02-2 Clinical therapeutics and good prescribing

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Clinical therapeutics and good prescribing SRJ Maxwell Principles of clinical pharmacology 14 Pharmacodynamics 14 Pharmacokinetics 17 Inter-individual variation in drug responses 19 Adverse outcomes of drug therapy 21 Adverse drug reactions 21 Drug interactions 23 Medication errors 24 Drug regulation and management 26 Drug development and marketing 26 Managing the use of medicines 27 Prescribing in practice 28 Decision-making in prescribing 28 Prescribing in special circumstances 31 Writing prescriptions 33 Monitoring drug therapy 34

14 • CLINICAL THERAPEUTICS AND GOOD PRESCRIBING strength of the chemical bond. Some drug–receptor interactions are irreversible, either because the affinity is so strong or because the drug modifies the structure of its molecular target. • Selectivity describes the propensity for a drug to bind to one target rather than another. Selectivity is a relative term, not to be confused with absolute specificity. It is common for drugs targeted at a particular subtype of receptor to exhibit some effect at other subtypes. For example, β-adrenoceptors can be subtyped on the basis of their responsiveness to the endogenous agonist noradrenaline (norepinephrine): the concentration of noradrenaline required to cause bronchodilatation (via β2-adrenoceptors) is ten times higher than that required to cause tachycardia (via β1-adrenoceptors). ‘Cardioselective’ β-blockers have anti-anginal effects on the heart (β1) but may still cause bronchospasm in the lung (β2) and are contraindicated for asthmatic patients. • Agonists bind to a receptor to produce a conformational change that is coupled to a biological response. As agonist concentration increases, so does the proportion of receptors occupied, and hence the biological effect. Partial agonists activate the receptor but cannot produce a maximal signalling effect equivalent to that of a full agonist, even when all available receptors are occupied. • Antagonists bind to a receptor but do not produce the conformational change that initiates an intracellular signal. A competitive antagonist competes with endogenous ligands to occupy receptor-binding sites, with the resulting antagonism depending on the relative affinities and concentrations of drug and ligand. Non-competitive antagonists inhibit the effect of an agonist by mechanisms other than direct competition for receptor binding with the agonist (e.g. by affecting post-receptor signalling). Dose–response relationships Plotting the logarithm of drug dose against drug response typically produces a

sigmoidal dose–response curve (Fig. 2.2). Progressive increases in drug dose (which, for most drugs, is proportional to the plasma drug concentration) produce increasing Prescribing medicines is the major tool used by doctors to restore or preserve the health of patients. Medicines contain drugs (the specific chemical substances with pharmacological effects), either alone or in combination with additional drugs, in a formulation mixed with other ingredients. The beneficial effects of medicines must be weighed against their cost and potential adverse drug reactions and interactions. The latter two factors are sometimes caused by injudicious prescribing decisions and by prescribing errors. The modern prescriber must meet the challenges posed by the increasing number of drugs and formulations available and of indications for prescribing them, and the greater complexity of treatment regimens followed by individual patients ('polypharmacy', a particular challenge in the ageing population). The purpose of this chapter is to elaborate on the principles and practice that underpin good prescribing (Box 2.1). Fig. 2.1 Pharmacokinetics and pharmacodynamics. Dosage regimen Plasma concentration Concentration at the site of action Pharmacological effects Pharmacokinetics 'what the body does to a drug' Monitoring Measure plasma drug concentration 'what a drug does to the body' Monitoring Measure clinical effects Time Concentration Pharmacodynamics Concentration Effect *These steps in particular take the patient's views into consideration to establish a therapeutic partnership (shared decision-making to achieve 'concordance'). 2.1 Steps in good prescribing • Make a diagnosis • Consider factors that might influence the patient's response to therapy (age, concomitant drug therapy, renal and liver function etc.) • Establish the therapeutic goal* • Choose the therapeutic approach* • Choose the drug and its formulation (the 'medicine') • Choose the dose, route and frequency • Choose the duration of therapy • Write an unambiguous prescription (or 'medication order') • Inform the patient about the treatment and its likely effects • Monitor treatment effects, both beneficial and harmful • Review/alter the prescription Principles of clinical pharmacology Prescribers need to understand what the drug does to the body (pharmacodynamics) and what the body does to the drug (pharmacokinetics) (Fig. 2.1). Although this chapter is focused on the most common drugs, which are synthetic small molecules, the same principles apply to the increasingly numerous 'biological' therapies (sometimes abbreviated to 'biologics') now in use, which include peptides, proteins, enzymes and monoclonal antibodies (see Box 4.2, p. 65). Pharmacodynamics Drug targets and mechanisms of action Modern drugs are usually discovered by screening compounds for activity either to stimulate or to block the function of a specific molecular target, which is predicted to have a beneficial effect in a particular disease (Box 2.2). Other drugs have useful but less selective chemical properties, such as chelators (e.g. for treatment of iron or copper overload), osmotic agents (used as diuretics in cerebral oedema) or general anaesthetics (that alter the biophysical properties of lipid membranes). The following characteristics of the interaction of drugs with receptors illustrate some of the important determinants of the effects of drugs: • Affinity describes the propensity for a drug to bind to a receptor and is related to the 'molecular fit' and the

Fig. 2.2 Dose–response curve. The green curve represents the beneficial effect of the drug. The maximum response on the curve is the Emax and the dose (or concentration) producing half this value (Emax/2) is the ED50 (or EC50). The red curve illustrates the dose–response relationship for the most important adverse effect of this drug. This occurs at much higher doses; the ratio between the ED50 for the adverse effect and that for the beneficial effect is the 'therapeutic index', which indicates how much margin there is for prescribers when choosing a dose that will provide

beneficial effects without also causing this adverse effect. Adverse effects that occur at doses above the therapeutic range are normally called ‘toxic effects’, while those occurring within the therapeutic range are ‘side-effects’ and those below it are ‘hyper-susceptibility effects’. Hypersusceptibility Side-effects

0.0001 0.001 0.01 0.1

Therapeutic index 100/0.1 = 1000 Drug dose (mg) Response (% of maximum) Toxic effects Adverse effect ED50 =100 mg Beneficial effect ED50 =0.1 mg Emax ED50 ED50 2.2 Examples of target molecules for drugs Drug target Description Examples Receptors Channel-linked receptors Ligand binding controls a linked ion channel, known as ‘ligand-gated’ (in contrast to ‘voltage-gated’ channels that respond to changes in membrane potential) Nicotinic acetylcholine receptor GABA receptor Sulphonylurea receptor G-protein-coupled receptors (GPCRs) Ligand binding affects one of a family of ‘G-proteins’ that mediate signal transduction either by activating intracellular enzymes (such as adenylate or guanylate cyclase, producing cyclic AMP or GMP, respectively) or by controlling ion channels Muscarinic acetylcholine receptor β-adrenoceptors Dopamine receptors 5-Hydroxytryptamine (5-HT, serotonin) receptors Opioid receptors Kinase-linked receptors Ligand binding activates an intracellular protein kinase that triggers a cascade of phosphorylation reactions Insulin receptor Cytokine receptors Transcription factor receptors Intracellular and also known as ‘nuclear receptors’; ligand binding promotes or inhibits gene transcription and hence synthesis of new proteins Steroid receptors Thyroid hormone receptors Vitamin D receptors Retinoid receptors PPARγ and α receptors Other targets Voltage-gated ion channels Mediate electrical signalling in excitable tissues (muscle and nervous system) Na+ channels Ca2+ channels Enzymes Catalyse biochemical reactions. Drugs interfere with binding of substrate to the active site or of co-factors Cyclo-oxygenase ACE Xanthine oxidase Transporter proteins Carry ions or molecules across cell membranes 5-HT re-uptake transporter Na+/K+ ATPase Cytokines and other signalling molecules Small proteins that are important in cell signalling (autocrine, paracrine and endocrine), especially affecting the immune response Tumour necrosis factors Interleukins Cell surface antigens Block the recognition of cell surface molecules that modulate cellular responses Cluster of differentiation molecules (e.g. CD20, CD80) (ACE = angiotensin-converting enzyme; AMP = adenosine monophosphate; ATPase = adenosine triphosphatase; GABA = γ-aminobutyric acid; GMP = guanosine monophosphate; PPAR = peroxisome proliferator-activated receptor)

16 • CLINICAL THERAPEUTICS AND GOOD PRESCRIBING therapeutic index is usually based on adverse effects that might require dose reduction or discontinuation. For most drugs, the therapeutic index is greater than 100 but there are some notable exceptions with therapeutic indices of less than 10 (e.g. digoxin, warfarin, insulin, phenytoin, opioids). The doses of such drugs have to be titrated carefully for individual patients to maximise benefits but avoid adverse effects. Desensitisation and withdrawal effects Desensitisation refers to the common situation in which the biological response to a drug diminishes when it is given continuously or repeatedly. It may be possible to restore the response by increasing the dose of the drug but, in some cases, the tissues may become completely refractory to its effect. • Tachyphylaxis describes desensitisation that occurs very rapidly, sometimes with the initial dose. This rapid loss of response implies depletion of chemicals that may be necessary for the pharmacological actions of the drug (e.g. a stored neurotransmitter released from a nerve terminal) or receptor phosphorylation. • Tolerance describes a more gradual loss of response to a drug that occurs over days or weeks. This slower

change implies changes in receptor numbers or the development of counter-regulatory physiological changes that offset the actions of the drug (e.g. accumulation of salt and water in response to vasodilator therapy). • Drug resistance is a term normally reserved for describing the loss of effectiveness of an antimicrobial (p. 116) or cancer chemotherapy drug. • In addition to these pharmacodynamic causes of desensitisation, reduced response may be the consequence of lower plasma and tissue drug concentrations as a result of altered pharmacokinetics (see below). When drugs induce chemical, hormonal and physiological changes that offset their actions, discontinuation may allow these changes to cause ‘rebound’ withdrawal effects (Box 2.3). response but only within a relatively narrow range of dose; further increases in dose beyond this range produce little extra effect. The following characteristics of the drug response are useful in comparing different drugs: • Efficacy describes the extent to which a drug can produce a target-specific response when all available receptors or binding sites are occupied (i.e. Emax on the dose–response curve). A full agonist can produce the maximum response of which the receptor is capable, while a partial agonist at the same receptor will have lower efficacy. Therapeutic efficacy describes the effect of the drug on a desired biological endpoint and can be used to compare drugs that act via different pharmacological mechanisms (e.g. loop diuretics induce a greater diuresis than thiazide diuretics and therefore have greater therapeutic efficacy). • Potency describes the amount of drug required for a given response. More potent drugs produce biological effects at lower doses, so they have a lower ED50. A less potent drug can still have an equivalent efficacy if it is given in higher doses. The dose–response relationship varies between patients because of variations in the many determinants of pharmacokinetics and pharmacodynamics. In clinical practice, the prescriber is unable to construct a dose–response curve for each individual patient. Therefore, most drugs are licensed for use within a recommended range of doses that is expected to reach close to the top of the dose–response curve for most patients. However, it is sometimes possible to achieve the desired therapeutic efficacy at doses towards the lower end of, or even below, the recommended range. Therapeutic index The adverse effects of drugs are often dose-related in a similar way to the beneficial effects, although the dose–response curve for these adverse effects is normally shifted to the right (Fig. 2.2). The ratio of the ED50 for therapeutic efficacy and for a major adverse effect is known as the ‘therapeutic index’. In reality, drugs have multiple potential adverse effects, but the concept of 2.3 Examples of drugs associated with withdrawal effects Drug Symptoms Signs Treatment Alcohol Anxiety, panic, paranoid delusions, visual and auditory hallucinations Agitation, restlessness, delirium, tremor, tachycardia, ataxia, disorientation, seizures Treat immediate withdrawal syndrome with benzodiazepines Barbiturates, benzodiazepines Similar to alcohol Similar to alcohol Transfer to long-acting benzodiazepine then gradually reduce dosage Glucocorticoids Weakness, fatigue, decreased appetite, weight loss, nausea, vomiting, diarrhoea, abdominal pain Hypotension, hypoglycaemia Prolonged therapy suppresses the hypothalamic–pituitary–adrenal axis and causes adrenal insufficiency requiring glucocorticoid replacement. Withdrawal should be gradual after prolonged therapy (p. 670) Opioids Rhinorrhoea, sneezing, yawning, lacrimation, abdominal and leg cramping, nausea, vomiting, diarrhoea Dilated pupils Transfer addicts to long-acting agonist methadone Selective serotonin re-uptake inhibitors (SSRIs) Dizziness, sweating, nausea, insomnia, tremor, delirium, nightmares Tremor Reduce SSRIs slowly to avoid withdrawal effects

Parenteral administration These routes avoid absorption via the gastrointestinal tract and first-pass metabolism in the liver: • Intravenous (IV). The IV route enables all of a dose to enter the systemic circulation reliably, without any concerns about absorption or first-pass metabolism (i.e. the dose is 100% bioavailable), and rapidly achieve a high plasma concentration. It is ideal for very ill patients when a rapid, certain effect is critical to outcome (e.g. benzathine benzylpenicillin for meningococcal meningitis). • Intramuscular (IM). IM administration is easier to achieve than the IV route (e.g. adrenaline (epinephrine) for acute anaphylaxis) but absorption is less predictable and depends on muscle blood flow. • Subcutaneous (SC). The SC route is ideal for drugs that have to be administered parenterally because of low oral bioavailability, are absorbed well from subcutaneous fat, and might ideally be injected by patients themselves (e.g. insulin, heparin). • Transdermal. A transdermal patch can enable a drug to be absorbed through the skin and into the circulation (e.g. oestrogens, nicotine, nitrates). Other routes of administration • Topical application of a drug involves direct administration to the site of action (e.g. skin, eye, ear). This has the advantage of achieving sufficient concentration at this site while minimising systemic exposure and the risk of adverse effects elsewhere. • Inhaled (INH) administration allows drugs to be delivered directly to a target in the respiratory tree, usually the small airways (e.g. salbutamol, beclometasone). However, a significant proportion of the inhaled dose may be absorbed from the lung or is swallowed and can reach the systemic circulation. The most common mode of delivery is the metered-dose inhaler but its success depends on some degree of manual dexterity and timing (see Fig. 17.23, p. 571). Patients who find these difficult may use a ‘spacer’ device to improve drug delivery. A special mode Pharmacokinetics Understanding ‘what the body does to the drug’ (Fig. 2.3) is extremely important for prescribers because this forms the basis on which the optimal route of administration and dose regimen are chosen and explains the majority of inter-individual variation in the response to drug therapy. Drug absorption and routes of administration Absorption is the process by which drug molecules gain access to the blood stream. The rate and extent of drug absorption depend on the route of administration (Fig. 2.3). Enteral administration These routes involve administration via the gastrointestinal tract: • Oral. This is the most common route of administration because it is simple, convenient and readily used by patients to self-administer their medicines. Absorption after an oral dose is a complex process that depends on the drug being swallowed, surviving exposure to gastric acid, avoiding unacceptable food binding, being absorbed across the small bowel mucosa into the portal venous system, and surviving metabolism by gut wall or liver enzymes (‘first-pass metabolism’). As a consequence, absorption is frequently incomplete following oral administration. The term ‘bioavailability’ describes the proportion of the dose that reaches the systemic circulation intact. • Buccal, intranasal and sublingual (SL). These routes have the advantage of enabling rapid absorption into the systemic circulation without the uncertainties associated with oral administration (e.g. organic nitrates for angina pectoris, triptans for migraine, opioid analgesics). • Rectal (PR). The rectal mucosa is occasionally used as a site of drug administration when the oral route is compromised because of nausea and vomiting or unconsciousness (e.g. diazepam in status epilepticus). Fig. 2.3 Pharmacokinetics summary. Most drugs are taken orally, are absorbed from the intestinal lumen and enter the portal venous system to be conveyed to the liver, where they may be subject to first-pass metabolism and/or excretion in bile. Active drugs then enter the systemic circulation, from which they may diffuse (or sometimes be actively transported) in and out of the interstitial and intracellular fluid compartments. Drug that remains in circulating plasma is subject to liver metabolism and renal excretion. Drugs excreted in bile may be reabsorbed, creating an enterohepatic circulation. First-pass metabolism in the liver is avoided if drugs are administered via the buccal or rectal mucosa, or parenterally (e.g. by

intravenous injection). I n t e r s t i t i a l

f l u i d Intracellular fluid Kidney Liver Parenteral Mouth Stomach Small intestine Large intestine Rectum Buccal Excretion in urine Excretion in faeces Portal venous system Intestinal wall enzymes Liver enzymes Metabolism Circulating plasma Rectal Oral

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sufficiently water-soluble to avoid reabsorption from the renal tubule. Drugs bound to plasma proteins are not filtered by the glomeruli. The pH of the urine is more acidic than that of plasma, so that some drugs (e.g. salicylates) become un-ionised and tend to of inhaled delivery is via a nebulised solution created by using pressurised oxygen

or air to break up solutions and suspensions into small aerosol droplets that can be directly inhaled from the mouthpiece of the device. Drug distribution Distribution is the process by which drug molecules transfer into and out of the blood stream. This is influenced by the drug’s molecular size and lipid solubility, the extent to which it binds to proteins in

plasma, its susceptibility to drug transporters expressed on cell surfaces, and its binding to its molecular target and to other cellular proteins (which can be irreversible). Most drugs diffuse passively across capillary walls down a concentration gradient into the interstitial fluid until the concentration of free drug molecules in the interstitial

fluid is equal to that in the plasma. As drug molecules in the blood are removed by metabolism or excretion, the plasma concentration falls, drug molecules diffuse back from the tissue compartment into the blood and eventually all will be eliminated. Note that this reverse movement of drug away from the tissues will be prevented if further drug

doses are administered and absorbed into the plasma. Volume of distribution The apparent volume of distribution (Vd) is the volume into which a drug appears to have distributed following intravenous injection. It is calculated from the equation Vd D C

where D is the amount of drug given and C0 is the initial plasma concentration (Fig. 2.4A). Drugs that are highly bound to plasma proteins may have a Vd below 10 L (e.g. warfarin, aspirin), while those that diffuse into the interstitial fluid but do not enter cells because they have low lipid solubility may have a Vd between 10 and 30 L (e.g. gentamicin, amoxicillin). It is an ‘apparent’ volume because those drugs that are lipid-soluble and highly tissue-bound may have a Vd of greater than 100 L (e.g. digoxin, amitriptyline). Drugs with a larger Vd have longer half-lives (see below), take longer to reach steady state on repeated administration and are eliminated more slowly from the body following discontinuation. Drug elimination Drug metabolism Metabolism is the process by which drugs are chemically altered from a lipid-soluble form suitable for absorption and distribution to a more water-soluble form that is necessary for excretion. Some drugs, known

as ‘prodrugs’, are inactive in the form in which they are administered but are converted to an active metabolite in vivo. Phase I metabolism involves oxidation, reduction or hydrolysis to make drug molecules suitable for phase II reactions or for excretion. Oxidation is by far the most common form of phase I reaction and chiefly involves members of the cytochrome P450 family of membrane-bound enzymes in the endoplasmic reticulum of hepatocytes. Phase II metabolism involves combining phase I metabolites with an endogenous substrate to form an inactive conjugate that is much more water-soluble. Reactions include glucuronidation, sulphation, acetylation, methylation and conjugation with glutathione. This is necessary to enable renal excretion, because lipid-soluble metabolites will simply diffuse back into the body after glomerular filtration (p. 349). Fig. 2.4 Drug concentrations in plasma following single and multiple drug dosing. A In this example of first-order kinetics following a single intravenous dose, the time period required for the plasma drug concentration to halve (half-life, t1/2) remains constant throughout the elimination process. B After multiple dosing, the plasma drug concentration rises if each dose is administered before the previous dose has been entirely cleared. In this example, the drug’s half-life is 30 hours, so that with daily dosing the peak, average and trough concentrations steadily increase as drug accumulates in the body (black line). Steady state is reached after approximately 5 half-lives, when the rate of elimination (the product of concentration and clearance) is equal to the rate of drug absorption (the product of rate of administration and bioavailability). The long half-life in this example means that it takes 6 days for steady state to be achieved and, for most of the first 3 days of treatment, plasma drug concentrations are below the therapeutic range. This problem can be overcome if a larger loading dose (red line) is used to achieve steady-state drug concentrations more rapidly. Time (hours) A constant fraction of drug is cleared in unit time t1/2= 8 hours C0 Plasma drug concentration

A Loading dose Dose Dose Dose Dose Dose Dose Dose Subtherapeutic Dose interval = 24 hours Time (days) Plasma drug concentration

Therapeutic range Adverse effects t1/2= 30 hours B

means that the effects of a new prescription, or dose titration, for a drug with a long half-life (e.g. digoxin – 36 hours) may not be known for a few days. In contrast, drugs with a very short half-life (e.g. dobutamine – 2 minutes) have to be given continuously by infusion but reach a new steady state within minutes. For drugs with a long half-life, if it is unacceptable to wait for 5 half-lives until concentrations within the therapeutic range are achieved, then an initial ‘loading dose’ can be given that is much larger than the maintenance dose and equivalent to the amount of drug required in the body at steady state. This achieves a peak plasma concentration close to the plateau concentration, which can then be maintained by successive maintenance doses. ‘Steady state’ actually involves fluctuations in drug concentrations, with peaks just after administration followed by troughs just prior to the next administration. The manufacturers of medicines recommend dosing regimens that predict that, for most patients, these oscillations result in troughs within the therapeutic range and peaks that are not high enough to cause adverse effects. The optimal dose interval is a compromise between convenience for the patient and a constant level of drug exposure. More frequent administration (e.g. 25 mg 4 times daily) achieves a smoother plasma concentration profile than 100 mg once daily but is much more difficult for

patients to sustain. A solution to this need for compromise in dosing frequency for drugs with half-lives of less than 24 hours is the use of ‘modified-release’ formulations. These allow drugs to be absorbed more slowly from the gastrointestinal tract and reduce the oscillation in plasma drug concentration profile, which is especially important for drugs with a low therapeutic index (e.g. levodopa). Inter-individual variation in drug responses Prescribers have numerous sources of guidance about how to use drugs appropriately (e.g. dose, route, frequency, duration) for many conditions. However, this advice is based on average dose–response data derived from observations in many individuals. When applying this information to an individual patient, prescribers must take account of inter-individual variability in response. Some of this variability is predictable and good prescribers are able to anticipate it and adjust their prescriptions accordingly to maximise the chances of benefit and minimise harm. Inter-individual variation in responses also mandates that effects of treatment should be monitored (p. 34). Some inter-individual variation in drug response is accounted for by differences in pharmacodynamics. For example, the beneficial natriuresis produced by the loop diuretic furosemide is often significantly reduced at a given dose in patients with renal impairment, while delirium caused by opioid analgesics is more likely in the elderly. Differences in pharmacokinetics more commonly account for different drug responses, however. Examples of factors influencing the absorption, metabolism and excretion of drugs are shown in Box 2.4. It is hoped that a significant proportion of the inter-individual variation in drug responses can be explained by studying genetic differences in single genes (‘pharmacogenetics’; Box 2.5) or the effects of multiple gene variants (‘pharmacogenomics’). The aim is to identify those patients most likely to benefit from specific treatments and those most susceptible to adverse effects. In this way, it may be possible to select drugs and dose regimens for individual patients to maximise the benefit-to-hazard ratio (‘personalised medicine’). be reabsorbed. Alkalination of the urine can hasten excretion (e.g. after a salicylate overdose; p. 138). For some drugs, active secretion into the proximal tubule lumen, rather than glomerular filtration, is the predominant mechanism of excretion (e.g. methotrexate, penicillin). Faecal excretion is the predominant route of elimination for drugs with high molecular weight, including those that are excreted in the bile after conjugation with glucuronide in the liver, and any drugs that are not absorbed after enteral administration. Molecules of drug or metabolite that are excreted in the bile enter the small intestine, where they may, if they are sufficiently lipid-soluble, be reabsorbed through the gut wall and return to the liver via the portal vein (see Fig. 2.3). This recycling between the liver, bile, gut and portal vein is known as ‘enterohepatic circulation’ and can significantly prolong the residence of drugs in the body. Elimination kinetics The net removal of drug from the circulation results from a combination of drug metabolism and excretion, and is usually described as ‘clearance’, i.e. the volume of plasma that is completely cleared of drug per unit time. For most drugs, elimination is a high-capacity process that does not become saturated, even at high dosage. The rate of elimination is therefore directly proportional to the drug concentration because of the ‘law of mass action’, whereby higher drug concentrations will drive faster metabolic reactions and support higher renal filtration rates. This results in ‘first-order’ kinetics, when a constant fraction of the drug remaining in the circulation is eliminated in a given time and the decline in concentration over time is exponential (Fig. 2.4A). This elimination can be described by the drug’s half-life (t1/2), i.e. the time taken for the plasma drug concentration to halve, which remains constant throughout the period of drug elimination. The significance of this phenomenon for prescribers is that the effect of increasing doses on plasma concentration is predictable – a doubled dose leads to a doubled concentration at all time points. For a few drugs in common use (e.g. phenytoin, alcohol), elimination capacity is exceeded (saturated) within the usual dose range. This is called ‘zero-order’

kinetics. Its significance for prescribers is that, if the rate of administration exceeds the maximum rate of elimination, the drug will accumulate progressively, leading to serious toxicity. Repeated dose regimens The goal of therapy is usually to maintain drug concentrations within the therapeutic range (see Fig. 2.2) over several days (e.g. antibiotics) or even for months or years (e.g. antihypertensives, lipid-lowering drugs, thyroid hormone replacement therapy). This goal is rarely achieved with single doses, so prescribers have to plan a regimen of repeated doses. This involves choosing the size of each individual dose and the frequency of dose administration. As illustrated in Figure 2.4B, the time taken to reach drug concentrations within the therapeutic range depends on the half-life of the drug. Typically, with doses administered regularly, it takes approximately 5 half-lives to reach a ‘steady state’ in which the rate of drug elimination is equal to the rate of drug administration. This applies when starting new drugs and when adjusting doses of current drugs. With appropriate dose selection, steady-state drug concentrations will be maintained within the therapeutic range. This is important for prescribers because it

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have larger body compartments into which drugs are distributed and may require higher doses Liver function • Metabolism of most drugs depends on several cytochrome P450 enzymes that are impaired in patients with advanced liver disease • Hypoalbuminaemia influences the distribution of drugs that are highly protein-bound Kidney function • Renal disease and the decline in renal function with ageing may lead to drug accumulation Gastrointestinal function • Small intestinal absorption of oral drugs may be delayed by reduced gastric motility • Absorptive capacity of the intestinal mucosa may be reduced in disease (e.g. Crohn's or coeliac disease) or after surgical resection Food • Food in the stomach delays gastric emptying and reduces the rate (but not usually the extent) of drug absorption • Some food constituents bind to certain drugs and prevent their absorption Smoking • Tar in tobacco smoke stimulates the oxidation of certain drugs Alcohol • Regular alcohol consumption stimulates liver enzyme synthesis, while binge drinking may temporarily inhibit drug metabolism Drugs • Drug–drug interactions cause marked variation in pharmacokinetics (see Box 2.11) 2.4 Patient-specific factors that influence pharmacokinetics

Adverse outcomes of drug therapy The decision to prescribe a drug always involves a judgement of the balance between therapeutic benefits and risk of an adverse outcome. Both prescribers and patients tend to be more focused on the former but a truly informed decision requires consideration of both. Adverse drug reactions Some important definitions for the adverse effects of drugs are: • Adverse event. A harmful event that occurs while a patient is taking a drug, irrespective of whether the drug is suspected of being the cause. • Adverse drug reaction (ADR). An unwanted or harmful reaction that is experienced following the administration of a drug or combination of drugs under normal conditions of use and is suspected to be related to the drug. An ADR will usually require the drug to be discontinued or the dose reduced. • Side-effect. Any effect caused by a drug other than the intended therapeutic effect, whether beneficial, neutral or harmful. The term 'side-effect' is often used interchangeably with 'ADR', although the former usually implies an ADR that occurs during exposure to normal therapeutic drug concentrations (e.g. vasodilator-induced ankle oedema). • Hypersensitivity reaction. An ADR that occurs as a result of an immunological reaction and often at exposure to subtherapeutic drug concentrations. Some of these reactions are immediate and result from the interaction of drug antigens with immunoglobulin E (IgE) on mast cells and basophils, which causes a release of vasoactive biomolecules (e.g. penicillin-related anaphylaxis). 'Anaphylactoid' reactions present similarly but occur through a direct non-immune-mediated release of the same mediators or result from direct complement activation (p. 75). Hypersensitivity reactions may occur via other mechanisms such as antibody-dependent (IgM or IgG), immune complex-mediated or cell-mediated pathways. • Drug toxicity. Adverse effects of a drug that occur because the dose or plasma concentration has risen above the therapeutic range, either unintentionally or intentionally (drug overdose; see Fig. 2.2 and p. 137). • Drug abuse. The misuse of recreational or therapeutic drugs that may lead to addiction or dependence, serious physiological injury (such as liver damage), psychological harm (abnormal behaviour patterns, hallucinations, memory loss) or death (p. 1184). Prevalence of ADRs ADRs are a common cause of illness, accounting in the UK for approximately 3% of consultations in primary care and 7% of emergency admissions to hospital, and affecting around 15% of hospital inpatients. Many 'disease' presentations are eventually attributed to ADRs, emphasising the importance of always taking a careful drug history (Box 2.6). Factors accounting for the rising prevalence of ADRs are the increasing age of patients, polypharmacy (higher risk of drug

interactions), increasing availability of over-the-counter medicines, increasing use of herbal or traditional medicines, and the increase in medicines available via the Internet that can be purchased without a prescription from a health-care professional. Risk factors for ADRs are shown in Box 2.7. 2.7 Risk factors for adverse drug reactions Patient factors • Elderly age (e.g. low physiological reserve) • Gender (e.g. ACE inhibitor-induced cough in women) • Polypharmacy (e.g. drug interactions) • Genetic predisposition (see Box 2.5) • Hypersensitivity/allergy (e.g. β-lactam antibiotics) • Diseases altering pharmacokinetics (e.g. hepatic or renal impairment) or pharmacodynamic responses (e.g. bladder instability) • Adherence problems (e.g. cognitive impairment) Drug factors • Steep dose–response curve (e.g. insulin) • Low therapeutic index (e.g. digoxin, cytotoxic drugs) Prescriber factors • Inadequate understanding of principles of clinical pharmacology • Inadequate knowledge of the patient • Inadequate knowledge of the prescribed drug • Inadequate instructions and warnings provided to patients • Inadequate monitoring arrangements planned (ACE = angiotensin-converting enzyme) 2.6 How to take a drug history Information from the patient (or carer) Use language that patients will understand (e.g. ‘medicines’ rather than ‘drugs’, which may be mistaken for drugs of abuse) while gathering the following information: • Current prescribed drugs, including formulations (e.g. modifiedrelease tablets), doses, routes of administration, frequency and timing, duration of treatment • Other medications that are often forgotten (e.g. contraceptives, over-the-counter drugs, herbal remedies, vitamins) • Drugs that have been taken in the recent past and reasons for stopping them • Previous drug hypersensitivity reactions, their nature and time course (e.g. rash, anaphylaxis) • Previous ADRs, their nature and time course (e.g. ankle oedema with amlodipine) • Adherence to therapy (e.g. ‘Are you taking your medication regularly?’) Information from GP medical records and/or pharmacist • Up-to-date list of medications • Previous ADRs • Last order dates for each medication Inspection of medicines • Drugs and their containers (e.g. blister packs, bottles, vials) should be inspected for name, dosage, and the number of dosage forms taken since dispensed (ADR = adverse drug reaction)

 2.9 DoTS classification of adverse drug reactions Category Example Dose Below therapeutic dose Anaphylaxis with penicillin In the therapeutic dose range Nausea with morphine At high doses Hepatotoxicity with paracetamol Timing With the first dose Anaphylaxis with penicillin Early stages of treatment Hyponatraemia with diuretics On stopping treatment Benzodiazepine withdrawal syndrome Significantly delayed Clear-cell cancer with diethylstilboestrol Susceptibility See patient factors in Box 2.7 (INR = international normalised ratio) 2.8 Drugs that are common causes of adverse drug reactions Drug or drug class Common adverse drug reactions ACE inhibitors (e.g. lisinopril) Renal impairment Hyperkalaemia Antibiotics (e.g. amoxicillin) Nausea Diarrhoea Anticoagulants (e.g. warfarin, heparin) Bleeding Antipsychotics (e.g. haloperidol) Falls Sedation Delirium Aspirin Gastrotoxicity (dyspepsia, gastrointestinal bleeding) Benzodiazepines (e.g. diazepam) Drowsiness Falls β-blockers (e.g. atenolol) Cold peripheries Bradycardia Calcium channel blockers (e.g. amlodipine) Ankle oedema Digoxin Nausea and anorexia Bradycardia Diuretics (e.g. furosemide, bendroflumethiazide) Dehydration Electrolyte disturbance (hypokalaemia, hyponatraemia) Hypotension Renal impairment Insulin Hypoglycaemia NSAIDs (e.g. ibuprofen) Gastrotoxicity (dyspepsia, gastrointestinal bleeding) Renal impairment Opioid analgesics (e.g. morphine) Nausea and vomiting Delirium Constipation (ACE = angiotensin-converting enzyme; NSAID = non-steroidal anti-inflammatory drug) ADRs are important because they reduce quality of life for patients, reduce adherence to and therefore efficacy of beneficial treatments, cause diagnostic confusion,

undermine the confidence of patients in their health-care professional(s) and consume health-care resources. Retrospective analysis of ADRs has shown that more than half could have been avoided if the prescriber had taken more care in anticipating the potential hazards of drug therapy. For example, non-steroidal anti-inflammatory drug (NSAID) use accounts for many thousands of emergency admissions, gastrointestinal bleeding episodes and a significant number of deaths. In many cases, the patients are at increased risk due to their age, interacting drugs (e.g. aspirin, warfarin) or a past history of peptic ulcer disease. Drugs that commonly cause ADRs are listed in Box 2.8. Prescribers and their patients ideally want to know the frequency with which ADRs occur for a specific drug. Although this may be well characterised for more common ADRs observed in clinical trials, it is less clear for rarely reported ADRs when the total numbers of reactions and patients exposed are not known. The words used to describe frequency can be misinterpreted by patients but widely accepted meanings include: very common (10% or more), common (1–10%), uncommon (0.1–1%), rare (0.01–0.1%) and very rare (0.01% or less). Classification of ADRs ADRs have traditionally been classified into two major groups: • Type A (‘augmented’) ADRs. These are predictable from the known pharmacodynamic effects of the drug and are dose-dependent, common (detected early in drug development) and usually mild. Examples include constipation caused by opioids, hypotension caused by antihypertensives and dehydration caused by diuretics. • Type B (‘bizarre’) ADRs. These are not predictable, are not obviously dose-dependent in the therapeutic range, are rare (remaining undiscovered until the drug is marketed) and often severe. Patients who experience type B reactions are generally ‘hyper-susceptible’ because of unpredictable immunological or genetic factors (e.g. anaphylaxis caused by penicillin, peripheral neuropathy caused by isoniazid in poor acetylators). This simple classification has shortcomings, and a more detailed classification based on dose (see Fig. 2.2), timing and susceptibility (DoTS) is now used by those analysing ADRs in greater depth (Box 2.9). The AB classification can be extended as a reminder of some other types of ADR: • Type C (‘chronic/continuous’) ADRs. These occur only after prolonged continuous exposure to a drug. Examples include osteoporosis caused by glucocorticoids, retinopathy caused by chloroquine, and tardive dyskinesia caused by phenothiazines. • Type D (‘delayed’) ADRs. These are delayed until long after drug exposure, making diagnosis difficult. Examples include malignancies that may emerge after immunosuppressive treatment post-transplantation (e.g. azathioprine, tacrolimus) and vaginal cancer occurring many years after exposure to diethylstilboestrol. • Type E (‘end-of-treatment’) ADRs. These occur after abrupt drug withdrawal (see Box 2.3). A teratogen is a drug with the potential to affect the development of the fetus in the first 10 weeks of intrauterine life (e.g. phenytoin, warfarin). The thalidomide disaster in the early 1960s highlighted the risk of teratogenicity and led to mandatory testing of all new drugs. Congenital defects in a live infant or aborted fetus should

of prescribers of a particular drug are issued with questionnaires concerning the clinical outcome for their patients, and the collection of population statistics. Many health-care systems routinely collect patient-identifiable data on prescriptions (a surrogate marker of exposure to a drug), health-care events (e.g. hospitalisation, operations, new clinical diagnoses) and other clinical data (e.g. haematology, biochemistry). As these records are linked, with appropriate safeguards for confidentiality and data protection, they are providing a much more powerful mechanism for assessing both the harms and benefits of drugs. All prescribers will inevitably see patients

experiencing ADRs caused by prescriptions written by themselves or their colleagues. It is important that these are recognised early. In addition to the features in Box 2.10, features that should raise suspicion of an ADR and the need to respond (by drug withdrawal, dosage reduction or reporting to the regulatory authorities) include: • concern expressed by a patient that a drug has harmed them • abnormal clinical measurements (e.g. blood pressure, temperature, pulse, blood glucose and weight) or laboratory results (e.g. abnormal liver or renal function, low haemoglobin or white cell count) while on drug therapy • new therapy started that could be in response to an ADR (e.g. omeprazole, allopurinol, naloxone) • the presence of risk factors for ADRs (see Box 2.7). Drug interactions A drug interaction has occurred when the administration of one drug increases or decreases the beneficial or adverse responses to another drug. Although the number of potential interacting drug combinations is very large, only a small number are common in clinical practice. Important drug interactions are most likely to occur when the affected drug has a low therapeutic index, steep dose–response curve, high first-pass or saturable metabolism, or a single mechanism of elimination. Mechanisms of drug interactions Pharmacodynamic interactions occur when two drugs produce additive, synergistic or antagonistic effects at the same drug target (e.g. receptor, enzyme) or physiological system (e.g. electrolyte excretion, heart rate). These are the most common interactions in clinical practice and some important examples are given in Box 2.11. Pharmacokinetic interactions occur when the administration of a second drug alters the concentration of the first at its site of action. There are numerous potential mechanisms: • Absorption interactions. Drugs that either delay (e.g. anticholinergic drugs) or enhance (e.g. prokinetic drugs) gastric emptying influence the rate of rise in plasma concentration of other drugs but not the total amount of drug absorbed. Drugs that bind to form insoluble complexes or chelates (e.g. aluminium-containing antacids binding with ciprofloxacin) can reduce drug absorption. • Distribution interactions. Co-administration of drugs that compete for protein binding in plasma (e.g. phenytoin and diazepam) can increase the unbound drug concentration, but the effect is usually short-lived due to increased elimination and hence restoration of the pre-interaction equilibrium. provoke suspicion of an ADR and a careful exploration of drug exposures (including self-medication and herbal remedies). Detecting ADRs – pharmacovigilance Type A ADRs become apparent early in the development of a new drug. By the time a new drug is licensed and launched on to a possible worldwide market, however, a relatively small number of patients (just several hundred) may have been exposed to it, meaning that rarer but potentially serious type B ADRs may remain undiscovered. Pharmacovigilance is the process of detecting (‘signal generation’) and evaluating ADRs in order to help prescribers and patients to be better informed about the risks of drug therapy. Drug regulatory agencies may respond to this information by placing restrictions on the licensed indications, reducing the recommended dose range, adding special warnings and precautions for prescribers in the product literature, writing to all health-care professionals or withdrawing the product from the market. Voluntary reporting systems allow health-care professionals and patients to report suspected ADRs to the regulatory authorities. A good example is the ‘Yellow Card’ scheme that was set up in the UK in response to the thalidomide tragedy. Reports are analysed to assess the likelihood that they represent a true ADR (Box 2.10). Although voluntary reporting is a continuously operating and effective early-warning system for previously unrecognised rare ADRs, its weaknesses include low reporting rates (only 3% of all ADRs and 10% of serious ADRs are ever reported), an inability to quantify risk (because the ratio of ADRs to prescriptions is unknown), and the influence of prescriber awareness on likelihood of reporting (reporting rates rise rapidly following publicity about potential ADRs). More systematic approaches to collecting information on ADRs include ‘prescription event monitoring’, in which a sample 2.10

TREND analysis of suspected adverse drug reactions Factor Key question Comment Temporal relationship What is the time interval between the start of drug therapy and the reaction? Most ADRs occur soon after starting treatment and within hours in the case of anaphylactic reactions Re-challenge What happens when the patient is re-challenged with the drug? Re-challenge is rarely possible because of the need to avoid exposing patients to unnecessary risk Exclusion Have concomitant drugs and other non-drug causes been excluded? ADR is a diagnosis of exclusion following clinical assessment and relevant investigations for non-drug causes Novelty Has the reaction been reported before? The suspected ADR may already be recognised and mentioned in the SPC approved by the regulatory authorities De-challenge Does the reaction improve when the drug is withdrawn or the dose is reduced? Most, but not all, ADRs improve on drug withdrawal, although recovery may be slow (SPC = summary of product characteristics)

24 • CLINICAL THERAPEUTICS AND GOOD PRESCRIBING consequences of drug–drug interactions by taking a careful drug history (see Box 2.6) before prescribing additional drugs, only prescribing for clear indications, and taking special care when prescribing drugs with a narrow therapeutic index (e.g. warfarin). When prescribing an interacting drug is unavoidable, good prescribers will seek further information and anticipate the potential risk. This will allow them to provide special warnings for the patient and arrange for monitoring, either of the clinical effects (e.g. coagulation tests for warfarin) or of plasma concentration (e.g. digoxin). Medication errors A medication error is any preventable event that may lead to inappropriate medication use or patient harm while the medication is in the control of the health-care professional or patient. Errors may occur in prescribing, dispensing, preparing solutions, administration or monitoring. Many ADRs are considered in retrospect to have been ‘avoidable’ with more care or forethought; in other words, an adverse event considered by one prescriber to be an unfortunate ADR might be considered by another to be a prescribing error. Medication errors are very common. Several thousand medication orders are dispensed and administered each day in a medium-sized hospital. Recent UK studies suggest that • Metabolism interactions. Many drugs rely on metabolism by different isoenzymes of cytochrome P450 (CYP) in the liver. CYP enzyme inducers (e.g. phenytoin, rifampicin) generally reduce plasma concentrations of other drugs, although they may enhance activation of prodrugs. CYP enzyme inhibitors (e.g. clarithromycin, cimetidine, grapefruit juice) have the opposite effect. Enzyme induction effects usually take a few days to manifest because of the need to synthesise new CYP enzyme, in contrast to the rapid effects of enzyme inhibition. • Excretion interactions. These primarily affect renal excretion. For example, drug-induced reduction in glomerular filtration rate (e.g. diuretic-induced dehydration, angiotensin-converting enzyme (ACE) inhibitors, NSAIDs) can reduce the clearance and increase the plasma concentration of many drugs, including some with a low therapeutic index (e.g. digoxin, lithium, aminoglycoside antibiotics). Less commonly, interactions may be due to competition for a common tubular organic anion transporter (e.g. methotrexate excretion may be inhibited by competition with NSAIDs). Avoiding drug interactions Drug interactions are increasing as patients are prescribed more medicines (polypharmacy). Prescribers can avoid the adverse 2.11 Common drug interactions Mechanism Object drug Precipitant drug Result Pharmaceutical* Chemical reaction Sodium bicarbonate Calcium gluconate Precipitation of insoluble calcium carbonate Pharmacokinetic Reduced absorption Tetracyclines Calcium, aluminium, and magnesium salts Reduced tetracycline absorption Reduced protein binding Phenytoin Aspirin Increased unbound and reduced total phenytoin plasma concentration Reduced metabolism: CYP3A4 Amiodarone Grapefruit juice Cardiac arrhythmias because of prolonged QT interval (p. 476) Warfarin Clarithromycin Enhanced

anticoagulation CYP2C19 Phenytoin Omeprazole Phenytoin toxicity CYP2D6 Clozapine Paroxetine Clozapine toxicity Xanthine oxidase Azathioprine Allopurinol Azathioprine toxicity Monoamine oxidase Catecholamines Monoamine oxidase inhibitors Hypertensive crisis due to monoamine toxicity Increased metabolism (enzyme induction) Ciclosporin St John's wort Loss of immunosuppression Reduced renal elimination Lithium Diuretics Lithium toxicity Methotrexate NSAIDs Methotrexate toxicity Pharmacodynamic Direct antagonism at same receptor Opioids Naloxone Reversal of opioid effects used therapeutically Salbutamol Atenolol Inhibits bronchodilator effect Direct potentiation in same organ system Benzodiazepines Alcohol Increased sedation ACE inhibitors NSAIDs Increased risk of renal impairment Indirect potentiation by actions in different organ systems Digoxin Diuretics Digoxin toxicity enhanced because of hypokalaemia Warfarin Aspirin, NSAIDs Increased risk of bleeding because of gastrotoxicity and antiplatelet effects Diuretics ACE inhibitors Blood pressure reduction (may be therapeutically advantageous) because of the increased activity of the renin–angiotensin system in response to diuresis *Pharmaceutical interactions are related to the formulation of the drugs and occur before drug absorption. (ACE = angiotensin-converting enzyme; NSAID = non-steroidal anti-inflammatory drug)

7–9% of hospital prescriptions contain an error, and most are written by junior doctors. Common prescribing errors in hospitals include omission of medicines (especially failure to prescribe regular medicines at the point of admission or discharge, i.e. 'medicines reconciliation'), dosing errors, unintentional prescribing and poor use of documentation (Box 2.12). Most prescription errors result from a combination of failures by the individual prescriber and the health-service systems in which they work (Box 2.13). Health-care organisations increasingly encourage reporting of errors within a 'no-blame culture' so that they can be subject to 'root cause analysis' using human error theory (Fig. 2.5). Prevention is targeted at the factors in Box 2.13, and can be supported by prescribers communicating and cross-checking with colleagues (e.g. when calculating doses adjusted for body weight, or planning appropriate monitoring after drug administration), and by health-care systems providing clinical pharmacist support (e.g. for checking the patient's previous medications and current prescriptions) and electronic prescribing (which avoids errors due to illegibility or serious dosing mistakes, and may be combined with a clinical decision support system to take account of patient characteristics and drug history, and provide warnings of potential contraindications and drug interactions). 2.13 Causes of prescribing errors Systems factors • Working hours of prescribers (and others) • Patient throughput • Professional support and supervision by colleagues • Availability of information (medical records) • Design of prescription forms • Distractions • Availability of decision support • Checking routines (e.g. clinical pharmacy) • Reporting and reviewing of incidents Prescriber factors Knowledge • Clinical pharmacology principles • Drugs in common use • Therapeutic problems commonly encountered • Knowledge of workplace systems Skills • Taking a good drug history • Obtaining information to support prescribing • Communicating with patients • Numeracy and calculations • Prescription writing Attitudes • Coping with risk and uncertainty • Monitoring of prescribing • Checking routines 2.12 Hospital prescribing errors Error type Approximate % of total Omission on admission

Underdose

Overdose

Strength/dose missing

Omission on discharge

Administration times incorrect/missing

Duplication

Product or formulation not specified

Incorrect formulation

No maximum dose

Unintentional prescribing

No signature

Clinical contraindication

Incorrect route

No indication

Intravenous instructions incorrect/missing

Drug not prescribed but indicated

Drug continued for longer than needed

Route of administration missing

Start date incorrect/missing

Risk of drug interaction < 0.5 Controlled drug requirements incorrect/missing < 0.5 Daily dose divided incorrectly < 0.5 Significant allergy < 0.5 Drug continued in spite of adverse effects < 0.5 Premature discontinuation < 0.5 Failure to respond to out-of-range drug level < 0.5 Fig. 2.5 Human error theory. Unintended errors may occur because the prescriber fails to complete the prescription correctly (a slip; e.g. writes the dose in ‘mg’ not ‘micrograms’) or forgets part of the action that is important for success (a lapse; e.g. forgets to co-prescribe folic acid with methotrexate); prevention requires the system to provide appropriate checking routines. Intended errors occur when the prescriber acts incorrectly due to lack of knowledge (a mistake; e.g. prescribes atenolol for a patient with known severe asthma because of ignorance about the contraindication); prevention must focus on training the prescriber. Planned action Prescribing Intended action Correct action Intended outcome Unintended action Lapse Slip Wrong plan selected (Causes include poor training and lack of experience) Correct plan known but not executed (Causes include workload, time pressures, distractions) Prescription not as intended Prescriber unaware

Prescription incomplete or forgotten Prescriber may remember Violation Mistake Prescription as intended but written based on the wrong principles or lack of knowledge Prescriber unaware Deliberate deviations from standard practice Prescriber aware

26 • CLINICAL THERAPEUTICS AND GOOD PRESCRIBING cell lines, molecular cloning and purification processes. After the patent for the originator product expires, other manufacturers may develop similar products (‘biosimilars’) that share similar pharmacological actions but are not completely identical. ‘Biosimilars’ are considered distinct from ‘generic’ medications, as complex biological molecules are more susceptible to differences in manufacturing processes than conventional small-molecule-type pharmaceuticals. The number of new drugs produced by the pharmaceutical industry has declined in recent years. The traditional approach of targeting membrane-bound receptors and enzymes with small molecules (see Box 2.2) is now giving way to new targets, such as complex second-messenger systems, cytokines, nucleic acids and cellular networks. These require novel therapeutic agents, which present new challenges for ‘translational medicine’, the discipline of converting scientific discoveries into a useful medicine with a well-defined benefit–risk profile (Box 2.15). Licensing new medicines New drugs are given a ‘market authorisation’, based on the evidence of quality, safety and efficacy presented by the manufacturer. The regulator not only will approve the drug but also will take great care to ensure that the accompanying information reflects the evidence that has been presented. The summary of product characteristics (SPC), or ‘label’, provides detailed information about indications, dosage, adverse effects, warnings, monitoring and so on. If approved, drugs can be made available with different levels of restriction: • Controlled drug (CD). These drugs are subject to strict legal controls on supply and possession, usually due to their abuse potential (e.g. opioid analgesics). 2.14 Clinical development of new drugs Phase I • Healthy volunteers (20–80) • These involve initial single-dose, ‘first-into-man’ studies, followed by repeated-dose studies. They aim to establish the basic pharmacokinetic and pharmacodynamic properties, and short-term safety • Duration: 6–12 months Phase II • Patients (100–200) • These investigate clinical effectiveness (‘proof of concept’), safety and dose–response relationship, often with a surrogate clinical endpoint, in the target patient group to determine the optimal dosing regimen for larger confirmatory studies • Duration: 1–2 years Phase III • Patients (100s–1000s) • These are large, expensive clinical trials that confirm safety and efficacy in the target patient population, using relevant clinical endpoints. They may be placebo-controlled studies or comparisons with other active compounds • Duration: 1–2 years Phase IV • Patients (100s–1000s) • These are undertaken after the medicine has been marketed for its first indication to evaluate new indications, new doses or formulations, long-term safety or cost-effectiveness Responding when an error is discovered All prescribers will make errors. When they do, their first duty is to protect the patient’s safety. This will involve a clinical review and the taking of any steps that will reduce harm (e.g. remedial treatment, monitoring, recording the event in the notes, informing colleagues). Patients should be informed if they have been exposed to potential harm. For errors that do not reach the patient, it is the prescriber’s duty to report them, so that others can learn from the experience and take the opportunity to reflect on how a similar incident might be avoided in the future. Drug regulation and management Given the powerful beneficial and potentially adverse effects of drugs, the production and use of medicines are strictly regulated (e.g. by the Food and Drug Administration in the USA, Medicines and Healthcare Products Regulatory Agency in the UK, and Central Drugs Standard Control Organisation in India). Regulators are responsible for licensing medicines, monitoring their safety (pharmacovigilance; p. 23), approving clinical trials, and inspecting and maintaining standards of drug development and

manufacture. In addition, because of the high costs of drugs and their adverse effects, health-care services must prioritise their use in light of the evidence of their benefit and harm, a process referred to as ‘medicines management’. Drug development and marketing Naturally occurring products have been used to treat illnesses for thousands of years and some remain in common use today. Examples include morphine from the opium poppy (Papaver somniferum), digitalis from the foxglove (Digitalis purpurea), curare from the bark of a variety of species of South American trees, and quinine from the bark of the Cinchona species. Although plants and animals remain a source of discovery, the majority of new drugs come from drug discovery programmes that aim to identify small-molecule compounds with specific interactions with a molecular target that will induce a predicted biological effect. The usual pathway for development of these small molecules includes: identifying a plausible molecular target by investigating pathways in disease; screening a large library of compounds for those that interact with the molecular target in vitro; conducting extensive medicinal chemistry to optimise the properties of lead compounds; testing efficacy and toxicity of these compounds in vitro and in animals; and undertaking a clinical development programme (Box 2.14). This process typically takes longer than 10 years and may cost up to US$1 billion. Manufacturers have a defined period of exclusive marketing of the drug while it remains protected by an original patent, typically 10–15 years, during which time they must recoup the costs of developing the drug. Meanwhile, competitor companies will often produce similar ‘me too’ drugs of the same class. Once the drug’s patent has expired, ‘generic’ manufacturers may step in to produce cheaper formulations of the drug. Paradoxically, if a generic drug is produced by only one manufacturer, the price may actually rise, sometimes substantially. Newer ‘biological’ products are based on large molecules (e.g. human recombinant antibodies) derived from complex manufacturing processes involving specific

Managing the use of medicines Many medicines meet the three key regulatory requirements of quality, safety and efficacy. Although prescribers are legally entitled to prescribe any of them, it is desirable to limit the choice so that treatments for specific diseases can be focused on the most effective and cost-effective options, prescribers (and patients) gain familiarity with a smaller number of medicines, and pharmacies can concentrate stocks on them. The process of ensuring optimal use of available medicines is known as ‘medicines management’ or ‘quality use of medicines’. It involves careful evaluation of the evidence of benefit and harm from using the medicine, an assessment of cost-effectiveness, and support for processes to implement the resulting recommendations. These activities usually involve both national (e.g. National Institute for Health and Care Excellence (NICE) in the UK) and local organisations (e.g. drug and therapeutics committees). Evaluating evidence The principles of evidence-based medicine are described on page 10. Drugs are often evaluated in high-quality randomised controlled trials, the results of which can be considered by systematic review (Fig. 2.6). Ideally, data are available not only for comparison with placebo but also for ‘head-to-head’ comparison with alternative therapies. Trials are conducted in selected patient populations, however, and are not representative of every clinical scenario, so extrapolation to individual patients is not always straightforward. Other subtle bias may be introduced because of the sources of funding (e.g. pharmaceutical industry) and the interests of the investigators in being involved in research that has a ‘positive’ impact. These biases may be manifest in the way the trials are conducted or in how they are interpreted or reported. A common example of the latter is the difference between relative and absolute risk of

clinical events reported in prevention trials. If a clinical event is encountered in the placebo arm at a rate of 1 in 50 patients (2%) but only 1 in 100 patients (1%) in the active treatment arm, then the impact of treatment can be described as either a 50% relative risk reduction or 1% absolute risk reduction. Although the former sounds more impressive, it is the latter that is of more importance to the • Prescription-only medicine (PoM). These are available only from a pharmacist and can be supplied only if prescribed by an appropriate practitioner. • Pharmacy (P). These are available only from a pharmacist but can be supplied without a prescription. • General sales list (GSL). These medicines may be bought ‘over the counter’ (OTC) from any shop and without a prescription. Although the regulators take great care to agree the exact indications for prescribing a medicine, based on the evidence provided by the manufacturer, there are some circumstances in which prescribers may direct its use outside the terms stated in the SPC (‘off-label’ prescribing). Common situations where this might occur include prescribing outside the approved age group (e.g. prescribing for children) or using an alternative formulation (e.g. administering a medicine provided in a solid form as an oral solution). Other important examples might include prescribing for an indication for which there are no approved medicines or where all of the approved medicines have caused unacceptable adverse effects. Occasionally, medicines may be prescribed when there is no marketing authorisation in the country of use. Examples include when a medicine licensed in another country is imported for use for an individual patient (‘unlicensed import’) or when a patient requires a specific preparation of a medicine to be manufactured (‘unlicensed special’). When prescribing is ‘off-label’ or ‘unlicensed’, there is an increased requirement for prescribers to be able to justify their actions and to inform and agree the decision with the patient. Drug marketing The marketing activities of the pharmaceutical industry are well resourced and are important in the process of recouping the massive costs of drug development. In some countries, such as the USA, it is possible to promote a new drug by direct-toconsumer advertising, although this is illegal in the countries of the European Union. A major focus is on promotion to prescribers via educational events, sponsorship of meetings, advertisements in journals, involvement with opinion leaders, and direct contact by company representatives. Such largesse has the potential to cause significant conflicts of interest and might tempt prescribers to favour one drug over another, even in the face of evidence on effectiveness or cost-effectiveness. 2.15 Novel therapeutic alternatives to conventional small-molecule drugs Approaches Therapeutic indications Challenges Monoclonal antibodies Targeting of receptors or other molecules with relatively specific antibodies Cancer Chronic inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease) Selectivity of action Complex manufacturing process Small interfering RNA (siRNA) Inhibition of gene expression Macular degeneration Delivery to target Gene therapy Delivery of modified genes that supplement or alter host DNA Cystic fibrosis Cancer Cardiovascular disease Delivery to target Adverse effects of delivery vector (e.g. virus) Stem cell therapy Stem cells differentiate and replace damaged host cells Parkinson’s disease Spinal cord injury Ischaemic heart disease Delivery to target Immunological compatibility Long-term effects unknown

 Implementing recommendations Many recommendations about drug therapy are included in clinical guidelines written by an expert group after systematic review of the evidence. Guidelines provide recommendations rather than obligations for prescribers and are helpful in promoting more consistent and higher-quality prescribing. They are often written without concern for cost-effectiveness, however, and may be limited by the quality of available evidence. Guidelines cannot anticipate the extent of the variation between individual patients who may, for example, have unexpected contraindications to

recommended drugs or choose different priorities for treatment. When deviating from respected national guidance, prescribers should be able to justify their practice. Additional recommendations for prescribing are often implemented locally or imposed by bodies responsible for paying for health care. Most health-care units have a drug and therapeutics committee (or equivalent) comprised of senior and junior medical staff, pharmacists and nurses, as well as managers (because of the implications of the committee's work for governance and resources). This group typically develops local prescribing policy and guidelines, maintains a local drug formulary and evaluates requests to use new drugs. The local formulary contains a more limited list than any national formulary (e.g. British National Formulary) because the latter lists all licensed medicines that can be prescribed legally, while the former contains only those that the health-care organisation has approved for local use. The local committee may also be involved, with local specialists, in providing explicit protocols for management of clinical scenarios. Prescribing in practice Decision-making in prescribing Prescribing should be based on a rational approach to a series of challenges (see Box 2.1). individual patient. It means that the number of patients that needed to be treated (NNT) for 1 to benefit (compared to placebo) was 100. This illustrates how large clinical trials of new medicines can produce highly statistically significant and impressive relative risk reductions and still predict a very modest clinical impact. Evaluating cost-effectiveness New drugs often represent an incremental improvement over the current standard of care but are usually more expensive. Health-care budgets are limited in every country and so it is impossible to fund all new medicines. This means that very difficult financial decisions have to be taken with due regard to the principles of ethical justice. The main approach taken is cost-effectiveness analysis (CEA), where a comparison is made between the relative costs and outcomes of different courses of action. CEA is usually expressed as a ratio where the denominator is a gain in health and the numerator is the cost associated with the health gain. A major challenge is to compare the value of interventions for different clinical outcomes. One method is to calculate the quality-adjusted life years (QALYs) gained if the new drug is used rather than standard treatment. This analysis involves estimating the 'utility' of various health states between 1 (perfect health) and 0 (dead). If the additional costs and any savings are known, then it is possible to derive the incremental cost-effectiveness ratio (ICER) in terms of cost/QALY. These principles are exemplified in Box 2.16. There are, however, inherent weaknesses in this kind of analysis: it usually depends on modelling future outcomes well beyond the duration of the clinical trial data that are available; it assumes that QALYs gained at all ages are of equivalent value; and the appropriate standard care against which the new drug should be compared is often uncertain. These pharmacoeconomic assessments are challenging and resource-intensive, and are undertaken at national level in most countries, e.g. in the UK by NICE. Fig. 2.6 Systematic review of the evidence from randomised controlled clinical trials. This forest plot shows the effect of warfarin compared with placebo on the likelihood of stroke in patients with atrial fibrillation in five randomised controlled trials that passed the quality criteria required for inclusion in a meta-analysis. For each trial, the purple box is proportionate to the number of participants. The tick marks show the mean odds ratio and the black lines indicate its 95% confidence intervals. Note that not all the trials showed statistically significant effects (i.e. the confidence intervals cross 1.0). However, the meta-analysis, represented by the black diamond, confirms a highly significant statistical benefit. The overall odds ratio is approximately 0.4, indicating a mean 60% risk reduction with warfarin treatment in patients with the characteristics of the participants in these trials. Odds ratio Favours treatment 0.1 0.2 0.5

Favours placebo 2.16 Cost-effectiveness analysis A clinical trial lasting 2 years compares two interventions for the treatment of colon cancer: • Treatment A: standard treatment, cost £1000/year, oral therapy • Treatment B: new treatment, cost £6000/year, monthly intravenous infusions, often followed by a week of nausea. The new treatment (B) significantly increases the average time to progression (18 months versus 12 months) and reduces overall mortality (40% versus 60%). The health economist models the survival curves from the trial in order to undertake a cost–utility analysis and concludes that: • Intervention A: allows an average patient to live for 2 extra years at a utility 0.7 = 1.4 QALYs (cost £2000) • Intervention B: allows an average patient to live for 3 extra years at a utility 0.6 = 1.8 QALYs (cost £18 000). The health economists conclude that treatment B provides an extra 0.4 QALYs at an extra cost of £16 000, meaning that the ICER = £40 000/QALY. They recommend that the new treatment should not be funded on the basis that their threshold for cost acceptability is £30 000/QALY. (ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year)

Excretion Drugs that depend on renal excretion for elimination (e.g. digoxin, aminoglycoside antibiotics) should be avoided in patients with impaired renal function if suitable alternatives exist. Efficacy Prescribers normally choose drugs with the greatest efficacy in achieving the goals of therapy (e.g. proton pump inhibitors rather than H2-receptor antagonists). It may be appropriate, however, to compromise on efficacy if other drugs are more convenient, safer to use or less expensive. Avoiding adverse effects Prescribers should be wary of choosing drugs that are more likely to cause adverse effects (e.g. cephalosporins rather than alternatives for patients allergic to penicillin) or worsen coexisting conditions (e.g. β-blockers as treatment for angina in patients with asthma). Features of the disease This is most obvious when choosing antibiotic therapy, which should be based on the known or suspected sensitivity of the infective organism (p. 116). Severity of disease The choice of drug should be appropriate to disease severity (e.g. paracetamol for mild pain, morphine for severe pain). Coexisting disease This may be either an indication or a contraindication to therapy. Hypertensive patients might be prescribed a β-blocker if they also have left ventricular impairment but not if they have asthma. Avoiding adverse drug interactions Prescribers should avoid giving combinations of drugs that might interact, either directly or indirectly (see Box 2.11). Patient adherence to therapy Prescribers should choose drugs with a simple dosing schedule or easier administration (e.g. the ACE inhibitor lisinopril once daily rather than captopril 3 times daily for hypertension). Cost Prescribers should choose the cheaper drug (e.g. a generic or biosimilar) if two drugs are of equal efficacy and safety. Even if cost is not a concern for the individual patient, it is important to remember that unnecessary expenditure will ultimately limit choices for other prescribers and patients. Sometimes a more costly drug may be appropriate (e.g. if it yields improved adherence). Genetic factors There are already a small number of examples where genotype influences the choice of drug therapy (see Box 2.5). Choosing a dosage regimen Prescribers have to choose a dose, route and frequency of administration (dosage regimen) to achieve a steady-state drug concentration that provides sufficient exposure of the target tissue without producing toxic effects. Manufacturers draw up dosage recommendations based on average observations in many patients but the optimal regimen that will maximise the benefit to harm ratio for an individual patient is never certain. Making a diagnosis Ideally, prescribing should be based on a confirmed diagnosis but, in reality, many prescriptions are based on the balance of probability, taking into account the differential diagnosis (e.g. proton pump

inhibitors for post-prandial retrosternal discomfort). Establishing the therapeutic goal The goals of treatment are usually clear, particularly when relieving symptoms (e.g. pain, nausea, constipation). Sometimes the goal is less obvious to the patient, especially when aiming to prevent future events (e.g. ACE inhibitors to prevent hospitalisation and extend life in chronic heart failure). Prescribers should be clear about the therapeutic goal against which they will judge success or failure of treatment. It is also important to establish that the value placed on this goal by the prescriber is shared by the patient (concordance). Choosing the therapeutic approach For many clinical problems, drug therapy is not absolutely mandated. Having taken the potential benefits and harms into account, prescribers must consider whether drug therapy is in the patient's interest and is preferred to no treatment or one of a range of alternatives (e.g. physiotherapy, psychotherapy, surgery). Assessing the balance of benefit and harm is often complicated and depends on various features associated with the patient, disease and drug (Box 2.17). Choosing a drug For most common clinical indications (e.g. type 2 diabetes, depression), more than one drug is available, often from more than one drug class. Although prescribers often have guidance about which represents the rational choice for the average patient, they still need to consider whether this is the optimal choice for the individual patient. Certain factors may influence the choice of drug: Absorption Patients may find some formulations easier to swallow than others or may be vomiting and require a drug available for parenteral administration. Distribution Distribution of a drug to a particular tissue sometimes dictates choice (e.g. tetracyclines and rifampicin are concentrated in the bile, and lincomycin and clindamycin in bones). Metabolism Drugs that are extensively metabolised should be avoided in severe liver disease (e.g. opioid analgesics). 2.17 Factors to consider when balancing benefits and harms of drug therapy • Seriousness of the disease or symptom • Efficacy of the drug • Seriousness of potential adverse effects • Likelihood of adverse effects • Efficacy of alternative drugs or non-drug therapies • Safety of alternative drugs or non-drug therapies

 Duration Some drugs require a single dose (e.g. thrombolysis post myocardial infarction), while for others the duration of the course of treatment is certain at the outset (e.g. antibiotics). For most, the duration will be largely at the prescriber's discretion and will depend on response and disease progression (e.g. analgesics, antidepressants). For many, the treatment will be long-term (e.g. insulin, antihypertensives, levothyroxine). Involving the patient Patients should, whenever possible, be engaged in making choices about drug therapy. Their beliefs and expectations affect the goals of therapy and help in judging the acceptable benefit/ harm balance when selecting treatments. Very often, patients may wish to defer to the professional expertise of the prescriber. Nevertheless, they play key roles in adherence to therapy and in monitoring treatment, not least by providing early warning of adverse events. It is important for them to be provided with the necessary information to understand the choice that has been made, what to expect from the treatment, and any measurements that must be undertaken (Box 2.20). A major drive to include patients has been the recognition that up to half of the drug doses for chronic preventative therapy are not taken. This is often termed 'non-compliance' but is more appropriately called 'non-adherence', to reflect a less paternalistic view of the doctor–patient relationship; it may or may not be intentional. Non-adherence to the dose regimen reduces the likelihood of benefits to the patient and can be costly in terms Rational prescribing involves treating each prescription as an experiment and gathering sufficient information to amend it if necessary. There are some general principles that should be followed, as described below. Dose titration Prescribers should generally start with a low dose and titrate this

slowly upwards as necessary. This cautious approach is particularly important if the patient is likely to be more sensitive to adverse pharmacodynamic effects (e.g. delirium or postural hypotension in the elderly) or have altered pharmacokinetic handling (e.g. renal or hepatic impairment), and when using drugs with a low therapeutic index (e.g. benzodiazepines, lithium, digoxin). There are some exceptions, however. Some drugs must achieve therapeutic concentration quickly because of the clinical circumstance (e.g. antibiotics, glucocorticoids, carbimazole). When early effect is important but there may be a delay in achieving steady state because of a drug's long half-life (e.g. digoxin, warfarin, amiodarone), an initial loading dose is given prior to establishing the appropriate maintenance dose (see Fig. 2.4). If adverse effects occur, the dose should be reduced or an alternative drug prescribed; in some cases, a lower dose may suffice if it can be combined with another synergistic drug (e.g. the immunosuppressant azathioprine reduces glucocorticoid requirements in patients with inflammatory disease). It is important to remember that the shape of the dose–response curve (see Fig. 2.2) means that higher doses may produce little added therapeutic effect and might increase the chances of toxicity. Route There are many reasons for choosing a particular route of administration (Box 2.18). Frequency Frequency of doses is usually dictated by a manufacturer's recommendation. Less frequent doses are more convenient for patients but result in greater fluctuation between peaks and troughs in drug concentration (see Fig. 2.4). This is relevant if the peaks are associated with adverse effects (e.g. dizziness with antihypertensives) or the troughs are associated with troublesome loss of effect (e.g. anti-Parkinsonian drugs). These problems can be tackled either by splitting the dose or by employing a modified-release formulation, if available. Timing For many drugs the time of administration is unimportant. There are occasionally pharmacokinetic or therapeutic reasons, however, for giving drugs at particular times (Box 2.19). Formulation For some drugs there is a choice of formulation, some for use by different routes. Some are easier to ingest, particularly by children (e.g. elixirs). The formulation is important when writing repeat prescriptions for drugs with a low therapeutic index that come in different formulations (e.g. lithium, phenytoin, theophylline). Even if the prescribed dose remains constant, an alternative formulation may differ in its absorption and bioavailability, and hence plasma drug concentration. These are examples of the small number of drugs that should be prescribed by specific brand name rather than 'generic' international non-proprietary name (INN). 2.18 Factors influencing the route of drug administration Reason Example Only one route possible Dobutamine (IV) Gliclazide (oral) Patient adherence Phenothiazines and thioxanthenes (2 weekly IM depot injections rather than daily tablets, in schizophrenia) Poor absorption Furosemide (IV rather than oral, in severe heart failure) Rapid action Haloperidol (IM rather than oral, in acute behavioural disturbance) Vomiting Phenothiazines (PR or buccal rather than oral, in nausea) Avoidance of first-pass metabolism Glyceryl trinitrate (SL, in angina pectoris) Certainty of effect Amoxicillin (IV rather than oral, in acute chest infection) Direct access to the site of action (avoiding unnecessary systemic exposure) Bronchodilators (INH rather than oral, in asthma) Local application of drugs to skin, eyes etc. Ease of access Diazepam (PR, if IV access is difficult in status epilepticus) Adrenaline (epinephrine) (IM, if IV access is difficult in acute anaphylaxis) Comfort Morphine (SC rather than IV in terminal care) (IM = intramuscular; INH = by inhalation; IV = intravenous; PR = per rectum; SC = subcutaneous; SL = sublingual)

Stopping drug therapy It is also important to review long-term treatment at regular intervals to assess whether continued treatment is required. Elderly patients are keen to reduce their

medication burden and are often prepared to compromise on the original goals of long-term preventative therapy to achieve this. Prescribing in special circumstances Prescribing for patients with renal disease Patients with renal impairment are readily identified by having a low estimated glomerular filtration rate (eGFR < 60 mL/min) based on their serum creatinine, age, sex and ethnic group (p. 386). This group includes a large proportion of elderly patients. If a drug (or its active metabolites) is eliminated predominantly by the kidneys, it will tend to accumulate and so the maintenance dose must be reduced. For some drugs, renal impairment makes patients more sensitive to their adverse pharmacodynamic effects. of wasted medicines and unnecessary health-care episodes. An important reason may be lack of concordance with the prescriber about the goals of treatment. A more open and shared decisionmaking process might resolve any misunderstandings at the outset and foster improved adherence, as well as improved satisfaction with health-care services and confidence in prescribers. Fully engaging patients in shared decision-making is sometimes constrained by various factors, such as limited consultation time and challenges in communicating complex numerical data. Writing the prescription The culmination of the planning described above is writing an accurate and legible prescription so that the drug will be dispensed and administered as planned (see ‘Writing prescriptions’ below). Monitoring treatment effects Rational prescribing involves monitoring for the beneficial and adverse effects of treatment so that the balance remains in favour of a positive outcome (see ‘Monitoring drug therapy’ below). 2.19 Factors influencing the timing of drug therapy Drug Recommended timing Reasons Diuretics (e.g. furosemide) Once in the morning Night-time diuresis undesirable Statins (e.g. simvastatin) Once at night HMG CoA reductase activity is greater at night Antidepressants (e.g. amitriptyline) Once at night Allows adverse effects to occur during sleep Salbutamol Before exercise Reduces symptoms in exercise-induced asthma Glyceryl trinitrate Paracetamol When required Relief of acute symptoms only Regular nitrate therapy (e.g. isosorbide mononitrate) Eccentric dosing regimen (e.g. twice daily at 8 a.m. and 2 p.m.) Reduces development of nitrate tolerance by allowing drug-free period each night Aspirin With food Minimises gastrotoxic effects Alendronate Once in the morning before breakfast, sitting upright Minimises risk of oesophageal irritation Tetracyclines 2 hours before or after food or antacids Divalent and trivalent cations chelate tetracyclines, preventing absorption Hypnotics (e.g. temazepam) Once at night Maximises therapeutic effect and minimises daytime sedation Antihypertensive drugs (e.g. amlodipine) Once in the morning Blood pressure is higher during the daytime (HMG CoA = 3-hydroxy-3-methylglutaryl-coenzyme A) 2.20 What patients need to know about their medicines* Knowledge Comment The reason for taking the medicine How the medicine works Reinforces the goals of therapy How to take the medicine May be important for the effectiveness (e.g. inhaled salbutamol in asthma) and safety (e.g. alendronate for osteoporosis) of treatment What benefits to expect May help to support adherence or prompt review because of treatment failure What adverse effects might occur Discuss common and mild effects that may be transient and might not require discontinuation Mention rare but serious effects that might influence the patient’s consent Precautions that improve safety Explain symptoms to report that might allow serious adverse effects to be averted, monitoring that will be required and potentially important drug–drug interactions When to return for review This will be important to enable monitoring *Many medicines are provided with patient information leaflets, which the patient should be encouraged to read.

 Examples of drugs that require extra caution in patients with renal disease are listed in Box 2.21. Prescribing for patients with hepatic disease The liver has a large capacity for drug metabolism and hepatic insufficiency has to be

advanced before drug dosages need to be modified. Patients who may have impaired metabolism include those with jaundice, ascites, hypoalbuminaemia, malnutrition or encephalopathy. Hepatic drug clearance may also be reduced in acute hepatitis, in hepatic congestion due to cardiac failure, and in the presence of intrahepatic arteriovenous shunting (e.g. in hepatic cirrhosis). There are no good tests of hepatic drugmetabolising capacity or of biliary excretion, so dosage should be guided by the therapeutic response and careful monitoring for adverse effects. The presence of liver disease also increases the susceptibility to adverse pharmacological effects of drugs. Some drugs that require extra caution in patients with hepatic disease are listed in Box 2.21. Prescribing for elderly patients The issues around prescribing in the elderly are discussed in Box 2.22. Prescribing for women who are pregnant or breastfeeding Prescribing in pregnancy should be avoided if possible to minimise the risk of adverse effects in the fetus. Drug therapy in pregnancy may, however, be required either for a pre-existing problem (e.g. epilepsy, asthma, hypothyroidism) or for problems that arise during pregnancy (e.g. morning sickness, anaemia, prevention of neural tube defects, gestational diabetes, hypertension). About 35% of women take drug therapy at least once during 2.23 Prescribing in pregnancy • Teratogenesis: a potential risk, especially when drugs are taken between 2 and 8 weeks of gestation (4–10 weeks from last menstrual period). Common teratogens include retinoids (e.g. isotretinoin), cytotoxic drugs, angiotensin-converting enzyme inhibitors, antiepileptics and warfarin. If there is inadvertent exposure, then the timing of conception should be established, counselling given and investigations undertaken for fetal abnormalities. • Adverse fetal effects in late gestation: e.g. tetracyclines may stain growing teeth and bones; sulphonamides displace fetal bilirubin from plasma proteins, potentially causing kernicterus; opioids given during delivery may be associated with respiratory depression in the neonate. • Altered maternal pharmacokinetics: extracellular fluid volume and Vd increase. Plasma albumin falls but other binding globulins (e.g. for thyroid and steroid hormones) increase. Glomerular filtration increases by approximately 70%, enhancing renal clearance. Placental metabolism contributes to increased clearance, e.g. of levothyroxine and glucocorticoids. The overall effect is a fall in plasma levels of many drugs. • In practice: Avoid any drugs unless the risk:benefit analysis is in favour of treating (usually the mother). Use drugs for which there is some record of safety in humans. Use the lowest dose for the shortest time possible. Choose the least harmful drug if alternatives are available. 2.22 Prescribing in old age • Reduced drug elimination: partly due to impaired renal function. • Increased sensitivity to drug effects: notably in the brain (leading to sedation or delirium) and as a result of comorbidities. • More drug interactions: largely as a result of polypharmacy. • Lower starting doses and slower dose titration: often required, with careful monitoring of drug effects. • Drug adherence: may be poor because of cognitive impairment, difficulty swallowing (dry mouth) and complex polypharmacy regimens. Supplying medicines in pill organisers (e.g. dosette boxes or calendar blister packs), providing automatic reminders, and regularly reviewing and simplifying the drug regimen can help. • Some drugs that require extra caution, and their mechanisms: Digoxin: increased sensitivity of Na+/K+ pump; hypokalaemia due to diuretics; renal impairment favours accumulation → increased risk of toxicity. Antihypertensive drugs: reduced baroreceptor function → increased risk of postural hypotension. Antidepressants, hypnotics, sedatives, tranquillisers: increased sensitivity of the brain; reduced metabolism → increased risk of toxicity. Warfarin: increased tendency to falls and injury and to bleeding from intra- and extracranial sites; increased sensitivity to inhibition of clotting factor synthesis → increased risk of bleeding. Clomethiazole, lidocaine, nifedipine, phenobarbital, propranolol, theophylline: metabolism reduced → increased risk of toxicity. Non-steroidal anti-inflammatory drugs: poor renal function → increased risk of renal impairment; susceptibility to

gastrotoxicity → increased risk of upper gastrointestinal bleeding. 2.21 Some drugs that require extra caution in patients with renal or hepatic disease Kidney disease Liver disease Pharmacodynamic effects enhanced ACE inhibitors and ARBs (renal impairment, hyperkalaemia) Metformin (lactic acidosis) Spironolactone (hyperkalaemia) NSAIDs (impaired renal function) Sulphonylureas (hypoglycaemia) Insulin (hypoglycaemia) Warfarin (increased anticoagulation because of reduced clotting factor synthesis) Metformin (lactic acidosis) Chloramphenicol (bone marrow suppression) NSAIDs (gastrointestinal bleeding, fluid retention) Sulphonylureas (hypoglycaemia) Benzodiazepines (coma) Pharmacokinetic handling altered (reduced clearance) Aminoglycosides (e.g. gentamicin) Vancomycin Digoxin Lithium Other antibiotics (e.g. ciprofloxacin) Atenolol Allopurinol Cephalosporins Methotrexate Opioids (e.g. morphine) Phenytoin Rifampicin Propranolol Warfarin Diazepam Lidocaine Opioids (e.g. morphine) (ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; NSAID = non-steroidal anti-inflammatory drug) pregnancy and 6% take drug therapy during the first trimester (excluding iron, folic acid and vitamins). The most commonly used drugs are simple analgesics, antibacterial drugs and antacids. Some considerations when prescribing in pregnancy are listed in Box 2.23.

Hospital discharge (‘to take out’) medicines Most patients will be prescribed a short course of their medicines at discharge. This prescription is particularly important because it usually informs future therapy at the point of transfer of prescribing responsibility to primary care. Great care is required to ensure that this list is accurate. It is particularly important to ensure that any hospital medicines that should be stopped are not included and that those intended to be administered for a short duration only are clearly identified. It is also important for any significant ADRs experienced in hospital to be recorded and any specific monitoring or review identified. Prescribing in primary care Most of the considerations above are equally applicable to primary care (GP) prescriptions. In many health-care systems, community prescribing is electronic, making issues of legibility irrelevant and often providing basic decision support to limit the range of doses that can be written and highlight potential drug interactions. Important additional issues more relevant to GP prescribing are: • Formulation. The prescription needs to carry information about the formulation for the dispensing pharmacist (e.g. tablets or oral suspension). • Amount to be supplied. In the hospital the pharmacist will organise this. Elsewhere it must be specified either as the precise number of tablets or as the duration of treatment. Creams and ointments should be specified in grams and lotions in mL. • Controlled drugs. Prescriptions for ‘controlled’ drugs (e.g. opioid analgesics, with potential for drug abuse) are subject to additional legal requirements. In the UK, they Drugs that are excreted in breast milk may cause adverse effects in the baby. Prescribers should always consult the summary of product characteristics for each drug or a reliable formulary when treating a pregnant woman or breastfeeding mother. Writing prescriptions A prescription is a means by which a prescriber communicates the intended plan of treatment to the pharmacist who dispenses a medicine and to a nurse or patient who administers it. It should be precise, accurate, clear and legible. The two main kinds of prescription are those written, dispensed and administered in hospital and those written in primary care (in the UK by a GP), dispensed at a community pharmacy and self-administered by the patient. The information supplied must include: • the date • the identification details of the patient • the name of the drug • the formulation • the dose • the frequency of administration • the route and method of administration • the amount to be supplied (primary care only) • instructions for labelling (primary care only) • the prescriber’s signature.

Prescribing in hospital Although GP prescribing is increasingly electronic, most hospital prescribing continues to be based around the prescription and administration record (the ‘drug chart’) (Fig. 2.7). A variety of charts are in use and prescribers must familiarise themselves with the local version. Most contain the following sections: • Basic patient information: will usually include name, age, date of birth, hospital number and address. These details are often ‘filled in’ using a sticky addressograph label but this increases the risk of serious error. • Previous adverse reactions/allergies: communicates important patient safety information based on a careful drug history and/or the medical record. • Other medicines charts: notes any other hospital prescription documents that contain current prescriptions being received by the patient (e.g. anticoagulants, insulin, oxygen, fluids). • Once-only medications: for prescribing medicines to be used infrequently, such as single-dose prophylactic antibiotics and other pre-operative medications. • Regular medications: for prescribing medicines to be taken for a number of days or continuously, such as a course of antibiotics, antihypertensive drugs and so on. • ‘As required’ medications: for prescribing for symptomatic relief, usually to be administered at the discretion of the nursing staff (e.g. antiemetics, analgesics). Prescribers should be aware of the risks of prescription error (Box 2.24 and see Box 2.13), ensure they have considered the rational basis for their prescribing decision described above, and then follow the guidance illustrated in Figure 2.7 in order to write the prescription. It is a basic principle that a prescription will be followed by a judgement as to its success or failure and any appropriate changes made (e.g. altered dosage, discontinuation or substitution). 2.24 High-risk prescribing moments • Trying to amend an active prescription (e.g. altering the dose/ timing) – always avoid and start again • Writing up drugs in the immediate presence of more than one prescription chart or set of notes – avoid • Allowing one’s attention to be diverted in the middle of completing a prescription – avoid • Prescribing ‘high-risk’ drugs (e.g. anticoagulants, opioids, insulin, sedatives) – ask for help if necessary • Prescribing parenteral drugs – take care • Rushing prescribing (e.g. in the midst of a busy ward round) – avoid • Prescribing unfamiliar drugs – consult the formulary and ask for help if necessary • Transcribing multiple prescriptions from an expired chart to a new one – take care to review the rationale for each medicine • Writing prescriptions based on information from another source such as a referral letter (the list may contain errors and some of the medicines may be the cause of the patient’s illness) – review the justification for each as if it is a new prescription • Writing up ‘to take out’ drugs (because these will become the patient’s regular medication for the immediate future) – take care and seek advice if necessary • Calculating drug doses – ask a colleague to perform an independent calculation or use approved electronic dose calculators • Prescribing sound-alike or look-alike drugs (e.g. chlorphenamine and chlorpromazine) – take care

 Fig. 2.7 Example of a hospital prescription and administration record (‘drug chart’). A Front page. The correct identification of the patient is critical to reducing the risk of an administration error. This page also clearly identifies other prescriptions charts in use and previous adverse reactions to drugs to minimise the risk of repeated exposure. Note also the codes employed by the nursing staff to indicate reasons why drugs may not have been administered. The patient’s name and date of birth should be written on each page of the chart. The patient’s weight and height may be required to calculate safe doses for many drugs with narrow therapeutic indices. B ‘Once-only medicines’. This area is used for prescribing medicines that are unlikely to be repeated on a regular basis. Note that the prescriber has written the names of all drugs legibly in block capitals. The generic international non-proprietary name (INN) should be used in preference to the brand name (e.g. write ‘SIMVASTATIN’, not ‘ZOCOR’). The

only exceptions are when variation occurs in the properties of alternative branded formulations (e.g. modified-release preparations of drugs such as lithium, theophylline, phenytoin and nifedipine) or when the drug is a combination product with no generic name (e.g. Kliovance). The only acceptable abbreviations for drug dose units are ‘g’ and ‘mg’. ‘Units’ (e.g. of insulin or heparin) and ‘micrograms’ must always be written in full, never as ‘U’ or ‘µg’ (nor ‘mcg’, nor ‘ug’). For liquid preparations write the dose in mg; ‘mL’ can be written only for a combination product (e.g. Gaviscon liquid) or if the strength is not expressed in weight (e.g. adrenaline (epinephrine) 1 in 1000). Use numbers/figures (e.g. 1 or ‘one’) to denote use of a sachet/enema but avoid prescribing numbers of tablets without specifying their strength. Always include the dose of inhaled drugs in addition to stating numbers of ‘puffs’, as strengths can vary. Widely accepted abbreviations for route of administration are: intravenous – ‘IV’; intramuscular – ‘IM’; subcutaneous – ‘SC’; sublingual – ‘SL’; per rectum – ‘PR’; per vaginam – ‘PV’; nasogastric – ‘NG’; inhaled – ‘INH’; and topical – ‘TOP’. ‘ORAL’ is preferred to per oram – ‘PO’. Care should be taken in specifying ‘RIGHT’ or ‘LEFT’ for eye and ear drops. The prescriber should sign and print their name clearly so that they can be identified by colleagues. The prescription should be dated and have an administration time. The nurse who administered the prescription has signed to confirm that the dose has been administered. OTHER MEDICINES CHARTS CODES FOR NON-ADMINISTRATION OF PRESCRIBED MEDICINE PREVIOUS ADVERSE REACTIONS (This must be completed before prescribing on this chart) Hospital/Ward: Consultant: Name of patient: Hospital number: (Attach printed label here) D.O.B.: Weight: Date Date Time Medicine (approved name) Dose Route Time given Given by Prescriber – sign and print If a dose is not administered as prescribed, intial and enter a code in the column with a circle drawn round the code according to the reason as shown below. Inform the responsible doctor of the appropriate timescale.

1. Patient refuses
2. Patient not present
3. Medicines not available – CHECK ORDERED
4. Asleep/drowsy
5. Administration route not available – CHECK FOR ALTERNATIVE
6. Vomiting/nausea
7. Time varied on doctor’s instructions
8. Once-only/as-required medicine given
9. Dose withheld on doctor’s instructions
10. Possible adverse reaction/side-effect Type of chart Medicine Description of reaction Completed by Date Height: If rewritten, date: DISCHARGE PRESCRIPTION PRESCRIPTION AND ADMINISTRATION RECORD Standard Chart ONCE-ONLY MEDICINES Date completed:– Completed by:– A B must contain the address of the patient and prescriber (not necessary on most hospital forms), the form and the strength of the preparation, and the total quantity of the preparation/number of dose units in both words and figures. • ‘Repeat prescriptions’. A large proportion of GP prescribing involves ‘repeat prescriptions’ for chronic medication. These are often generated automatically, although the prescriber remains responsible for regular review and for ensuring that the benefit-to-harm ratio remains favourable. Monitoring drug therapy Prescribers should measure the effects of the drug, both beneficial and harmful, to inform decisions about dose titration (up or down), discontinuation or substitution of treatment. Monitoring can be achieved subjectively by asking the patient about symptoms or, more objectively, by measuring a

clinical effect. Alternatively, if the pharmacodynamic effects of the drug are difficult to assess, the plasma drug concentration may be measured, on the basis that it will be closely related to the effect of the drug (see Fig. 2.2).

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REGULAR MEDICINES AS-REQUIRED THERAPY C D Drug (approved name) Dose Date Time

Prescriber–sign and print Notes Start date Pharmacy Route Drug (approved name) Dose Prescriber–sign and print Notes Start date Pharmacy Route Drug (approved name) Dose and frequency Prescriber–sign and print Start date Indication/notes Pharmacy Route Date Time Dose Initials Date Time Dose Initials Drug (approved name) Dose and frequency Prescriber–sign and print Start date Indication/notes Pharmacy Route Date Time Dose Initials Date Time Dose Initials Drug (approved name) Dose Prescriber–sign and print Notes Start date Pharmacy Route C 'Regular medicines'. This area is used for prescribing medicines that are going to be given regularly. In addition to the name, dose and route, a frequency of administration is required for each medicine. Widely accepted Latin abbreviations for dose frequency are: once daily – 'OD'; twice daily – 'BD'; 3 times daily – 'TDS'; 4 times daily – 'QDS'; as required – 'PRN'; in the morning – 'OM' (omni mane); at night – 'ON' (omni nocte); and immediately – 'stat'. The hospital chart usually requires specific times to be identified for regular medicines that coincide with nursing drug rounds and these can be circled. If treatment is for a known time period, cross off subsequent days when the medicine is not required. The 'notes' box can be used to communicate additional important information (e.g. whether a medicine should be taken with food, type of inhaler device used, and anything else that the drug dispenser should know). State here the times for peak/trough plasma levels for drugs requiring therapeutic monitoring. Prescriptions should be discontinued by drawing a vertical line at the point of discontinuation, horizontal lines through the remaining days on the chart, and diagonal lines through the drug details and administration boxes. This action should be signed and dated and a supplementary note written to explain it (e.g. describing any adverse effect). In this example, amlodipine has been discontinued because of ankle oedema. There is room for the ward pharmacist to sign to indicate that the prescription has been reviewed and that a supply of the medicine is available. The administration boxes allow the nurse to sign to confirm that the dose has been given. Note that these boxes also allow for recording of reasons for non-administration (in this example '2' indicates that the patient was not present on the ward at the time) and the prevention of future administration by placing an 'X' in the box. D 'As-required medicines'. These prescriptions leave the administration of the drug to the discretion of the nursing staff. The prescription must describe clearly the indication, frequency, minimal time interval between doses, and maximum dose in any 24-hour period (in this case, the maximum daily dose of paracetamol is 4 g). Fig. 2.7, cont'd Clinical and surrogate endpoints Ideally, clinical endpoints are measured directly and the drug dosage titrated to achieve the therapeutic goal and avoid toxicity (e.g. control of ventricular rate in a patient with atrial fibrillation). Sometimes this is impractical because the clinical endpoint is a future event (e.g. prevention of myocardial infarction by statins or resolution of a chest infection with antibiotics); in these circumstances, it may be possible to select a 'surrogate' endpoint that will predict success or failure. This may be an intermediate step in the pathophysiological process (e.g. serum cholesterol as a surrogate for risk of myocardial infarction) or a

36 • CLINICAL THERAPEUTICS AND GOOD PRESCRIBING Interpreting the result A target range is provided for many drugs, based on average thresholds for therapeutic benefit and toxicity. Inter-individual variability means that these can be used only as a guide. For instance, in a patient who describes symptoms that could be consistent with toxicity but has a drug concentration in the top half of the target range, toxic effects should still be suspected. Another important consideration is that some drugs are heavily protein-bound (e.g. phenytoin) but only the unbound drug is pharmacologically active. Patients with hypoalbuminaemia may therefore have a therapeutic or even toxic concentration of unbound drug, despite a low 'total' concentration. Further information Websites bnf.org The British National Formulary (BNF) is a key reference resource for UK NHS prescribers, with a list of licensed drugs, chapters on prescribing in renal failure, liver disease, pregnancy and during breastfeeding, and appendices on drug interactions. cochrane.org The Cochrane Collaboration is a leading international body that provides evidence-based reviews (around 7000 so far). evidence.nhs.uk NHS Evidence provides a wide range of health information relevant to delivering quality patient care. icp.org.nz The Interactive Clinical Pharmacology site is designed to increase understanding of principles in clinical pharmacology. medicines.org.uk/emc/ The electronic Medicines Compendium (eMC) contains up-to-date, easily accessible information about medicines licensed by the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA). nice.org.uk The UK National Institute for Health and Care Excellence makes recommendations to the UK NHS on new and existing medicines, treatments and procedures. who.int/medicines/en/ The World Health Organisation Essential Medicines and Pharmaceutical Policies. measurement that follows the pathophysiology, even if it is not a key factor in its progression (e.g. serum C-reactive protein as a surrogate for resolution of inflammation in chest infection). Such surrogates are sometimes termed 'biomarkers'. Plasma drug concentration The following criteria must be met to justify routine monitoring by plasma drug concentration: • Clinical endpoints and other pharmacodynamic (surrogate) effects are difficult to monitor. • The relationship between plasma concentration and clinical effects is predictable. • The therapeutic index is low. For drugs with a high therapeutic index, any variability in plasma concentrations is likely to be irrelevant clinically. Some examples of drugs that fulfil these criteria are listed in Box 2.25. Measurement of plasma concentration may be useful in planning adjustments of drug dose and frequency of administration; to explain an inadequate therapeutic response (by identifying subtherapeutic concentration or incomplete adherence); to establish whether a suspected ADR is likely to be caused by the drug; and to assess and avoid potential drug interactions. Timing of samples in relation to doses The concentration of drug rises and falls during the dosage interval (see Fig. 2.4B). Measurements made during the initial absorption and distribution phases are unpredictable because of the rapidly changing concentration, so samples are usually taken at the end of the dosage interval (a 'trough' or 'pre-dose' concentration). This measurement is normally made in steady state, which usually takes five half-lives to achieve after the drug is introduced or the dose changed (unless a loading dose has been given). 2.25 Drugs commonly monitored by plasma drug concentration Drug Half-life (hrs)* Comment Digoxin

Steady state takes several days to achieve. Samples should be taken 6 hrs post dose. Measurement is useful to confirm the clinical impression of toxicity or non-adherence but clinical effectiveness is better assessed by ventricular heart rate. Risk of toxicity increases progressively at concentrations > 1.5 μg/L, and is likely at concentrations > 3.0 μg/L (toxicity is more likely in the presence of hypokalaemia) Gentamicin

Measure pre-dose trough concentration (should be < 1 µg/mL) to ensure that accumulation (and the risk of nephrotoxicity and ototoxicity) is avoided; see Fig. 6.18 (p. 122) Levothyroxine

> 120 Steady state may take up to 6 weeks to achieve (p. 640) Lithium

Steady state takes several days to achieve. Samples should be taken 12 hrs post dose. Target range 0.4–1 mmol/L Phenytoin

Measure pre-dose trough concentration (should be 10–20 mg/L) to ensure that accumulation is avoided. Good correlation between concentration and toxicity. Concentration may be misleading in the presence of hypoalbuminaemia Theophylline (oral)

Steady state takes 2–3 days to achieve. Samples should be taken 6 hrs post dose. Target concentration is 10–20 mg/L but its relationship with bronchodilator effect and adverse effects is variable Vancomycin

Measure pre-dose trough concentration (should be 10–15 mg/L) to ensure clinical efficacy and that accumulation and the risk of nephrotoxicity are avoided (p. 123) *Half-lives vary considerably with different formulations and between patients.

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