache* 1993; **33:** 284.
2. Solomon GD, Pearson E. Sertraline in the management of headache. *Clin Pharmacol Ther* 1994; **55:** 130.
3. Jung AC, *et al.* The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 1997; **12:** 384–9.
4. d'Amato CC, *et al.* Fluoxetine for migraine prophylaxis: a double-blind trial. *Headache* 1999; **39:** 716–19.

Hot flushes. HRT with oestrogens is usually the mainstay of acute treatment for symptoms such as hot flushes associated with the menopause (see p.2077); however, HRT has potentially tumour-stimulating effects and may be unsuitable in some patients, particularly those with a history of breast cancer (see Malignant Neoplasms, under Precautions of HRT, p.2075). Preliminary studies have shown that some SSRIs (fluoxetine, paroxetine, and sertraline) have a modest effect on alleviating hot flushes and may be an alternative to HRT in peri- and postmenopausal women and in women with a history of breast cancer.[1-4] However, there is some concern that the SSRI paroxetine may interact with tamoxifen treatment in patients with breast cancer (see Antidepressants under Interactions in Tamoxifen, p.774 for details).

In addition, paroxetine has been tried in the treatment of hot flushes in men receiving anti-androgen therapy for prostate cancer.[5]

The serotonergic antidepressant venlafaxine has also been tried with some success in men and women with hot flushes in whom other treatments were unsuitable.[6]

1. Stearns V, *et al.* Paroxetine controlled release in the treatment of menopausal hot flashes: a randomized controlled trial. *JAMA* 2003; **289:** 2827–34.
2. Kockler DR, McCarthy MW. Antidepressants as a treatment for hot flashes in women. *Am J Health-Syst Pharm* 2004; **61:** 287–92.
3. De Sloover Koch Y, Ernst ME. Selective serotonin-reuptake inhibitors for the treatment of hot flashes. *Ann Pharmacother* 2004; **38:** 1293–6.
4. Stearns V, *et al.* Paroxetine is an effective treatment for hot flashes: results from a prospective randomized clinical trial. *J Clin Oncol* 2005; **23:** 6919–30. Correction. *ibid.*; 8549.
5. Loprinzi CL, *et al.* Pilot evaluation of paroxetine for treating hot flashes in men. *Mayo Clin Proc* 2004; **79:** 1247–51.
6. Schober CE, Ansani NT. Venlafaxine hydrochloride for the treatment of hot flashes. *Ann Pharmacother* 2003; **37:** 1703–7.

Hyperactivity. When drug therapy is indicated for attention deficit hyperactivity disorder (ADHD—p.2148) initial treatment is usually with a central stimulant. SSRIs such as fluoxetine have produced beneficial effects as an adjunct to central stimulants in small numbers of patients with comorbid disorders such as depression or obsessive-compulsive disorder;[1-3] although there is insufficient evidence to assess their efficacy in ADHD alone.

1. Gammon GD, Brown TE. Fluoxetine and methylphenidate in combination for treatment of attention deficit disorder and comorbid depressive disorder. *J Child Adolesc Psychopharmacol* 1993; **3:** 1–10.
2. Bussing R, Levin GM. Methamphetamine and fluoxetine treatment of a child with attention-deficit hyperactivity disorder and obsessive-compulsive disorder. *J Child Adolesc Psychopharmacol* 1993; **3:** 53–8.
3. Finding RL. Open-label treatment of comorbid depression and attentional disorders with co-administration of serotonin reuptake inhibitors and psychostimulants in children, adolescents and adults: a case series. *J Child Adolesc Psychopharmacol* 1996; **6:** 165–75.

Hypochondriasis. SSRIs may be of benefit in patients with hypochondriasis.[1] Fluoxetine in an initial dose of 20 mg daily gradually increased up to 80 mg daily produced some beneficial

results in 10 of 14 patients with hypochondriasis (p.954) who completed 12 weeks of treatment.[2] Fluvoxamine[3] and paroxetine[4] have also been tried.

1. Fallon BA, *et al.* The pharmacotherapy of hypochondriasis. *Psychopharmacol Bull* 1996; **32:** 607–11.
2. Fallon BA, *et al.* Fluoxetine for hypochondriacal patients without major depression. *J Clin Psychopharmacol* 1993; **13:** 438–41.
3. Fallon BA, *et al.* An open trial of fluvoxamine for hypochondriasis. *Psychosomatics* 2003; **44:** 298–303.
4. Oosterbaan DB, *et al.* An open study of paroxetine in hypochondriasis. *Prog Neuropsychopharmacol Biol Psychiatry* 2001; **25:** 1023–33.

Hypotension. SSRIs have been used in patients with neurally mediated hypotension refractory to standard treatment (see p.1174), although evidence of benefit is mainly anecdotal. However, a small study[1] found that paroxetine reduced the incidence of both tilt-induced and spontaneous syncope.

See also Orthostatic Hypotension, below.

1. Di Girolamo E, *et al.* Effects of paroxetine hydrochloride, a selective serotonin reuptake inhibitor, on refractory vasovagal syncope: a randomized, double-blind, placebo-controlled study. *J Am Coll Cardiol* 1999; **33:** 1227–30.

Obesity. Fluoxetine has been tried with some success as part of the management of obesity (p.2149). Fluoxetine's mechanism of action in obesity is unknown. Serotonin is believed to be involved in the regulation of satiety[1] but fluoxetine has also been shown to increase resting energy expenditure and raise basal body temperature.[2] A common dose for fluoxetine in the management of obesity has been 60 mg daily; it appears that fluoxetine has a dose-related effect on weight loss.[3] Reviews[1,4,5] agree that fluoxetine can aid weight reduction in the short term but after 16 to 20 weeks some patients have started to regain weight and its long-term efficacy remains to be established. Troublesome adverse effects can occur.[1] Some patients treated with fluoxetine for depression have experienced an increase of appetite and some have gained weight. There has been a report[6] of a patient who lost weight during treatment with fluoxetine for depression despite an increased appetite and food intake.

1. Anonymous. Fluoxetine (Prozac) and other drugs for treatment of obesity. *Med Lett Drugs Ther* 1994; **36:** 107–8.
2. Bross R, Hoffer LJ. Fluoxetine increases resting energy expenditure and basal body temperature in humans. *Am J Clin Nutr* 1995; **61:** 1020–5.
3. Levine LR, *et al.* Use of fluoxetine, a selective serotonin-uptake inhibitor, in the treatment of obesity: a dose-response study. *Int J Obes* 1989; **13:** 635–45.
4. Bray GA. Use and abuse of appetite-suppressant drugs in the treatment of obesity. *Ann Intern Med* 1993; **119:** 707–13.
5. Mayer LE, Walsh BT. The use of selective serotonin reuptake inhibitors in eating disorders. *J Clin Psychiatry* 1998; **59** (suppl 15): 28–34.
6. Fichtner CG, Braun BG. Hyperphagia and weight loss during fluoxetine treatment. *Ann Pharmacother* 1994; **28:** 1350–2.

Orthostatic hypotension. Although orthostatic hypotension has been reported in some patients taking SSRIs, there has been a report[1] that fluoxetine 20 mg daily for 6 to 8 weeks produced beneficial effects in 4 of 5 patients with chronic symptomatic orthostatic hypotension (p.1530) refractory to other treatment. Modest benefits have also been seen in patients with orthostatic hypotension associated with parkinsonism.[2]

1. Grubb BP, *et al.* Fluoxetine hydrochloride for the treatment of severe refractory orthostatic hypotension. *Am J Med* 1994; **97:** 366–8.
2. Montastruc JL, *et al.* Fluoxetine in orthostatic hypotension of Parkinson's disease: a clinical and experimental pilot study. *Fundam Clin Pharmacol* 1998; **12:** 398–402.

Pain. SSRIs have been tried in the treatment of painful disorders including fibromyalgia and diabetic neuropathy.

See also Headache, above.

References.

1. Goldenberg D, *et al.* A randomized, double-blind crossover trial of fluoxetine and amitriptyline in the treatment of fibromyalgia. *Arthritis Rheum* 1996; **39:** 1852–9.
2. Jung AC, *et al.* The efficacy of selective serotonin reuptake inhibitors for the management of chronic pain. *J Gen Intern Med* 1997; **12:** 384–9.
3. Smith AJ. The analgesic effects of selective serotonin reuptake inhibitors. *J Psychopharmacol* 1998; **12:** 407–13.
4. Anderberg UM, *et al.* Citalopram in patients with fibromyalgia–a randomized, double-blind, placebo-controlled study. *Eur J Pain* 2000; **4:** 27–35.
5. Shimodozono M, *et al.* Reduction of central poststroke pain with the selective serotonin reuptake inhibitor fluvoxamine. *Int J Neurosci* 2002; **112:** 1173–81.
6. Arnold LM, *et al.* A randomized, placebo-controlled, double-blind, flexible-dose study of fluoxetine in the treatment of women with fibromyalgia. *Am J Med* 2002; **112:** 191–7.

Parkinsonism. It has been suggested that fluoxetine might be of use in the management of selected patients with Parkinson's disease (p.791) who have levodopa-induced dyskinesias unresponsive to other measures.[1] However, although fluoxetine has been reported to have produced beneficial results in such patients[2] there has also been a report of increased disability in patients with Parkinson's disease given fluoxetine.[3] Extrapyramidal effects have also been reported in other patients taking fluoxetine (see under Adverse Effects, above). Fluoxetine has been tried in parkinsonism-related orthostatic hypotension (above).

1. Giron LT, Koller WC. Methods of managing levodopa-induced dyskinesias. *Drug Safety* 1996; **14:** 365–74.
2. Durif F, *et al.* Levodopa-induced dyskinesias are improved by fluoxetine. *Neurology* 1995; **45:** 1855–8.
3. Steur ENHJ. Increase of Parkinson disability after fluoxetine medication. *Neurology* 1993; **43:** 211–3.

Pathological crying or laughing. Inappropriate or uncontrolled crying or laughing can occur in patients with lesions in certain areas of the brain. Attempts at treatment have mostly been with antidepressant drugs, including SSRIs. Beneficial effects have been claimed for fluoxetine in a number of uncontrolled studies and reports.[1-4]

1. Seliger GM, *et al.* Fluoxetine improves emotional incontinence. *Brain Inj* 1992; **6:** 267–70.
2. Sloan RL, *et al.* Fluoxetine as a treatment for emotional lability after brain injury. *Brain Inj* 1992; **6:** 315–19.
3. Hanger HC. Emotionalism after stroke. *Lancet* 1993; **342:** 1235–6.
4. Tsai WC, *et al.* Treatment of emotionalism with fluoxetine during rehabilitation. *Scand J Rehabil Med* 1998; **30:** 145–9.

Peripheral vascular disease. Anecdotal reports[1,2] and a small pilot study[3] of fluoxetine (in a daily dose of 20 to 60 mg) suggest it may produce favourable therapeutic responses in patients with Raynaud's syndrome (see Vasospastic Arterial Disorders, p.1188).

1. Bolte MA, Avery D. Case of fluoxetine-induced remission of Raynaud's phenomenon—a case report. *Angiology* 1993; **44:** 161–3.
2. Jaffe IA. Serotonin reuptake inhibitors in Raynaud's phenomenon. *Lancet* 1995; **345:** 1378.
3. Coleiro B, *et al.* Treatment of Raynaud's phenomenon with the selective serotonin reuptake inhibitor fluoxetine. *Rheumatology (Oxford)* 2001; **40:** 1038–43.

Premenstrual syndrome. Fluoxetine is used to control both the psychological and somatic symptoms of women with premenstrual dysphoric syndrome, a severe form of premenstrual syndrome (p.2099). Other SSRIs also appear to be useful, although evidence is so far more limited.

References.

1. Romano S, *et al.* The role of fluoxetine in the treatment of premenstrual dysphoric disorder. *Clin Ther* 1999; **21:** 615–33.
2. Eriksson E. Serotonin reuptake inhibitors for the treatment of premenstrual dysphoria. *Int Clin Psychopharmacol* 1999; **14** (suppl 2): S27–S33.
3. Dimmock PW, *et al.* Efficacy of selective serotonin-reuptake inhibitors in premenstrual syndrome: a systematic review. *Lancet* 2000; **356:** 1131–6.
4. Carr RR, Ensom MHH. Fluoxetine in the treatment of premenstrual dysphoric disorder. *Ann Pharmacother* 2002; **36:** 713–17.
5. Pearlstein T. Selective serotonin reuptake inhibitors for premenstrual dysphoric disorder: the emerging gold standard. *Drugs* 2002; **62:** 1869–85.
6. Wyatt KM, *et al.* Selective serotonin reuptake inhibitors for premenstrual syndrome. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2002 (accessed 24/11/05).
7. Luisi AF, Pawasauskas JE. Treatment of premenstrual dysphoric disorder with selective serotonin reuptake inhibitors. *Pharmacotherapy* 2003; **23:** 1131–40.

Sexual dysfunction. Impotence or ejaculatory problems have been reported as adverse effects of SSRIs (see Effects on Sexual Function in Adverse Effects, above). Such properties of the SSRIs have been studied as a potential form of treatment for men with premature ejaculation[1-3] (p.2181). The relative effects of the SSRIs on delaying ejaculation have also been studied.[4] Paroxetine was found to cause the strongest delay, followed by fluoxetine and then sertraline; fluvoxamine caused a slight delay although the effect was not significantly different from that seen with placebo. (Citalopram was unavailable at the time of the study; later studies of its effect have been conflicting[3].)

1. Waldinger MD, *et al.* Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry* 1994; **151:** 1377–9.
2. Mendels J, *et al.* Sertraline treatment for premature ejaculation. *J Clin Psychopharmacol* 1995; **15:** 341–6.
3. Moreland AJ, Makela EH. Selective serotonin-reuptake inhibitors in the treatment of premature ejaculation. *Ann Pharmacother* 2005; **39:** 1296–1301.
4. Waldinger MD, *et al.* Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine and sertraline. *J Clin Psychopharmacol* 1998; **18:** 274–81.

Preparations

BP 2008: Fluoxetine Capsules; Fluoxetine Oral Solution;
USP 31: Fluoxetine Capsules; Fluoxetine Delayed-Release Capsules; Fluoxetine Oral Solution; Fluoxetine Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Alental; Animex-On; Anzolden; Captaton; Eburnate; Equilibrane; Faboxetina; Felixina; Fibrotina; Fluopiram; Foxetin; Lapsus; Mitilase; Nervosal; Neupax; Neuro Laz; Prozac; Saurat; ***Austral.:*** Auscap; Erocap†; Fluohexal; Fluoxebell; Lovan; Prozac; Zactin; ***Austria:*** Felicium; Fluctine; Fluoxenorm; Fluoxibene; Fluoxistad; Fluoxityrol†; Flux; Fluxil; FluxoMed; Mutan; NuFluo; Positivum; ***Belg.:*** Docfluoxetine; Fluox; Fluoxemed; Fluoxone; Fontex; Prosimed; Prozac; ***Braz.:*** Daforin; Deprax; Depress; Eufor; Fluox; Fluxene; Nortec; Prozac; Prozen; Psiquial; Verotina; ***Canad.:*** FXT; Prozac; ***Chile:*** Actan; Alentol; Anisimol; Clinium; Dominium; Pragmaten; Prozac; Sostac; Tremafarm†; ***Cz.:*** Deprenon†; Deprex; Floxet; Flumirex†; Fluocim†; Fluogal†; Fluoxin; Fluval†; Fluxonil†; Fluzak; Framex†; Magrilan; Milezin†; Portal; Prozac; ***Denm.:*** Afeksin; Flutin; Fluxantin†; Folizol; Fondur†; Fonigen†; Fontex; Fonzac; ***Fin.:*** Fluoxal†; Fluxantin†; Fontex†; Seromex; Seronil; ***Fr.:*** Prozac; ***Ger.:*** Fluctin; Fluneurin; Fluox; Fluox-Puren; Fluoxa†; Fluoxe-Q; FluoxeLich; Fluoxemerck†; Fluoxgamma; Fluxet; Fysionorm†; ***Gr.:*** Dagrilan; Dinalexin; Exostrept; Flonital; Fluocalm; Fluxadir; Fokeston; Hapilux; Ladose; Orthon; Sartuzin; Sofelin; Stephadilat-S; Stressless; Thiramil; Zinovat; ***Hong Kong:*** Atd; CP-Fluoxet; Deprexin; Fluxetin; Fluxil; Magrilan†; Nopres; Plazeron†; Provatine†; Prozac; Qualisac; ***Hung.:*** Deprexin; Fefluzin†; Floxet; FluWinox; Portal; Prozac; ***India:*** Depzac; Fludac; Flufran†; Nuzac; Platin; ***Indon.:*** Andep; Ansi; Antiprestin; Courage; Elizac; Kalxetin; Lodep; Nopres; Noxetine; Oxipres; Prozac; ZAC; Zactin; ***Irl.:*** Affex; Biozac; Gerozac; Norzac; Prozac; Prozamel; Prozatan; Prozit; ***Israel:*** Affectine; Flutine; Prizma; Prozac; ***Ital.:*** Azur; Clexiclor; Cloriflox; Deprexen; Diesan; Flotina; Fluoxeren; Fluoxin†; Grinflux†; Ibixetin†; Ipsumor; Prozac; Serezac†; Xeredien; Zafluox†; ***Malaysia:*** Fluran; Fluxetil; Prozac; Salipax; ***Mex.:*** Aponeusak†; Auroken†; Axtin; Deprozin; Farmaxetina; Flocet; Florexal; Fluctine; Fluneurin; Fluoxac; Fluralex; Flutinax; Indozul; Lebensart; Ovisen; Prozac; Quanilene; Regultron; Siquial; Ulmely; Zatin; ***Neth.:*** Fluoxstad; Flustad; Prozac; ***Norw.:*** Fontex; ***NZ:*** Fluox; Plinzene; Prozac; ***Philipp.:*** Adepssir; Deprexone; Deprizac; Prozac; ***Pol.:*** Andepin; Bioxetin; Deprexetin; Salipax; Seronil; ***Port.:*** Digassim; Mizac†; Nodepe†; Prozac; Psipax; Salipax; Selectus; Tuneluz; ***Rus.:*** Apo-Fluoxetine (Апо-Флуоксетин); Fluval (Флувал); Framex (Фрамекс); Portal (Портал); Prodep (Продеп); Proflusak (Профлузак); Prozac (Прозак); ***S.Afr.:*** Deprozan; Lorien; Nuzak; Prohexal; Prozac; Ranflocs; Sanzur†; ***Singapore:*** Deprexin; Fluxetil†; Fluxetin; Fluxil; Foxtin; Magrilan; Prozac; Zactin; ***Spain:*** Adofen; Astrin†; Augort†; Lecimar; Luramon; Nodepe; Prozac; Reneuron; Zaxetina†; ***Swed.:*** Fluxantin†; Fontex; Seroscand†; ***Switz.:*** Fluctine; Fluesco; Fluocim; fluox-basan†; Fluoxifar; Flusol; ***Thai.:*** Actisac†; Anzac; Atd†; Dawnex; Deproxin; Flulox; Flumed; Fluoxine; Flusac; Flutine; Fluxetil; Fluxetin; Fluzac; Hapilux†; Loxetine; Magrilan; Oxetine; Oxsac; Prodep; Prozac; Unprozy; ***Turk.:*** Depreks; Fulsac; Loksetin; Prozac; Seronil; Zedprex; ***UAE:*** Flutin; ***UK:*** Prozac; Prozit; ***USA:*** Prozac; Sarafem; ***Venez.:*** Anoxen; Antipres; Fluxet; Fluzac; Prozac; Psiquial.

Multi-ingredient: ***Arg.:*** Combined†; Symbyax†; ***Chile:*** Symbyax; ***India:*** Fludep Plus; ***Mex.:*** Symbyax; ***USA:*** Symbyax.

Fluvoxamine Maleate *(BANM, USAN, rINNM)*

DU-23000; Fluvoksamiinimaleaatti; Fluvoksamin Maleat; Fluvoxamine, maléate de; Fluvoxamini maleas; Fluvoxaminmaleat; Maleato de fluvoxamina. (*E*)-5-Methoxy-4′-trifluoromethylvalerophenone *O*-2-aminoethyloxime maleate.

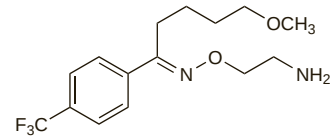
Флувоксамина Малеат

$C_{15}H_{21}F_3N_2O_2,C_4H_4O_4$ = 434.4.

CAS — 54739-18-3 (fluvoxamine); 61718-82-9 (fluvoxamine maleate).

ATC — N06AB08.

ATC Vet — QN06AB08.



(fluvoxamine)

Pharmacopoeias. In *Eur.* (see p.vii) and *US.*

Ph. Eur. 6.2 (Fluvoxamine Maleate). A white or almost white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in methyl alcohol.

USP 31 (Fluvoxamine Maleate). A white to off-white, crystalline powder. Sparingly soluble in water; freely soluble in alcohol and in chloroform; practically insoluble in solvent ether. Protect from light.

Adverse Effects, Treatment, and Precautions

As for SSRIs in general (see Fluoxetine, p.391).

Bradycardia with ECG changes has been noted with fluvoxamine (but see also Effects on the Cardiovascular System in Adverse Effects of Fluoxetine, p.392).

It is recommended that fluvoxamine should be withdrawn in patients who have increased serum liver enzyme concentrations.

Fluvoxamine may need to be given with caution to patients with hepatic or renal impairment, and to the elderly (see under Uses and Administration, below).

Incidence of adverse effects. The UK CSM has reported[1] that between 25 September 1986 and 23 March 1988 it had received 961 reports of adverse reactions, including 5 deaths, associated with the use of fluvoxamine. The most frequently reported reactions were nausea (183) and vomiting (101). Other reactions included dizziness, somnolence, agitation, headache, tremor, and, during the first few days, worsening of anxiety. There were 13 reports of convulsions. Reports of appetite stimulation and antimuscarinic reactions were unusual. The effects sometimes resolved with time or dose reduction.

The safety profile of fluvoxamine has been reviewed.[2] For a comparison of the adverse reaction profiles of other SSRIs including fluoxetine with that of fluvoxamine, see Incidence of Adverse Effects, under Adverse Effects of Fluoxetine, p.391.

1. CSM. Fluvoxamine (Faverin): adverse reaction profile. *Current Problems 22* 1988. Also available at: http:// www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2024429&RevisionSelectionMethod=LatestReleased (accessed 04/08/08)
2. Wagner W, *et al.* Fluvoxamine: a review of its safety profile in world-wide studies. *Int Clin Psychopharmacol* 1994; **9:** 223–7.