intervals of 4–7 days to usual dose of 75–100 mg daily according to response; CHILD not recommended

Short-term adjunctive management of severe anxiety, 15–20 mg daily in divided doses; max. 40 mg daily; CHILD not recommended

By deep intramuscular injection, psychoses, mania, prochlorperazine mesilate 12.5–25 mg 2–3 times daily; CHILD not recommended

By rectum in suppositories, psychoses, mania, the equivalent of prochlorperazine maleate 25 mg 2–3 times daily; CHILD not recommended

Preparations
Section 4.6

PROMAZINE HYDROCHLORIDE

Indications: see under Dose

Cautions: see notes above; also cerebral arteriosclerosis

Contra-indications: see notes above

Side-effects: see notes above; also haemolytic anaemia

Dose: *by mouth*, short-term adjunctive management of psychomotor agitation, 100–200 mg 4 times daily; CHILD not recommended

Agitation and restlessness in elderly, 25–50 mg 4 times daily

By intramuscular injection, short-term adjunctive management of psychomotor agitation, 50 mg (25 mg in elderly or debilitated), repeated if necessary after 6–8 hours; CHILD not recommended

Promazine (Non-proprietary) PoM

Tablets, coated, promazine hydrochloride 25 mg, net price 20 = 49p; 50 mg, 20 = 87p. Label: 2

Available from Biorex

Oral solution, promazine hydrochloride 25 mg/5 mL, net price 150 mL = £1.60; 50 mg/5 mL, 150 mL = £2.06. Label: 2

Available from Rosemont

Injection, promazine hydrochloride 50 mg/mL. Net price 1-mL amp = 30p

Note. May be difficult to obtain

SULPIRIDE

Indications: schizophrenia

Cautions: see notes above; also excited, agitated, or aggressive patients (even low doses may aggravate symptoms)

Contra-indications: see notes above; also porphyria (section 9.8.2)

Side-effects: see notes above; also hepatitis

Dose: 200–400 mg twice daily; max. 800 mg daily in predominantly negative symptoms, and 2.4 g daily in mainly positive symptoms; ELDERLY, lower initial dose, increased gradually according to response; CHILD under 14 years not recommended

Sulpiride (Non-proprietary) PoM

Tablets, sulpiride 200 mg, net price 100-tab pack = £14.12; 400 mg, 100-tab pack = £36.29. Label: 2

Available from Alpharma, APS, CP, Generics, IVAX

Dolmatil® (Sanofi-Synthelabo) PoM

Tablets, both scored, sulpiride 200 mg, net price 100-tab pack = £13.85; 400 mg (f/c), 100-tab pack = £36.29. Label: 2

Sulpitil® (Pharmacia) PoM

Tablets, scored, sulpiride 200 mg. Net price 28-tab pack = £4.29; 112-tab pack = £12.85. Label: 2

Sulpor® (Rosemont) PoM

Oral solution, sugar-free, lemon- and aniseed-flavoured, sulpiride 200 mg/5 mL, net price 150 mL = £27.00. Label: 2

THIORIDAZINE

Indications: under specialist supervision, second-line treatment of schizophrenia in adults (see Contra-indications, below)

Cautions: see notes above; ECG screening and electrolyte measurement before treatment, after each dose increase and at 6-month intervals; also monitor for visual defects on prolonged use; avoid in porphyria (section 9.8.2)

Contra-indications: see notes above

CARDIOTOXICITY. Thioridazine is associated with QT-interval prolongation and increased risk of ventricular arrhythmias. The CSM has advised that thioridazine should be restricted to second-line treatment of schizophrenia in adults under specialist supervision. Thioridazine is **contra-indicated** in patients with:

- significant cardiac disease, such as angina, bradycardia, second- or third-degree heart block, cardiac failure;
- history of ventricular arrhythmia;
- QT-interval prolongation or a family history of the condition;
- uncorrected hypokalaemia or hypomagnesaemia;
- concomitant use with other drugs known to cause QT-interval prolongation;
- reduced cytochrome P450 2D6 activity;
- concomitant use with drugs that inhibit or are metabolised by cytochrome P450 2D6.

Side-effects: see notes above; less sedating than chlorpromazine, and extrapyramidal symptoms and hypothermia rarely occur; more likely to induce hypotension and increased risk of cardiotoxicity and prolongation of QT interval (see above); pigmentary retinopathy (with reduced visual acuity, brownish colouring of vision, and impaired night vision) occurs rarely with high doses; sexual dysfunction, particularly retrograde ejaculation, may occur

Dose: 50–300 mg daily (initially in divided doses); max. 600 mg daily (in hospital patients only); CHILD not recommended

Thioridazine (Non-proprietary) PoM

Tablets, coated, thioridazine hydrochloride 25 mg, net price 20 = 35p; 50 mg, 20 = £1.02; 100 mg, 20 = £1.57. Label: 2

Available from Alpharma, DDSA (*Rideril®*), Hillcross, IVAX

Oral solution, thioridazine (as hydrochloride) 25 mg/5 mL. Net price 500-mL = £2.67. Label: 2

Available from Hillcross, Rosemont

Melleril® (Novartis) PoM

Tablets, all f/c, thioridazine hydrochloride 10 mg, net price 84-tab pack = £1.01; 25 mg, 84-tab pack = £1.66; 50 mg, 84-tab pack = £3.23; 100 mg, 84-tab pack = £6.24. Label: 2

Suspension 25 mg/5 mL, thioridazine 25 mg/5 mL, net price 300 mL = £1.96. Label: 2

Suspension 100 mg/5 mL, thioridazine 100 mg/5 mL, net price 300 mL = £7.14. Label: 2

Note. These suspensions should not be diluted but the two preparations may be mixed with each other to provide intermediate strengths

Syrup, brown, thioridazine (as hydrochloride) 25 mg/5 mL, net price 300 mL = £1.98. Label: 2

TRIFLUOPERAZINE

Indications: see under Dose; anti-emetic (section 4.6)

Cautions: see notes above

Contra-indications: see notes above

Side-effects: see notes above; extrapyramidal symptoms more frequent, especially at doses exceeding 6 mg daily; pancytopenia; thrombocytopenia; hyperpyrexia; anorexia

Dose: *by mouth* (reduce initial doses in elderly by at least half)

Schizophrenia and other psychoses, short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, initially 5 mg twice daily, *or* 10 mg daily in modified-release form, increased by 5 mg after 1 week, then at intervals of 3 days, according to the response; CHILD up to 12 years, initially up to 5 mg daily in divided doses, adjusted according to response, age, and bodyweight

Short-term adjunctive management of severe anxiety, 2–4 mg daily in divided doses *or* 2–4 mg daily in modified-release form, increased if necessary to 6 mg daily; CHILD 3–5 years up to 1 mg daily, 6–12 years up to 4 mg daily

Trifluoperazine (Non-proprietary) PoM

Tablets, coated, trifluoperazine (as hydrochloride) 1 mg, net price 20 = 57p; 5 mg, 20 = 87p. Label: 2

Available from most generic manufacturers

Oral solution, trifluoperazine (as hydrochloride) 5 mg/5 mL. Net price 200-mL = £11.07. Label: 2

Available from Rosemont (sugar-free)

Stelazine® (Goldshield) PoM

Tablets, both blue, f/c, trifluoperazine (as hydrochloride) 1 mg, net price 20 = 61p; 5 mg, 20 = 87p. Label: 2

Spansules® (= capsules m/r), all clear/yellow, enclosing dark blue, light blue, and white pellets, trifluoperazine (as hydrochloride) 2 mg, net price 60-cap pack = £4.36; 10 mg, 30-cap pack = £2.83; 15 mg, 30-cap pack = £4.27. Label: 2, 25

Syrup, yellow, sugar-free, trifluoperazine (as hydrochloride) 1 mg/5 mL. Net price 200-mL pack = £2.95. Label: 2

ZUCLOPENTHIXOL ACETATE

Indications: short-term management of acute psychosis, mania, or exacerbations of chronic psychosis

Cautions: see notes above; avoid in porphyria (section 9.8.2)

Contra-indications: see notes above

Side-effects: see notes above

Dose: *by deep intramuscular injection* into the gluteal muscle or lateral thigh, 50–150 mg (elderly 50–100 mg), if necessary repeated after 2–3 days (1 additional dose may be needed 1–2 days after the first injection); max. cumulative dose 400 mg per course and max. 4 injections; max. duration of treatment 2 weeks—if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, *or* to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate; CHILD not recommended

Clopixol Acuphase® (Lundbeck) PoM

Injection (oily), zuclopenthixol acetate 50 mg/mL. Net price 1-mL amp = £5.20; 2-mL amp = £10.03

ZUCLOPENTHIXOL DIHYDROCHLORIDE

Indications: schizophrenia and other psychoses, particularly when associated with agitated, aggressive, or hostile behaviour

Cautions: see notes above; avoid in porphyria (section 9.8.2)

Contra-indications: see notes above; apathetic or withdrawn states

Side-effects: see notes above; urinary frequency or incontinence; weight loss (less common than weight gain)

Dose: initially 20–30 mg daily in divided doses, increasing to a max. of 150 mg daily if necessary; usual maintenance dose 20–50 mg daily; ELDERLY (or debilitated) initially quarter to half adult dose; CHILD not recommended

Clopixol® (Lundbeck) PoM

Tablets, all f/c, pink, zuclopenthixol (as dihydrochloride) 2 mg, net price 20 = 62p; 10 mg, 20 = £1.73; 25 mg, 20 = £3.47. Label: 2

Depot injection (zuclopenthixol decanoate): section 4.2.2

Atypical antipsychotics

The 'atypical antipsychotics' **amisulpride, clozapine, olanzapine, quetiapine, risperidone,** and **zotepine** may be better tolerated than other antipsychotics; extrapyramidal symptoms and prolactin elevation may be less frequent than with older antipsychotics.

The atypical antipsychotics may be used as first-line treatment for schizophrenia, but clozapine is licensed for the treatment of schizophrenia only in patients unresponsive to, or intolerant of, conventional antipsychotic drugs. It can cause agranulocytosis and its use is restricted to patients registered with the Clozaril Patient Monitoring Service (see under Clozapine, below).

Sertindole has been suspended following reports of arrhythmias and sudden cardiac death; it remains available on a named-patient basis (from Lundbeck—*Serdolect®*) for patients already stabilised on the drug in whom other antipsychotics are inappropriate.

CAUTIONS AND CONTRA-INDICATIONS. While most atypical antipsychotics have not generally been associated with prolongation of the QT interval, caution should be exercised if they are prescribed with other drugs known to increase the QT interval. Atypical antipsychotics should be used with caution in patients with cardiovascular disease, or a history of epilepsy; they should be used with caution in the elderly; **interactions:** Appendix 1 (antipsychotics).

and lens opacities, and purplish pigmentation of the skin, cornea, conjunctiva, and retina

Overdosage: for poisoning with phenothiazines and related compounds, see Emergency Treatment of Poisoning, p. 26.

CLASSIFICATION OF ANTIPSYCHOTICS. The **phenothiazine** derivatives can be divided into 3 main groups.

Group 1: chlorpromazine, levomepromazine (methotrimeprazine), and promazine, generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.

Group 2: pericyazine, pipotiazine, and thioridazine, generally characterised by moderate sedative effects, marked antimuscarinic effects, but fewer extrapyramidal side-effects than groups 1 or 3.

Group 3: fluphenazine, perphenazine, prochlorperazine, and trifluoperazine, generally characterised by fewer sedative effects, fewer antimuscarinic effects, but more pronounced extrapyramidal side-effects than groups 1 and 2.

Drugs of other chemical groups tend to resemble the phenothiazines of *group 3*. They include the **butyrophenones** (benperidol and haloperidol); **diphenylbutylpiperidines** (pimozide); **thioxanthenes** (flupentixol and zuclopenthixol); **substituted benzamides** (sulpiride); **oxypertine**; and **loxapine**.

For details of the newer antipsychotic drugs amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine, see under Atypical antipsychotics , p. 181.

CHOICE. As indicated above, the various drugs differ somewhat in predominant actions and side-effects. Selection is influenced by the degree of sedation required and the patient's susceptibility to extrapyramidal side-effects. However, the differences between antipsychotic drugs are less important than the great variability in patient response; moreover, tolerance to secondary effects such as sedation usually develops. The atypical antipsychotics may be appropriate if extrapyramidal side-effects are a particular concern (see under Atypical Antipsychotics, below). Clozapine is used for schizophrenia when other antipsychotics are ineffective or not tolerated.

Prescribing of more than one antipsychotic at the same time is **not** recommended; it may constitute a hazard and there is no significant evidence that side-effects are minimised.

Chlorpromazine is still widely used despite the wide range of adverse effects associated with it. It has a marked sedating effect and is useful for treating violent patients without causing stupor. Agitated states in the elderly can be controlled without confusion, a dose of 10 to 25 mg once or twice daily usually being adequate.

Flupentixol (flupenthixol) and **pimozide** (see CSM advice p. 179) are less sedating than chlorpromazine.

Sulpiride in high doses controls florid positive symptoms, but in lower doses it has an alerting effect on apathetic withdrawn schizophrenics.

Fluphenazine, haloperidol, and **trifluoperazine** are also of value but their use is limited by the high incidence of extrapyramidal symptoms. Haloperidol may be preferred for the rapid control of hyperactive psychotic states. It is less hypotensive than chlorpromazine and is therefore also popular for agitation in the elderly, despite the high incidence of extrapyramidal side-effects.

Thioridazine is associated with rare reports of ventricular arrhythmia and it is now restricted for use as second-line treatment for schizophrenia in adults; it should be prescribed under specialist supervision only.

Promazine is not sufficiently active by mouth to be used as an antipsychotic drug; it has been used to treat agitation and restlessness in the elderly (see Other uses, below).

Loxapine causes relatively little sedation; in overdosage it has a high potential for serious neurological and cardiac toxicity.

OTHER USES. Nausea and vomiting (section 4.6), choreas, motor tics (section 4.9.3), and intractable hiccup (see under Chlorpromazine Hydrochloride and under Haloperidol). **Benperidol** is used in deviant antisocial sexual behaviour but its value is not established.

Psychomotor agitation and, in the elderly, agitation and restlessness, should be investigated for an underlying cause; they can be managed with low doses of chlorpromazine or haloperidol used for short periods. The use of promazine for agitation and restlessness in the elderly has declined. Olanzapine and risperidone may be effective for agitation and restlessness in the elderly [unlicensed].

Equivalent doses of oral antipsychotics

These equivalences are intended **only** as an approximate guide; individual dosage instructions should **also** be checked; patients should be carefully monitored after **any** change in medication

Antipsychotic	Daily dose
Chlorpromazine	100 mg
Clozapine	50 mg
Haloperidol	2–3 mg
Loxapine	10–20 mg
Pimozide	2 mg
Risperidone	0.5–1 mg
Sulpiride	200 mg
Thioridazine	100 mg
Trifluoperazine	5 mg

Important. These equivalences must **not** be extrapolated beyond the max. dose for the drug. Higher doses require careful titration in specialist units and the equivalences shown here may not be appropriate.

DOSAGE. After an initial period of stabilisation, in most patients, the long half-life of antipsychotic drugs allows the total daily oral dose to be given as a single dose. For the advice of The Royal College of Psychiatrists on doses above the BNF upper limit, see p. 174.

BENPERIDOL

Indications: control of deviant antisocial sexual behaviour (but see notes above)

Cautions: see notes above; also manufacturer advises regular blood counts and liver function tests during long-term treatment

Contra-indications: see notes above

Side-effects: see notes above

Dose: 0.25–1.5 mg daily in divided doses, adjusted according to the response; ELDERLY (or debilitated) initially half adult dose; CHILD not recommended

Anquil® (Concord) PoM

Tablets, benperidol 250 micrograms. Net price 100-tab pack = £26.13. Label: 2

CHLORPROMAZINE HYDROCHLORIDE

WARNING. Owing to the risk of contact sensitisation, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care

Indications: see under Dose; antiemetic in palliative care (section 4.6)

Cautions: see notes above; also patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection

Contra-indications: see notes above

Side-effects: see notes above; also intramuscular injection may be painful, cause hypotension and tachycardia, and give rise to nodule formation

Dose: *by mouth*,

Schizophrenia and other psychoses, mania, short-term adjunctive management of severe anxiety, psychomotor agitation, excitement, and violent or dangerously impulsive behaviour initially 25 mg 3 times daily (*or* 75 mg at night), adjusted according to response, to usual maintenance dose of 75–300 mg daily (but up to 1 g daily may be required in psychoses); ELDERLY (or debilitated) third to half adult dose; CHILD (childhood schizophrenia and autism) 1–5 years 500 micrograms/kg every 4–6 hours (max. 40 mg daily); 6–12 years third to half adult dose (max. 75 mg daily)

Intractable hiccup, 25–50 mg 3–4 times daily

By deep intramuscular injection, (for relief of acute symptoms but see also Cautions and Side-effects), 25–50 mg every 6–8 hours; CHILD, 1–5 years 500 micrograms/kg every 6–8 hours (max. 40 mg daily); 6–12 years 500 micrograms/kg every 6–8 hours (max. 75 mg daily)

Induction of hypothermia (to prevent shivering), *by deep intramuscular injection*, 25–50 mg every 6–8 hours; CHILD 1–12 years, initially 0.5–1 mg/kg, followed by maintenance 500 micrograms/kg every 4–6 hours

By rectum in suppositories as chlorpromazine base 100 mg every 6–8 hours [unlicensed]

Note. For equivalent therapeutic effect 100 mg chlorpromazine base given *rectally* as a suppository ≡ 20–25 mg chlorpromazine hydrochloride *by intramuscular injection* ≡ 40–50 mg of chlorpromazine base or hydrochloride *by mouth*

Chlorpromazine (Non-proprietary) PoM

Tablets, coated, chlorpromazine hydrochloride 10 mg, net price 56-tab pack = 71p; 25 mg, 28-tab pack = 96p; 50 mg, 28-tab pack = 95p; 100 mg, 28-tab pack = £1.15. Label: 2, 11

Available from Antigen, APS, DDSA (*Chloractil®*), Hillcross, IVAX

Oral solution, chlorpromazine hydrochloride 25 mg/5 mL, net price 150 mL = £1.35, 100 mg/5 mL, 150 mL = £3.76. Label: 2, 11

Available from Hillcross, Rosemont

Injection, chlorpromazine hydrochloride 25 mg/mL, net price 1-mL amp = 60p; 2-mL amp = 60p

Available from Antigen

Suppositories, chlorpromazine 100 mg. Label: 2, 11

'Special order' [unlicensed] product; contact Martindale or regional hospital manufacturing unit

Largactil® (Hawgreen) PoM

Tablets, all off-white, f/c, chlorpromazine hydrochloride 10 mg. Net price 56-tab pack = 71p; 25 mg, 56-tab pack = 98p; 50 mg, 56-tab pack = £2.05; 100 mg, 56-tab pack = £3.81. Label: 2, 11

Syrup, brown, chlorpromazine hydrochloride 25 mg/5 mL. Net price 100-mL pack = £1.11. Label: 2, 11

Suspension forte, orange, sugar-free, chlorpromazine hydrochloride 100 mg (as embonate)/5 mL. Net price 100-mL pack = £2.56. Label: 2, 11

Injection, chlorpromazine hydrochloride 25 mg/mL. Net price 2-mL amp = 67p

FLUPENTIXOL

(Flupenthixol)

Indications: schizophrenia and other psychoses, particularly with apathy and withdrawal but not mania or psychomotor hyperactivity; depression (section 4.3.4)

Cautions: see notes above; avoid in porphyria (section 9.8.2)

Contra-indications: see notes above; also excitable and overactive patients

Side-effects: see notes above; less sedating but extrapyramidal symptoms frequent

Dose: psychosis, initially 3–9 mg twice daily adjusted according to the response; max. 18 mg daily; ELDERLY (or debilitated) initially quarter to half adult dose; CHILD not recommended

Depixol® (Lundbeck) PoM

Tablets, yellow, s/c, flupentixol 3 mg (as dihydrochloride). Net price 20 = £2.99. Label: 2

Depot injection (flupentixol decanoate): section 4.2.2

FLUPHENAZINE HYDROCHLORIDE

Indications: see under Dose

Cautions: see notes above

Contra-indications: see notes above

Side-effects: see notes above; less sedating and fewer antimuscarinic or hypotensive symptoms, but extrapyramidal symptoms, particularly dystonic reactions and akathisia, more frequent; systemic lupus erythematosus

Dose: schizophrenia and other psychoses, mania, initially 2.5–10 mg daily in 2–3 divided doses, adjusted according to response to 20 mg daily; doses above 20 mg daily (10 mg in elderly) only with special caution; CHILD not recommended

Short-term adjunctive management of severe anxiety, psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, initially 1 mg twice daily, increased as necessary to 2 mg twice daily; CHILD not recommended

Moditen® (Sanofi-Synthelabo) PoM

Tablets, all s/c, fluphenazine hydrochloride 1 mg (pink), net price 20 = £1.06; 2.5 mg (yellow), 20 = £1.33; 5 mg, 20 = £1.77. Label: 2

Modecate® PoM

Section 4.2.2

ease, hepatic impairment; **interactions:** Appendix 1 (barbiturates and primidone)

DRIVING. Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications: insomnia caused by pain; porphyria (section 9.8.2), pregnancy, breast-feeding; children, young adults, elderly and debilitated patients, also patients with history of drug or alcohol abuse

Side-effects: include hangover with drowsiness, dizziness, ataxia, respiratory depression, hypersensitivity reactions, headache, particularly in elderly; paradoxical excitement and confusion occasionally precede sleep; **overdosage:** see Emergency Treatment of Poisoning, p. 25

Dose: see under preparations below

Amytal® (Flynn) CD

Tablets, amobarbital (amylobarbitone) 50 mg, net price 20 = £1.84. Label: 19

Dose: 100–200 mg at bedtime (**important:** but see also contra-indications)

Sodium Amytal® (Flynn) CD

Capsules, both blue, amobarbital (amylobarbitone) sodium 60 mg, net price 20 = £3.43; 200 mg, 20 = £6.75. Label: 19

Dose: 60–200 mg at bedtime (**important:** but see also contra-indications)

Soneryl® (Concord) CD

Tablets, pink, scored, butobarbital (butobarbitone) 100 mg. Net price 56-tab pack = £10.65. Label: 19

Dose: 100–200 mg at bedtime (**important:** but see also contra-indications)

■ Preparations containing secobarbital (quinalbarbitone)

Note. Secobarbital (quinalbarbitone) is in schedule 2 of the Misuse of Drugs Regulations 1985; receipt and supply must therefore be recorded in the CD register.

Seconal Sodium® (Flynn) CD

Capsules, both orange, secobarbital (quinalbarbitone) sodium 50 mg, net price 20 = £5.30; 100 mg, 20 = £6.96. Label: 19

Dose: 100 mg at bedtime (**important:** but see also contra-indications)

Tuinal® (Flynn) CD

Capsules, orange/blue, a mixture of amobarbital (amylobarbitone) sodium 50 mg, secobarbital (quinalbarbitone) sodium 50 mg. Net price 20 = £3.88. Label: 19

Dose: 1–2 capsules at bedtime (**important:** but see also contra-indications)

Note. Prescriptions need only specify 'Tuinal capsules'

denotes preparations that are considered to be less suitable for prescribing (see p. vi)

4.2 Drugs used in psychoses and related disorders

Advice of Royal College of Psychiatrists on doses above BNF upper limit

Unless otherwise stated, doses in the BNF are licensed doses—any higher dose is therefore **unlicensed** (for an explanation of the significance of this, see p. 1).

1. Consider alternative approaches including adjuvant therapy and newer or atypical neuroleptics such as clozapine.
2. Bear in mind risk factors, including obesity—particular caution is indicated in older patients especially those over 70.
3. Consider potential for drug interactions—see **interactions:** Appendix 1 (antipsychotics).
4. Carry out ECG to exclude untoward abnormalities such as prolonged QT interval; repeat ECG periodically and reduce dose if prolonged QT interval or other adverse abnormality develops.
5. Increase dose slowly and not more often than once weekly.
6. Carry out regular pulse, blood pressure, and temperature checks; ensure that patient maintains adequate fluid intake.
7. Consider high-dose therapy to be for limited period and review regularly; abandon if no improvement after 3 months (return to standard dosage).

Important: When prescribing an antipsychotic for administration on an emergency basis, the intramuscular dose should be **lower** than the corresponding oral dose (owing to absence of first-pass effect), particularly if the patient is very active (increased blood flow to muscle considerably increases the rate of absorption). The prescription should specify the dose for **each route** and should **not** imply that the same dose can be given by mouth or by intramuscular injection. The dose of antipsychotic for emergency use should be reviewed at least **daily**.

4.2.1 Antipsychotic drugs

Antipsychotic drugs are also known as 'neuroleptics' and (misleadingly) as 'major tranquillisers'. Antipsychotic drugs generally tranquillise without impairing consciousness and without causing paradoxical excitement but they should not be regarded merely as tranquillisers. For conditions such as schizophrenia the tranquillising effect is of secondary importance.

In the short term they are used to quieten disturbed patients whatever the underlying psychopathology, which may be schizophrenia, brain damage, mania, toxic delirium, or agitated depression. Antipsychotic drugs are used to alleviate severe anxiety but this too should be a short-term measure.

SCHIZOPHRENIA. Antipsychotic drugs relieve florid psychotic symptoms such as thought disorder, hallucinations, and delusions, and prevent relapse. Although they are usually less effective in apathetic withdrawn patients, they sometimes appear to have an activating influence. For example, haloperidol may restore an acutely ill schizophrenic, who was previously withdrawn or even mute and akinetic, to normal activity and social behaviour. Patients with acute schizophrenia generally respond better than those with chronic symptoms.

Long-term treatment of a patient with a definite diagnosis of schizophrenia may be necessary even after the first episode of illness in order to prevent the manifest illness from becoming chronic. Withdrawal of drug treatment requires careful surveillance because the patient who appears well on medication may suffer a disastrous relapse if treatment is withdrawn inappropriately. In addition the need for continuation of treatment may not become immediately evident because relapse is often delayed for several weeks after cessation of treatment.

Antipsychotic drugs are considered to act by interfering with dopaminergic transmission in the brain by blocking dopamine D_2 receptors, which may give rise to the extrapyramidal effects described below, and also to hyperprolactinaemia. Antipsychotic drugs may also affect cholinergic, alpha-adrenergic, histaminergic, and serotonergic receptors.

CAUTIONS AND CONTRA-INDICATIONS. Antipsychotics should be used with **caution** in patients with hepatic impairment (Appendix 2), renal impairment (Appendix 3), cardiovascular disease, Parkinson's disease (may be exacerbated by antipsychotics), epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis, prostatic hypertrophy, or a personal or family history of angle-closure glaucoma (avoid chlorpromazine, pericyazine and prochlorperazine in these conditions). Caution is also required in severe respiratory disease and in patients with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops). Antipsychotics should be used with caution in the elderly, who are particularly susceptible to postural hypotension and to hyper- or hypothermia in very hot or cold weather. Serious consideration should be given before prescribing these drugs for elderly patients. As photosensitisation may occur with higher dosages, patients should avoid direct sunlight.

Antipsychotic drugs may be **contra-indicated** in comatose states, CNS depression, and phaeochromocytoma. Most antipsychotics are best avoided during pregnancy, unless essential (Appendix 4) and it is advisable to discontinue breast-feeding during treatment (Appendix 5); **interactions:** Appendix 1 (antipsychotics)

DRIVING. Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced

WITHDRAWAL. Withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse.

SIDE-EFFECTS. Extrapyramidal symptoms are the most troublesome. They occur most frequently with the piperazine phenothiazines (fluphenazine, perphenazine, prochlorperazine, and trifluoperazine), the butyrophenones (benperidol, and haloperidol), and the depot preparations. They are easy to recognise but cannot be predicted accurately because they depend on the dose, the type of drug, and on individual susceptibility.

Extrapyramidal symptoms consist of:

- *parkinsonian symptoms* (including tremor), which may occur more commonly in adults or the elderly and may appear gradually;
- *dystonia* (abnormal face and body movements) and *dyskinesia*, which occur more commonly in children or young adults and appear after only a few doses;
- *akathisia* (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated; and
- *tardive dyskinesia* (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, but it may develop on short-term treatment with low doses—short-lived tardive dyskinesia may occur after withdrawal of the drug.

Parkinsonian symptoms remit if the drug is withdrawn and may be suppressed by the administration of **antimuscarinic** drugs (section 4.9.2). However, routine administration of such drugs is not justified because not all patients are affected and because they may unmask or worsen tardive dyskinesia.

Tardive dyskinesia is of particular concern because it may be irreversible on withdrawing therapy and treatment is usually ineffective. However, some manufacturers suggest that drug withdrawal at the earliest signs of tardive dyskinesia (fine vermicular movements of the tongue) may halt its full development. Tardive dyskinesia occurs fairly frequently, especially in the elderly, and treatment must be carefully and regularly reviewed.

Hypotension and interference with temperature regulation are dose-related side-effects and are liable to cause dangerous falls and hypothermia or hyperthermia in the elderly.

Neuroleptic malignant syndrome (hyperthermia, fluctuating level of consciousness, muscular rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating, and urinary incontinence) is a rare but potentially fatal side-effect of some drugs. Discontinuation of the antipsychotic is essential because there is no proven effective treatment, but cooling, bromocriptine, and dantrolene have been used. The syndrome, which usually lasts for 5–7 days after drug discontinuation, may be unduly prolonged if depot preparations have been used.

Other side-effects include: drowsiness; apathy; agitation, excitement and insomnia; convulsions; dizziness; headache; confusion; gastro-intestinal disturbances; nasal congestion; antimuscarinic symptoms (such as dry mouth, constipation, difficulty with micturition, and blurred vision); cardiovascular symptoms (such as hypotension, tachycardia, and arrhythmias); ECG changes (cases of sudden death have occurred); endocrine effects such as menstrual disturbances, galactorrhoea, gynaecomastia, impotence, and weight gain; blood dyscrasias (such as agranulocytosis and leucopenia), photosensitisation, contact sensitisation and rashes, and jaundice (including cholestatic); corneal

Chloral Elixir, Paediatric, BP PoM
(Chloral Oral Solution, Paediatric)
Elixir, chloral hydrate 4% in a suitable vehicle with a blackcurrant flavour. Extemporaneous preparations should be recently prepared according to the following formula: chloral hydrate 200 mg, water 0.1 mL, blackcurrant syrup 1 mL, syrup to 5 mL. Net price 100 mL = 95p. Label: 1, 27
Dose: up to 1 year 5 mL, taken well diluted with water at bedtime

Welldorm® (S&N Hlth.) PoM
Tablets, blue-purple, f/c, cloral betaine 707 mg (≡ chloral hydrate 414 mg). Net price 30-tab pack = £2.43. Label: 19, 27
Dose: 1–2 tablets with water or milk at bedtime, max. 5 tablets (2 g chloral hydrate) daily
Elixir, red, chloral hydrate 143.3 mg/5 mL. Net price 150-mL pack = £2.05. Label: 19, 27
Dose: 15–45 mL (0.4–1.3 g chloral hydrate) with water or milk, at bedtime, max. 70 mL (2 g chloral hydrate) daily; CHILD 1–1.75 mL/kg (30–50 mg/kg chloral hydrate), max. 35 mL (1 g chloral hydrate) daily

TRICLOFOS SODIUM

Indications: insomnia (short-term use)
Cautions: see Chloral Hydrate
Contra-indications: see Chloral Hydrate
Side-effects: see Chloral Hydrate but less gastric irritation
Dose: see under preparation below

Triclofos Oral Solution, BP PoM
(Triclofos Elixir)
Oral solution, triclofos sodium 500 mg/5 mL. Net price 300 mL = £28.23. Label: 19
Available from Celltech
Dose: 10–20 mL (1–2 g triclofos sodium) at bedtime; CHILD up to 1 year 25–30 mg/kg, 1–5 years 2.5–5 mL (250–500 mg triclofos sodium), 6–12 years 5–10 mL (0.5–1 g triclofos sodium)

denotes preparations that are considered to be less suitable for prescribing (see p. vi)

Clomethiazole

Clomethiazole (chlormethiazole) may be a useful hypnotic for elderly patients because of its freedom from hangover but, as with all hypnotics, routine administration is undesirable and dependence occurs. It is indicated for use as a hypnotic only in the elderly (and for *very short-term use* in younger adults to attenuate alcohol withdrawal symptoms, see section 4.10).

CLOMETHIAZOLE

(Chlormethiazole)
Indications: see under Dose; alcohol withdrawal (section 4.10)
Cautions: cardiac and respiratory disease (confusional state may indicate hypoxia); history of drug abuse; marked personality disorder; elderly; excessive sedation may occur (particularly with higher doses); hepatic impairment (especially if severe since sedation can mask hepatic coma); renal impairment; avoid prolonged use (and abrupt withdrawal thereafter); **interactions:** Appendix 1 (anxiolytics and hypnotics)
DRIVING. Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced
Contra-indications: acute pulmonary insufficiency; alcohol-dependent patients who continue to drink
Side-effects: nasal congestion and irritation (increased nasopharyngeal and bronchial secretions), conjunctival irritation, headache; rarely, paradoxical excitement, confusion, dependence, gastro-intestinal disturbances, rash, urticaria, bullous eruption, anaphylaxis, alterations in liver enzymes
Dose: severe insomnia in the elderly (short-term use), 1–2 capsules (*or* 5–10 mL syrup) at bedtime; CHILD not recommended
Restlessness and agitation in the elderly, 1 capsule (*or* 5 mL syrup) 3 times daily
Alcohol withdrawal, initially 2–4 capsules, if necessary repeated after some hours;
day 1 (first 24 hours), 9–12 capsules in 3–4 divided doses;
day 2, 6–8 capsules in 3–4 divided doses;
day 3, 4–6 capsules in 3–4 divided doses; then gradually reduced over days 4–6; total treatment for not more than 9 days
Note. For an equivalent therapeutic effect 1 capsule ≡ 5 mL syrup

Heminevrin® (AstraZeneca) PoM
Capsules, grey-brown, clomethiazole base 192 mg in an oily basis. Net price 60-cap pack = £4.34. Label: 19
Syrup, sugar-free, clomethiazole edisilate 250 mg/5 mL. Net price 300-mL pack = £3.63. Label: 19

Antihistamines

Some **antihistamines** such as diphenhydramine (section 3.4.1) and promethazine are on sale to the public for occasional insomnia; their prolonged duration of action may often lead to drowsiness the following day. The sedative effect of antihistamines may diminish after a few days of continued treatment; antihistamines are associated with headache, psychomotor impairment and antimuscarinic effects.

Promethazine is also popular for use in children, but the use of hypnotics in children is not usually justified.

PROMETHAZINE HYDROCHLORIDE

Indications: night sedation and insomnia (short-term use); other indications (section 3.4.1, section 4.6)
Cautions: section 3.4.1
Contra-indications: section 3.4.1
Side-effects: section 3.4.1
Dose: *by mouth*, 25 mg at bedtime increased to 50 mg if necessary; CHILD under 2 years not recommended, 2–5 years 15–20 mg, 5–10 years 20–25 mg, at bedtime

Preparations
Section 3.4.1

Alcohol

Alcohol is a poor hypnotic because its diuretic action interferes with sleep during the latter part of the night. With chronic use, alcohol disturbs sleep patterns and causes insomnia; **interactions:** Appendix 1 (alcohol).

4.1.2 Anxiolytics

Benzodiazepine anxiolytics can be effective in alleviating anxiety states. Although these drugs are often prescribed to almost anyone with stress-related symptoms, unhappiness, or minor physical disease, their use in many situations is unjustified. In particular, they are not appropriate for treating depression or chronic psychosis. In bereavement, psychological adjustment may be inhibited by benzodiazepines. In children anxiolytic treatment should be used only to relieve acute anxiety (and related insomnia) caused by fear (e.g. before surgery).

Anxiolytic treatment should be limited to the lowest possible dose for the shortest possible time (see CSM advice, section 4.1). Dependence is particularly likely in patients with a history of alcohol or drug abuse and in patients with marked personality disorders.

Anxiolytics, particularly the benzodiazepines, have been termed 'minor tranquillisers'. This term is misleading because not only do they differ markedly from the antipsychotic drugs ('major tranquillisers') but their use is by no means minor. Antipsychotics, in low doses, are also sometimes used in severe anxiety for their sedative action but long-term use should be avoided in view of a possible risk of tardive dyskinesia (section 4.2.1).

Some antidepressants (section 4.3) are licensed for use in anxiety and related disorders; see section 4.3 for a comment on their role in generalised anxiety disorder and panic disorders. The use of antihistamines (e.g. hydroxyzine, section 3.4.1) for their sedative effect in anxiety is not considered to be appropriate.

Benzodiazepines

Benzodiazepines are indicated for the *short-term relief of severe anxiety* but long-term use should be avoided (see p. 166). Diazepam, alprazolam, chlordiazepoxide, clobazam, and clorazepate have a sustained action. Shorter-acting compounds such as **lorazepam** and **oxazepam** may be preferred in patients with hepatic impairment but they carry a greater risk of withdrawal symptoms.

In *panic disorders* (with or without agoraphobia) resistant to antidepressant therapy (section 4.3), a benzodiazepine (lorazepam 3–5 mg daily or clonazepam 1–2 mg daily (section 4.8.1) [both unlicensed]) may be used; alternatively a benzodiazepine may be used as short-term adjunctive therapy at the start of antidepressant treatment to prevent the initial worsening of symptoms.

Diazepam or lorazepam are very occasionally administered intravenously for the *control of panic attacks*. This route is the most rapid but the procedure is not without risk (section 4.8.2) and should be used only when alternative measures have failed. The intramuscular route has no advantage over the oral route.

For guidelines on benzodiazepine withdrawal, see p. 166.

DIAZEPAM

Indications: short-term use in anxiety or insomnia, adjunct in acute alcohol withdrawal; status epilepticus (section 4.8.2); febrile convulsions (section 4.8.3); muscle spasm (section 10.2.2); perioperative use (section 15.1.4.1)
Cautions: respiratory disease, muscle weakness (special care in myasthenia gravis), history of drug or alcohol abuse, marked personality disorder, pregnancy and breast-feeding (Appendixes 4 and 5); reduce dose in elderly and debilitated, and in hepatic impairment (avoid if severe, Appendix 2), renal impairment (Appendix 3); avoid prolonged use (and abrupt withdrawal thereafter); special precautions for intravenous injection (section 4.8.2); porphyria (section 9.8.2); **interactions:** Appendix 1 (anxiolytics and hypnotics)
DRIVING. Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced
Contra-indications: respiratory depression; acute pulmonary insufficiency; sleep apnoea syndrome; severe hepatic impairment; not for chronic psychosis; should not be used alone in depression or in anxiety with depression; myasthenia gravis; avoid injections containing benzyl alcohol in neonates (see under preparations below)
Side-effects: drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression (see also section 4.1); muscle weakness; *occasionally:* headache, vertigo, hypotension, salivation changes, gastrointestinal disturbances, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice reported; skin reactions; on intravenous injection, pain, thrombophlebitis, and rarely apnoea; **overdosage:** see Emergency Treatment of Poisoning, p.25
Dose: *by mouth*, anxiety, 2 mg 3 times daily increased if necessary to 15–30 mg daily in divided doses; ELDERLY (or debilitated) half adult dose
Insomnia associated with anxiety, 5–15 mg at bedtime
CHILD night terrors and somnambulism, 1–5 mg at bedtime
By intramuscular injection or slow intravenous injection (into a large vein, at a rate of not more than 5 mg/minute), for severe acute anxiety, control of acute panic attacks, and acute alcohol withdrawal, 10 mg, repeated if necessary after not less than 4 hours
Note. Only use intramuscular route when oral and intravenous routes not possible; special precautions for intravenous injection see section 4.8.2
By intravenous infusion—section 4.8.2
By rectum as rectal solution, acute anxiety and agitation, 500 micrograms/kg repeated after 12 hours as required; ELDERLY 250 micrograms/kg; CHILD not recommended
CHILD febrile convulsions, see p. 239
By rectum as suppositories, anxiety when oral route not appropriate, 10–30 mg (higher dose divided); dose form not appropriate for less than 10 mg

Rapifen® (Janssen-Cilag) CD
Injection, alfentanil (as hydrochloride) 500 micrograms/mL. Net price 2-mL amp = 72p; 10-mL amp = £3.31
Intensive care injection, alfentanil (as hydrochloride) 5 mg/mL. To be diluted before use. Net price 1-mL amp = £2.65

FENTANYL

Indications: analgesia during operation, enhancement of anaesthesia; respiratory depressant in assisted respiration; analgesia in other situations (section 4.7.2)
Cautions: see section 4.7.2 and notes above
Contra-indications: see section 4.7.2 and notes above
Side-effects: see section 4.7.2 and notes above
Dose: *by intravenous injection*, with spontaneous respiration, 50–200 micrograms, then 50 micrograms as required; CHILD 3–5 micrograms/kg, then 1 microgram/kg as required
With assisted ventilation, 0.3–3.5 mg, then 100–200 micrograms as required; CHILD 15 micrograms/kg, then 1–3 micrograms/kg as required

Sublimaze® (Janssen-Cilag) CD
Injection, fentanyl (as citrate) 50 micrograms /mL. Net price 2-mL amp = 24p; 10-mL amp = £1.17
Available as a generic from Antigen

REMIFENTANIL

Indications: supplementation of general anaesthesia during induction and analgesia during maintenance of anaesthesia (consult product literature for use in patients undergoing cardiac surgery)
Cautions: see section 4.7.2 and notes above
Contra-indications: see section 4.7.2 and notes above
Side-effects: see section 4.7.2 and notes above
Dose: induction, *by intravenous infusion*, 0.5–1 microgram/kg/minute, *with or without* an initial bolus *by intravenous injection* (of a solution containing 20–250 micrograms/mL) over not less than 30 seconds, 1 microgram/kg
Note. If patient is to be intubated more than 8 minutes after start of intravenous infusion, intial intravenous injection dose is unnecessary
Maintenance in ventilated patients, *by intravenous infusion*, 0.05–2 micrograms/kg/minute according to anaesthetic technique and adjusted according to response; supplemental doses in light anaesthesia, *by intravenous injection* every 2–5 minutes
Maintenance in spontaneous respiration anaesthesia, *by intravenous infusion*, initially 40 nanograms/kg/minute adjusted according to response, usual range 25–100 nanograms/kg/minute
CHILD 1–12 years, maintenance, *by intravenous infusion*, 0.05–1.3 micrograms/kg/minute (*with or without* an initial bolus *by intravenous injection* over not less than 30 seconds, 1 microgram/kg/minute) according to anaesthetic technique and adjusted according to response

Ultiva® (Elan) PoM
Injection, powder for reconstitution, remifentanil (as hydrochloride), net price 1-mg vial = £5.50; 2-mg vial = £11.00; 5-mg vial = £27.50

15.1.5 Muscle relaxants

Muscle relaxants used in anaesthesia are also known as **neuromuscular blocking drugs**. By specific blockade of the neuromuscular junction they enable light levels of anaesthesia to be employed with adequate relaxation of the muscles of the abdomen and diaphragm. They also relax the vocal cords and allow the passage of a tracheal tube. Their action differs from the muscle relaxants acting on the spinal cord or brain which are used in musculoskeletal disorders (section 10.2.2).

Patients who have received a muscle relaxant should **always** have their respiration assisted or controlled until the drug has been inactivated or antagonised (section 15.1.6).

Non-depolarising muscle relaxants

Non-depolarising muscle relaxants (also known as competitive muscle relaxants) compete with acetylcholine for receptor sites at the neuromuscular junction and their action may be reversed with anticholinesterases such as neostigmine (section 15.1.6). Non-depolarising muscle relaxants may be divided into the **aminosteroid** group which includes pancuronium, rocuronium and vecuronium, and the **benzylisoquinolinium** group which includes atracurium, cisatracurium, gallamine and mivacurium.

Non-depolarising muscle relaxants have a slower onset of action than suxamethonium. These drugs can be classified by their duration of action as short-acting (15–30 minutes), intermediate-acting (30–40 minutes) and long-acting (60–120 minutes), although duration of action is dose-dependent. Drugs with a shorter or intermediate duration of action, such as atracurium and vecuronium, are more widely employed than those with a longer duration of action such as pancuronium.

Non-depolarising muscle relaxants have no sedative or analgesic effects and are not considered to be a triggering factor for malignant hyperthermia.

For patients receiving intensive care and who require tracheal intubation and mechanical ventilation, a non-depolarising muscle relaxant is chosen according to its onset of effect, duration of action and side-effects. Rocuronium, with a rapid onset of effect, may facilitate intubation. Atracurium or cisatracurium may be suitable for long-term muscle relaxation since their duration of action is not dependent on elimination by the liver or the kidneys.

CAUTIONS. Allergic cross-reactivity between neuromuscular blocking agents has been reported; caution is advised in cases of hypersensitivity to these drugs. Their activity is prolonged in patients with myasthenia gravis and in hypothermia, therefore lower doses are required. Resistance may develop in patients with burns who may require increased doses; low plasma cholinesterase activity in these patients requires dose titration for mivacurium. **Interactions:** Appendix 1 (muscle relaxants)

SIDE-EFFECTS. Benzylisoquinolinium non-depolarising muscle relaxants (except cisatracurium) are associated with histamine release which can cause flushing, hypotension, tachycardia, bronchospasm and rarely, anaphylactoid reactions. Aminosteroid muscle relaxants are not associated with histamine release. Drugs possessing vagolytic activity can counteract any bradycardia that occurs during surgery.

Atracurium is a mixture of 10 isomers and is a benzylisoquinolinium muscle relaxant with an intermediate duration of action. It undergoes non-enzymatic metabolism which is independent of liver and kidney function, thus allowing its use in patients with hepatic or renal impairment. Cardiovascular effects are associated with significant histamine release.

Cisatracurium is a single isomer of atracurium. It is more potent and has a slightly longer duration of action than atracurium and provides greater cardiovascular stability because cisatracurium lacks histamine-releasing effects.

Mivacurium, a benzylisoquinolinium muscle relaxant, has a short duration of action. It is metabolised by plasma cholinesterase and muscle paralysis is prolonged in individuals deficient in this enzyme. It is not associated with vagolytic activity or ganglionic blockade although histamine release may occur, particularly with rapid injection.

Pancuronium, an aminosteroid muscle relaxant, has a long duration of action and is often used in patients receiving long-term mechanical ventilation in intensive care units. It lacks a histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia and hypertension.

Rocuronium exerts an effect within 2 minutes and has the most rapid onset of any of the competitive muscle relaxants. It is an aminosteroid muscle relaxant with an intermediate duration of action. It is reported to have minimal histamine-releasing and cardiovascular effects; high doses produce mild vagolytic activity.

Vecuronium, an aminosteroid muscle relaxant, has an intermediate duration of action. It does not generally produce histamine release and lacks cardiovascular effects.

Gallamine has vagolytic and sympathomimetic properties and frequently increases pulse rate and blood pressure. It is rarely used since the other neuromuscular blocking drugs have a more predictable response and it should be avoided in patients with renal impairment.

ATRACURIUM BESILATE

(Atracurium Besylate)

Indications: muscle relaxation for surgery (short to intermediate duration)
Cautions: see notes above
Side-effects: see notes above
Dose: *by intravenous injection*, ADULT and CHILD over 1 month initially 300–600 micrograms/kg, then 100–200 micrograms/kg as required
By intravenous infusion, 5–10 micrograms/kg/minute (300–600 micrograms/kg/hour)

Atracurium (Non-proprietary) PoM
Injection, atracurium besilate 10 mg/mL, net price 2.5-mL amp = £1.85; 5-mL amp = £3.37; 25-mL amp = £14.45
Available from Faulding DBL

Tracrium® (GlaxoWellcome) PoM
Injection, atracurium besilate 10 mg/mL, net price 2.5-mL amp = £1.78; 5-mL amp = £3.23; 25-mL amp = £13.88

CISATRACURIUM

Indications: muscle relaxation for surgery (intermediate duration)
Cautions: see notes above
Side-effects: see notes above
Dose: *by intravenous injection*, intubation, 150 micrograms/kg; maintenance, 30 micrograms/kg approx. every 20 minutes
CHILD over 2 years, initially, 100 micrograms/kg; maintenance, 20 micrograms/kg approx. every 9 minutes
By intravenous infusion, ADULT and CHILD over 2 years, initially, 3 micrograms/kg/minute, *then after stabilisation*, 1–2 micrograms/kg/minute; dose reduced by up to 40% if used with enflurane or isoflurane
CHILD under 2 years not recommended

Nimbex® (GlaxoWellcome) PoM
Injection, cisatracurium (as besilate) 2 mg/mL, net price 2.5-mL amp = £2.20, 10-mL amp = £8.12
Forte injection, cisatracurium (as besilate) 5 mg/mL, net price 30-mL vial = £33.43

GALLAMINE TRIETHIODIDE

Indications: muscle relaxation for surgery (intermediate duration)
Cautions: see notes above
Contra-indications: renal impairment
Side-effects: see notes above
Dose: *by intravenous injection*, 80–120 mg, then 20–40 mg as required; NEONATE, 600 micrograms/kg; CHILD, 1.5 mg/kg

Flaxedil® (Concord) PoM
Injection, gallamine triethiodide 40 mg/mL. Net price 2-mL amp = £4.97

denotes preparations that are considered to be less suitable for prescribing (see p. vi)

MIVACURIUM

Indications: muscle relaxation for surgery (short duration)
Cautions: see notes above; low plasma cholinesterase activity
Side-effects: see notes above
Dose: *by intravenous injection*, 70–250 micrograms/kg; maintenance 100 micrograms/kg every 15 minutes; CHILD 2–6 months initially 150 micrograms/kg, 7 months–12 years initially 200 micrograms/kg; maintenance (CHILD 2 months–12 years) 100 micrograms/kg every 6–9 minutes
Note. Doses up to 150 micrograms/kg may be given over 5–15 seconds, higher doses should be given over 30 seconds. In patients with asthma, cardiovascular disease or

Nitrous oxide

Nitrous oxide is used for maintenance of anaesthesia and, in sub-anaesthetic concentrations, for analgesia. For anaesthesia it is commonly used in a concentration of 50 to 70% in oxygen as part of a balanced technique in association with other inhalational or intravenous agents. Nitrous oxide is unsatisfactory as a sole anaesthetic owing to lack of potency, but is useful as part of a combination of drugs since it allows a significant reduction in dosage.

A mixture of nitrous oxide and oxygen containing 50% of each gas (*Entonox®*, *Equanox®*) is used to produce analgesia without loss of consciousness. Self-administration using a demand valve is popular in obstetric practice, for changing painful dressings, as an aid to postoperative physiotherapy, and in emergency ambulances.

Nitrous oxide may have a deleterious effect if used in patients with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in the presence of a pneumothorax which may enlarge to compromise respiration.

Exposure of patients to nitrous oxide for prolonged periods, either by continuous or by intermittent administration, may result in megaloblastic anaemia owing to interference with the action of vitamin B_{12}. For the same reason, exposure of theatre staff to nitrous oxide should be minimised. Depression of white cell formation may also occur.

NITROUS OXIDE

Indications: see notes above

Cautions: see notes above; **interactions:** Appendix 1 (anaesthetics, general)

Side-effects: see notes above

Dose: using a suitable anaesthetic apparatus, a mixture with 25–30% oxygen for *maintenance* of light anaesthesia

Analgesic, as a mixture with 50% oxygen, according to the patient's needs

15.1.3 Antimuscarinic drugs

Antimuscarinic drugs are used (less commonly nowadays) as premedicants to dry bronchial and salivary secretions which are increased by intubation, by surgery to the upper airways, and by some inhalational anaesthetics. They are also used before or with neostigmine (section 15.1.6) to prevent bradycardia, excessive salivation, and other muscarinic actions of neostigmine. They are also used to prevent bradycardia and hypotension associated with agents such as halothane, propofol, and suxamethonium.

Atropine is now rarely used for premedication but still has an emergency role in the treatment of vagotonic side-effects. For its role in acute arrhythmias after myocardial infarction, see section 2.3.1; see also cardiopulmonary resuscitation algorithm, section 2.7.3.

Hyoscine effectively reduces secretions and also provides a degree of amnesia, sedation and antiemesis. Unlike atropine it may produce bradycardia rather than tachycardia. In some patients, especially the elderly, hyoscine may cause the central anticholinergic syndrome (excitement, ataxia, hallucinations, behavioural abnormalities, and drowsiness).

Glycopyrronium produces good drying of salivary secretions. When given intravenously it produces less tachycardia than atropine. It is widely used with neostigmine for reversal of non-depolarising muscle relaxants (section 15.1.5).

Phenothiazines have too little drying activity to be effective when used alone.

ATROPINE SULPHATE

Indications: drying secretions, reversal of excessive bradycardia; with neostigmine for reversal of non-depolarising neuromuscular block; antispasmodic (section 1.2); bradycardia (section 2.3.1); eye (section 11.5)

Cautions: cardiovascular disease; see also section 1.2; **interactions:** Appendix 1 (antimuscarinics)

DURATION OF ACTION. Since atropine has a shorter duration of action than neostigmine, late unopposed bradycardia may result; close monitoring of the patient is necessary

Side-effects: tachycardia; see also section 1.2

Dose: premedication, *by intravenous injection*, 300–600 micrograms immediately before induction of anaesthesia, and in incremental doses of 100 micrograms for the treatment of bradycardia

By intramuscular injection, 300–600 micrograms 30–60 minutes before induction; CHILD 20 micrograms/kg

For control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block, *by intravenous injection*, 0.6–1.2 mg

Arrhythmias after myocardial infarction, see section 2.3.1; see also cardiopulmonary resuscitation algorithm, inside back cover

Atropine (Non-proprietary) PoM

Injection, atropine sulphate 600 micrograms/mL, net price 1-mL amp = 47p

Note. Other strengths also available

Injection, prefilled disposable syringe, atropine sulphate 100 micrograms/mL, net price 5 mL = £4.16, 10 mL = £4.66, 30 mL = £8.52

Available from Celltech (*Min-I-Jet®*)

Injection, prefilled disposable syringe, atropine sulphate 200 micrograms/mL, net price 5 mL = £4.24; 300 micrograms/mL, 10 mL = £4.32

Available from Aurum

■ With morphine

See under Morphine Salts (section 4.7.2)

GLYCOPYRRONIUM BROMIDE

Indications: see under Atropine Sulphate

Cautions: cardiovascular disease; see also Atropine sulphate (section 1.2); **interactions:** Appendix 1 (antimuscarinics)

Side-effects: see under Atropine Sulphate

Dose: premedication, *by intramuscular or intravenous injection*, 200–400 micrograms, *or* 4–5 micrograms/kg to a max. of 400 micrograms; CHILD *by intramuscular or* preferably *by intravenous injection*, 4–8 micrograms/kg to a max. of 200 micrograms

Intra-operative use, *by intravenous injection*, as for premedication, repeated if necessary

Control of muscarinic side-effects of neostigmine in reversal of non-depolarising neuromuscular block, *by intravenous injection*, 200 micrograms per 1 mg of neostigmine, *or* 10–15 micrograms/kg with neostigmine 50 micrograms/kg; CHILD 10 micrograms/kg with neostigmine 50 micrograms/kg

Robinul® (Anpharm) PoM

Injection, glycopyrronium bromide 200 micrograms/mL, net price 1-mL amp = 60p; 3-mL amp = £1.01

Available as a generic from Antigen

■ With neostigmine metilsulphate

Section 15.1.6

HYOSCINE HYDROBROMIDE

(Scopolamine Hydrobromide)

Indications: drying secretions, amnesia; other indications (section 4.6)

Cautions: see under Atropine Sulphate; avoid in the elderly (see notes above)

Contra-indications: porphyria (section 9.8.2)

Side-effects: see under Atropine Sulphate; bradycardia

Dose: premedication, *by subcutaneous or intramuscular injection*, 200–600 micrograms 30–60 minutes before induction of anaesthesia, usually with papaveretum

Hyoscine (Non-proprietary) PoM

Injection, hyoscine hydrobromide 400 micrograms/mL, net price 1-mL amp = £2.70; 600 micrograms/mL, 1-mL amp = £2.81

■ With papaveretum

See under papaveretum (section 4.7.2)

15.1.4 Sedative and analgesic peri-operative drugs

These drugs are given to allay the apprehension of the patient in the pre-operative period (including the night before operation), to relieve pain and discomfort when present, and to augment the action of subsequent anaesthetic agents. A number of the drugs used also provide some degree of pre-operative amnesia. The choice will vary with the individual patient, the nature of the operative procedure, the anaesthetic to be used and other prevailing circumstances such as outpatients, obstetrics, recovery facilities etc. The choice would also vary in elective and emergency operations.

PREMEDICATION IN CHILDREN. Oral administration is preferred to injections where possible but is not altogether satisfactory; the rectal route should only be used in exceptional circumstances. Oral alimemazine (trimeprazine) is still used but when given alone it may cause postoperative restlessness when pain is present.

Atropine or hyoscine is often given orally to children, but may be given intravenously immediately before induction.

The use of a suitable local anaesthetic cream (section 15.2) should be considered to avoid pain at injection site.

ANAESTHESIA AND DRIVING. See section 15.1.

15.1.4.1 Anxiolytics and neuroleptics

Anxiolytic benzodiazepines are widely used whereas neuroleptics such as **chlorpromazine** (section 4.2.1) are rarely used in the UK for premedication although chlorpromazine was used to prevent shivering in induction of hypothermia. **Alimemazine (trimeprazine)** (section 3.4.1) is still occasionally used as a premedicant for children (but see section 15.1.4).

Benzodiazepines

Benzodiazepines possess useful properties for premedication including relief of anxiety, sedation, and amnesia; short-acting benzodiazepines taken by mouth are the most common premedicants. They have no analgesic effect so an opioid analgesic may sometimes be required for pain.

Benzodiazepines can alleviate anxiety at doses that do not necessarily cause excessive sedation and they are of particular value during short procedures or during operations under local anaesthesia (including dentistry). Amnesia reduces the likelihood of any unpleasant memories of the procedure (although benzodiazepines, particularly when used for more profound sedation, can sometimes induce sexual fantasies). Benzodiazepines are also used in intensive care units for sedation, particularly in those receiving assisted ventilation.

Benzodiazepines may occasionally cause marked respiratory depression and facilities for its treatment are essential; flumazenil (section 15.1.7) is used to antagonise the effects of benzodiazepines.

Diazepam is used to produce mild sedation with amnesia. It is a long-acting drug with active metabolites and a second period of drowsiness can occur several hours after its administration. Peri-operative use of diazepam in children is not generally recommended; its effect and timing of response are unreliable and paradoxical effects may occur.

Diazepam is relatively insoluble in water and preparations formulated in organic solvents are painful on intravenous injection and give rise to a high incidence of venous thrombosis (which may not be noticed for several days after the injection). Intramuscular injection of diazepam is painful and absorption is erratic. An emulsion preparation for intravenous injection is less irritant and is followed by a negligible incidence of venous thrombosis; it is not suitable for intramuscular injection. Diazepam is also available as a rectal solution.

Temazepam is given by mouth and has a shorter duration of action and a more rapid onset than diazepam given by mouth. It has been used as a premedicant in inpatient and day-case surgery; anxiolytic and sedative effects last about 90 minutes although there may be residual drowsiness.

Lorazepam produces more prolonged sedation than temazepam and it has marked amnesic effects.

NAUSEA AND VOMITING. Haloperidol is given in a *subcutaneous infusion* dose of 2.5–10 mg/24 hours.

Levomepromazine (methotrimeprazine) causes sedation in about 50% of patients; it is given in a *subcutaneous infusion dose* of 25–200 mg/24 hours, although lower doses of 5–25 mg/24 hours may be effective with less sedation.

Cyclizine is particularly liable to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility, below); it is given in a *subcutaneous infusion dose* of 150 mg/24 hours.

Metoclopramide may cause skin reactions; it is given in a *subcutaneous infusion dose* of 30–100 mg/24 hours.

Octreotide (section 8.3.4.3), which stimulates water and electrolyte absorption and inhibits water secretion in the small bowel, can be used by subcutaneous infusion, in a dose of 300–600 micrograms/24 hours to reduce intestinal secretions and vomiting.

BOWEL COLIC AND EXCESSIVE RESPIRATORY SECRETIONS. Hyoscine hydrobromide effectively reduces respiratory secretions and is sedative (but occasionally causes paradoxical agitation); it is given in a *subcutaneous infusion dose* of 0.6–2.4 mg/24 hours.

Hyoscine butylbromide is effective in bowel colic, is less sedative than hyoscine hydrobromide, but is not always adequate for the control of respiratory secretions; it is given in a *subcutaneous infusion dose* of 20–60 mg/24 hours (**important:** this dose of *hyoscine butylbromide* must not be confused with the much lower dose of *hyoscine hydrobromide*, above).

Glycopyrronium 0.6–1.2 mg/24 hours may also be used.

RESTLESSNESS AND CONFUSION. Haloperidol has little sedative effect; it is given in a *subcutaneous infusion dose* of 5–15 mg/24 hours.

Levomepromazine (methotrimeprazine) has a sedative effect; it is given in a *subcutaneous infusion dose* of 50–200 mg/24 hours.

Midazolam is a sedative and an antiepileptic, and is therefore suitable for a very restless patient; it is given in a *subcutaneous infusion dose* of 20–100 mg/24 hours.

CONVULSIONS. If a patient has previously been receiving an antiepileptic *or* has a primary or secondary cerebral tumour *or* is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. Midazolam is the benzodiazepine antiepileptic of choice for *continuous subcutaneous infusion*, and is given in a dose of 20–40 mg/24 hours.

PAIN CONTROL. Diamorphine is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under Mixing and Compatibility, below). The table below gives the approximate doses of *morphine by mouth* (as oral solution or standard formulation tablets or as modified-release tablets) equivalent to *diamorphine by injection* (intramuscularly or by subcutaneous infusion).

MIXING AND COMPATIBILITY. The general principle that injections should be given into separate sites (and should not be mixed) does not apply to the use of syringe drivers in palliative care. Provided that there is evidence of compatibility, selected injections can be mixed in syringe drivers. Not all types of medication can be used in a subcutaneous infusion. In particular, chlorpromazine, prochlorperazine and diazepam are **contra-indicated** as they cause skin reactions at the injection site; to a lesser extent cyclizine and levomepromazine (methotrimeprazine) may also sometimes cause local irritation.

In theory injections dissolved in water for injections are more likely to be associated with pain (possibly owing to their hypotonicity). The use of physiological saline (sodium chloride 0.9%) however increases the likelihood of precipitation when more than one drug is used; moreover subcutaneous infusion rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

Diamorphine can be given by subcutaneous infusion in a strength of up to 250 mg/mL; up to a strength of 40 mg/mL either *water for injections* or *physiological saline* (sodium chloride 0.9%) is a suitable diluent—above that strength only *water for injections* is used (to avoid precipitation).

The following can be mixed with *diamorphine:*

Cyclizine[1]	Hyoscine hydrobromide
Dexamethasone[2]	Levomepromazine
Haloperidol[3]	Metoclopramide[4]
Hyoscine butylbromide	Midazolam

Subcutaneous infusion solution should be monitored regularly both to check for precipitation (and discoloration) and to ensure that the infusion is running at the correct rate.

PROBLEMS ENCOUNTERED WITH SYRINGE DRIVERS. The following are problems that may be encountered with syringe drivers and the action that should be taken:

- if the subcutaneous infusion runs *too quickly* check the rate setting and the calculation;
- if the subcutaneous infusion runs *too slowly* check the start button, the battery, the syringe driver, the cannula, and make sure that the injection site is not inflamed;
- if there is an *injection site reaction* make sure that the site does not need to be changed—firmness or swelling at the site of injection is not in itself an indication for change, but pain or obvious inflammation is.

1. Cyclizine may precipitate at concentrations above 10 mg/mL *or* in the presence of physiological saline *or* as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also liable to precipitate after 24 hours.
2. Special care is needed to avoid precipitation of dexamethasone when preparing.
3. Mixtures of haloperidol and diamorphine are liable to precipitate after 24 hours if haloperidol concentration is above 2 mg/mL.
4. Under some conditions metoclopramide may become discoloured; such solutions should be discarded.

Equivalent doses of morphine sulphate by mouth (as oral solution *or* standard tablets *or* as modified-release tablets) *or* of diamorphine hydrochloride by intramuscular injection *or by* subcutaneous infusion

These equivalences are approximate only and may need to be adjusted according to response

ORAL MORPHINE		PARENTERAL DIAMORPHINE	
Morphine sulphate oral solution or standard tablets	Morphine sulphate modified-release tablets	Diamorphine hydrochloride by intramuscular injection	Diamorphine hydrochloride by subcutaneous infusion
every 4 hours	**every 12 hours**	**every 4 hours**	**every 24 hours**
5 mg	20 mg	2.5 mg	15 mg
10 mg	30 mg	5 mg	20 mg
15 mg	50 mg	5 mg	30 mg
20 mg	60 mg	7.5 mg	45 mg
30 mg	90 mg	10 mg	60 mg
40 mg	120 mg	15 mg	90 mg
60 mg	180 mg	20 mg	120 mg
80 mg	240 mg	30 mg	180 mg
100 mg	300 mg	40 mg	240 mg
130 mg	400 mg	50 mg	300 mg
160 mg	500 mg	60 mg	360 mg
200 mg	600 mg	70 mg	400 mg

If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection of diamorphine equivalent to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection *subcutaneously*—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle).

To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.

Prescribing for the elderly

Old people, especially the very old, require special care and consideration from prescribers. *Medicines for Older People*, a component document of the National Service Framework for Older People,[1] describes how to maximise the benefits of medicines and how to avoid excessive, inappropriate, or inadequate consumption of medicines by older people.

POLYPHARMACY. Elderly patients often receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as adverse reactions, and may affect compliance (see Taking medicines to best effect under General guidance). Moreover, symptoms such as headache, sleeplessness, and lightheadedness which may be associated with social stress, as in widowhood, loneliness, and family dispersal can lead to further prescribing, especially of psychotropics. The use of drugs in such cases can at best be a poor substitute for effective social measures and at worst pose a serious threat from adverse reactions. Whilst unnecessary medication should be avoided, elderly patients should not be denied effective treatments such as those for stroke prophylaxis in atrial fibrillation or for osteoporosis.

1. Department of Health. National Service Framework for Older People. London: Department of Health, March 2001

FORM OF MEDICINE. Frail elderly patients may have difficulty swallowing tablets; if left in the mouth, ulceration may develop. They should always be encouraged to take their tablets or capsules with enough fluid, and in some cases it may be helpful to discuss with the patient the possibility of prescribing the drug as a liquid if available.

MANIFESTATIONS OF AGEING. In very old subjects, manifestations of normal ageing may be mistaken for disease and lead to inappropriate prescribing. For example, drugs such as prochlorperazine are commonly misprescribed for giddiness due to age-related loss of postural stability. Not only is such treatment ineffective but the patient may experience serious side-effects such as parkinsonism, postural hypotension, and confusion.

SELF-MEDICATION. Self-medication with over-the-counter products or with drugs prescribed for a previous illness (or even for another person) may be an added complication. Discussion with both the patient and relatives as well as a home visit may be needed to establish exactly what is being taken.

SENSITIVITY. The ageing nervous system shows increased *susceptibility* to many commonly used drugs, such as opioid analgesics, benzodiazepines, antipsychotics, and antiparkinsonian drugs, all of which must be used with caution. Similarly, other organs may also be more susceptible to the effects of drugs such as antihypertensives and NSAIDs.

icines to the infant's feed, since the drug may interact with the milk or other liquid in it; moreover the ingested dosage may be reduced if the child does not drink all the contents.

Parents must be warned to keep **all** medicines out of the reach of children, see Safety in the Home, p. 2.

Rare paediatric conditions

Information on substances such as *biotin* and *sodium benzoate* used in rare metabolic conditions can be obtained from:

Drug Information Centre, Alder Hey Children's Hospital, Liverpool L12 2AP. Telephone (0151) 252 5381;

Pharmacy, Great Ormond Street Hospital for Children, Great Ormond St, London, WC1N 3JH. Telephone (020) 7405 9200

Dosage in Children

Children's doses in the BNF are stated in the individual drug entries as far as possible, except where paediatric use is not recommended, information is not available, or there are special hazards.

Doses are generally based on body-weight (in kilograms) or the following age ranges:

first month (neonate)
up to 1 year (infant)
1–5 years
6–12 years

Unless the age is specified, the term 'child' in the BNF includes persons aged 12 years and younger.

DOSE CALCULATION. Children's doses may be calculated from adult doses by using age, body-weight, or body-surface area, or by a combination of these factors. The most reliable methods are those based on body-surface area.

Body-weight may be used to calculate doses expressed in mg/kg. Young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Other problems need to be considered. For example, calculation by body-weight in the obese child may result in much higher doses being administered than necessary; in such cases, dose should be calculated from an ideal weight, related to height and age.

Body-surface area (BSA) estimates are more accurate for calculation of paediatric doses than body-weight since many physiological phenomena correlate better to body-surface area. The average body-surface area of a 70-kilogram human is about 1.8 m^2. Thus, to calculate the dose for a child the following formula may be used:

Approximate dose for patient =

$$\frac{\text{surface area of patient } (m^2) \times \text{adult dose}}{1.8}$$

More precise body-surface values may be calculated from height and weight by means of a nomogram (e.g. J. Insley, *A Paediatric Vade-Mecum*, 13th Edition, London, Arnold, 1996); see also BNF Inside back covers.

Where the dose for children is not stated, prescribers should seek advice from a drug information centre or refer to a current edition of a specialist text on the use of medicines in children.

DOSE FREQUENCY. Antibacterials are generally given at regular intervals throughout the day. Some flexibility should be allowed in children to avoid waking them during the night. For example, the night-time dose may be given at the parent's bedtime.

Where new or potentially toxic drugs are used, the manufacturers' recommended doses should be carefully followed.

Prescribing in palliative care

Palliative care is the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems, is paramount to provide the best quality of life for patients and their families. Careful assessment of symptoms and needs of the patient should be undertaken by a multidisciplinary team.

Specialist palliative care is available in most areas as day hospice care, home care teams (often known as Macmillan teams), in-patient hospice care, and hospital teams. Many acute hospitals and teaching centres now have consultative, hospital-based teams.

Hospice care of terminally ill patients has shown the importance of symptom control and psychosocial support of the patient and family. Families should be included in the care of the patient if they wish.

Many patients wish to remain at home with their families. Although some families may at first be afraid of caring for the patient at home, support can be provided by community nursing services, social services, voluntary agencies and hospices together with the general practitioner. The family may be reassured by the knowledge that the patient will be admitted to a hospital or hospice if the family cannot cope.

DRUG TREATMENT. The number of drugs should be as few as possible, for even the taking of medicine may be an effort. Oral medication is usually satisfactory unless there is severe nausea and vomiting, dysphagia, weakness, or coma, in which case parenteral medication may be necessary.

Pain

Analgesics are more effective in preventing pain than in the relief of established pain; it is important that they are given regularly.

The non-opioid analgesics **aspirin** or **paracetamol** given regularly will often make the use of opioids unnecessary. Aspirin (or other NSAIDs if preferred) may also control the pain of *bone secondaries*; naproxen, flurbiprofen, and indometacin (section 10.1.1) are valuable and if necessary can be given rectally. Radiotherapy, bisphosphonates (section 6.6.2) and radioactive isotopes of **strontium** (*Metastron*® available from Amersham) may also be useful for pain due to bone metastases.

An opioid such as **codeine** or **dextropropoxyphene**, alone or in combination with a non-opioid analgesic at adequate dosage, may be helpful in the control of moderate pain if non-opioids alone are not sufficient. If these preparations are not controlling the pain, **morphine** is the most useful opioid analgesic. Alternatives to morphine are **hydromorphone, oxycodone** (section 4.7.2) and transdermal **fentanyl** (see below and section 4.7.2). Initiation of an opioid analgesic should not be delayed by concern over a theoretical likelihood of psychological dependence (addiction).

Equivalent single doses of strong analgesics

These equivalences are intended **only** as an approximate guide; patients should be carefully monitored after **any** change in medication and dose titration may be required

Analgesic	Dose
Morphine salts (oral)	10 mg
Diamorphine hydrochloride (intramuscular)	3 mg
Hydromorphone hydrochloride	1.3 mg
Oxycodone	5 mg

ORAL ROUTE. Morphine is given *by mouth* as an oral solution or as standard ('immediate release') tablets regularly every 4 hours, the initial dose depending largely on the patient's previous treatment. A dose of 5–10 mg is enough to replace a weaker analgesic (such as paracetamol or co-proxamol), but 10–20 mg or more is required to replace a strong one (comparable to morphine itself). If the first dose of morphine is no more effective than the previous analgesic, the next dose should be increased by 50%, the aim being to choose the lowest dose which prevents pain. The dose should be adjusted with careful assessment of the pain and the use of adjuvant analgesics (such as NSAIDs) should also be considered. Although morphine in a dose of 5–20 mg is usually adequate there should be no hesitation in increasing it stepwise according to response to 100 mg or occasionally up to 500 mg or higher if necessary. It may be possible to omit the overnight dose if double the usual dose is given at bedtime.

If pain occurs between regular doses ('breakthrough pain'), an additional dose ('rescue dose') should be given. An additional dose should also be given 30 minutes before an activity that causes pain (e.g. wound dressing). Fentanyl lozenges are also licensed for breakthrough pain.

When the pain is controlled and the patient's 24-hour morphine requirement is established, the daily dose can be given as a single dose or in 2 divided doses as a *modified-release preparation*.

Preparations suitable for twice daily administration include *MST Continus*® tablets or suspension, and *Zomorph*® capsules. Preparations that allow administration of the total daily morphine requirement as a single dose include *MXL*® capsules. *Morcap SR*® capsules may be given either twice daily or as a single daily dose.

The starting dose of modified-release preparations designed for twice daily administration is usually 10–20 mg every 12 hours if no other analgesic (or only paracetamol) has been taken previously, but to replace a weaker opioid analgesic (such as co-proxamol) the starting dose is usually 20–30 mg every 12 hours. Increments should be made to the dose, not to the frequency of administration, which should remain at every 12 hours.

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The effective dose of modified-release preparations can alternatively be determined by giving the oral solution of morphine every 4 hours in increasing doses until the pain has been controlled, and then transferring the patient to the same total 24-

PRESCRIBING DRUGS LIKELY TO CAUSE DEPENDENCE OR MISUSE. The prescriber has three main responsibilities:

1. To avoid creating dependence by introducing drugs to patients without sufficient reason. In this context, the proper use of the morphine-like drugs is well understood. The dangers of other controlled drugs are less clear because recognition of dependence is not easy and its effects, and those of withdrawal, are less obvious. Perhaps the most notable result of uninhibited prescribing is that a very large number of patients in the country take tablets which do them neither much good nor much harm, but are committed to them indefinitely because they cannot readily be stopped.
2. To see that the patient does not gradually increase the dose of a drug, given for good medical reasons, to the point where dependence becomes more likely. This tendency is seen especially with hypnotics and anxiolytics (for CSM advice see section 4.1). The prescriber should keep a close eye on the amount prescribed to prevent patients from accumulating stocks that would enable them to arrange their own dosage or even that of their families and friends. A minimal amount should be prescribed in the first instance, or when seeing a new patient for the first time.
3. To avoid being used as an unwitting source of supply for addicts. Methods include visiting more than one doctor, fabricating stories, and forging prescriptions.

Patients under temporary care should be given only small supplies of drugs unless they present an unequivocal letter from their own doctors. Doctors should also remember that their own patients may be doing a collecting round with other doctors, especially in hospitals. It is sensible to decrease dosages steadily or to issue weekly or even daily prescriptions for small amounts if it is apparent that dependence is occurring.

The stealing and misuse of prescription forms could be minimised by the following precautions:

(a) do not leave unattended if called away from the consulting room or at reception desks; do not leave in a car where they may be visible; when not in use, keep in a locked drawer within the surgery and at home;

(b) draw a diagonal line across the blank part of the form under the prescription;

(c) write the quantity in words and figures when prescribing drugs prone to abuse; this is obligatory for controlled drugs (see Prescriptions, above);

(d) alterations are best avoided but if any are made they should be clear and unambiguous; add initials against altered items;

(e) if prescriptions are left for collection they should be left in a safe place in a sealed envelope.

TRAVELLING ABROAD. Prescribed drugs listed in schedules 4 and 5 to the Misuse of Drugs Regulations 1985 are not subject to import or export licensing but doctors are advised that patients intending to carry Schedule 2 and 3 drugs abroad may require an export licence. This is dependent upon the amount of drug to be exported and further details may be obtained from the Home Office by telephoning (020) 7273 3806. Applications for licences should be sent to the Home Office, Drugs Branch, Queen Anne's Gate, London SW1H 9AT.

There is no standard application form but applications must be supported by a letter from a doctor giving details of:

- the patient's name and current address;
- the quantities of drugs to be carried;
- the strength and form in which the drugs will be dispensed;
- the dates of travel to and from the United Kingdom.

Ten days should be allowed for processing the application.

Individual doctors who wish to take Controlled Drugs abroad while accompanying patients, may similarly be issued with licences. Licences are not normally issued to doctors who wish to take Controlled Drugs abroad solely in case a family emergency should arise.

These import/export licences for named individuals do not have any legal status outside the UK and are only issued to comply with the Misuse of Drugs Act and facilitate passage through UK Customs and Excise control. For clearance in the country to be visited it would be necessary to approach that country's consulate in the UK.

Misuse of Drugs Act

The Misuse of Drugs Act, 1971 prohibits certain activities in relation to 'Controlled Drugs', in particular their manufacture, supply, and possession. The penalties applicable to offences involving the different drugs are graded broadly according to the *harmfulness attributable to a drug when it is misused* and for this purpose the drugs are defined in the following three classes:

Class A includes: alfentanil, cocaine, dextromoramide, diamorphine (heroin), dipipanone, lysergide (LSD), methadone, methylenedioxymethamfetamine (MDMA, 'ecstasy'), morphine, opium, pethidine, phencyclidine, and class B substances when prepared for injection

Class B includes: oral amphetamines, barbiturates, cannabis, cannabis resin, codeine, ethylmorphine, glutethimide, pentazocine, phenmetrazine, and pholcodine

Class C includes: certain drugs related to the amphetamines such as benzfetamine and chlorphentermine, buprenorphine, diethylpropion, mazindol, meprobamate, pemoline, pipradrol, most benzodiazepines, androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin

The Misuse of Drugs Regulations 2001 define the classes of person who are authorised to supply and possess controlled drugs while acting in their professional capacities and lay down the conditions under which these activities may be carried out. In the regulations drugs are divided into five schedules each specifying the requirements governing such activities as import, export, production, supply, possession, prescribing, and record keeping which apply to them.

Schedule 1 includes drugs such as cannabis and lysergide which are not used medicinally. Possession and supply are prohibited except in accordance with Home Office authority.

Schedule 2 includes drugs such as diamorphine (heroin), morphine, pethidine, secobarbital, glutethimide, amfetamine, and cocaine and are subject to the full controlled drug requirements relating to prescriptions, safe custody (except for secobarbital), the need to keep registers, etc. (unless exempted in schedule 5).

Schedule 3 includes the barbiturates (except secobarbital, now schedule 2), buprenorphine, diethylpropion, flunitrazepam, mazindol, meprobamate, pentazocine, phentermine, and temazepam. They are subject to the special prescription requirements (except for phenobarbital and temazepam, see p. 7) but not to the safe custody requirements (except for buprenorphine, diethylpropion, flunitrazepam, and temazepam) nor to the need to keep registers (although there are requirements for the retention of invoices for 2 years).

Schedule 4 includes in Part I benzodiazepines (except flunitrazepam and temazepam which are in schedule 3) that are subject to minimal control. Part II includes androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements.

Schedule 5 includes those preparations which, because of their strength, are exempt from virtually all Controlled Drug requirements other than retention of invoices for two years.

Notification of drug misusers

Doctors are expected to report on a standard form cases of drug misuse to their regional or national drug misuse database or centre—see below for contact telephone numbers. The National Drugs Treatment Monitoring System was introduced in England in April 2001; regional centres replace the Regional Drug Misuse Databases. A similar system has been introduced in Wales.

A report (notification) to their regional or national drug misuse database or centre should be made when a patient starts treatment for drug misuse. In England and Wales further information is collected in Spring, including whether or not patients are continuing to receive treatment. All types of problem drug misuse should be reported including opioid, benzodiazepine, and CNS stimulant.

The regional or national drug misuse database or centres are now the only national and local source of epidemiological data on people presenting with problem drug misuse; they provide valuable information to those working with drug misusers and those planning services for them. The databases cannot, however, be used as a check on multiple prescribing for drug addicts because the data are anonymised.

Enquiries about the regional or national drug misuse database or centres (including requests for supplies of notification forms) can be made by contacting one of the centres listed below:

ENGLAND

North West

Merseyside and Cheshire: telephone (0151) 231 4319; fax (0151) 231 4320

North Western: telephone (0161) 772 3782; fax (0161) 772 3445

Northern and Yorkshire

Telephone (0113) 295 1337; fax (0113) 295 1310

South East (West) and Eastern

Telephone (01865) 226734; fax (01865) 226652

South West

Telephone (0117) 918 6880; fax (0117) 918 6883

Thames and South East (East)

Telephone (020) 7594 0811; fax (020) 7594 0866

Trent

Telephone (0116) 225 6360; fax (0116) 225 6370

West Midlands

Telephone (0121) 580 4331; fax (0121) 525 7980

SCOTLAND

Telephone (0131) 551 8715; fax (0131) 551 1392

WALES

Telephone (029) 2082 6260; fax (029) 2082 5473

In **Northern Ireland**, the Misuse of Drugs (Notification of and Supply to Addicts) (Northern Ireland) Regulations 1973 require doctors to send particulars of persons whom they consider to be addicted to certain controlled drugs to Chief Medical Officer of the Department of Health and Social Services. The Northern Ireland contacts are:

Medical contact:
Dr Ian McMaster
C3 Castle Buildings
Belfast BT4 3PP
Telephone (028) 9052 2421
Fax (028) 9052 0781

Administrative contact:
Health Promotion Branch
C4.22 Castle Buildings
Belfast BT4 3PP
Telephone (028) 9052 0532

Prescribing of diamorphine (heroin), dipipanone, and cocaine for addicts

The Misuse of Drugs (Supply to Addicts) Regulations 1997 require that only medical practitioners who hold a special licence issued by the Home Secretary may prescribe, administer or supply diamorphine, dipipanone[1] (*Diconal*®) or cocaine in the treatment of drug addiction; other practitioners must refer any addict who requires these drugs to a treatment centre. Whenever possible the addict will be introduced by a member of staff from the treatment centre to a pharmacist whose agreement has been obtained and whose pharmacy is conveniently sited for the patient. Prescriptions for weekly supplies will be sent to the pharmacy by post and will be dispensed on a daily basis as indicated by the doctor. If any alterations of the arrangements are requested by the addict, the portion of the prescription affected must be represcribed and not merely altered. *General practitioners and other doctors may still prescribe diamorphine, dipipanone, and cocaine for patients (including addicts) for relief of pain due to organic disease or injury without a special licence.*

For guidance on prescription writing, see p. 7.

1. Dipipanone in *Diconal*® tablets has been much misused by opioid addicts in recent years. Doctors and others should be suspicious of people who ask for the tablets, especially if temporary residents.