Chapter 1

Adherence

Introduction to adherence

What is adherence?

'To be taken as directed' is an instruction that frequently appears on medicine labels. It suggests that a patient will obey the doctor's 'orders' without question. However, as most pharmacists are well aware, patients frequently choose not to 'take as directed'.

'Compliance' is a term used to describe whether or not a patient takes their medicines as directed. It implies a paternalistic relationship between the doctor (or other healthcare professional) and the patient, with little, if any, discussion or negotiation.

'Concordance' is a two-way exchange between healthcare professional and patient. The patient participates in both the consultation and the decision-making process, and the patient's preferences and beliefs are taken into account. However, this rarely happens in full in a busy general practitioner's (GP's) surgery, hospital ward, or out-patient clinic.

'Adherence' is somewhere between compliance and concordance. The healthcare professional accepts that the patient's beliefs, preferences, and prior knowledge influence medicine-taking and attempts to address this. However, adherence interventions are frequently made after the prescription is written and the patient might not have had much influence on the choice of drug. Consequently, pharmacists and specialist nurses tend to have a bigger role in facilitating adherence than doctors.

Concordance requires a high level of resources and a multidisciplinary effort. However, adherence support can be carried out by pharmacists to some extent in their everyday practice. Thus this discussion will concentrate on adherence.

Why is adherence important?

It is estimated that, on average, 50% of patients on long-term therapy do not take their medicines 'as directed'. The costs of this are potentially significant on both personal and public levels. It is estimated that up to 30% of drug-related hospital admissions result from non-adherence. In one study, 91% of non-adherent renal transplant patients experienced organ rejection or death compared with 18% of adherent patients.[1] The cost of wasted medicines and ↑ health expenditure to treat uncontrolled disease represent a significant public cost.

Why do patients not take their medicines?

Numerous studies have attempted to identify the causes of non-adherence and many factors have been identified (Table 1.1). Different factors are relevant to different diseases or settings; for example, cost is an issue in the USA (because patients have to pay for medicines/health insurance) but rarely in the UK. The reasons for non-adherence generally fall into two categories:

- involuntary or behavioural (e.g. simply forgetting)
- voluntary or cognitive (e.g. concerns about side effects).

1 De Geest S *et al.* (1995). Incidence, determinants, and consequences of subclinical noncompliance with immunosuppressive therapy in renal transplant patients. *Transplantation* **59**: 340–7.

Pharmaceutical manufacturers tend to concentrate on behavioural factors—producing combination tablets or once-daily versions of their medicines, which are supposedly easier to take. There is evidence to suggest that adherence is reduced if the dose frequency is more than three times daily, but no data are available to support once-daily over twice-daily dosing. Patients might prefer combination products or once-daily dosing, but preference does not necessarily relate to adherence. Once-daily dosing could, in fact, lead to a worse therapeutic outcome because missing one dose means missing a whole day's therapy.

Many adherence strategies focus on cognitive issues. Intuitively it seems right that if patients do not adhere because of fears or misconceptions about their medicines, addressing these issues should improve adherence. However, it is not clear whether non-adherent patients lack knowledge and understanding or whether these are the patients who fail to seek advice.

Ultimately, it is the patient's, not the healthcare professional's, agenda that influences whether or not they take their medicines.

Table 1.1 Factors reported to affect adherence

Ability to attend appointments
Age
Beliefs about medicines
Chaotic lifestyle
Complexity of regimen
Concerns about confidentiality
Cost
Cultural practices or beliefs
Depression
Educational status
Frequency of doses
Gender
Health beliefs and attitudes (towards self and others)
Impact on daily life
Language (if the patient's first language is different from that of healthcare professional's)
Literacy
Manual dexterity
Past or current experience of side effects
Satisfaction with healthcare
Self-esteem
Side effects
Socioeconomic status

Assessing adherence

Various methods of measuring adherence have been developed, but none of them is entirely satisfactory.

- Treatment response—the most clinically relevant method of assessing adherence. If the patient has been taking their medicines, logically their health should improve (assuming that the choice of therapy was appropriate). A reasonably non-invasive and simple marker of treatment success is necessary (e.g. measuring blood pressure (BP) or cholesterol levels). However, some markers might only show recent adherence (e.g. blood glucose levels).
- Therapeutic drug monitoring (TDM)—this has limited use for assessing adherence. If serum levels are within the therapeutic range, recent, but not long-term, adherence can be assumed. Sub-therapeutic levels can be an indicator of erratic or recent non-adherence, but could also reflect malabsorption of the drug or a drug interaction.
- Medicines event monitoring systems (MEMSs)—these are special bottle caps that record each time the bottle is opened. The information can be downloaded so that each time and date the bottle was opened can be read. However, MEMS caps can only record whether the bottle has been opened, not whether any drug (or how much) was taken out of the bottle. Ideally, they should be used in conjunction with some form of patient diary so that if the bottle is opened or not opened for some reason (e.g. taking out two doses at once), this can be recorded. MEMS caps are expensive and are usually only used in clinical trials. Blister-packed medicines have to be popped into a suitable container, which can be time consuming and inconvenient.
- Pharmacy records (refills)—these can be used to check whether the patient collects the correct quantity of tablets each time, so that they do not run out if they have been taking their drugs correctly. However, this system cannot determine whether the patient actually takes the tablets.
- Patient self-report—the patient should be asked (in a non-judgemental way) whether they have missed or delayed any doses, and if so, how many. Patients tend to overestimate their level of adherence and could give the answer they feel the enquirer wants to hear rather than a true picture. However, patient self-report correlates well with other measures and is relatively cheap and easy to do.

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Strategies to improve adherence

Numerous strategies have been used to attempt to improve adherence, but there is little evidence that any of them are effective in the long term. Interventions to support adherence are discussed here.

Monitored dose systems (MDSs)

MDSs ('dosette boxes') are useful for patients who might have difficulty understanding or following instructions—because of language, learning, or memory problems. Different types of box are available and it is important to ensure that the patient has the dexterity required to use them. There is no guarantee that the patient will actually take their tablets, but MDSs provide a useful check for whether or not a dose has been taken—if the tablets are still there, clearly the dose has been missed, but an absence of tablets doesn't necessarily mean that the tablets have been swallowed.

MDSs are time consuming to fill and pharmacists must ensure that if a patient starts to use an MDS in hospital, a continuing supply of filled MDSs can be ensured in the community. MDSs can only be used for solid-dose formulations and are not suitable for hygroscopic tablets (e.g. sodium valproate), 'as required' drugs (e.g. analgesics), or variable-dose medicines (e.g. warfarin).

Alarms

Alarms, bleeps, and phone calls have all been used to remind patients to take their medicines. Many patients find it useful to set the alarm on their mobile phone because this is less obvious than a special alarm. Text messaging has also been used to remind patients to take their tablets, but this requires a system to be set up to send the messages and should only be done with the patient's consent.

Refill/follow-up reminders

Patients who attend follow-up clinics and collect refill or repeat prescriptions are more likely to adhere to their medication regimen. Adherence support should not just concentrate on medicine-taking, but also ensure that the patient adheres to other therapies, out-patient appointments, etc. Keeping the patient engaged with the whole of their care could be the most important adherence intervention.

Regimen simplification

Patients who have to take their medicines more than three times daily are less likely to adhere fully to their regimen. Further complications, such as having to take medicines with food or on an empty stomach, make adherence even harder. Ideally, the regimen should be simplified to three times daily or less, with times that fit in with the patient's lifestyle.

Written and oral patient information

Bombarding the patient with drug information can be counterproductive, but well thought out advice is important. Much of this can be done when handing out the medicine. A simple explanation of the dosage schedule and probable side effects should be given with every prescription handover. Remember that patients might not understand terms that seem

obvious to a healthcare professional. For example, 'take two tablets twice daily' could be interpreted as 'take one tablet morning and evening' (i.e. two tablets in 24h). Clearly stating that the patient should 'take two tablets in the morning and two tablets in the evening' helps to clarify exactly what is expected.

Manufacturers' patient information leaflets are frequently complex and beyond the reading ability of many patients. A list of side effects can scare patients and confirm the belief that the medicine could do more harm than good. A brief explanation of common side effects and what to do about them, in addition to reassurance that the patient is unlikely to experience other less common side effects listed, can be of considerable benefit.

For more complex or problematic therapies, it might be necessary to spend a substantial amount of time discussing treatment with the patient. This is often a task for specialist pharmacists (where available) in hospitals or GP's surgeries. The patient should be given time to express their fears and beliefs and to ask questions about therapy. Two-way communication between patient and healthcare professional has the following benefits.

- Improves patient satisfaction with care.
- Improves patients' knowledge of their condition and treatment.
- Increases the level of adherence.
- Improves health outcomes.
- Leads to fewer medication-related problems.

Verbal information should be backed up with written information. For many chronic diseases, there is a wealth of literature available from the Pharmaceutical Industry or self-help organizations (e.g. Diabetes UK). It might be appropriate to write tailor-made patient information for certain drugs or therapies.

Comprehensive management

This involves a multidisciplinary approach, which encompasses all the strategies outlined in this section. It is potentially complex, labour intensive (with associated costs), and not feasible or necessary in many situations. However, it is appropriate for some diseases and treatments (e.g. diabetes mellitus and antiretrovirals). Some schemes can be quite intensive and care must be taken that patients do not lose autonomy as a result of the scheme. Expert patient schemes are a good example of comprehensive disease self-management (alongside conventional care), whereby patients are taught by their peers. See http://www.nhs.uk/conditions/Expert-patients-programme-/Pages/Introduction.aspx. These schemes deal with complete management of the disease, not just drug therapy.

Adherence counselling

Pharmacists involved in adherence counselling should ideally employ the communication skills discussed in Chapter 4 (see 📖 p.94).

When discussing treatment with the patient for the first time, it is important to establish what they already know and any beliefs they hold. Possible questions to ask the patient include the following.

- Tell me anything you already know about the disease/treatment.
- What have the doctors already told you?
- Have you read/found any information about the disease/treatment (e.g. on the internet)?

Having established baseline knowledge, the pharmacist can then proceed to fill in gaps and attempt to correct any misconceptions. The latter must be done tactfully, in order not to undermine patient self-confidence and their confidence in others (bear in mind that the most cited sources of medicines information are family and friends). A checklist of information that could be provided is shown in Box 1.1, but this should be tailored according to the setting and patient's needs.

Sometimes it is useful to provide written information (to complement verbal information) at the beginning of the session so that you can go through the information with the patient, but sometimes it is better to supply written information at the end so that the patient is not distracted by what they have in their hand. Suggest other sources of information, such as self-help organizations and suitable websites, and provide your contact details for further questions.

When questioning the patient about the level of adherence, it is important to do so in a non-judgemental way. A reasonably accurate picture of adherence, and whether the patient's lifestyle affects it, can be obtained if the patient is asked how many doses they have missed or delayed:

- in the past month
- in the past week
- over a weekend.

This method tends to give a more realistic idea of adherence, but patients tend to underestimate how many doses they have missed. It is also important to confirm that the correct dose (e.g. number of tablets) has been taken and that any food restrictions have also been adhered to.

If the patient has been non-adherent, ask them why they think they missed doses and if they can think of ways to overcome this. Work together with the patient to find strategies to overcome non-adherence. Ask the patient to tell you in their own words why adherence is important and reflect this back, correcting any inaccuracies as you do so. Verify that the patient understands the regimen—e.g. ask the patient 'Tell me exactly how you take your medicines'. Try to find something positive to say about their adherence, even if this is saying something along the lines of 'I'm glad you've told me about these problems with taking your tablets . . .'.

Give positive reinforcement to patients who are fully adherent and encourage any improvements. Be careful not to be patronizing! If you have access to any results that could reflect adherence (e.g. BP readings and glycosylated haemoglobin (HbA_{1c})), show the patient these results, and explain how they reflect improvement in control of the disease.

Box 1.1 Checklist of medication information for patients

Basic information

- Drug name (generic and trade name), strength, and formulation
- How it works—non-technical explanation
- Why it is important to keep taking the treatment correctly

Using the treatment

- How much to use—e.g. number of tablets
- How often to use—e.g. twice daily, about 12h apart
- Special information—e.g. with food or drink plenty of water
- Storage—e.g. in the original container, in the fridge, or expiry date

Side effects

- Common side effects—e.g. when they might occur and what to do about them
- Managing side effects (e.g. taking drugs with food might reduce nausea or using over-the-counter drug treatments for symptom control)
- Serious side effects—e.g. what to do and whether to contact clinic (provide a phone number, if appropriate), local doctor, or hospital

Drug interactions

Any drugs that the patient should avoid/be cautious with—in particular, mention over-the-counter medicines, herbal and traditional medicines and recreational drugs

Other

- Availability
- Cost (per month/per year)
- Monitoring—e.g. frequency of tests and costs of tests

Further reading

NICE guideline: Medicine adherence, http://guidance.nice.org.uk/CG76/NICEGuidance/pdf/English.

A competency framework for shared decision making with patients http://www.keele.ac.uk/pharmacy/npcplus/medicinespartnershipprogramme/medicinespartnershipprogrammepublications/acompetencyframeworkforshareddecision-making/.

Writing patient information leaflets

Written information is an important supplement to the verbal information on medicines and disease that pharmacists provide. Patient information leaflets help patients retain the information discussed and provide a source of information for future reference. In the European Union, pharmacists are required to distribute the patient information leaflets supplied by the pharmaceutical industry with each drug when it is dispensed, but additional information might also be required.

Pharmacy-generated patient information leaflets can be used to describe the following.

- The disease and how it could affect the patient's daily life.
- Disease prevention—e.g. stopping smoking.
- Treatment or treatment options if there is more than one.
- Details of drug therapy, including the following.
  - Dose and regimen.
  - The importance of continuing chronic therapy even if the patient feels well.
  - Side effects—e.g. risks and benefits, and what to do if they occur.
  - Drug interactions—e.g. over-the-counter and herbal medicines, food, alcohol, and recreational drugs.
  - Other special considerations—e.g. use in pregnancy and lactation.
  - Further sources of information and support—e.g. pharmacy contact details, self-help organizations, and websites.

Before you start

- Discuss the following with patients.
  - Do they feel they need additional information? What information would they like?
  - What are they worried about?
  - What type of leaflet design do they prefer?
- Don't reinvent the wheel! Check whether a leaflet covering the topic you intend to write about is already available—useful sources are the pharmaceutical industry and patient organizations.
- Look at other leaflets and see how they have been written.
  - Does the style and layout fit what you want to do?
  - Do you find it easy to read and understand?
  - What good/bad aspects of design and content can you learn from these?
- Check whether your hospital or primary care trust has guidelines on writing patient information leaflets. Some organizations require leaflets to be written in a standard format and the final version to be approved by a senior manager.
- Check what facilities there are for printing and distribution and what funding is available. There is no point spending hours producing a full-colour leaflet that requires professional printing if the funds will only stretch to a black and white photocopy.
- Talk to your organization's information technology adviser/medical illustration department—they might have access to computer programs that will make designing the leaflet much easier.

Content

- State the aim of the leaflet at the beginning—e.g. 'This leaflet is for people starting treatment for . . .'.
- Be relevant—decide on the scope of the information you are providing and stick to that. Don't get sidetracked into providing information that is not directly relevant to the aim. The leaflet should provide sufficient detail that the reader can understand the main points but not so much that it becomes confusing and the main points are lost.
- Be accurate—the leaflet must include the most up to date information available and should also address the following points.
  - Be consistent with current guidelines or best practice.
  - Give an honest description of risks and benefits.
  - Where there is a lack of clear evidence, explain that this is the case.
  - Be updated as new information becomes available or guidelines are updated.
- Be understandable, acceptable, and accessible to the audience.
  - Apply the rules for clear writing discussed in Chapter 4 (see 📖 p.86).
  - Consider the target group—are there any religious or cultural issues that could influence the content? How can you make the leaflet accessible to patients with visual impairment or who do not speak English? Be careful about getting leaflets translated because sometimes the meaning can be inadvertently changed.
  - Get patient's opinions on the content—check that they understand/interpret the information correctly, tone and style are acceptable (see Box 1.2), layout and presentation are easy to follow, and they think that it covers all the relevant issues.

Box 1.2 Patient preferences for tone and style of written information

Likes	*Dislikes*
• Positive tone	• Negative tone
• Friendly	• Stress on what could go wrong
• Encouraging	• Unrealistic
• Reassuring	• Over-optimistic
• Non-alarmist	• Misleading
• Honest	• Patronizing
• Practical	• Childish
• Understanding	• Cold
• Not condescending	
• Talking to you personally	
• Using 'you' a lot	
• Warm	

Design and layout

Once you have drafted the text, think about how best it can be presented (Fig. 1.1). Use the guidance in Chapter 4 (see 📖 p.88) on font type and basic layout.

Large amounts of type on an A4-size sheet of paper is hard work for anyone to read. A5 size (ideally a single side) is the maximum size that should be used. If you have a lot of information to present, use an A5 or smaller booklet format or a three-fold A4 leaflet.

Graphics can be helpful to break up the text and 'signpost' new ideas, but be careful not to overdo it so that the graphics overwhelm the text. Graphics must be relevant to the text. Ensure that graphics are culturally acceptable and bear in mind that some stylized pictures or icons could be interpreted differently by people of different cultures (e.g. a crescent moon to indicate night time might be interpreted as a religious symbol).

Review and update regularly

The leaflet should state the author's name and job title, the date of production, and a future review date. Depending on what new information becomes available, it might be necessary to update the leaflet sooner than the review date. If the information is significantly out of date, the leaflet should be withdrawn from use until an updated version is available.

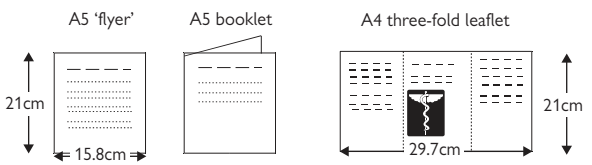

Fig. 1.1 Writing reports: design and layout.

Chapter 2

Adverse drug reactions and drug interactions

Introduction to ADRs

Adverse drug reactions (ADRs), also known as 'side effects', 'adverse drug events', or 'drug misadventures', are a frequent cause of morbidity in hospital and the community. They have a significant cost both financially and in terms of quality of life. Few studies of ADRs have been carried out in the community so the effect on primary care is harder to assess, but studies in the hospital environment have shown the following.

- ADRs occur in 10–20% of patients in hospital.
- ADRs are responsible for 5% of admissions to hospital.
- ADRs might be responsible for 1 in 1000 deaths in medical wards.
- ADRs are the most common cause of iatrogenic injury in hospital patients.

The World Health Organization (WHO) defines an ADR as follows:
'*a drug-related event that is noxious and unintended and occurs at doses used in humans for prophylaxis, diagnosis or therapy of disease or for the modification of physiological function.*'

However, this definition does not take into account the following scenarios, all of which can also cause ADRs:

- overdose (including prescribing or administration errors)
- therapeutic failure
- drug interactions
- drug withdrawal.

Pharmacists have an important role in identifying, reporting, and preventing ADRs.

Classification of ADRs

A number of classification systems exist, but the most widely accepted is to group ADRs as either type A (predictable) or type B (unpredictable) reactions. This system is not ideal because some types of reaction (e.g. teratogenic effects) do not fit easily into either category. However, it is a useful system in most cases because immediate management of the ADR and future drug choices can be guided by the ADR type.

Type A reactions

An exaggerated, but otherwise normal, pharmacological action. Type A reactions have the following characteristics:

- largely predictable
- usually dose-dependent
- incidence and morbidity high
- mortality low.

Examples of type A reactions include respiratory depression with opioid analgesia, cough with angiotensin-coverting enzyme (ACE) inhibitors, and withdrawal effects with benzodiazepines or alcohol.

Type B reactions

Idiosyncratic, aberrant, or bizarre drug effects that are unrelated to the pharmacology of the drug. Type B reactions have the following characteristics:

- usually unpredictable
- might not be picked up by toxicological screening
- not necessarily dose-related
- incidence and morbidity low
- mortality high.

Type B reactions are most commonly immunological (e.g. penicillin allergy).

Adverse reactions: drug or disease?

Determining whether or not a symptom is an ADR can be difficult, especially if the patient has multiple pathologies. Experience has shown that pharmacists tend to blame the drug and doctors to blame the disease. Questions to ask are as follows.

- Is there another explanation for the symptom (e.g. disease-related)?
- Is this a previously reported side effect of this drug? How common is it? This is harder to assess for new drugs because there is less information available.
- Is the timing right? Most ADRs occur soon after starting a drug, although some ADRs (e.g. hepatotoxicity) might be delayed. The onset of some hypersensitivity reactions (e.g. penicillin rash) can be delayed for up to 10 days after starting the drug. This can cause confusion, especially if the antibiotic course has been completed before the rash appears.
- Is the dose excessive? Check serum levels if available. Check renal function—was the dose too high if renal function is impaired? If the symptom can be explained as a type A reaction and the dose is high for whatever reason, it is more probable that the reaction is drug-induced.
- Does the symptom resolve on stopping the drug or reducing the dose (de-challenge)? Type A reactions are usually dose-dependent and so will worsen on dose increase, but rapidly resolve or improve on dose reduction or drug withdrawal. Type B reactions are dose-independent and will rarely resolve with dose reduction. Drug withdrawal is necessary, but if symptoms are caused by immunological effects (rather than direct drug action) it could take some days or weeks for symptoms to resolve.
- Does the symptom recur on restarting the drug (re-challenge)? Remember that re-challenge can be especially hazardous for type B reactions and is usually not advised.

If the answer to the first question is 'no' and the answer to (most of) the other questions is 'yes', it is highly probable that the event is an ADR.

Factors predisposing to ADRs

Factors that predispose to ADRs are many and varied, and some are related only to specific disease–drug interactions, such as rash with amoxicillin in patients with glandular fever. However, the following factors are generally considered to ↑ patient risk:

- age
- renal impairment
- hepatic impairment
- 'frailty'
- polypharmacy
- ♀
- previous history of ADRs
- genetics.

The first four factors predispose to type A reactions because they are determinants of drug toxicity, but the remaining factors predispose to type A or type B reactions.

Helping patients understand the risk of ADRs

Terms such as 'common' and 'uncommon' are used to describe levels of risk of ADRs in patient information leaflets and summaries of product characteristics. The terms are standardized by the European Union according to the reported frequency found in clinical trials for example (Table 2.1), but patients routinely overestimate the level of risk that these terms are intended to imply.

The following strategies should help in communicating risk to patients.

- Avoid using verbal descriptors such as 'common'.
- Use frequencies rather than percentages—e.g. 1 person in every 1000 rather than 0.1%.
- Use the same denominator throughout—i.e. 1 in 1000 and 10 in 1000 rather than 1 in 1000 and 1 in 100.
- Give both positive and negative information—e.g. 95 out 100 patients did not get the side effect and 5 patients did.
- Give information about baseline risk—e.g.
  - The risk of deep vein thrombosis (DVT) in non-pregnant women who are not taking the combined oral contraceptive (COC) is 5 cases per 100 000 women per year.
  - The risk of DVT in pregnancy is 60 cases per 100 000 pregnancies.
  - The risk of DVT in women taking the COC is 15–25 cases per 100 000 per year.

Table 2.1 Terminology as standardized by the European Union according to reported frequency in clinical trials

EU terminology	Level of risk
Very common	>10%
Common	1–10%
Uncommon	0.1–1%
Rare	0.01–0.1%
Very rare	<0.015%

Reporting ADRs

Most ADRs are not reported and this can lead to delays in identifying important reactions. The reasons for failure to report ADRs have been called the 'seven deadly sins' (Box 2.1). Pharmacists should attempt to address these and encourage their medical and nursing colleagues to report ADRs, in addition to sending in their own reports.

The regulatory authorities in many countries have systems for reporting ADRs, and it is important to find out how ADRs are reported and whether pharmacists can submit reports. In the UK, doctors, dentists, pharmacists, nurses, and patients can report ADRs to the Medicines and Healthcare products Regulatory Agency (MHRA) through the yellow card scheme. New drugs are labelled with a black inverted triangle in the *British National Formulary* (*BNF*), and the MHRA requests that all ADRs to these drugs are reported. For established drugs, unusual or significant reactions should be reported. Yellow card data can be accessed online.[1]

Box 2.1 Failure to report ADRs: the 'seven deadly sins'

1. **Complacency**—a mistaken belief that only safe drugs are allowed onto the market and that these will not cause serious ADRs
2. **Fear** of involvement in litigation, or of a loss of patient confidence
3. **Guilt** that a patient has been harmed by a prescribed treatment
4. **Ambition**—to collect and publish a personal series of cases
5. **Ignorance** of what should be reported or how to make a report
6. **Diffidence**—a reluctance to report an effect for which there is only a suspicion that it is drug-related
7. **Lethargy**—this may include a lack of time or interest, inability to find a report card, etc.

1 http://www.yellowcard.mhra.gov.uk

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Drug interactions

Drug interactions occur when the effect of a drug is altered by the co-administration of any of the following:

- another drug.
- food.
- drink.

The outcome of this is as follows:

- frequently clinically insignificant
- sometimes beneficial
- occasionally potentially harmful.

Mechanisms of drug interactions

Interactions can be caused by pharmacokinetic mechanisms (i.e. the handling of the drug in the body is affected) or pharmacodynamic mechanisms (i.e. related to the pharmacology of the drug). Sometimes the interaction can be caused by more than one mechanism, although usually one mechanism is more significant. The majority of interactions are caused by the following mechanisms.

Pharmacokinetic mechanisms

Absorption

One drug will ↑ or ↓ the absorption of another. This is most frequently due to one drug or compound interacting with another—by adsorption, chelation or complexing—to form a product that is poorly absorbed. This can be beneficial (e.g. activated charcoal adsorbs certain poisons) or problematic (e.g. antacids and tetracyclines).

Changes in gastric pH affect the absorption of certain drugs—e.g. ketoconazole and itraconazole require an acidic environment to be absorbed; thus proton pump inhibitors can ↓ absorption and an acidic drink such as fruit juice or soft drinks (especially Coca Cola®) will ↑ absorption.

Most drugs are absorbed from the upper part of the small intestine. Thus changes in gut motility potentially affect absorption. Usually the total amount absorbed is unaffected, but the rate of absorption might be altered. This effect is used in some combination migraine products—e.g. including metoclopramide (an antiemetic) speeds up the rate of absorption of the analgesic.

Distribution

Some drugs are bound to proteins in the serum. Only free (unbound) drug is active. Protein binding is a competitive effect, so one drug can displace the other from protein binding sites. This interaction is only an issue with highly protein bound drugs and is only significant if most of the drug remains in the plasma rather than being distributed into tissues (i.e. a low volume of distribution). Displacement of drug from protein binding sites often only causes a small 'blip' in drug levels before equilibrium is restored (because the free drug is also now available for metabolism and excretion), but it could be significant for drugs with a narrow therapeutic index (e.g. warfarin).

Metabolism

Accounts for the majority of clinically significant pharmacokinetic interactions. Induction or inhibition of the cytochrome P450 (CYP450) system leads to changes in drug levels. CYP450 represents a large group of isoenzymes; drugs are rarely metabolized by a single enzyme, although one usually predominates. Equally, drugs can induce or inhibit several enzymes and some drugs can induce some enzymes and inhibit others (e.g. efavirenz). In addition, some (but not all) enzyme inhibitors or inducers can induce or inhibit their own metabolism.

When only two drugs are involved, the effect is fairly easy to predict, even if each drug is likely to affect the metabolism of the other. However, if three or more drugs, all of which are inducers or inhibitors, are involved, the effect is almost impossible to predict, and this type of combination should be avoided if possible.

The full effects of enzyme induction and inhibition do not occur immediately.

- Enzyme induction takes about 2–3wks to develop and wear off.
- Enzyme inhibition takes only a few days.

Thus, it might be necessary to delay dose adjustment or TDM until a few days (inhibition) or at least a week (induction) after starting or stopping the offending drug(s).

An emerging area of study is drug interactions involving induction or inhibition of p-glycoprotein. This probably includes interactions involving ↑ in bioavailability because it affects drug metabolism in the gut wall—e.g. grapefruit juice ↑ levels of ciclosporin by inhibiting gut wall metabolism.

Excretion

Some drugs interfere with excretion (usually renal) of other drugs. If both drugs are excreted by the same active transport system in the kidney tubule, the excretion of each drug is ↓ by the other. This might be used as a beneficial effect—e.g. probenecid has been used to prolong the half-life of penicillin—or be problematic—e.g. methotrexate and non-steroidal anti-inflammatory drugs (NSAIDs).

Pharmacodynamic interactions

These occur if the pharmacological effects of two drugs are additive or opposing.

- Additive—the desired or adverse effects of the two drugs are the same. This can be beneficial or potentially harmful (e.g. ↑ sedation with alcohol plus hypnotics).
- Synergism—which is a form of additive effect. In this instance the combination of the two drugs has a greater effect than just an additive effect (e.g. ethambutol ↑ the effectiveness of other anti-tubercular drugs).
- Antagonism—at receptor level (e.g. a β-blocker should be prescribed with caution to an asthmatic patient who uses a β-agonist inhaler) or because of opposing effects (e.g. the desired effects of diuretics could be, at least partly, opposed by fluid retention caused by NSAIDs).

Predicting drug interactions

- Are the desired or adverse effects of the two drugs similar or opposing?
- If there is no information available for the drugs in question, are there reports of drug interactions for other drugs in the same class?
- Are both drugs metabolized by the liver and, if so, by which enzymes? Information on which drugs are metabolized by which CYP450 enzymes might be listed in the summary of product characteristics and can also be found on the following websites:
  - www.hiv-druginteractions.org
  - medicine.iupui.edu/flockhart/
- Drugs that are predominantly renally cleared are unlikely to interact with enzyme inducers and inhibitors.

Managing drug interactions

- Check whether or not the drug combination is new.
- If the patient has already been taking the drug combination, have they tolerated it? If yes, there is probably no need to change therapy, although monitoring might be required.
- Is the interaction potentially serious (e.g. significant risk of toxicity or ↓ drug effect)—in which case seek alternatives.
- Is the interaction potentially of low to moderate significance—in which case it might only be necessary to monitor side effects and therapeutic effect, or arrange TDM.
- Remember that some drugs in the same class can have different potentials to cause interactions (e.g. ranitidine versus cimetidine).
- Remember that not only do interactions occur when a drug is started, but unwanted effects can also occur when a drug is stopped.
- The elderly are at greater risk of drug interactions, because of polypharmacy and impaired metabolism and excretion. Additive side effects can be a particular problem.
- Be aware of high-risk drugs and always check for potential interactions with these drugs:
  - enzyme inhibitors and inducers (e.g. erythromycin, rifampicin, phenytoin, and protease inhibitors)
  - drugs with a narrow therapeutic index (e.g. warfarin, digoxin, lithium, phenytoin, theophylline, and gentamicin).
- Remember that interactions can occur with non-prescription drugs, which the patient might not tell you about:
  - herbal or traditional medicines
  - over-the-counter medicines
  - recreational drugs, including alcohol, tobacco, and drugs obtained by other means, such as sildenafil purchased on the internet.

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