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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 always more effective in preventing the development of pain than in the relief of established pain.

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 indomethacin (section 10.1.1) are valuable and if necessary can be given rectally. Radiotherapy, radioactive isotopes of **strontium** (*Metastron*® available from Amersham) and bisphosphonates (section 6.6.2) 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.

ORAL ROUTE. Morphine is given *by mouth* as an **oral solution** 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 it should be increased by 50%, the aim being to choose the lowest dose which prevents pain. Although 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. If pain occurs between doses the next dose due is increased; in the interim an additional dose is given. The dose should be adjusted with careful assessment of the pain and the use of other drugs (such as NSAIDs) should also be considered.

Modified-release preparations of morphine are an alternative to the oral solution. Depending on the formulation of the modified-release preparation, the total daily morphine requirement may be given in two equal doses or as a single dose.

Preparations suitable for twice daily administration include *MST Continus*® tablets or suspension, *Oramorph*® *SR* tablets, 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.

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-hour dose of morphine given as the modified-release preparation (divided into two portions for 12-hourly administration). The first dose of the modified-release preparation is given 4 hours after the last dose of the oral solution.[1]

Morphine, as oral solution or standard formulation tablets, should be prescribed for breakthrough pain.

PARENTERAL ROUTE. If the patient becomes unable to swallow, the equivalent intramuscular dose of morphine is half the oral solution dose; in the case of the modified-release tablets it is half the total 24-hour dose (which is then divided into 6 portions to be given every 4 hours). **Diamorphine** is preferred for injection because being more soluble it can be given in a smaller volume. The equivalent intramuscular (or subcutaneous) dose of diamorphine is only about a quarter to a third of the oral dose of morphine; *subcutaneous infusion via syringe driver* can be useful (for details, see p. 14).

1. Studies have indicated that administration of the last dose of the *oral solution* with the first dose of the *modified-release tablets* is not necessary.

RECTAL ROUTE. Morphine is also available for *rectal administration* as suppositories; alternatively **oxycodone** suppositories can be obtained on special order.

TRANSDERMAL ROUTE. Transdermal preparations of fentanyl are available (section 4.7.2). Careful conversion from oral morphine to transdermal fentanyl is necessary; a 25 micrograms/hr patch is equivalent to a total dose of morphine up to 135 mg/24 hours.

GASTRO-INTESTINAL PAIN. The pain of *bowel colic* may be reduced by loperamide 2–4 mg 4 times daily. Hyoscine hydrobromide may also be helpful, given sublingually at a dose of 300 micrograms 3 times daily as *Kwells*® (Roche Consumer Health) tablets. For the dose by subcutaneous infusion using a syringe driver, see p. 14.

Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiflatulent (section 1.1.1) and by domperidone 10 mg 3 times daily before meals.

MUSCLE SPASM. The pain of muscle spasm can be helped by a muscle relaxant such as diazepam 5–10 mg daily or baclofen 5–10 mg 3 times daily.

NERVE PAIN. Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone 8 mg daily, which reduces oedema around the tumour, thus reducing compression.

Dysaesthetic or stabbing pain resulting from nerve irritation may be reduced by amitriptyline 25–75 mg at night, or by carbamazepine 200 mg 3 times daily.

Nerve blocks may be considered when pain is localised to a specific area. **Transcutaneous electrical nerve stimulation** (TENS) may also provide useful relief of pain.

MISCELLANEOUS CONDITIONS

Non-licensed indications or routes

Several recommendations in this section involve non-licensed indications or routes.

RAISED INTRACRANIAL PRESSURE. Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone 16 mg daily for 4 to 5 days, subsequently reduced to 4–6 mg daily if possible.

INTRACTABLE COUGH. Intractable cough may be relieved by moist inhalations or may require regular administration of an oral morphine hydrochloride (or sulphate) solution in an initial dose of 5 mg every 4 hours. Methadone linctus should be avoided as it has a long duration of action and tends to accumulate.

DYSPNOEA. Dyspnoea may be relieved by regular oral morphine hydrochloride (or sulphate) solution in carefully titrated doses, starting at 5 mg every 4 hours. Diazepam 5–10 mg daily may be helpful; a corticosteroid, such as dexamethasone 4–8 mg daily, may also be helpful if there is bronchospasm or partial obstruction.

EXCESSIVE RESPIRATORY SECRETION. Excessive respiratory secretion (death rattle) may be reduced by subcutaneous injection of hyoscine hydrobromide 400–600 micrograms every 4 to 8 hours; care must however be taken to avoid the discomfort of dry mouth. For the dose by subcutaneous infusion using a syringe driver, see next page.

RESTLESSNESS AND CONFUSION. Restlessness and confusion may require treatment with haloperidol 1–3 mg by mouth every 8 hours. Chlorpromazine 25–50 mg by mouth every 8 hours is an alternative, but causes more sedation. Methotrimeprazine is also used occasionally for restlessness. For the dose by subcutaneous infusion using a syringe driver, see next page.

HICCUP. Hiccup due to gastric distension may be helped by a preparation incorporating an antacid with an antiflatulent (see section 1.1.1). If this fails, metoclopramide 10 mg every 6 to 8 hours by mouth or by intramuscular injection can be added; if this also fails, chlorpromazine 10–25 mg every 6 to 8 hours can be tried.

ANOREXIA. Anorexia may be helped by prednisolone 15–30 mg daily or dexamethasone 2–4 mg daily.

CONSTIPATION. Constipation is a very common cause of distress and is almost invariable after administration of an opioid. It should be prevented if possible by the regular administration of laxatives; a faecal softener with a peristaltic stimulant (e.g. co-danthramer), or lactulose solution with a senna preparation should be used (section 1.6.2 and section 1.6.3).

FUNGATING GROWTH. Fungating growth may be treated by cleansing with a mixture of 1 part of 4% povidone–iodine skin cleanser solution and 4 parts of liquid paraffin. Oral administration of metronidazole (section 5.1.11) may eradicate the anaerobic bacteria responsible for the odour of fungating tumours; topical application (section 13.10.1.2) is also used.

CAPILLARY BLEEDING. Capillary bleeding may be reduced by applying gauze soaked in adrenaline solution 1 mg/mL (1 in 1000).

DRY MOUTH. Dry mouth may be relieved by good mouth care and measures such as the sucking of ice or pineapple chunks or the use of artificial saliva (section 12.3.5); dry mouth associated with candidiasis can be treated by oral preparations of nystatin or miconazole (section 12.3.2); alternatively, fluconazole can be given by mouth (section 5.2). Dry mouth may be caused by certain medication including, opioids, antimuscarinic drugs (e.g. hyoscine), antidepressants and some anti-emetics; if possible, an alternative preparation should be considered.

PRURITUS. Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as emollients. In the case of obstructive jaundice, further measures include administration of cholestyramine or an anabolic steroid, such as stanozolol 5–10 mg daily; antihistamines can be helpful (section 3.4.1).

CONVULSIONS. Patients with cerebral tumours or uraemia may be susceptible to convulsions. Prophylactic treatment with phenytoin or carbamazepine (section 4.8.1) should be considered. When oral medication is no longer possible, diazepam as suppositories 10–20 mg every 4 to 8 hours, or phenobarbitone by injection 50–200 mg twice daily is continued as prophylaxis. For the use of midazolam by subcutaneous infusion using a syringe driver, see below.

DYSPHAGIA. A corticosteroid such as dexamethasone 8 mg daily may help, temporarily, if there is an obstruction due to tumour. See also under Dry Mouth.

NAUSEA AND VOMITING. Nausea and vomiting are very common in patients with advanced cancer. The cause should be diagnosed before treatment with anti-emetics (section 4.6) is started. 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.

Nausea and vomiting may also occur in the initial stages of morphine therapy but can be prevented by giving an anti-emetic such as haloperidol 1.5 mg daily (or twice daily if nausea continues) or prochlorperazine (section 4.6). An anti-emetic is usually only necessary for the first 4 or 5 days therefore fixed-combination opioid preparations containing an anti-emetic are not recommended since they lead to unnecessary anti-emetic therapy (often with undesirable drowsiness). For the administration of anti-emetics by subcutaneous infusion using a syringe driver, see below.

For the treatment of nausea and vomiting associated with cancer chemotherapy, see section 8.1.

INSOMNIA. Patients with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics are used. Benzodiazepines, such as temazepam, may be useful (section 4.1.1).

HYPERCALCAEMIA. See section 9.5.1.2.

SYRINGE DRIVERS

Although drugs can usually be administered *by mouth* to control the symptoms of advanced cancer, the parenteral route may sometimes be necessary. If the parenteral route is necessary, repeated administration of *intramuscular injections* can be difficult in a cachectic patient. This has led to the use of a portable syringe driver to give a *continuous subcutaneous infusion*, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Indications for the **parenteral route** are:

- the patient is unable to take medicines by mouth owing to *nausea and vomiting, dysphagia, severe weakness,* or *coma;*
- there is *malignant bowel obstruction* in patients for whom further surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube);
- occasionally when the patient *does not wish* to take regular medication by mouth.

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

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 30–60 mg/24 hours.

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).

RESTLESSNESS AND CONFUSION. **Haloperidol** has little sedative effect; it is given in a *subcutaneous infusion dose* of 5–30 mg/24 hours.

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 on the next page gives the approximate doses of *morphine by mouth* (as oral solution or standard 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 **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]
Dexamethasone[2]
Haloperidol[3]
Hyoscine butylbromide
Hyoscine hydrobromide
Methotrimeprazine
Metoclopramide[4]
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.

Syringe driver rate settings. Staff using syringe drivers should be adequately trained and different rate settings should be clearly identified and differentiated; incorrect use of syringe drivers is a common cause of drug errors.

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.

POLYPHARMACY. Elderly patients are apt to receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as other adverse reactions. 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.

FORM OF MEDICINE. 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 advisable to prescribe 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 drug-induced parkinsonism, postural hypotension, and mental 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 relatives and a home visit may be needed to establish exactly what is being taken.

SUSCEPTIBILITY. The ageing nervous system shows increased *susceptibility* to many commonly used drugs, such as opioid analgesics, benzodiazepines, and antiparkinsonian drugs, all of which must be used with caution.

PHARMACOKINETICS

While drug distribution and metabolism may be significantly altered, the most important effect of age is reduction in renal clearance, frequently aggravated by the effects of prostatism, nephrosclerosis, or chronic urinary tract infection. Many aged patients thus possess only *limited reserves of renal function, excrete drugs slowly*, and are *highly susceptible to nephrotoxic drugs*. Acute illness may lead to rapid reduction in renal clearance, especially if accompanied by dehydration. Hence, a patient stabilised on a drug with a narrow margin between the therapeutic and the toxic dose (e.g. digoxin) may rapidly develop adverse effects in the aftermath of a myocardial infarction or a respiratory tract infection.

The net result of pharmacokinetic changes is that tissue concentrations are commonly increased by over 50%, and aged and debilitated patients may show even larger changes.

ADVERSE REACTIONS

Adverse reactions often present in the elderly in a vague and non-specific fashion. *Mental confusion* is often the presenting symptom (caused by almost any of the commonly used drugs). Other common manifestations are *constipation* (with antimuscarinics and many tranquillisers) and postural *hypotension* and *falls* (with diuretics and many psychotropics).

HYPNOTICS. Many hypnotics with long half-lives have serious hangover effects of drowsiness, unsteady gait, and even slurred speech and confusion. Those with short half-lives should be used but they too can present problems (section 4.1.1). Short courses of hypnotics are occasionally useful for helping a patient through an acute illness or some other crisis but every effort must be made to avoid dependence.

DIURETICS. Diuretics are overprescribed in old age and should not be used on a long-term basis to treat simple gravitational oedema which will usually respond to increased movement, raising the legs, and support stockings. A few days of diuretic treatment may speed the clearing of the oedema but it should rarely need continued drug therapy.

NSAIDs. Bleeding associated with *aspirin* and *other NSAIDs* is more common in the elderly who are more likely to have a fatal or serious outcome. NSAIDs are also a special hazard in patients with cardiac disease or renal impairment which may again place the elderly at particular risk.

Owing to the *increased susceptibilty of the elderly* to the *side-effects of NSAIDs* the following recommendations are made:

- for *osteoarthritis, soft-tissue lesions and back pain* first try measures such as weight reduction, warmth, exercise and use of a walking stick;
- for *osteoarthritis, soft tissue lesions, back pain and rheumatoid arthritis* avoid giving an NSAID unless *paracetamol* (alone or with a *low dose* of an opioid analgesic as in co-codamol 8/500 or co-dydramol 10/500) has failed to relieve the pain adequately;
- where a paracetamol preparation has failed to relieve the pain adequately *add a very low dose of an NSAID* to the paracetamol preparation (starting with ibuprofen). For advice on prophylaxis of NSAID-induced peptic ulcers (where continued treatment with NSAIDs is necessary), see section 1.3.
- if an NSAID is considered necessary monitor the patient for gastro-intestinal bleeding for 4 weeks (and for a similar time on switching to another NSAID). For the management of NSAID-associated peptic ulcers, see section 1.3.
- do not give two NSAIDs at the same time.

OTHER DRUGS. Other drugs which commonly cause adverse reactions are *antiparkinsonian drugs, antihypertensives, psychotropics*, and *digoxin*; the usual maintenance dose of digoxin in very old patients is 125 micrograms daily (62.5 micrograms is often inadequate, and toxicity is common in those given 250 micrograms).

Drug-induced blood disorders are much more common in the elderly. Therefore drugs with a tendency to cause bone marrow depression (e.g. *co-trimoxazole, mianserin*) should be avoided unless there is no acceptable alternative.

The elderly generally require a lower maintenance dose of *warfarin* than younger adults; once again, the outcome of bleeding tends to be more serious.

GUIDELINES

First always question whether a drug is indicated at all.

LIMIT RANGE. It is a sensible policy to prescribe from a limited range of drugs and to be thoroughly familiar with their effects in the elderly.

REDUCE DOSE. Dosage should generally be substantially lower than for younger patients and it is common to start with about 50% of the adult dose. Some drugs (e.g. chlorpropamide) should be avoided altogether.

REVIEW REGULARLY. Review repeat prescriptions regularly. It may be possible to stop the drug (e.g. digoxin can often be withdrawn) or it may be necessary to reduce the dose to match diminishing renal function.

SIMPLIFY. Simplify regimens. Elderly patients cannot normally cope with more than three different drugs and, ideally, these should not be given more than twice daily. In particular, regimens which call for a confusing array of dosage intervals should be avoided.

EXPLAIN CLEARLY. Write full instructions on every prescription (*including* repeat prescriptions) so that containers can be properly labelled with full directions. Avoid imprecisions like 'as directed'. Child-resistant containers may be unsuitable.

REPEATS AND DISPOSAL. Instruct patients what to do when drugs run out, and also how to dispose of any that are no longer necessary. Try to prescribe matching quantities.

If these guidelines are followed most elderly people will cope adequately with their own medicines. If not then it is essential to enrol the help of a third party, usually a relative or a friend.

PoM **Parvolex®** (Evans)

Injection, acetylcysteine 200 mg/mL. Net price 10-mL amp = £2.65

METHIONINE

Indications: paracetamol overdosage, see notes above

Dose: by mouth, 2.5 g initially, followed by 3 further doses of 2.5 g every 4 hours

Methionine (Non-proprietary)

Tablets, DL-methionine 250 mg. Net price course of 40 tabs = £12.27

Available from Norton

ANALGESICS (OPIOID)

Opioids (narcotic analgesics) cause varying degrees of coma, respiratory depression, and pinpoint pupils. The specific antidote **naloxone** is indicated if there is coma or bradypnoea. Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. Alternatively, it may be given by continuous intravenous infusion, the rate of administration being adjusted according to response.

CO-PROXAMOL. Combinations of dextropropoxyphene and paracetamol (co-proxamol) are frequently taken in overdosage. The initial features are those of acute opioid overdosage with coma, respiratory depression, and pinpoint pupils. Patients may die of acute cardiovascular collapse before reaching hospital (particularly if alcohol has also been consumed) unless adequately resuscitated or given **naloxone** as antidote to the dextropropoxyphene. Paracetamol hepatotoxicity may develop later and should be anticipated and treated as indicated above.

NALOXONE HYDROCHLORIDE

Indications: overdosage with opioids; for post-operative respiratory depression, see section 15.1.7

Cautions: physical dependence on opioids; cardiac irritability; naloxone is short-acting, see notes above

Dose: by intravenous injection, 0.8–2 mg repeated at intervals of 2–3 minutes to a max. of 10 mg if respiratory function does not improve (then question diagnosis); CHILD 10 micrograms/kg; subsequent dose of 100 micrograms/kg if no response

By subcutaneous or intramuscular injection, as intravenous injection but only if intravenous route not feasible (onset of action slower)

By continuous intravenous infusion, 2 mg diluted in 500 mL intravenous infusion solution at a rate adjusted according to the response

IMPORTANT. Doses used in acute opioid overdosage may not be appropriate for the management of opioid-induced respiratory depression and sedation in those receiving palliative care and in chronic opioid use, see also section 15.1.7 for management of postoperative

PoM **Naloxone** (Non-proprietary)

Injection, naloxone hydrochloride 400 micrograms/mL. Net price 1-mL amp = 74p

Available from Antigen, Faulding DBL

PoM **Min-i-Jet® Naloxone** (IMS)

Injection, naloxone hydrochloride 400 micrograms/mL. Net price 1-mL disposable syringe = £5.23; 2-mL disposable syringe = £9.74

PoM **Narcan®** (Du Pont)

Injection, naloxone hydrochloride 400 micrograms/mL, net price 1-mL amp = £4.79

Neonatal preparations —section 15.1.7

ANTIDEPRESSANTS

Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Metabolic acidosis may complicate severe poisoning; delirium with confusion, agitation, and visual and auditory hallucinations, is common during recovery.

Symptomatic treatment and activated charcoal by mouth may reasonably be given in the home before transfer but hospital admission is strongly advised, and supportive measures to ensure a patent airway and adequate ventilation during transfer are mandatory. Intravenous diazepam may be required for control of convulsions (preferably in emulsion form). Although arrhythmias are worrying, some will respond to correction of hypoxia and acidosis; the use of anti-arrhythmic drugs is best avoided. Diazepam given by mouth is usually adequate to sedate delirious patients but large doses may be required.

ANTIMALARIALS

Overdosage with chloroquine and hydroxychloroquine is extremely hazardous and difficult to treat. Urgent advice from a poisons information centre is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable). Quinine overdosage is also a severe hazard and calls for urgent advice from a poisons information centre.

BETA-BLOCKERS

Therapeutic overdosages with beta-blockers may cause lightheadedness, dizziness, and possibly syncope due to impaired circulation secondary to bradycardia and hypotension; heart failure may be precipitated or exacerbated. These complications are most likely in patients with pre-existing conduction system disorders or impaired myocardial function. Bradycardia is the most common arrhythmia caused by beta-blockers, but sotalol occasionally induces ventricular tachyarrhythmias (sometimes of the torsades de pointes type). The effects of massive overdosage may vary from one beta-blocker to another; propranolol overdosage in particular may cause coma and convulsions.

Acute massive overdosage must be managed in hospital and expert advice should be obtained.

lation is mandatory. An intravenous injection of atropine is required to treat bradycardia and hypotension (3 mg for an adult, 40 micrograms/kg for a child). Cardiogenic shock unresponsive to atropine is probably best treated with an intravenous injection of glucagon 50–150 micrograms/kg [unlicensed indication and dose] in glucose 5% (with precautions to protect the airway in case of vomiting). A further dose of glucagon (or an intravenous infusion) may be required if the response is not maintained. If glucagon is not available, intravenous isoprenaline or intravenous prenalterol [not on UK market] are alternatives to glucagon.

HYPNOTICS AND ANXIOLYTICS

BARBITURATES. These cause drowsiness, coma, respiratory depression, hypotension, and hypothermia. The duration and depth of cerebral depression vary greatly with the drug, the dose, and the tolerance of the patient. The severity of poisoning is often greater with a large dose of barbiturate hypnotics than with the longer-acting phenobarbitone. The majority of patients survive with supportive measures alone. Charcoal haemoperfusion is the treatment of choice for the small minority of patients with very severe barbiturate poisoning who fail to improve, or who deteriorate despite good supportive care.

BENZODIAZEPINES. Benzodiazepines taken alone cause drowsiness, ataxia, dysarthria, and occasionally minor and short-lived depression of consciousness. They potentiate the effects of other central nervous system depressants taken concomitantly. Flumazenil, a benzodiazepine antagonist, may be used in the *differential diagnosis* of unclear cases of multiple drug overdose but expert advice is essential since adverse effects may occur (e.g. convulsions in patients dependent on benzodiazepines).

IRON SALTS

Iron poisoning is commonest in childhood and is usually accidental. The symptoms are nausea, vomiting, abdominal pain, diarrhoea, haematemesis, and rectal bleeding. Hypotension, coma, and hepatocellular necrosis occur later. Mortality is reduced with intensive and specific therapy with **desferrioxamine**, which chelates iron. The stomach should be emptied at once by gastric lavage. The serum-iron concentration is measured as an emergency and intravenous desferrioxamine given to chelate absorbed iron in excess of the expected iron binding capacity. In severe toxicity intravenous desferrioxamine should be given *immediately* without waiting for the result of the serum-iron measurement (contact a poisons information centre for advice).

DESFERRIOXAMINE MESYLATE

(Deferoxamine Mesilate)

Indications: removal of iron from the body in poisoning; for use in chronic iron overload, see section 9.1.3

Side-effects: anaphylactic reactions, and hypotension when given too rapidly by intravenous injection

Dose: by continuous intravenous infusion, up to 15 mg/kg/hour; max. 80 mg/kg in 24 hours

PoM **Desferal®** (Novartis)

Injection, powder for reconstitution, desferrioxamine mesylate. Net price 500-mg vial = £3.70

LITHIUM

Most cases of lithium intoxication occur as a complication of long-term therapy and are caused by reduced excretion of the drug due to a variety of factors including dehydration, deterioration of renal function, infections, and co-administration of diuretics or NSAIDs (or other drugs that interact). Acute deliberate overdoses may also occur with delayed onset of symptoms (12 hours or more) due to slow entry of lithium into the tissues and continuing absorption from modified-release formulations.

The early clinical features are non-specific and may include apathy and restlessness which could be confused with mental changes due to the patient's depressive illness. Vomiting, diarrhoea, ataxia, weakness, dysarthria, muscle twitching, and tremor may follow. Severe poisoning is associated with convulsions, coma, renal failure, electrolyte imbalance, dehydration, and hypotension.

Therapeutic lithium concentrations are within the range of 0.4–1.0 mmol/litre; concentrations in excess of 2.0 mmol/litre are usually associated with serious toxicity and such cases may need treatment with haemodialysis (if there is renal failure). In acute overdosage much higher serum concentrations may be present without features of toxicity and measures to increase urine production are usually all that are necessary. Otherwise treatment is supportive with special regard to electrolyte balance, renal function, and control of convulsions.

PHENOTHIAZINES AND RELATED DRUGS

Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias (particularly with thioridazine) may complicate poisoning. Dystonic reactions can occur with therapeutic doses, (particularly with prochlorperazine and trifluoperazine) and convulsions may occur in severe cases. Arrhythmias may respond to correction of hypoxia and acidosis but anti-arrhythmic drugs may also be needed. Dystonic reactions are rapidly abolished by injection of drugs such as benztropine or procyclidine (see section 4.9.2).

STIMULANTS

AMPHETAMINES. These cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. The early stages can be controlled by chlorpromazine and, if necessary, beta-blockers. Later, tepid sponging, anticonvulsants, and artificial respiration may be needed. Amphetamine excretion can be increased by forced

Chlorpromazine is widely used. 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.

Flupenthixol and **pimozide** (see CSM advice p. 168) 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 was formerly popular for treating the elderly as there is a reduced incidence of extrapyramidal symptoms. However, there is a high incidence of antimuscarinic effects and possibly an increased risk of cardiotoxicity.

Promazine is not sufficiently active by mouth to be used as an antipsychotic drug.

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.

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[1]
Haloperidol	2–3 mg[2]
Loxapine	10–20 mg
Pimozide	2 mg[3]
Risperidone	0.5–1 mg
Sulpiride	200 mg
Thioridazine	100 mg
Trifluoperazine	5 mg

1. The prescribing of clozapine needs to comply with the Clozaril Patient Monitoring Service, see p. 171
2. In specialist psychiatric units where very high doses are required the equivalent dose of haloperidol might be up to 10 mg
3. See also the CSM warning concerning pimozide dose, p. 168

IMPORTANT. These equivalences must not be extrapolated beyond the max. dose for the drug.

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.

[redacted]

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 terminal illness), section 4.6; peri-operative use, see section 15.1.4.1

Cautions: cardiovascular and cerebrovascular disease, respiratory disease, parkinsonism, epilepsy (possibly avoid), acute infections, pregnancy, breast-feeding, renal and hepatic impairment (avoid if severe), history of jaundice, leucopenia (blood counts if unexplained infection or fever), hypothyroidism, myasthenia gravis, prostatic hypertrophy, angle-closure glaucoma; caution in elderly particularly in very hot or very cold weather; avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection; **interactions:** Appendix 1 (antipsychotics)

DRIVING. Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications: coma caused by CNS depressants; bone-marrow depression; avoid in phaeochromocytoma

Side-effects: extrapyramidal symptoms (reversed by dose reduction or antimuscarinic drugs) and, on prolonged administration, occasionally tardive dyskinesia; hypothermia (occasionally pyrexia), drowsiness, apathy, pallor, nightmares, insomnia, depression, and, more rarely, agitation, EEG changes, convulsions; 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; respiratory depression; endocrine effects such as menstrual disturbances, galactorrhoea, gynaecomastia, impotence, and weight gain; sensitivity reactions such as agranulocytosis, leucopenia, leucocytosis, and haemolytic anaemia, photosensitisation (more common with chlorpromazine than with other antipsychotics), contact sensitisation and rashes, jaundice (including cholestatic) and alterations in liver function; neuroleptic malignant syndrome; lupus erythematosus-like syndrome reported; with prolonged high dosage, corneal and lens opacities and purplish pigmentation of the skin, cornea, conjunctiva, and retina; intramuscular injection may be painful, cause hypotension and tachycardia (see Cautions), and give rise to nodule formation; **overdosage:** see Emergency Treatment of Poisoning, p. 23

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*

PoM **Chlorpromazine** (Non-proprietary)

Tablets, coated, chlorpromazine hydrochloride 10 mg, net price 20 = 14p; 25 mg, 20 = 15p; 50 mg, 20 = 27p; 100 mg, 20 = 31p. Label: 2, 11

Available from Antigen, APS, DDSA (Chloractil®), Hillcross, Norton

Oral solution, chlorpromazine hydrochloride 25 mg/5 mL, net price 100 mL = 58p, 100 mg/5 mL, 100 mL = £1.41. Label: 2, 11

Available from Hillcross, Rosemont

Injection, chlorpromazine hydrochloride 25 mg/mL, net price 1-mL amp = 32p; 2-mL amp = 37p

Available from Antigen

Suppositories, chlorpromazine 100 mg. Label: 2, 11

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

PoM **Largactil®** (Rhône-Poulenc Rorer)

Tablets, all off-white, f/c, chlorpromazine hydrochloride 10 mg. Net price 56-tab pack = 39p; 25 mg, 56-tab pack = 54p; 50 mg, 56-tab pack = £1.13; 100 mg, 56-tab pack = £2.10. Label: 2, 11

Syrup, brown, chlorpromazine hydrochloride 25 mg/5 mL. Net price 100-mL pack = 61p. Label: 2, 11

Suspension forte, orange, sugar-free, chlorpromazine hydrochloride 100 mg (as embonate)/5 mL. Net price 100-mL pack = £1.41. Label: 2, 11

Injection, chlorpromazine hydrochloride 25 mg/mL. Net price 2-mL amp = 37p

BENPERIDOL

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

Cautions; Contra-indications; Side-effects: see under Haloperidol

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

PoM **Anquil®** (Janssen-Cilag)

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

DROPERIDOL

Indications: see under Dose

Cautions; Contra-indications; Side-effects: see under Haloperidol

Dose: by mouth, tranquillisation and emergency control in mania, 5–20 mg repeated every 4–8 hours if necessary (elderly, initially half adult dose); CHILD, 0.5–1 mg daily

By intramuscular injection, up to 10 mg repeated every 4–6 hours if necessary (elderly, initially half adult dose); CHILD, 0.5–1 mg daily

By intravenous injection, 5–15 mg repeated every 4–6 hours if necessary (elderly, initially half adult dose)

Cancer chemotherapy-induced nausea and vomiting, *by intramuscular or intravenous injection,* 1–10 mg 30 minutes before starting therapy, followed by *continuous intravenous infusion* of 1–3 mg/hour *or* 1–5 mg *by intramuscular or intravenous injection* every 1–6 hours as necessary; CHILD *by intramuscular or intravenous injection,* 20–75 micrograms/kg

Premedication, *by intramuscular injection,* up to 10 mg 60 minutes before operation; CHILD 200–500 micrograms/kg

Neuroleptanalgesia, *by intravenous injection,* 5–15 mg at induction with an opioid analgesic; CHILD 200–300 micrograms/kg

PoM **Droleptan®** (Janssen-Cilag)

Tablets, yellow, scored, droperidol 10 mg. Net price 50-tab pack = £12.30. Label: 2

Oral liquid, sugar-free, droperidol 1 mg/mL. Net price 100-mL pack (with graduated cap) = £4.47; 500-mL pack = £21.25. Label: 2

Injection, droperidol 5 mg/mL. Net price 2-mL amp = 90p

FLUPENTHIXOL

(Flupentixol)

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

Cautions; Contra-indications; Side-effects: see under Chlorpromazine Hydrochloride but less sedating; extrapyramidal symptoms more frequent (25% of patients); avoid in senile confusional states, excitable and overactive patients; porphyria (see section 9.8.2)

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

Depression, see section 4.3.4