Chapter 11

Patient-specific issues

Medicines for children: introduction

Children represent a significant proportion of patients in both primary and secondary care. In the UK, the National Service Framework (NSF) for Children[1] lists a number of areas in which pharmacists can have an important role. These include the following areas.

- Developing and providing high-quality medicines information, especially with respect to unlicensed use or formulations.
- Promoting concordance.
- Ensuring good communication between primary and secondary care, especially with respect to unusual or unlicensed preparations.
- Advising on clinically appropriate, safe, and cost-effective use of medicines in children.

It is important to remember that children are not small adults, and neither are they a homogenous group. Drug handling in children can be quite different to that in adults and can also be different at different ages. For medical and pharmaceutical purposes, children are usually grouped according to the following ages:

- Premature—born before 40wks gestation.
- Neonate—≤4wks old (if premature, add the number of weeks premature, e.g. if born 2wks premature, the baby would be considered a neonate until it was 6wks old).
- Infant—4wks to 2 years.
- Child—2 years to (usually) 12 years.
- Adolescent—(usually) 12–18 years.

From 12 years old onwards, drug handling and dosing is usually the same as for adults, but adolescents require special consideration in terms of social and emotional needs.

1 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4090566.pdf.

This page intentionally left blank

Medicines for children: pharmacodynamics and pharmacokinetics

Virtually all pharmacokinetic parameters change with age. An understanding of how drug handling changes with age is essential to avoid toxicity or underdosing.

Tips on making medicine more palatable for children are given in Table 11.1

Absorption

GI absorption may be slower in newborns and infants than in adults. Newborns have a prolonged gastric emptying time. Lower levels of gastric acid in newborns might ↓ absorption of some drugs (e.g. itraconazole). Drugs that bind to calcium or magnesium should not be given at the same time as milk feeds.

Intramuscular absorption requires muscle movement to stimulate blood flow and so could be erratic in newborns who are relatively immobile. In addition, blood supply to the muscles is very variable.

Topical absorption of agents is enhanced in neonates and infants because the skin is thinner and better hydrated. This age group also has a proportionally larger body surface area for weight than older children. Thus, topical agents applied over a large area can provide a significant systemic dose.

Distribution

Total body water changes with age:

- premature—80% of body weight
- newborn—70% of body weight
- children—60–65% of body weight
- adults—60% of body weight.

This affects the volume of distribution of water-soluble drugs, and higher doses per kilogram might be required for premature or newborn infants.

Protein binding

In neonates, protein binding of drugs is less than in adults, but within a few months after birth it is similar to adult levels. ↓ protein binding might account for the ↑ sensitivity of neonates to some drugs (e.g. theophylline).

Metabolism

Premature and newborn infants metabolize drugs more slowly than adults. However, young children have a faster metabolic rate, which ↓ to adult levels with ↑ age. Thus doses of highly metabolized drugs are proportionally lower per kilogram for neonates and infants and higher for young children. As the child grows, doses should be frequently recalculated not only to allow for differing rates of drug metabolism, but also to allow for ↑ height and weight.

Premature infants and neonates have immature renal function, with the neonatal GFR usually ~30% of the adult rate. Thus doses should be ↓ accordingly. After infancy, plasma clearance of some drugs is significantly ↑ because of both ↑ hepatic elimination and ↑ renal excretion.

Table 11.1 Tips on making medicines more palatable

- Chill the medicine (but do not freeze it)*
- Take the medicine through a straw
- Use an oral syringe to direct the medicine towards the back of the mouth and away from the tongue (and therefore away from the highest concentration of taste buds)
- Chocolate disguises many flavours—try mixing the medicine with a small amount of chocolate milk, spread, or syrup*
- Coat the tongue and roof of the mouth with a spoonful of peanut butter or chocolate spread before taking the medicine.
- Suck an ice cube or ice lolly immediately before taking the medicine
- Brush teeth after taking the dose
- Eat strongly flavoured food after the dose—e.g. crisps, Marmite®, or citrus fruit (small amounts of these foods should not adversely affect drug absorption)

*Check drug compatibility and storage temperature requirements.

Medicines for children: licensing

Up to 40% of prescribing in children is unlicensed or 'off licence'—ie the drug is not licensed for use in that age range, route, dose or indication. Extemporaneous preparations and imported and specials products are effectively 'named patient' and thus unlicensed. Until such time as a wider range of formulations is available or drug manufacturers do the relevant trials to obtain licences for paediatric use or indications, this is an unavoidable practice. The Royal College of Paediatrics and Child Health and the Neonatal and Paediatric Pharmacists Group (NPPG) have issued a joint declaration stating the following:

> 'The informed use of unlicensed medicines, or of licensed medicines for unlicensed applications, is necessary in paediatric practice.'

Pharmacists should ensure that licensed preparations are used wherever possible. If there is no alternative, they should ensure that both prescribers and parents (and the child, as appropriate) are informed of unlicensed or off-label use. It is especially important to ensure that parents or carers do not feel that the medicine is 'sub-standard' or 'second best' because it is unlicensed. In general, it is not considered necessary to obtain formal consent for the use of unlicensed medicines in this context. The NPPG has produced leaflets suitable for parents and older children to explain the need to use unlicensed and off-label medicines. These are available on the NPPG website (see also 📖 p.214). Local guidelines on documentation and consent for use of unlicensed medicines should be complied with.

It is important that pharmacists ensure a continued supply of unlicensed, extemporaneous and special medicines by liaising with and providing product information to GPs and community pharmacists.

This page intentionally left blank

Medicines for children: calculating children's doses

A reputable reference source should be used for children's doses. Different sources quote doses in different ways and it is important to be clear how the dose is calculated to avoid the risk of overdose. Doses are usually quoted as follows:

- The total dose in mg/kg body weight per day, and the number of doses it should be divided into.
- The individual dose in mg/kg body weight per dose, and the number of doses that should be given each day.

Most doses are based on weight, although doses based on body surface area are more accurate because this takes into account the child's overall size (Table 11.2). Body surface area dosing is more frequent for drugs if accurate dosing is critical (e.g. cytotoxic drugs). Nomograms for calculating body surface area can be found in paediatric drugs handbooks, or the following equation can be used:

$$\text{body surface area } (m^2) = \sqrt{\frac{\text{body weight (kg)} \times \text{height (cm)}}{3600}}$$

Very rarely it is impossible to find a published and validated children's dose for a drug, in which case it can be estimated from the adult dose based on physiological or pharmacokinetic factors[1] or using approximate proportions (Table 11.3). This should only be used as a last resort. This method tends to give an underdose. Calculated doses should usually be rounded up, rather than down, and the dose titrated according to clinical response, as necessary.

1 Bartelink IH *et al.* (2006) Guidelines on paediatric dosing on the basis of development physiology and pharmacokinetic considerations. *Clinical Pharmacokinetics* **45**: 1077–97.

Table 11.2 Approximate surface area and weight*

	Weight (kg)	Surface area (m^2)
Newborn	3	0.2
1 year	10	0.5
3 years	15	0.6
5 years	20	0.7
9 years	30	1.0
14 years	50	1.5
Adult	70	1.7

*Note that many children in developing countries might only weigh 60–80% of the average weight.

Table 11.3 Estimating children's doses as a proportion of the adult doses*

Weight	Age	Proportion of adult dose
3–5kg	0–5 months	1/8
6–10kg	6 months–1 year	1/4
11–20kg	1–6 years	1/3
21–30kg	7–10 years	1/2
>30kg	11–15 years	3/4

*Note that this method tends to result in an underdose.

Medicines for children: adherence

Counselling on medicine use and adherence issues is important for children. Parents might be familiar with taking medicines themselves but this doesn't necessarily mean that they will cope with giving medicines to their child, especially if they are distressed by the child's diagnosis or the child is uncooperative. The toddler age group is often the most difficult because at this age they can be uncooperative but lack the language ability and insight needed for parents to reason with them.

- Wherever possible and within the child's level of understanding, pharmacists should aim to involve the child in discussions about their medicines.
- Ideally, counselling about medicine use and adherence should involve both parents (or two carers), especially if the therapy is complex and/or long term. As appropriate, also involve school nurses, for example, although it is best to avoid giving doses during school time if at all possible.
- The most appropriate delivery form should be selected. Most parents find an oral syringe easy to use but some children can object to this, and once measured the medicine might have to be transferred to a spoon.
- Parents and carers might find it easier to give the medicine mixed with a small amount of food or drink. They should be taught how to do this correctly so that the child takes the full dose. Medicines should not be added to baby's bottle feeds because the full quantity might not be taken.
- Be aware that some patient information leaflets might be for indications other than the one for which the medicine is being used.
- Explain to the child why they need to take their medicine in simple terms, allowing for any limitations on disclosure of the diagnosis—e.g. a child may not have been told that they have HIV but might have been told that they need medicine to help them fight infection.
- Encourage parents to involve the child in the administration process. From quite a young age (and with appropriate supervision and support), children can be taught to measure doses of liquid medicines, make up a dosette box, or even self-administer insulin.
- Help parents to think ahead to how medicines will be administered during the school day or on a school or youth organization residential event. Tailoring the regimen to once-daily or twice-daily dosing means that drug administration during school hours can usually be avoided.
- Adolescents might wish to discuss their medicines without their parents present. Non-adherence in adolescents is not uncommon as a way of expressing independence and requires sensitive handling.

Further reading

Paediatric Formulary Committee (2011). *British National Formulary for Children* London: Pharmaceutical Press. http://www.bnfc.org

Royal College of Paediatrics and Child Health and the Neonatal Paediatric Pharmacists Group (2003). *Medicines for Children*. London: RCPCH Publications Ltd.

Advice on administering medicines to children, formulae for extemporaneous preparation. http://www.pharminfotech.co.nz

Neonatal and Paediatric Pharmacists Group. http://www.nppg.scot.nhs.uk

National Paediatric Drug Information Advisory Line (DIAL). http://www.dial.org.uk

This page intentionally left blank

‘Pill school’: teaching children how to take tablets and capsules

Preparation

- Discuss the child’s ability to swallow food, especially hard or chewy food, with the parents. Ask whether they think the child would be able to swallow tablets or capsules.
- Ask whether the child has had any previous experience of taking tablets and capsules and whether this was successful.
- Check any dietary issues with respect to the placebo capsules to be used, e.g. allergies to food colouring or consumption of gelatin products.
- Ask parents to ensure that the child has not eaten or drunk anything immediately before the session so that they are not too full to swallow the capsules or water.
- Arrange the appointment for a time when the child will be alert and cooperative—e.g. not straight after school or nursery when they may be tired.
- Advise parents and other healthcare workers not to tell the child in advance what the session is about because this might create anxiety and resistance.
- To avoid possible disruption, ensure that the child has been to the toilet before starting the session.

Equipment

- Prepare a series of capsule shells of different sizes containing sugar strands and place in bottles labelled with the sizes. Place some loose sugar strands in a bottle. Keep bottles and labels hidden from the child’s view.
- Two cups (one for the child and one for you) and a bottle of water.
- Two small trays or containers (e.g. weighing boats), one on which to place capsules and one to use if the child spits out a capsule.
- Tissues for mopping-up purposes.

Environment

- The room should be quiet, without distractions such as books or toys.
- Have only one other person present (as a chaperone) and ask them to sit behind the child out of view. Advise them not to intervene at any stage. Ideally, this should not be a parent.
- Sit across the table from the child.

Process

- Explain the purpose of the session to the child in simple terms. Talk enthusiastically and mention good things about taking tablets or capsules—e.g. avoiding bad-tasting medicine.
- Show the bottle of sugar strands and place a few on the tray. Ask the child to show you that they can swallow these.
- Place two of the smallest capsules on the tray. Explain to the child that now you want them to try swallowing the sugar strands inside

a capsule. Explain how to swallow a capsule without chewing and demonstrate this.
  - Sit or stand upright.
  - Take a breath.
  - Put the pill in the middle of your tongue.
  - Take a mouthful of water and swallow.
  - Keep your head straight.
- Show the child that you have swallowed the capsule by opening your mouth and sticking out your tongue. Make the process fun, but be firm if necessary.
- Ask the child to show you that they can do the same with the other capsule.
- Get them to show you that their mouth is empty by opening their mouth and sticking out their tongue. Praise the child for their success.
- If the child has been successful, repeat the process with the next size of capsule, again demonstrating how to swallow it if necessary. State that it is the next capsule, not that it is larger. Give praise and encouragement at each stage.
- If the child has difficulties swallowing a capsule at any stage, get them to spit it out. Encourage them to try again with the same size of capsule.
- If the child is unsuccessful at the second attempt or if they refuse to try again, stop the session. Do not pressure the child because this could create an association between capsule taking and distress. Praise the child for trying hard.
- At the end of the session, if the parents have not been present, bring them into the room so that the child can demonstrate successful capsule swallowing.
- Give the parents a supply of the largest size swallowed and written instructions on how to take capsules for further practice at home.
- Explain to the child that the medicines they will take could look different to the sample capsules but they should be able to swallow them in the same way.

After the session

- Discuss the child's achievement with medical staff.
- Review current or planned medication to establish whether it can be dispensed as tablets or capsules of a suitable size and shape.
- Bear in mind that uncoated and/or round tablets are harder to swallow than capsules, coated tablets, or oval/capsule-shaped tablets.

Medicines for elderly people: introduction

Elderly people are high consumers of medicines, both prescribed and non-prescribed. In the UK, 50% of NHS drug expenditure is consumed by medicines for older people. Much prescribing for elderly people is done as 'repeats' and without regular review. This can frequently lead to inappropriate or unnecessary therapy, including prescribing for 'diseases' that are actually ADRs.

In the UK, the NSF for Older People[1] has a specific section on medicines management, with the following primary aims.

- Ensuring that older people gain maximum benefit from their medication to maintain or ↑ their quality and duration of life.
- Ensuring that older people do not suffer unnecessarily from illness caused by excessive, inappropriate, or inadequate consumption of medicines.

Elderly people are at ↑ risk of medication-related problems.

- ↑ risk of ADRs (many preventable) caused by polypharmacy, drug interactions, and changes in pharmacokinetics and pharmacodynamics.
- Underprescribing of some medicines—e.g. thrombolysis in MI.
- Non-adherence.
- Repeat medicines not being reviewed, leading to unnecessary long-term therapy and stockpiling.
- Difficulty in accessing the surgery and/or pharmacy.

1 http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4071283.pdf.

This page intentionally left blank

Medicines for elderly people: pharmacokinetics and pharmacodynamics

Physiological changes that occur with age affect drug handling and sensitivity. Predicting at what age these changes become significant is almost impossible because people 'age' at different rates, depending on environmental, social, and other factors. However, the pharmacist should be alert to possible changes in drug handling and sensitivity in any patient >75 years of age.

Absorption

- Ageing rarely has a significant effect on absorption. Delayed gastric emptying ↑ time to peak concentrations (C_{max}) but is rarely clinically significant.
- ↓ production of gastric acid can lead to ↓ absorption of drugs that require an acid environment for absorption (e.g. itraconazole), but can slightly ↑ the amount absorbed of drugs that are broken down by gastric acid (e.g. penicillins).
- Bioavailability of levopdopa is ↑ in elderly people, possibly because of ↓ levels of dopa decarboxylase in the gastric mucosa.
- ↓ regional blood flow might ↓ the rate of absorption of drugs administered by the intramuscular or subcutaneous route, but the total amount absorbed is the same.

Distribution

- Lean body mass ↓ with age, leading to ↑ levels of drugs distributed in the muscle (e.g. digoxin).
- Adipose tissue ↑ up to the age of 85 years, leading to ↑ tissue levels and thus prolonged duration of effect of lipid-soluble drugs (e.g. diazepam). Patients >85 years tend to lose adipose tissue.
- ↓ in total body water leads to ↑ in the serum concentration of water-soluble drugs (e.g. gentamicin and digoxin).
- ↓ serum albumin leads to ↑ levels of free drug for highly protein-bound drugs (e.g. NSAIDs, sulphonylureas, and warfarin). In the acute phase, homeostatic mechanisms usually counteract the ↑ drug effects. ↑ level of free drug also means ↑ amounts for clearance, so the effect is rarely significant in the long term.

Metabolism

Elderly people can have up to a 40% ↓ in hepatic blood flow. Drugs with high first-pass metabolism can be significantly affected (see 📖 p.180). There might be up to 60% ↓ in metabolism of some drugs, such as NSAIDs and anticonvulsants, leading to ↑ concentration, duration of action, and possibly accumulation.

Excretion

The natural ageing process between the ages of 20 and 80 years leads to a 30–35% loss of functioning of glomeruli, with a consequent up to 50%

loss of normal renal function. Serum creatinine levels might be normal or near normal because of ↓ muscle mass, but creatinine clearance will be ↓. Acute illness and dehydration can cause a rapid decline in renal function, which can be exacerbated by the use of potentially nephrotoxic drugs, including high-dose antibacterials. Even a fairly well elderly patient may tolerate a combination of potentially nephrotoxic drugs (e.g. diuretic plus NSAID), but the addition of one more nephrotoxic drug (e.g. an antibacterial) can tip the balance towards renal impairment.

It is advisable to calculate the creatinine clearance (using the Cockroft and Gault equation (see Table 10.5)) for any patient >70 years who is prescribed renally cleared or potentially nephrotoxic drugs. Remember that drugs such as morphine have active metabolites that are renally cleared. Drugs that rely on excretion into the urine for their effect—notably nitrofurantoin—can be ineffective in elderly people.

Pharmacodynamic changes

As the body ages, there is a natural loss of function at a cellular level. This can lead to ↑ or ↓ drug sensitivity. Changes in receptor–drug interactions can occur—e.g. there is a ↓ response to both β-adrenoceptor agonists and β-adrenoceptor antagonists.

Homeostatic responses can be blunted in old age—e.g. postural hypotension is more likely to be caused by blunting of reflex tachycardia, and cardiac failure might result from fluid overload caused by over-enthusiastic rehydration or NSAIDs combined with ↓ cardiac output and renal function.

There is ↑ susceptibility to CNS effects of drugs. Even drugs that are not normally associated with CNS effects can cause such symptoms in the elderly, e.g. histamine H_2 receptor antagonists and diuretics. These effects can occur without changes in kinetics, probably because of ↑ CNS penetration or altered drug response. For example, confusion and dis-orientation are more common in elderly people receiving benzodiazepines, antidepressants, and NSAIDs, even at standard doses. In addition, changes in kinetics can lead to CNS effects not usually seen in younger people—e.g. ↓ renal function can lead to confusion associated with ↑ levels of drugs such as ciprofloxacin and aciclovir.

Medicines for elderly people: medication review

See also 🕮 *p.62.*

Regular medication review is an essential, but often overlooked, aspect of care of the elderly. Both hospital and community pharmacists are ideally placed to do this. Ideally, elderly patients should have their medication reviewed on admission to hospital, and in the community all patients >75 years should have their drugs reviewed at least annually. Prioritize those at highest risk of medication-related problems.

- Elderly patients taking four or more drugs.
- Elderly patients recently discharged from hospital.
- Elderly patients taking 'high-risk' medicines.
  - Hypnotics—drowsiness and falls.
  - Diuretics—dehydration, renal failure and confusion caused by hypokalaemia.
  - NSAIDs—fluid retention and GI bleeds.
  - Antihypertensives—falls resulting from postural hypotension.
  - Digoxin—nausea and vomiting. Confusion could be missed as signs of toxicity.
  - Warfarin—bruising and bleeding.

Other factors that can ↑ the risk of medication-related problems are as follows.

- Social—lack of home support.
- Physical—poor vision, hearing, and dexterity.
- Mental—confusion, depression, and difficulty in understanding instructions.

Elderly patients are often high users of over-the-counter medicines and the pharmacist should be alert to this. Many over-the-counter drugs can:

- be unnecessary
- ↑ the risk of drug interactions
- ↑ the risk of additive side effects
- be an indicator for ADRs to other medicines (e.g. high antacid consumption could point to NSAID-induced gastric irritation).

Medication reviews should include partners and carers (formal and informal) if possible, and the results should be fed back to the GP and other relevant healthcare workers. If patients are attending the clinic for a review, they should be asked to bring all medications with them ('brown-bag review'). This enables the pharmacist to check for the following.

- Stockpiling.
- Out-of-date medicines.
- Problems with reading or interpretation of medicine labels.
- Strategies for self-administration—e.g. marking containers or transferring medicines to other containers.
- Problems with manipulation—e.g. opening bottle caps or using technologically difficult products, such as inhalers or eye drops.
- Use of over-the-counter or herbal medicines.

The NO TEARS tool is useful model both for medication review and when considering initiating a new drug.[1]

- **N**eed and indication.
  - Is the drug really necessary?
  - Is it being used to treat an adverse effect?
  - Can it be stopped?
- **O**pen questions.
  - Ask non-directed questions about the medication.
    — Any problems?
    — Tell me how/when you take these medicines?
- **T**ests and monitoring.
  - Ensure that appropriate monitoring is being done for both desired effect and checking for ADRs.
    Where possible ensure that tests, such as TDM and INR, are done beforehand so that the results can be used to inform the review.
  - Check adherence.
- **E**vidence and guidelines.
  - Ensure that treatment is evidence-based and complies with up-to-date local and national guidelines.
- **A**DRs.
  - Ask about ADRs.
  - Check whether a medicine is being used to treat side effects and, if possible, stop or change the causative drug.
- **R**isk reduction and prevention.
  - Pay special attention to 'high-risk' drugs. Are they really necessary?
  - Could the dose be reduced?
  - If initiating a drug, start at the lowest dose and cautiously titrate according to the response.
- **S**implification and switches.
  - Could a change of drug or formulation simplify the regimen or make self-administration easier?

1 Lewis T (2004). Using the NO TEARS tool for medication review. *British Medical Journal*, **329**: 434.

Dealing with injecting drug users in hospital

Injecting drug users and people who misuse other drugs, including alcohol, can present behavioural, in addition to medical, challenges on admission to hospital. An awareness of the issues involved is important, but equally healthcare staff should not assume that all drug misusers are 'difficult' patients. Drugs of misuse include the following:

- opioids
- benzodiazepines
- other prescription or over-the-counter drugs (e.g. anticholinergics)
- cocaine
- cannabis
- alcohol.

Managing behaviour

- Don't assume that all drug misusers will misbehave. Treat the patient with respect, as you would any other patient. A suspicious or negative manner from the healthcare professional is more likely to generate negative behaviour from the patient.
- Remove temptation—ensure that all drug cupboards and trolleys are locked and drug deliveries are put away immediately.
- Use a firm no-nonsense approach. Guidelines or a contract for acceptable behaviour might be helpful (see 📖 p.75).
- Liaise with local addiction teams for advice and support.

Patients who misuse drugs on the ward

Healthcare professionals should be aware that patients (or their visitors) might misuse drugs on the ward. Indicators for this are as follows.

- Large numbers of visitors and/or visitors at odd times.
- Signs of intoxication or a behaviour change, often after receiving visitors or temporarily leaving the ward.
- Actual evidence (e.g. empty syringe).

Management depends on local policy, but this type of behaviour should not be tolerated. A senior doctor or nurse will normally be the member of staff who addresses this issue with the patient. Other healthcare staff should ensure that their dealings with the patient are consistent with agreed management policies. A suggested approach is as follows.

- Do not condone or tolerate the behaviour; make it clear that it is unacceptable.
- Give a warning that the behaviour will not be tolerated and the patient will be discharged if it is repeated.
- Consider limiting the number of visitors and the time during which they can visit.
- Involve hospital security or the police, especially if the safety of other patients or healthcare staff is compromised.
- Liaise with senior managers/hospital legal advisers to ensure that action taken is within the law.

Handling illegal drugs

Pharmacists could be asked to take possession of illegal drugs that ward staff have taken from a patient. This might include schedule 1 drugs, which normally require a license for possession. However, UK law allows pharmacists to take possession of illegal (including schedule 1) drugs for the following purposes:

- destruction of the drug.
- handing the drug over to the police.

In this situation, it can be difficult to maintain the patient's rights and confidentiality while remaining within the law.

If a sufficiently large quantity is involved, such that it is clear that the drug is not just for personal use, it might be deemed that the public interest outweighs patient confidentiality and the police should be called. The decision to involve the police should only be taken after consultation with senior management and legal advisers.

If the quantity involved is small and clearly for personal use, the drugs should be destroyed. The patient's authority is required to remove and destroy the drug, and if they refuse to hand it over, consideration should be given to discharging the patient or involving the police. Returning the drug to the patient is not an option, because this would make the pharmacist guilty of unlawful supply of a controlled drug.

Managing patients who are opioid dependent

Patients who are maintained on opioid-replacement therapy (e.g. methadone or buprenorphine) in the community should have this continued in hospital.

- Verify the dose independently—e.g. by contacting the GP, addictions service, or community pharmacist.
- Notify the community pharmacist of the patient's admission (to ensure the patient doesn't 'double up' by obtaining supplies from the community, in addition to the hospital supply) and discharge (to ensure that community supply is restarted).
- Liaise with the GP and addictions service to ensure a consistent approach.
- As a rule, it is best to avoid providing more than one or two doses of replacement therapy on discharge. Liaise with the GP/community pharmacist to ensure that valid prescription is available for therapy to be continued in the community after discharge.
- Avoid prescribing other opioids if at all possible, especially short-acting opioids (e.g. pethidine).
- Benzodiazepines should only be prescribed if medically indicated (e.g. for alcohol withdrawal). If night sedation is required, prescribe in accordance with local addictions service guidance.
- If a dose adjustment of the replacement therapy is required (e.g. because of drug interactions), liaise with the local addictions service.

Patients dependent on opioids who are not on replacement therapy require careful management.

- Methadone or buprenorphine should only be prescribed if there are objective signs of withdrawal (Table 11.4).

- The dose should be titrated according to objective withdrawal symptoms, not according to the patient's reported use of street opioids.
- A suggested regimen is as follows.

Day 1

- Objective signs of withdrawal—methadone 20mg single dose (stat).
- Further signs of withdrawal—methadone 10mg single dose can be repeated after 4h.
- Maximum dose of methadone in the first 24h is usually 40–50mg.

Day 2 onwards

- Total dose given in the first 24h should be prescribed as a single daily dose.
- Up to two additional doses of methadone (10mg) can be given every 24h if further objective signs of withdrawal occur. Rewrite the maintenance dose each day to include additional doses until dose titration is achieved.
- A dose of methadone 80mg daily is usually considered the maximum maintenance dose, but some centres use higher doses.
- At all times, doses should only be ↑ if there are objective signs of withdrawal. Bear in mind that methadone has a long half-life, and so it takes several days to reach steady-state concentrations.
- Additional doses should not be prescribed 'as required' (prn)—the patient should be assessed each time by a doctor and any extra doses (if needed) prescribed as a single dose.
- If the patient wishes to continue replacement therapy after discharge, they should be referred to the local addictions service as soon as possible.
- Patients who do not wish to continue replacement therapy might require a rapid reduction of the therapy before discharge. Note that these patients will usually return to using street opioids on discharge; thus the risk of withdrawal is minimal.

It is advisable for hospitals to produce written guidelines on opioid replacement therapy in consultation with the local addictions service. This ensures continuity of care and can also be a great help to junior doctors, who may be pressurized by patients to prescribe replacement therapy inappropriately.

Managing alcohol withdrawal

See 📖 p.610.

Management of concurrent illness

In general, concurrent illnesses in patients who misuse drugs should be managed in the same way as for any other patient. However, the following points should be considered.

- Avoid opioids, benzodiazepines, and other drugs that could be misused.
- Be aware that enzyme inducers and inhibitors can affect methadone levels.
- If the patient has a chaotic lifestyle, avoid drugs with a narrow therapeutic index—e.g. daily low molecular weight heparin is preferable to warfarin for deep vein thrombosis (DVT).

Table 11.4 Withdrawal scale from opiates

Methadone is indicated if score ≥7		
Objective signs		
Sweating		
	None	0 ☐
	Clammy	1 ☐
	Sweaty	2 ☐
	Running sweat	3 ☐
Retching		
	None	0 ☐
	Mild	1 ☐
	Moderate	2 ☐
	Vomiting and retching	3 ☐
Gooseflesh		
	None	0 ☐
	Some	1 ☐
	Moderate	2 ☐
	Severe, with piloerection and shivers	3 ☐
Lacrymation		
	None	0 ☐
	Watery eyes; no tears	1 ☐
	Some tears	2 ☐
	Crying	3 ☐
Score /12		
Record values of:		
Pulse (record value).	Below 80–0	☐
	Over 80	☐
BP (record value).		

Pain control

Pain should be managed in the same way as for any other patient. Many doctors assume that patients on opioid replacement therapy require less analgesia, and the patient might insist that they require extra analgesia because of tolerance. If the patient is experiencing pain, it is clear that the replacement therapy is not blocking all opioid receptors and analgesia is required. Ideally, opioids—both weak and strong—should be avoided. If an opioid is required, a long-acting opioid is preferred. Tramadol has no advantage over codeine in this setting.

Because buprenorphine is a partial antagonist, it can present a specific problem in patients who require opioid analgesia (e.g. postoperatively). It might be appropriate to convert the patient to an equivalent dose of morphine before surgery. The local addiction service should be contacted for advice.

Discharge prescriptions for opioid-replacement therapy

Injecting drug users who are stabilized with methadone (IV or oral) or buprenorphine (Subutex®) might require a supply on discharge from hospital. It is usually not advisable to give more than a 24–48h discharge supply, especially if the patient usually gets their supply on a daily basis from the community pharmacist. Sometimes there can be a delay before a prescription for a community pharmacy supply can be arranged (e.g. at weekends or on bank holidays). On these occasions, it might be appropriate to use a prescription issued by the hospital, which can be dispensed in the community (FP10(HP) in the UK).

Things to consider

- Could an alternative arrangement be made—e.g. could the patient attend the ward/out-patient clinic for a supply?
- In the UK, only Home Office registered doctors can prescribe diamorphine, cocaine, or dipipanone to injecting drug users, but any doctor can prescribe any other replacement therapy.
- Close liaison with the local addiction service/GP/community pharmacist is important to ensure continuity of care.

Writing the prescription (guidelines refer to UK law)

- Normal writing rules for controlled drug prescriptions apply.
- FP10(HP) prescriptions cannot be used for instalment prescribing. If a daily pick-up is required, a separate prescription must be written for each day.
- FP10(MDA)[1] prescriptions can be used by any doctor to write instalment prescriptions. The prescription must specify the total quantity required, the amount of the instalments to be dispensed, and the intervals to be observed between instalments.
- A maximum of 14 days' supply of schedule 2 controlled drugs can be prescribed by instalments for the treatment of substance misuse.
- FP10 prescriptions have a potential street value and may be sold to other injecting drug users. Consider posting or delivering the prescription to the community pharmacy, rather than handing it to the patient. Check normal practice with the local addiction service/GP.

1 HBP(A), HBP or GP10 in Scotland, WP10 (MDA) or WP10(HP)Ad in Wales.

Surgical patient and nil by mouth (NBM) issues

It is imperative that a comprehensive DHx is undertaken for all patients admitted to hospital for surgery. The DHx should include regular, if needed, and recently stopped or withheld medications. Over-the-counter and herbal products need to be documented.

- Medicines used to control life-threatening conditions should be continued.
- Optimize the treatment of chronic diseases before admission for surgery—e.g. for asthma and COPD.
- For surgical emergencies, e.g. abdominal aortic aneurysm (AAA), it might not be possible to optimize drug therapy preoperatively and the pharmacist needs to highlight any possible complications relating to a recently administered drug that otherwise should have been stopped or dose-modified.

In general, with the exception of those drugs noted in this section, few drugs need to be stopped before surgery.

NBM period

- Patients are at risk of aspirating their stomach contents during general anaesthesia. They are usually prevented from eating within 6h of surgery. However, clear fluids leave the stomach within 2h of ingestion, and thus free clear fluids that enable a patient to take routine medication are allowed up to 2h presurgery.
- After surgery, oral medicines can be restarted at their previous pre-operative dose as soon as the patient can swallow small amounts of fluid.
- If a patient is likely to be NBM for a long time (e.g. surgeon's plan and postoperative nausea and vomiting (PONV)), the drug can be given by an alternative route—e.g. rectal, transdermal, parenteral, or feeding tube delivery.
- Drugs with a long half-life (e.g. levothyroxine) or long duration of action (e.g. antidepressants) shouldn't cause a problem if they have to be omitted for several days.

Reviewing a patient's medication during the NBM period

The risks and benefits must be considered when deciding to continue or suspend medication. For example, the consequences of stopping long-term therapy for conditions such as osteoporosis or osteoarthritis in the NBM period might be considered non-problematic in the majority of patients.

To avoid interrupting appropriate long-term therapies, oral medicines can be administered with sips of clear oral fluid in the NBM period.

The anaesthetist should be contacted if there is any doubt about a patient's specific medication plan—e.g. if a drug is known to have potential interaction with anaesthetic agents.

There are a few significant interactions between drugs used during surgery and routine medications that require the drugs not to be administered concurrently. This is usually managed by the anaesthetist, by their choice of anaesthetic technique. Significant interactions are as follows.

- Enflurane can precipitate seizure activity in patients taking tricyclic antidepressants.
- Pethidine can precipitate fatal 'excitatory' reactions in patients taking monoamine oxidase inhibitors and can cause serotonin syndrome in patients taking SSRIs.
- The effects of suxamethonium can be prolonged by neostigmine.
- The metabolism of midazolam is significantly decreased by protease inhibitors and efavirenz.

Controversial therapy for surgical patients

Hormone-replacement therapy (HRT)

Women on HRT had an ↑ risk of developing venous thromboembolism (VTE) after major surgery compared with controls. The MHRA advise that there is no need to stop HRT unless patients have other predisposing risk factors for VTE; such patients require suitable thromboprophylaxis.

For patients with predisposing risk factors, HRT should be stopped 4wks before major surgery.

Combined oral contraceptives *(see 🕮 p.463)*

Again, there is an ↑ risk of VTE in patients having therapy with COCs. Therapy should be discontinued 4wks before major elective surgery and all leg surgery. However, the risks and consequences of pregnancy versus VTE must be discussed with patients.

COCs should be restarted at the first menses that occurs at least 2wks after full mobilization.

Tamoxifen

Patients on tamoxifen therapy have a higher risk of VTE after surgery. However, tamoxifen treatment for breast cancer should be continued during surgery unless directed by the patient's oncologist, and close monitoring of VTE symptoms for 3 months post surgery should be planned.

Patients having tamoxifen treatment for fertility should have treatment suspended 6wks before major surgery.

Methotrexate

Fluid restriction, hypovolaemia, and renal hypoperfusion can result in ↓ clearance; it is advisable to suspend methotrexate for 2days before surgery and check renal function before recommencing therapy.

Monoamine oxidase inhibitors

MAOIs can result in hypertensive crisis if used concurrently with interacting drugs (e.g. pethidine, dextromethorphan, and pentazocine). They are usually withdrawn 2wks before surgery. However, the risk of psychiatric relapse must be considered. If necessary, MAOIs can be substituted with a short-acting form, such as moclobemide (which can be withheld on the morning of surgery). If withdrawal is not possible, avoid pethidine and indirectly acting sympathomimetics—use isoprenaline instead. Phentolamine can be used to ↓ BP in the event of a hypertensive crisis.

Corticosteroids

Stress caused by surgery is associated with ↑ cortisol production. Prolonged corticosteroid therapy, especially at high doses, can cause adrenal atrophy, an impaired stress response, and risk of hypoadrenal crisis, manifesting in circulatory collapse and shock.

The risk of HPA (hypothalmic–pituary–adrenal) axis suppression should be considered if patients have been on steroids for 1–2wks before surgery or within the last 6 months. The dose and duration of steroids determines the risk, in addition to the type of surgery. Therefore these patients will require IV hydrocortisone cover. The usual dose is 50–100mg of hydrocortisone given preoperatively, intraoperatively (if necessary), and every 6–8h for 2–3 days after surgery. Normal preoperative steroid doses should be restarted 2 days after surgery (no gradual dose reduction is needed from postoperative cover).

Lithium

Lithium prolongs the action of depolarizing and non-depolarizing muscle relaxants. Ideally, stop therapy 24–72h before major surgery, but therapy can continue during minor surgery. If it is not possible to stop therapy, ensure adequate fluid intake during and after surgery. Monitor U&E regularly; measure lithium blood levels if necessary.

Diuretics

Omit K^+-sparing diuretics on the morning of surgery because ↓ kidney perfusion in the immediate postoperative period can predispose to hyperkalaemia. Thiazide and loop diuretics need not be omitted. Any electrolyte imbalance should be corrected before surgery.

β-blockers

Anaesthesia and surgery can provoke tachycardia and ↑ BP in patients with hypertension. β-blockers can help to suppress these effects and therefore are usually continued perioperatively.

Antiplatelet drugs

Aspirin/clopidogrel should be stopped when the risks of postoperative bleeding are high or if the consequences of, even minor, bleeding are significant (e.g. retinal and intracranial bleeding). This must be balanced against the risk of precipitating thromboembolic complications if these drugs are stopped, particularly in patients with unstable angina. If low-dose aspirin or clopidogrel are stopped, this is generally 7–10 days before surgery to enable recovery of adequate platelet function. It is not usually necessary to stop dipyridamole before surgery, but if complete absence of antiplatelet effect is desired, it should be stopped 24h before surgery.

Anti-Parkinson's drugs

There is a small risk of arrhythmias or hypertension during anaesthesia in patients with Parkinson's disease. However, anaesthesia can worsen symptoms of Parkinson's disease after surgery and uncontrolled symptoms ↓ mobility and impede recovery. These drugs should be continued wherever possible. Procyclidine can be given by injection to relieve rigidity and tremor if the patient is unable to take oral medication after surgery.

Antipsychotics and anxiolytics

Generally these agents are continued to avoid relapse of the condition. Antipsychotics can ↓ anaesthetic requirements and potentiate arrhythmias. However, clozapine should be stopped 24h before surgery. Therefore if the patient is on the morning list, do not give medication on the day before surgery, in addition to the day of surgery itself. There are no withdrawal problems associated with doing this. If the patient is unable to take clozapine for >2 days because of being NBM, the drug must be gradually re-titrated up from the starting dose (12.5mg once or twice daily).

Oral hypoglycaemics

For major surgery, most patients with type 2 diabetes benefit from IV insulin therapy, especially if a prolonged NBM period is expected or if the stress from surgery has led to unacceptable hyperglycaemia.

However, the following guidance can aid your patient management.

- Glibenclamide—switch to a sulphonylurea with a shorter half-life 3 days before surgery or switch to soluble insulin.
- Gliclazide/glipizide/tolbutamide—omit therapy on the day of surgery.
- Metformin—to ↓ the risk of lactic acidosis, withdraw the drug 48–72h before surgery and restabilize 48h after surgery.

This page intentionally left blank

Chapter 12

Pharmaceutical calculations

Concentrations

Pharmaceutical preparations consist of a number of different ingredients in a vehicle. The ingredients can be solid, liquid, or gas.

'Concentration' is an expression of the ratio of the amount of an ingredient to the amount of product. Concentrations can be expressed in several ways.

- Solutions of solids in liquids, denoted by w/v.
- Solutions of liquids in liquids, denoted by v/v.
- Admixtures of liquids in solids (v/w) or solids combined with solids (w/w).

Concentrations are expressions of ratios and are written in different formats that can cause confusion. Formats traditionally used are as follows:

- amount strengths
- ratio strengths
- ppm (parts per million)
- percentage strength.

Amount strengths

A preparation contains 900mg of sodium chloride dissolved in water to make a final volume of 100mL. The concentration of this solution can be written as an amount strength in units of 900mg/100mL, 9mg/mL, 0.9g/100mL, or 9g/L.

Ratio strengths

Convention states that when ratio strength represents a solid in a liquid, involving units of weight and volume, the weight is expressed in grams and the volume in millilitres.

A 1 in 50 sodium chloride in water preparation is a solid in a liquid (w/v) ratio strength. This means that the solution contains 1g of sodium chloride made up to 50mL with water.

A 14 in 100 sulphuric acid in water preparation is a liquid in liquid (v/v) ratio strength, i.e. 14mL of sulphuric acid in 86mL of water.

Parts per million (ppm)

This expression is used when the ratio of ingredient to product is very small, by convention 1ppm weight in volume is 1g in 1000000mL. 1ppm weight in weight is 1mg per 1000000mg or 1g per 1000000g. In volume, it is 1mL in 1000000mL or 1L in 1000000L.

Percentage strength

'Percentage' in pharmaceutical calculations is quantified as the amount of ingredient in 100 parts of the product.

By convention, % w/v indicates the number of grams of ingredient in 100mL of product. Therefore 900mg of sodium chloride made up to 100mL with water can be expressed as 0.9g in 100mL and the percentage strength is 0.9% w/v.

A 1 in 1000 adrenaline injection is equivalent to 0.1% w/v or, by convention, 1g of adrenaline made up to 1000mL with water.

A 1 in 10 000 adrenaline injection is equivalent to 0.01% w/v or, by convention, 1g of adrenaline made up to 10000mL with water.

Calculations

For example, how many millilitres of a 1 in 50 w/v solution are required to make 500mL of a 0.02% solution?

By convention, 1 in 50 means 1g in 50mL and 0.02% w/v means 0.02g in 100mL. Let the number of millilitres of the 1 in 50 solution be *y* and let the amount of ingredient in grams in 500mL of 0.02% solution be *x*. The amount of ingredient in grams in *y*mL of a 1 in 50 solution will also be *x*.

Setting up proportional sets

For 1 in 50:

Ingredient (g)	1	*x*	1g
Product (mL)	50	*y*	to 50mL

For 500mL of 0.02%:

Ingredient (g)	0.02	*x*	0.02g
Product (mL)	100	500	to 100mL

By 'spotting' $x = 0.1$; substitute into the first pair of proportional sets.
For 1 in 50

Ingredient (g)	1	0.1	1g
Product (mL)	50	*y*	to 50mL

By 'spotting' $y = 5$. Therefore 5mL of a 1 in 50 w/v solution is required to make 500mL of a 0.02% w/v solution.

Alternatively, how many grams in 500mL of 0.02% solution?

0.02% = 0.02g in 100mL
in 500mL = 0.02 x 5
= 0.1g

1 in 50 solution, by convention 1g in 50mL
Then, to calculate the volume containing 0.1g, 1/10 of 1g or 1/10 of 50mL = 5mL.

Moles and millimoles

The atomic and molecular weights of a drug can be used as methods of defining the amount of drug. The substance can be atoms, molecules, or ions; a mole is the weight expressed in grams. The mole is the SI base unit for the amount of a substance—e.g. the atomic weight of iron is 56 and 1 mole of iron weighs 56g.

The molecular weight of a drug (e.g. sodium chloride) is the sum of all the atomic weights of the individual atoms in the molecule. A molecule of sodium chloride consists of one sodium ion and one chloride ion :

- 1mole sodium ions weighs 23g
- 1mole chloride ions weighs 35.5g
- hence the molecular weight of sodium chloride is 58.5g

In the same way that the system of weights and volumes have multiples and subdivisions (e.g. milli, micro, and nano), so the mole has similar subdivisions and multiples:

- 1mole contains 1000 millimoles (mmol)
- 1mmol contains 1000 micromoles (mcmol)
- 1micromol contains 1000 nanomoles (nmol)
- 1nanomol contains 1000 picomoles (pmol)

Amount of substance concentration

In clinical chemistry, laboratory results are usually written in terms of mol/L (or mmol/L or micromol/L).

Example

How many millimoles of sodium chloride are there in a litre of sodium chloride 0.9% w/v?

First calculate the weight of sodium chloride in a litre:
0.9g in 100mL
=0.9g×10 in 1000mL
=9g in 1000mL.

For the molecule sodium chloride: 1mole = 58.5g
58.5g = 1000mmol
9/58.5 = *x*/1000
x = 9000/58.5
x = 153mmoL.

Alternatively, to calculate the number of millimoles contained in 1g of substance, use the following formula:

$$\text{mmol} = \frac{1000 \times \text{number of specified units in one unit (atom, molecule or ion)}}{\text{atomic, molecular, or ionic weight}}$$

Number of mmol of sodium in 1g of sodium chloride (molecular weight = 58.5):

$$\text{mmol} = \frac{1000 \times 1}{58.5}$$
$$= 17\text{mmol in 1g or } 153\text{mmol in 9g}$$

For $CaCl_2.2H_2o$ (molecular weight = 147)

$$\text{mmol of calcium in 1g } CaCl_2 2H_2o = \frac{1000 \times 1}{147} = 6.8\text{mmol}$$

$$\text{mmol of chloride in 1g } CaCl_2 2H_2o = \frac{1000 \times 2}{147} = 13.6\text{mmol}$$

$$\text{mmol of water in 1g } CaCl_2 2H_2o = \frac{1000 \times 2}{147} = 13.6\text{mmol}$$

i.e. each gram of $CaCl_2.2H_2O$ represents 6.8mmol of calcium, 13.6mmol of chloride, and 13.6mmol of water of crystallization.

Practical issues involving pharmaceutical calculations

- Always work from a written master copy.
  - Calculate the amounts of ingredients for 200mL Chloral Mixture BP 1988:

Ingredients	Master formula	Scaled quantities
Chloral hydrate	1g	20g
Syrup	2mL	40mL
Water	To 10mL	To 200mL

- Use double checks: 1 is 1/10 of 10 and 20 is 1/10 of 200.
- Don't forget your units: 1g = 1000mg = 1 000 000micrograms.

Preparing dilutions

- Ensure correct choice of diluent.
- Calculate dilution factor.
- Correctly express the concentration of the diluted product on the label.

Example 1

Calculate the amount of benzalkonium chloride solution BP 2004 needed to prepare a 150mL of a solution of benzalkonium chloride 10% w/v. Benzalkonium chloride solution BP 2004 is a 50% w/v concentration.

Calculation of dilution factor

Method 1

$$\frac{\text{Strength of concentrate}}{\text{Strength of dilute solution}} = \text{dilution factor}$$

$$\frac{\text{Strength of concentrate}}{\text{Strength of dilute solution}} = \frac{50\%\ \text{w/v}}{10\%\ \text{w/V}} = 5 \text{ times}$$

$$\text{To prepare dilute solution} = \frac{\text{final volume}}{\text{dilution factor}}$$

$$150 / 5 = 30\text{mL of concentrate solution}$$

The diluted solution is obtained by using 30mL of BP solution and diluting with 120mL of water.

Method 2

Product of volume and concentration:

$V_c \times C_c = V_d \times C_d$ where

$V_c \times 50 = 150 \times 10$

$V_c = 150/5$

$V_c = 30\text{mL}$

V_c = volume of concentrated solution
C_c = concentration of concentrate
V_d = volume of diluted solution
C_d = concentration of diluted solution

Example 2

Calculate the quantity of potassium permanganate 0.25% w/v solution that is required to produce 100mL of a 0.0125% w/v solution of potassium permanganate.

Calculation of dilution factor

$V_c \times C_c = V_d \times C_d$

V_c = volume of concentrated solution = unknown
C_c = concentration of concentrate = 0.25%
V_d = volume of diluted solution = 100mL
C_d = concentration of diluted solution = 0.0125%

$V_c \times 0.25\% = 100\text{mL} \times 0.0125\%$
$V_c = 1.25/0.25$
$= 5\text{mL}$

Dilution instructions

5mL of potassium permanganate solution 0.25% w/v must be diluted to 100mL with water to produce a 0.0125% w/v solution.

Pharmaceutical calculations involving drug administration

Calculations

- Calculations usually involve fairly straightforward theory, but difficulties can arise as a result of interruptions, tiredness, or lack of experience.
- In preparing infusions, the mathematics normally involves translating units such as micrograms/kg body weight/min into a practical number of millilitres of diluted infusion solution per hour.

Examples

A patient requires a parenteral loading dose of 0.5mg of digoxin. Digoxin is available as an injection containing 250micrograms/mL. How many millilitres of injection will supply the required dose?
First convert mg to micrograms:
0.5mg = 500micrograms

Setting up a proportional set

Weight of digoxin (mg)	250	500
Volume of injection (mL)	1	*y*

250 multiplied by 2 gives 500, so 1 is multiplied by 2 to give $y = 2$.

Because the injection contains 250micrograms in 1mL, a 500micrograms dose will be provided in 2mL.

ITU prepare dobutamine as a standard concentration of 250mg in 50mL 5% dextrose solution. You need to confirm that the prescribed 5micrograms/kg/body weight/min dose for a 70kg patient is correctly delivered by the volumetric hourly rate set by the nurse.

Standard concentration = 250mg in 50mL (patient 70kg)

To calculate the hourly rate: = 5micrograms x kg body weight × min
= 5 × 70 × 60(min)
= 21 000micrograms/h

Concentration of dobutamine (convert to micrograms) = 250mg in 50mL
= 250 × 1000 (micrograms) in 50mL
= 250 000micrograms in 50mL
= 5000micrograms in 1mL

Volume per hour requires 21 000micrograms to be administered
= (21 000micrograms/h)/(5000micrograms/mL)
= 4.2mL/h