5 Adverse drug reactions

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Key points

- An adverse drug reaction is an unintended noxious response occurring after the normal use of a drug, which is suspected to be associated with the drug.
- Adverse drug reactions can be classified as type A, which are most common and related to the drug's pharmacological effect, or type B, which are rare and unpredictable, although other classes of reaction can be identified.
- Few adverse reactions are identified during pre-marketing studies; therefore, pharmacovigilance systems to detect new adverse drug reactions are essential.
- Spontaneous reporting schemes are a common method of pharmacovigilance which depend primarily on health professionals.
- Patients are encouraged to contribute to post-marketing surveillance schemes in some countries.
- Adverse drug reactions are a significant cause of morbidity and mortality, are responsible for approximately 1 in 20 hospital admissions and are a considerable financial burden on health systems.
- Predisposing factors for adverse drug reactions include age, female gender, ethnicity, genetic factors, co-morbidities and concomitant medication.
- Many adverse drug reactions may be preventable through rational prescribing and careful monitoring of drug therapy.
- Health professionals need to be able to identify and assess adverse drug reactions and play a major role in preventing their occurrence.
- Patients want to receive information about adverse drug reactions; therefore, communicating the risks of using medicines is an important skill for health professionals.

Introduction

All medicines with the ability to produce a desired therapeutic effect also have the potential to cause unwanted adverse effects. Health professionals should have an awareness of the burden that adverse drug reactions (ADRs) place on health services and the public, the identification and avoidance of ADRs and their important role in post-marketing surveillance of medicines to ensure their continued safety.

Risks associated with medicinal substances are documented throughout history; for example, William Withering's 1785 account provides a meticulous description of the adverse effects of digitalis. However, it was the thalidomide disaster that captured public attention and brought about major regulatory changes in drug safety. Thalidomide was first marketed by Chemie Grünenthal in 1957 and distributed in the UK by Distillers Ltd, whose chief medical advisor stated, 'If all the details of this are true, then it is a most remarkable drug. In short, it is impossible to give a toxic dose.' In 1958, thalidomide was recommended for use in pregnant and nursing mothers without supporting evidence. An Australian doctor, Jim McBride, and a German doctor, Widukund Lenz, independently associated thalidomide exposure with serious birth defects and thalidomide was withdrawn in December 1961. Thalidomide left behind between 8000 and 12,000 deformed children and an unknown number of deaths *in utero*.

The 1970s saw another unexpected and serious adverse reaction. The cardioselective beta-adrenergic receptor blocker practolol, launched in June 1970, was initially associated with rashes, some of which were severe. A case series of psoriasis-like rashes linked to dry eyes, including irreversible scarring of the cornea, led other doctors to report eye damage, including corneal ulceration and blindness, to regulators. Cases of sclerosing peritonitis, a bowel condition associated with significant mortality, were also reported. Practolol had remained on the market for 4 years; over 100,000 people had been treated and hundreds were seriously affected.

Some adverse effects can be more difficult to differentiate from background events occurring commonly in the population. The COX-II selective non-steroidal anti-inflammatory drugs (NSAIDs), celecoxib (introduced 1998) and rofecoxib (introduced 1999), were marketed on the basis of reduced gastro-intestinal ADRs in comparison to other non-selective NSAIDs. Apparent excesses of cardiovascular events, which were noted during clinical trials and in elderly patient groups, were ascribed to the supposed cardio-protective effects of comparator drugs. However, in September 2004, a randomised controlled trial of rofecoxib in the prevention of colorectal cancer showed the drug to be associated with a significantly increased risk of cardiovascular events. Celecoxib was also associated with a dose-related increased risk of cardiovascular events in clinical trials. Rofecoxib was voluntarily withdrawn from the market. Further research has provided evidence of thrombotic risk with non-selective NSAIDs, in particular diclofenac. This risk appears to extend to all NSAID users, irrespective of baseline cardiovascular risk.

Not all drug safety issues are related to real effects. In 1998, a widely-publicised paper by Andrew Wakefield and co-authors, later retracted, alleged a link between MMR vaccine and autism, and led to a crisis in parental confidence in the vaccine. This had a detrimental effect on vaccination rates, resulting in frequent outbreaks of measles and mumps, despite epidemiological and virological studies showing no link between MMR vaccine and autism. The MMR vaccine controversy illustrates how media reporting of drug safety information can influence patients' views of medicines and can cause significant harm. Poor presentation of drug safety issues in the media often creates anxiety in patients about medicines which they may be using, regardless of their benefits.

Assessing the safety of drugs

When drugs are newly introduced to the market, their safety profile will be provisional. While efficacy and evidence of safety must be demonstrated for regulatory authorities to permit marketing, it is not possible to discover the complete safety profile of a new drug prior to its launch. Pre-marketing clinical trials involve on average 2500 patients, with perhaps a hundred patients using the drug for longer than a year. Therefore, pre-marketing trials do not have the power to detect important reactions that occur at rates of 1 in 10,000, or fewer, drug exposures. Often, only pharmacologically predictable ADRs with short onset times may be identified in clinical trials, nor can pre-marketing trials detect ADRs which are separated in time from drug exposure. Additionally, patients within trials are often carefully selected, without the multiple disease states or complex drug histories of patients in whom the drug will eventually become used. Furthermore, the patient's perspective is also frequently excluded from clinical trial safety assessments, with ADRs being assessed only by the clinicians who run them (Basch, 2010). For these reasons, rare and potentially serious adverse effects often remain undetected until a wider population is exposed to the drug. The vigilance of health professionals is an essential factor in discovering these new risks, together with regulatory authorities who continuously monitor reports of adverse effects throughout the lifetime of a marketed medicinal product.

As a result of this monitoring, the safety profile of established drugs is often well known, although new risks are occasionally identified. However, an important part of the therapeutic management of medical conditions is the minimisation of these well-known risks through rational prescribing and careful monitoring of drug therapy. Current evidence suggests that this could be improved.

Definitions

Having clear definitions of what constitutes an ADR is important. The World Health Organization (WHO) defines an ADR as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function' (WHO, 1972). The use of the phrase 'at doses normally used in man' distinguishes the noxious effects of drugs during normal medical use from toxic effects caused by poisoning. Whether an effect is considered noxious depends on both the drug's beneficial effects and the severity of the disease for which it is being used. There is no need to prove a pharmacological mechanism for any noxious response to be termed an ADR.

The terms ADR and adverse drug effect can be used interchangeably; adverse reaction applies to the patient's point of view, while adverse effect applies to the drug. The terms suspected ADR or reportable ADR are commonly used in the context of reporting ADRs to regulatory authorities, for example, through the UK's Yellow Card Scheme, operated by the Medicines and Healthcare Regulatory Authority (MHRA). Although the term 'side effect' and ADR are often used synonymously, the term 'side effect' is distinct from ADR. A side effect is an unintended effect of a drug related to its pharmacological properties and can include unexpected benefits of treatment.

The WHO definition has been criticised for excluding the potential for contamination of a product, ADRs that include an element of error, and ADRs associated with pharmacologically inactive excipients in a product. The use of the term 'drug' also excluded the use of complementary and alternative treatments, such as herbal products. In an attempt to overcome these points, the following definition of an ADR was proposed, 'An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regime, or withdrawal of the product' (Edwards and Aronson, 2000).

It is important also to avoid confusion with the term adverse drug event (ADE). An ADR in a patient is an adverse outcome that is attributed to a suspected action of a drug, whereas an ADE is an adverse outcome that occurs after the use of a drug, but which may or may not be linked to use of the drug. It therefore follows that all ADRs are ADEs, but that not all ADEs will be ADRs. This distinction is important in the assessment of the drug safety literature, since the term ADE can be used when it is not possible to suggest a causal link between a drug treatment and an adverse outcome. The suspicion of a causal relationship between the drug and the adverse effect is central to the definition of an ADR.

Classification of ADRs

Classification systems for ADRs are useful for educational purposes, for those working within a regulatory environment and for clarifying thinking on the avoidance and management of ADRs.

Rawlins–Thompson classification

The Rawlins–Thompson system of classification divides ADRs into two main groups: Type A and Type B (Rawlins, 1981). Type A reactions are the normal, but quantitatively exaggerated, pharmacological effects of a drug. They include

the primary pharmacological effect of the drug, as well as any secondary pharmacological effects of the drug, for example, ADRs caused by the antimuscarinic activity of tricyclic antidepressants. Type A reactions are most common, accounting for 80% of reactions.

Type B reactions are qualitatively abnormal effects, which appear unrelated to the drug's normal pharmacology, such as hepatoxicity from isoniazid. They are more serious in nature, more likely to cause deaths, and are often not discovered until after a drug has been marketed. The Rawlins–Thompson classification has undergone further elaboration over the years (Table 5.1) to take account of ADRs that do not fit within the existing classifications (Edwards and Aronson, 2000).

The DoTS system

The DoTS classification is based on *Do*se relatedness, *T*iming and patient *S*usceptibility (Aronson and Ferner, 2003). In contrast to the Rawlins–Thompson classification, which is defined only by the properties of the drug and the reaction, the DoTS classification provides a useful template to examine the various factors that both describe a reaction and influence an individual patient's susceptibility.

DoTS first considers the dose of the drug, as many adverse effects are clearly related to the dose of the drug used. For example, increasing the dose of a cardiac glycoside will increase the risk of digitalis toxicity. In DoTS, reactions are divided into toxic effects (effects related to the use of drugs outside of their usual therapeutic dosage), collateral effects (effects occurring within the normal therapeutic use of the drug) and hyper-susceptibility reactions (reactions occurring in sub-therapeutic doses in susceptible patients). Collateral effects include reactions not related to the expected pharmacological effect of the drug or off-target reactions of the expected therapeutic effect in other body systems. It is worth noting that approximately 20% of newly marketed drugs have their dosage recommendations reduced after marketing, often due to drug toxicity.

The time course of a drug's presence at the site of action can influence the likelihood of an ADR occurring. For example, rapid infusion of furosemide is associated with transient hearing loss and tinnitus, and a constant low dose of methotrexate is more toxic than equivalent intermittent bolus doses. DoTS categorises ADRs as either time-independent reactions or time-dependent reactions. Time-independent reactions occur at any time within the treatment period, regardless of the length of course. Time-dependent reactions range from rapid and immediate reactions, to those reactions which can be delayed.

The final aspect of the DoTS classification system is susceptibility, which includes factors such as genetic predisposition, age, sex, altered physiology, disease and exogenous factors such as drug interactions (Table 5.2)

Factors affecting susceptibility to ADRs

Awareness of the factors which increase the risk of ADRs is key to reducing the burden on individual patients by informing prescribing decisions. The risk that drugs pose to patients

Table 5.1 Extended Rawlins–Thompson classification of adverse drug reactions

Type of reaction	Features	Examples
Type A: Augmented pharmacological effect	Common Predictable effect Dose-dependent Low morbidity Low mortality	Bradycardia associated with a beta-adrenergic receptor antagonist
Type B: Bizarre effects not related to pharmacological effect	Uncommon Unpredictable Not dose-dependent High morbidity High mortality	Anaphylaxis associated with a penicillin antibiotic
Type C: Dose-related and time-related	Uncommon Related to the cumulative dose	Hypothalamic pituitary–adrenal axis suppression by corticosteroids
Type D: Time-related	Uncommon Usually dose-related Occurs or becomes apparent some time after use of the drug	Carcinogenesis
Type E: Withdrawal	Uncommon Occurs soon after withdrawal of the drug	Opiate withdrawal syndrome
Type F: Unexpected failure of therapy	Common Dose-related Often cause by drug interactions	Failure of oral contraceptive in presence of enzyme inducer

Table 5.2 DoTS system of ADR classification

Dose relatedness	Time relatedness	Susceptibility
Toxic effects: ADRs that occur at doses higher than the usual therapeutic dose *Collateral effects*: ADRs that occur at standard therapeutic doses *Hypersusceptability reactions*: ADRs that occur at sub-therapeutic doses in susceptible patients	*Time-independent reactions*: ADRs that occur at any time during treatment. *Time-dependent reactions*: *Rapid reactions* occur when a drug is administered too rapidly. *Early reactions* occur early in treatment then abate with continuing treatment (tolerance). *Intermediate reactions* occur after some delay, but if reaction does not occur after a certain time, little or no risk exists. *Late reactions* risk of ADR increases with continued-to-repeated exposure, including withdrawal reactions. *Delayed reactions* occur some time after exposure, even if the drug is withdrawn before the ADR occurs.	Raised susceptibility may be present in some individuals, but not others. Alternatively, susceptibility may follow a continuous distribution – increasing susceptibility with impaired renal function. *Factors include*: genetic variation, age, sex, altered physiology, exogenous factors (interactions) and disease.

varies dependent on the population exposed and the individual characteristics of patients. Some reactions may be unseen in some populations, outside of susceptible subjects. Other reactions may follow a continuous distribution in the exposed population. Although many susceptibilities may not be known, a number of general factors which affect susceptibility to ADRs and others which affect the propensity of specific drugs to cause ADRs have been elucidated.

Age

Elderly patients may be more prone to ADRs, with age-related decline in both the metabolism and elimination of drugs from the body. They also have multiple co-morbidities and are, therefore, exposed to more prescribed drugs. Chronological age is, therefore, arguably a marker for altered physiological responses to drugs and for the presence of co-morbidities and associated drug use rather than a risk *per se*. As the population ages, the mitigation of preventable ADRs in the elderly will become increasingly important.

Children differ from adults in their response to drugs. Neonatal differences in body composition, metabolism and other physiological parameters can increase the risk of specific adverse reactions. Higher body water content can increase the volume of distribution for water-soluble drugs, reduced albumin and total protein may result in higher concentrations of highly protein bound drugs, while an immature blood–brain barrier can increase sensitivity to drugs such as morphine. Differences in drug metabolism and elimination and end-organ responses can also increase the risk. Chloramphenicol, digoxin, and ototoxic antibiotics such as streptomycin are examples of drugs that have a higher risk of toxicity in the first weeks of life.

Older children and young adults may also be more susceptible to ADRs, a classic example being the increased risk of extrapyramidal effects associated with metoclopramide. The use of aspirin was restricted in those under the age of 12, after an association with Reye's syndrome was found in epidemiological studies. Additionally, children can be exposed to more adverse effects due to the heightened probability of dosing errors and the relative lack of evidence for both safety and efficacy.

Gender

Women may be more susceptible to ADRs. In addition, there are particular adverse reactions that appear to be more common in women than men. For example, impairment of concentration and psychiatric adverse events associated with the anti-malarial mefloquine are more common in females.

Females are more susceptible to drug-induced torsade de pointes, a ventricular arrhythmia linked to ventricular fibrillation and death. Women are also over-represented in reports of torsades de pointes associated with cardiovascular drugs (such as sotalol) and erythromycin. This increased susceptibility in women is thought to be due to their longer QTc interval compared to men.

Co-morbidities and concomitant medicines use

Reductions in hepatic and renal function substantially increase the risk of ADRs. A recent study examining factors that predicted repeat admissions to hospital with ADRs in older patients showed that co-morbidities such as congestive cardiac failure, diabetes, and peripheral vascular, chronic pulmonary, rheumatological, hepatic, renal, and malignant diseases were strong predictors of readmissions for ADRs, while advancing age was not. Reasons for this could be pharmacokinetic and pharmacodynamic changes associated with pulmonary, cardiovascular, renal and hepatic insufficiency, or drug interactions because of multiple drug therapy (Zhang et al., 2009).

Ethnicity

Ethnicity has also been linked to susceptibility to ADRs, due to inherited traits of metabolism. It is known, for example, that the cytochrome P450 genotype, involved in drug metabolism, has varied distribution among people of differing ethnicity. For example, CYP2C9 alleles associated with poor metabolism can affect warfarin metabolism and increase the risk of toxicity. This occurs more frequently in white individuals compared to black individuals.

Examples of ADRs linked to ethnicity include the increased risk of angioedema with the use of ACE inhibitors in black patients (McDowell et al., 2006), the increased propensity of white and black patients to experience central nervous system ADRs associated with mefloquine compared to patients of Chinese or Japanese origin, and differences in the pharmacokinetics of rosuvastatin in Asian patients which may expose them to an increased risk of myopathy. However, susceptibility based on ethnicity could be associated with genetic or cultural factors and ethnicity can be argued to be a poor marker for a patient's genotype.

Pharmacogenetics

Pharmacogenetics is the study of genetic variations that influence an individual's response to drugs, and examines polymorphisms that code for drug transporters, drug-metabolising enzymes and drug receptors. A greater understanding of the genetic basis of variations that affect an individual's response to drug therapy has promised to lead to a new era of personalised medicine. Arguably, pharmacogenetics has yet to deliver on an appreciable scale, the reduction in ADRs that was predicted. However, there are some important examples of severe ADRs that may be avoided with knowledge of a patient's genetic susceptibility.

As already noted, major genetic variation is found in the cytochrome CYP450 group of isoenzymes. This can result in either inadequate responses to drugs, or increased risk of ADRs. Clinically relevant genetic variation has been seen in CYP2D6, CYP2C9, CYP2C19 and CYP3A5. A large effect on the metabolism of drugs can occur with CYP2C9, which accounts for 20% of total hepatic CYP450 content.

The narrow therapeutic index of warfarin, its high inter-individual variability in dosing and the serious consequences of toxicity have made it a major target of pharmacogenomic research. Studies of genetic polymorphisms influencing the toxicity of warfarin have focused on CYP2C9, which metabolises warfarin and vitamin K epoxide reductase (VKOR), the target of warfarin anticoagulant activity. Genetic variation in the VKORC1 gene, which encodes VKOR, influences warfarin dosing by a threefold greater extent than CYP2C9 variants. In 2007, the U.S. Food and Drug Administration (FDA) changed the labelling requirement for warfarin, advising that a lower initial dose should be considered in people with certain genetic variations. However, concerns remain because genetic variation only accounts for a proportion of the variability in drug response and clinicians may obtain a false sense of reassurance from genetic testing leading to complacency in monitoring of therapy. In addition, there appears to be little evidence of additional benefit (Laurence, 2009), in terms of preventing major bleeding events, compared to careful monitoring of the INR (see chapter 23)

A success story for pharmacogenetics is the story of the nucleoside analogue reverse transcriptase inhibitor (NRTI) abacavir. Hypersensitivity skin reactions to abacavir are a particular problem in the treatment of human immunodeficiency virus (HIV) infection. Approximately 5–8% of patients taking abacavir develop a severe hypersensitivity reaction, including symptoms such as fever, rash, arthralgia, headache, vomiting and other gastro-intestinal and respiratory disturbances. Early reports that only a subset of patients was affected, a suspected familial predisposition, the short onset time (within 6 weeks of starting therapy), and an apparent lower incidence in African patients led to suspicion of a genetic cause. Subsequent research revealed a strong predictive association with the human leukocyte antigen HLA-B*5701 allele in Caucasian and Hispanic patients. The presence of the allele can be used to stratify the predicted risk of hypersensitivity as high risk (>70%) for carriers of HLA-B*5701 and low risk (<1%) for non-carriers of HLA-B*5701. Evidence from the practical use of HLA-B*5701 screening has shown substantial falls in the incidence of hypersensitivity reactions, as well as a more general improved compliance with the medication (Lucas et al., 2007).

Another example of a success story for pharmacogenetics involves the cutaneous ADRs Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). Both are serious reactions associated with substantial morbidity and mortality in which up to 40% of patients with TEN may die. SJS and TEN have been associated with numerous drugs, although the incidence of these reactions is extremely rare. Anti-epileptic drugs, such as carbamazepine and phenytoin, are known causes of SJS and TEN. The reactions are more common in South East Asian populations, including those from China, Thailand, Malaysia, Indonesia, the Philippines and Taiwan and, to a lesser extent, India and Japan. The presence of HLA allele, HLA-B*1502, for which genetic testing is available, indicates an increased risk of skin reactions for carbamazepine, phenytoin, oxcarbamazepine and lamotrigine. The FDA has recommended HLA-B*1502 screening before using carbamazepine and phenytoin in South East Asian individuals.

Erythrocyte glucose-6-phophatase dehydrogenase (G6PD) deficiency

G6PD deficiency is present in over 400 million people worldwide. It is a sex-linked inherited enzyme deficiency, leading to susceptibility to haemolytic anaemia. Patients with low levels of G6PD are predisposed to haemolysis with oxidant drugs such as primaquine, sulphonamides and nitrofurantoin. There are many variants of the genotype, leading to varied susceptibilities in individuals.

Porphyrias

The porphyrias are a heterogeneous group of inherited disorders of haem biosynthesis. The disorders are transmitted as autosomal dominants, with the exception of the rare congenital porphyria, which is recessive. The effects of drugs are of most importance in patients with acute porphyrias, in which certain commonly prescribed agents may precipitate life-threatening attacks. Other trigger factors include alcohol and changes in sex hormone balance. In the acute porphyrias, patients develop abdominal and neuropsychiatric disturbances, and they excrete in their urine excessive amounts of the porphyrin precursors 5-aminolaevulinic acid (ALA) and porphobilinogen.

A number of drugs may induce excess porphyrin synthesis. However, it is extremely difficult to predict whether or not a drug may cause problems in patients with porphyria and the only factors shown to be clearly linked with porphyrinogenicity are lipid solubility and membrane fluidisation, that is, the ability to disrupt the phospholipid bilayer of the cell membrane. A number of commonly used drugs induce ALA synthase in the liver, but there is wide variation between porphyric patients in their sensitivity to drugs which may trigger attacks. Thus, whereas a single dose of a drug may be sufficient to trigger an acute attack in one patient, another may require a number of relatively large doses of the same drug to produce any clinically significant effect. Lists of drugs which are known to be unsafe and drugs which are thought to be safe for use in acute porphyria are available in the British National Formulary.

Immunological reactions

The immune system is able to recognise drugs as foreign substances, leading to allergic reactions. Smaller drug molecules (<600 Da) can bind with proteins to trigger an immune response, or larger molecules can trigger an immune response directly. The immune response is not related to the pharmacological action of the drug and prior exposure to the drug is required. Immunological reactions are often distinct recognisable responses.

Allergic reactions range from rashes, serum sickness and angioedema to the life-threatening bronchospasm and hypotension associated with anaphylaxis. Patients with a history of atopic or allergic disorders are at higher risk. Immunological (hypersensitivity) reactions are split into four main types (Table 5.3).

Formulation issues contributing to ADRs

Although ADRs caused by product formulation issues are rare, because of stringent regulatory control, examples have occurred and regulatory authorities remain vigilant for such problems. In 1937, the S.E. Massengill Company in the USA developed a liquid preparation of an early antibiotic sulphanilamide which contained 72% diethylene glycol. Over a 2-week period, 353 patients received the elixir, 30% of whom died, including 34 children. Sadly, episodes of diethylene glycol poisoning have been reported in contemporary times, in countries which include Nigeria, India, Argentina and Haiti. In 2006, cough medicines made using glycerin contaminated with diethylene glycol, sourced from China, were responsible for the suspected deaths of over 300 people in Panama.

Osmosin was a slow-release preparation of indometacin which used a novel osmotic pump to deliver the drug through a laser-drilled hole in an impervious tablet. Osmosin was withdrawn in 1983 after 36 fatal gastro-intestinal haemorrhages, suspected to be caused by the tablet becoming lodged against the mucosa of the gastro-intestinal tract and exposing the mucosa to high localised concentrations of indometacin.

Adverse reactions have also been associated with excipient changes. In Australia and New Zealand, a decision to change

Table 5.3 Classification of immunological (hypersensitivity) reactions

Classification	Mechanism	Symptoms/signs and examples
Type I (immediate)	Drug/IgE complex to mast cells release of histamine and leukotrienes.	Pruritis, urticaria, bronchoconstriction, angioedema, hypotension, shock, for example, penicillin anaphylaxis.
Type II (cytotoxic)	IgG and complement binding to (usually) red blood cell. Cytotoxic T-cells lyse the cell.	Haemolytic anaemia and thrombocytopaenia, for example, associated with cephalosporins, penicillins and rifampicin.
Type III (immune complex)	Drug antigen and IgG or IgM form immune complex, attracting macrophages and complement activation.	Cutaneous vasculitis, serum sickness, for example, associated with chlorpromazine and sulphonamides.
Type IV (delayed type)	Antigen presentation with major histocompatibility complex protein to T-cells and cytokine and inflammatory mediator release.	Usually occur after 7–20 days. Macular rashes and organ failure, including Stevens–Johnson syndrome and toxic epidermal necrolysis, for example, associated with neomycin and sulphonamides.

the formulation of phenytoin to one used in the USA led to previously stable patients developing severe adverse reactions, including coma. In the US formulation calcium sulphate dihydrate was replaced with lactose. Unfortunately, it was subsequently found that the calcium salt slowed absorption of phenytoin, while the lactose in the new formulation increased its absorption.

Although excipients are often referred to as inert substances, serious adverse reactions such as anaphylaxis and angioedema have been reported to these substances. Sweeteners, flavourings, colouring agents/dyes and preservatives have all been associated with adverse reactions (Kumar, 2003).

Epidemiology of ADRs

ADRs are widespread, as shown by both systematic reviews and large-scale studies. A review of 69 studies from many countries in 2002 found that ADRs were responsible for an estimated 2.6% of admissions to hospitals and that between 3.5% and 7.3% of in-patients may suffer an ADR. More recent data, however, shows these to be under-estimates. A prospective study (Pirmohamed et al., 2004) found that 6.5% out of 18,820 admissions to medical units were caused by ADRs, with 2.3% of patients dying as a result. A similar prospective study of 3695 in-patient episodes found that 14.7% of those admitted to medical or surgical wards experienced an ADR during their stay. These were more common in women, older patients and in those admitted to surgical wards (Davies et al., 2009).

In primary care, estimates for the incidence of ADRs are more difficult to obtain. Some studies have relied on patients' reports of ADRs, either to postal questionnaires or telephone surveys. These provide varying estimates in ADR incidence and prevalence, but are hampered by the lack of information about non-responders. Nonetheless, estimates are of the order of 25% in the USA (Ghandi et al., 2003) and 30% in the UK (Jarernsiripornkul et al., 2002). A systematic review in 2007 found an incidence of overall ADEs, including ADRs, of 14.9 per 1000 person-months in primary care settings.

A widely quoted figure is that ADRs are between the fourth and sixth leading cause of death in the USA. This is based on an extrapolation of a meta-analysis of studies carried out in the USA, which showed that the incidence of serious ADRs causing hospital admission or occurring during admissions was 6.7% and resulted in an incidence of fatal ADRs of 0.32% (Lazarou et al., 1998). The study has been criticised for its methodology; however, more recent work from Sweden has identified that ADRs were responsible for 3% of deaths there (Wester et al., 2008), while in England ADRs were shown to occur in 0.4% of all patients admitted to hospital. This latter study showed that mortality was higher in those experiencing an ADR than in those who did not. Furthermore, the median length of stay in patients who experienced an ADR was 20 days compared to 8 days and costs associated with in-patient ADRs were calculated to be £171 million annually for the NHS in England (Davies et al., 2009). Costs to the NHS associated with admissions due to ADRs have been estimated as £466 million annually (Pirmohamed et al., 2004).

Pharmacovigilance and epidemiological methods in ADR detection

As already noted, the inherent weaknesses of pre-marketing studies mean that post-marketing surveillance of medicines is essential to detect previously unnoticed adverse effects of treatment. The science of this process is called pharmacovigilance and has been defined as 'the study of the safety of marketed drugs under the practical conditions of clinical use in large communities'. Pharmacovigilance is concerned with the detection, assessment and prevention of adverse effects or any other possible drug-related problems, with the ultimate goal of achieving rational and safe therapeutic decisions in clinical practice.

Spontaneous reporting

Pharmacovigilance uses multiple methods, but the following will focus on spontaneous reporting systems. Spontaneous reporting systems collect data about suspected ADRs in a central database. Cases are not collected in a systematic manner, but accumulate through reports submitted spontaneously by people who make a connection between a drug and a suspected drug-induced event. In the UK, the spontaneous reporting scheme is the Yellow Card scheme. In some countries reporting is a voluntary activity, in others reporting is a legal requirement. There is no evidence that such a requirement increases reporting rates.

Spontaneous reporting has a number of advantages. It is relatively cheap to administer, can follow a product throughout its life and can also accept reports to over-the-counter medication and herbal treatments. Such schemes are, however, passive surveillance systems, which rely on the ability of health professionals to recognise possible ADRs and to distinguish these from symptoms related to underlying disease. It is important to emphasise that only a suspicion of a causal link between a drug and an adverse event is required, not confirmation of the association. One disadvantage of spontaneous reporting systems is their inability to quantify the risk. Such systems supply a numerator (the number of reports), but estimates of the incidence of reactions cannot be made because the population exposed to the drug cannot be ascertained accurately. Furthermore, only a minority of reactions are reported. Spontaneous reports are, however, an important form of evidence leading to drug withdrawals and are crucial for hypothesis generation.

Signal detection

A signal can be described as a possible causal relationship between an adverse event and a drug, which was previously unknown. One useful analogy for signal detection in a

spontaneous reporting database is to think of a radio signal, which is disguised by the background radio 'noise'. Statistical methods of signal generation can be thought of as methods of tuning in to capture the radio signal from the background noise.

Statistical approaches scan the data accumulated through spontaneous reports for 'drug–adverse event pairs' that are disproportionately present within the database as a whole. Such calculations can be run automatically by modern computer systems, providing the opportunity to scan large databases for potential signals of new ADRs. Only rarely will a signal provide such strong evidence that a restriction on use of the drug or its withdrawal is immediately required.

However, while these mathematical approaches do develop hypotheses and give the illusion of an objective estimate of risk, they are not conclusive in themselves. A signal could be due to causes other than the drug. Confounding factors such as particular groups of patients being 'channelled' into receiving a drug can influence reporting. Similarly, reports may be received and analysed by a varied set of people with differing levels of understanding, competence, training, experience and awareness. There is also a tendency for reporting rates to be higher with newly introduced drugs, while articles in the media, regulatory action and even legal cases can provoke reporting of particular reactions. For that reason, the strength of the signal also depends on the quality of the individual spontaneous reports.

Causality assessment

The assessment of whether a drug is responsible for a suspected ADR is of great importance in both the regulatory environment and within the pharmaceutical industry. Reporters to spontaneous reporting schemes are requested to submit suspected ADRs and such reports contain variable levels of information. For example, since re-challenge with the suspected drug is often ethically unacceptable, very few reports contain such information.

As already noted, while a safety signal can arise from the accumulation of reported cases of the event in a database, causality assessment of individual cases may influence the subsequent decision-making process. However, often causality is difficult to prove in pharmacovigilance and a high degree of suspicion may be all that is necessary for regulatory action.

One of the most common methods of causality assessment in use is unstructured clinical assessment, also known as global introspection. Expert review of clinical information is undertaken and a judgement is made about the likelihood of the reaction being due to drug exposure. The assessment of complex situations, often with missing information, is open to variation between different assessors and studies have shown marked disagreement between experts. The WHO international monitoring centre uses global introspection for case assessment, assigning standardised causality categories to suspected ADRs (Table 5.4).

A number of alternative methods of assessing causality have been developed using standardised decision algorithms in an attempt to increase objectivity and reduce assessor bias.

Table 5.4 WHO causality categories for ADRs

Category	Description
Certain	Pharmacologically definitive, with re-challenge if necessary
Probably/likely	Reasonable temporal relationship, unlikely to be attributed to disease processes or other drugs, with reasonable dechallenge response
Possible	Reasonable temporal relationship, but could be explained by concurrent disease or drugs. No information on withdrawal
Unlikely	Temporal relationship improbable, concurrent disease or drugs provide plausible explanation
Conditional/unclassified	An event which requires more data for assessment
Unassessable/ unclassifiable	An event that cannot be judged because of insufficient/contradictory information which cannot be supplemented or verified

One of those most commonly used to assess causality is the Naranjo algorithm. This uses a questionnaire and points are added or taken away based on the responses to each question, such as '*Did the adverse reaction reappear when the drug was re-administered?*' The total score is then used to place the assessed reaction on the following scale: definite, probable, possible or doubtful. Algorithms may be less open to the effects of confounding variables, such as underlying disease states or concomitant drugs, but variation in assessor judgements still occur.

Yellow Card Scheme

The UK's Yellow Card Scheme was established in 1964 following the thalidomide tragedy. The Scheme is operated by the Medicines and Health care Products Regulatory Authority (MHRA). Health care professionals and coroners can submit reports of suspected ADRs using a Yellow Card (found in the British National Formulary) or using an on-line form (http://www.yellowcard.gov.uk). An association between the medicine and the event does not have to be confirmed. A suspicion is sufficient for a report to be submitted. The MHRA request that all serious suspected ADRs are reported by health care professionals concerning established medicines (drugs and vaccines). For newer drugs and vaccines, all suspected ADRs should be reported, even if minor events. Newer medicines under intensive surveillance are identified with an inverted black triangle symbol in product information and standard prescribing texts. Black triangle status is generally maintained for at least 2 years, but the period varies, depending on how much information is obtained about a product's continued

safety. All suspected ADRs occurring in children should be reported even if the medicine has been used off-label.

Information from Yellow Card reports is entered into a database, suspected reactions are categorised using the internationally accepted Medical Dictionary for Regulatory Affairs (MedDRA) and the resultant signals generated by the combined reports are then assessed for causality. Where there is a valid signal which may be an ADR, further work may be required to assess the association further. This could involve requesting further details from reporters, contacting manufacturers, reviewing the literature or conducting pharmacoepidemiological studies. The MHRA estimates that about 40% of the safety signals investigated by the Agency are generated from spontaneous reports.

When new ADRs are identified and an association confirmed, the MHRA may take action in the form of changes to the Summary of Product Characteristics (SmPC) and/or the patient information leaflet (PIL), restricting usage or withdrawing marketing authorisation for the medicine. Withdrawal of marketing authorisation or change in use requires that prescribers and suppliers be informed immediately, but such information is also usually publicised in the media; hence, patients are often aware of these actions and may present with requests for information and advice.

Unfortunately, spontaneous reporting systems, including the Yellow Card Scheme, suffer from severe under-reporting. A systematic review estimated this to be between 82% and 98% (Hazell and Shakir, 2006). There are a variety of reasons for this, including lack of certainty that the medicine caused the symptom, but it is important to emphasise that such certainty is not required. There is also no requirement to provide the patient name or contact details, only those of the actual reporter; hence, confidentiality, also cited as a reason for under-reporting, is no longer an issue. Furthermore, the MHRA have systems in place to check for duplicate reports covering the same incident, thereby eliminating concern about two people submitting reports about the same event in a given patient.

Direct patient reporting

Patients have been permitted to report directly to MHRA since October 2005, with the number of reports increasing steadily since then. Respondents to a survey of UK patient reporters indicated that the facility to report was important and most had an understanding of the purpose of reporting. Many considered it provided an opportunity to influence the content of PILs so that other patients may be better informed. However, there remains a need to further increase awareness of direct patient reporting among both the public and health professionals.

Despite the limited awareness of direct patient reporting, in the main people find it relatively easy to report suspected ADRs (McLernon et al., 2011). The majority of people who reported a suspected ADR identified it as such through issues relating to timing, as outlined in the causality methods used by pharmacovigilance experts, or by accessing information about the medicine from the PIL (Krska et al., 2011). There are a number of countries world-wide which accept patient reports. It has been suggested that these advantages include faster signal generation, avoiding the filtering effect of interpretation of events by health professionals and not least, maintaining the number of reports at a time when reporting by health professionals may be reducing.

A comparison of the content of patient reports submitted to MHRA in the first 2 years of the scheme indicated they were more likely to describe the impact of the ADR than in reports submitted by health professionals. Comparisons of the ADR reports submitted indicated a wider range of ADRs were reported by patients to more medicines. However, the proportion of reactions judged serious by MHRA was similar between both patients and health professionals. Overall, patient reports make a useful contribution to pharmacovigilance.

Published case reports

The first suspicions of a less common or unpredictable reaction may often be seen in a case report from a practitioner. As seen by the cases of thalidomide and practolol, astute and vigilant clinicians submitting case reports to the medical press has been of importance in drug safety. Case reports have been described as a form of non-systematic voluntary reporting. However, reports are not solicited and their appearance in the medical literature is in the gift of medical editors. Editors may demand a causal link, or a case series, requiring higher standards of investigation than regulatory agencies demand from a spontaneous report. These high standards can prevent case histories from reaching publication and deter many clinicians. Furthermore, the time it takes for a case report about a suspected ADR to be published could be several months, during which time more patients may be exposed to the potential risk.

Cohort studies

Cohort studies are prospective pharmacoepidemiological studies that monitor a large group of patients taking a particular drug over a period of time. Ideally such studies compare the incidence of a particular adverse event in two groups of patients, those taking the drug of interest and, another group, matched for all important characteristics except the use of the drug. These studies can indicate the relative risks associated with the adverse event in people exposed to the drug being studied.

Case–control studies

Case–control studies compare the extent of drug usage in a group of patients who have experienced the adverse event with the extent of usage among a matched control group who are similar in potentially confounding factors, but have not experienced the event. By comparing the prevalence of drug taking between the groups, it may be possible to identify whether significantly more people who experienced the event also took a particular drug. Examples of associations which have been established by case–control studies are Reye's

syndrome and aspirin and the relationship between maternal diethylstilboestrol ingestion and vaginal adenocarcinoma in female offspring. Case–control studies are an effective method of confirming whether or not a drug causes a given reaction once a suspicion has been raised. Being retrospective, they rely on good record-keeping about drug use and are not capable of detecting previously unsuspected adverse reactions.

Roles of health professionals

Ensuring medicines are used safely is fundamental to the role of all health professionals who prescribe, supply, administer, monitor or advise on their use. When selecting a medicine for an individual patient, whether this is to be prescribed or sold, the health professional should take account of all relevant patient factors, which may predispose to an ADR. As outlined above, this includes co-morbidities, concomitant drugs, renal and liver function and genetic predisposition. Importantly, it is invaluable to have information about the patient's ADR history. Studies have repeatedly shown that this is poorly documented, leading to inappropriate re-use of medicines which have previously caused problems. Hence, another important role of all health professionals is the documentation of identified ADRs. The patient may have information about this if documentation is insufficient; therefore, questioning the patient about his/her ability to tolerate specific medicines or extracting a full ADR history should be considered at every opportunity.

Identifying and assessing ADRs in clinical practice

Outside the pharmacovigilance environment of companies and regulatory agencies, the identification of potential ADRs is an essential component of clinical practice. Although assessments in practice may lack the formality of expert or algorithmic assessment, they are likely to take into account similar factors, such as whether the clinical event is commonly drug related, the temporal relationship with drug use, a dose relationship and exclusion of other possible causes. A list of such factors is set out in Box 5.1.

There are many triggers which can lead to the suspicion of an ADR. For example, changes in medicines, dose reduction, prescription of medicines used to treat allergic reactions or those frequently used to counteract the effects of other drugs. Simple questioning of patients could easily be incorporated into many aspects of routine care to increase the chances of detecting potential ADRs.

The process of identifying an ADR then involves making a judgement about whether or not a particular event such as a symptom, condition or abnormal test result could be related to a drug used in the patient experiencing the event. The prior experiences of the patient with other medicines should also be taken into consideration.

Every opportunity should be taken to question patients about their experience, to determine whether they perceive any adverse events which could be due to medicines. While routinely asking simple questions is important, it is of equal value to develop a positive attitude towards the patients' perception of suspected ADRs. There is some evidence that health professionals may dismiss patients who report that they have experienced an ADR, but many patients identify such problems appropriately, using factors such as onset, effect of dose change, effect of de-challenge or even re-challenge, as well as the information sources freely accessible to them (Krska et al., 2011). To ascertain whether a symptom reported by a patient can be reasonably suspected of being an ADR requires careful questioning.

As stated above, the MHRA encourage reporting of all serious suspected ADRs to established drugs and all suspected ADRs to new drugs or vaccines. If not reporting themselves, health professionals should consider encouraging others to report. For example, a community pharmacist may have insufficient information to complete a Yellow Card as fully as possible, so may encourage a general practitioner to report. Alternatively, a hospital pharmacist may report on behalf of a consultant clinician. Encouraging others to report also extends to providing information about reporting and educating others, including patients, to report. Community pharmacies and general medical practices should all have a supply of Yellow Cards for patients, but patients may require advice and support in completing these. Pharmacists in particular, because of their role in dispensing prescriptions, may also be involved in educating and supporting others in preventing ADRs and in developing methods to detect ADRs through prescription monitoring.

Box 5.1 Factors that may raise or suppress suspicion of a drug-induced event (Shakir, 2004)

The *temporal relationship* between the exposure to the drug and the subsequent event
The *clinical and pathological characteristics of the event* – events which are known to be related to drug use, rather than disease processes
The *pharmacological plausibility* – based on the observer's knowledge of pharmacology
Existing information in published drug information sources – whether or not the event has been noted by others
Concomitant medication – which may be considered the cause of an event
Underlying and concurrent illnesses – may alter the event or be considered the cause of the event
De-challenge – disappearance of symptoms after dose reduction or cessation of therapy
Re-challenge – reappearance of symptoms after dose increases or recommencement of therapy
Patient characteristics and previous medical history – past history of the patient may colour the view of the event
The potential for *drug interactions*

Preventing ADRs

The majority of ADRs are thought to be preventable; hence, there is potential to dramatically reduce the costs associated with ADRs and possibly also deaths. Assessing preventability is a difficult area, since it involves judgements and many

different methods have been developed for making these judgements. The approach of Hallas et al. (1990) is widely used, providing definitions of avoidability which range from definite (due to a procedure inconsistent with present-day knowledge or good medical practice) to unevaluable (poor data or conflicting evidence). Recent estimates suggest that between 53% and 72% of hospital admissions due to ADEs are preventable, while a meta-analysis (Beijer and de Blaey, 2002) showed that 88% of ADRs causing hospital admission in the elderly were preventable. However, not all ADRs are absolutely preventable and assessments using hindsight are unlikely to replicate clinical decision making at the point of prescribing. Preventability also varies from those with clear solutions, such as the prescribing of a teratogenic drug to a female of child bearing age, to those where the drug increases the risk of an event that occurs within the population.

ADRs can be prevented by checking previous ADR history, minimising the use of drugs known to carry a high risk of ADRs and tailoring drug selection to individuals based on the factors which predispose them to ADRs. Strategies are still required to minimise the burden of ADRs, but many recent initiatives have the potential to do so. For example, electronic decision support, increasing regular review of medicines, improved sharing of information about patients between health care providers and the increasing availability of guidance on drug selection and appropriate use should all increase rational prescribing, which may have an effect on the incidence of ADRs.

Monitoring therapy

Monitoring the effects of drugs either by direct measurement of serum concentration or by measurement of physiological markers is another potential mechanism to reduce the risk of ADRs. For example, it has been estimated that one in four of preventable drug-related hospital admissions are caused by failure to monitor renal function and electrolytes (Howard et al., 2003).

Clozapine, used for the management of treatment resistant schizophrenia and psychosis, is associated with significant risk of agranulocytosis. Mandatory monitoring of white blood cell counts has effectively eliminated the risk of fatal agranulocytosis.

Ideally, advice on monitoring should be clear, provide an evidence-based frequency of monitoring and acceptable values. However, robust evidence for the optimal monitoring frequency is limited, hampering specific guidance on monitoring. Guidelines vary between various expert bodies and drug information sources. An examination of the adequacy of manufacturers' advice on monitoring for haematological ADRs found that advice was too vague to be useful to prescribers (Ferner et al., 2005).

Currently, monitoring is often neglected, although practitioners may take greater care when treating the elderly and those with more co-morbidities (McDowell., 2010). Warfarin remains one of the top 10 drugs involved in drug-induced admissions, despite a clearly defined monitoring requirement.

Explaining risks to patients

Numerous studies have shown that patients want to receive information about side effects, although one study comparing patients' views to those of health professionals found that the latter viewed providing side effect information as of much less importance than patients did in receiving it. One of the main sources of information about ADRs is the PIL, which must be provided every time a medicine is prescribed or supplied. Ultimately, patients then have to make a decision about whether or not to use the medicine. Therefore, they have a right to receive understandable information about the potential for harm that a medicine may cause, to enable them to make an informed decision. While there may still be debate about whether the provision of information on side effects encourages reduced adherence to taking medicines or spurious reporting of adverse effects, it is clear that this information is useful to patients and its availability will increase. Patients do use the PIL when suspected adverse events are experienced, to assist in ascribing the cause of the problem; therefore, as outlined above, side effect information should be understandable and there is now a requirement to test information leaflets with patients prior to granting a marketing authorisation for a medicine.

Patients increasingly access a wide range of information sources about medicines and ADRs themselves; indeed, they are actively encouraged to do so. Hence, they may question judgements about the selection of individual products they have been prescribed or sold. In this situation, the health professional must be able to interpret the information accessed by the patient to ensure it is unbiased and accurate.

The EU recommends using verbal terms to describe the risk of experiencing an ADR, ranging from '*very common*' (for rates of more than 1 in 10) to '*very rare*' (for rates of less than 1 in 10,000). The MHRA advocates combining words with frequencies, for example, '*Common (affects more than 1 in 100 persons)*'. Studies show that patients tend to over-estimate the risk when these are described using words only and that patients differ in their understanding of what the terms mean. Percentages, particularly those below 1%, are also not understood by everybody. This lack of understanding of the risks of experiencing an ADR can potentially reduce willingness to use the medicine.

Another approach is the use of pictures, such as faces, graphs or charts. One example is the 'Paling palette', which is a grid of 1000 stick figures to convey information on the chances of experiencing a particular outcome. A similar method is a 'Cates plot' which is a grid of 100 faces or 1000 faces for rarer events, coloured differently and either smiling or downcast depending on the outcome. An example of a Cates plot is provided in Fig. 5.1. These types of icon grids are mainly used to convey the potential benefits and risks of a particular action, but can also be used to explain the risks of getting a side effect. Cates plots have been used to good effect by the UK's National Prescribing Centre. However, there are people who do not find these easy to understand (Ancker et al., 2006).

Much work has been undertaken on risk communication. It is important to appreciate that, when communicating information

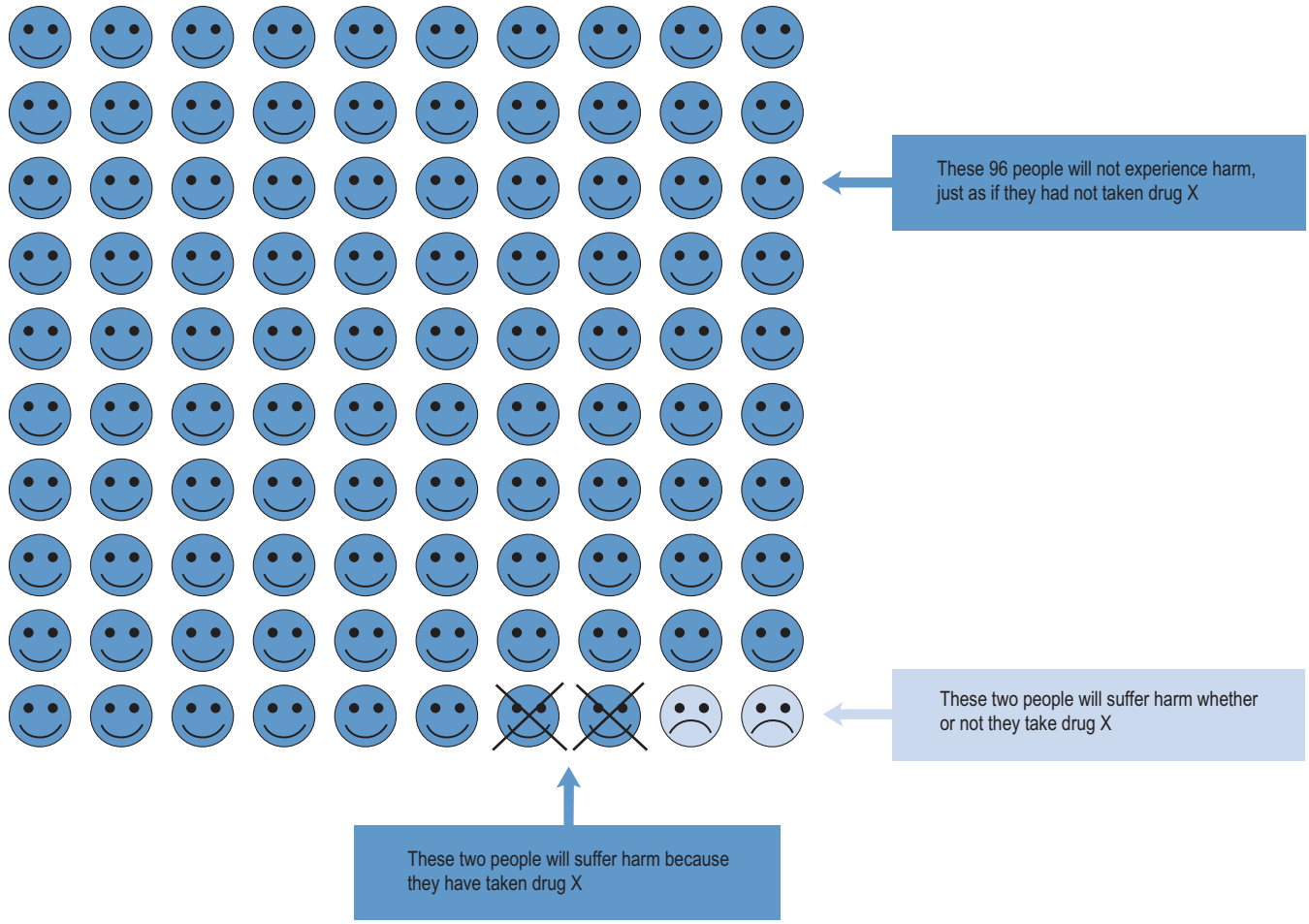

Fig. 5.1 Acute coronary syndrome (ACS) patient decision aid: aspirin plus clopidogrel versus aspirin alone. Copyright National Prescribing Centre, reproduced by permission.

about potential ADRs, how risks are perceived will be affected by the relationship between the health professional and the patient, the patient's prior experience and beliefs, how information is framed and the context in which it is given. Patients may also have views on the acceptability of ADRs, which should be taken into account when selecting a product for an individual. An ADR which is viewed as minor by health professionals may be considered to reduce quality of life by one patient, while another patient may be happy to accept this for the potential benefit the medicine offers. Even when drugs are withdrawn from the market for safety reasons, significant numbers of patients will feel they were willing to accept the harm–benefit of the drug. Communicating the harms and benefits of medicines is, therefore, an important role of health professionals.

Case studies

Case 5.1

Mr KM is a fairly active 69-year-old. He has regularly presented his repeat prescription for atenolol 50 mg daily, aspirin 75 mg daily and simvastatin 40 mg daily to the same community pharmacy for several years. Last month diltiazem SR 60 mg twice daily was added, as he had been getting increasing angina symptoms. He asks for a topical product to treat neck pain, which has developed in the last few days which he puts down to a 'frozen shoulder'.

Questions

1. Could this be an ADR and why did it develop now?
2. Is it appropriate to change to another statin?
3. What actions should the pharmacist take?

Answers

1. Neck pain, 'frozen shoulder' and such descriptions are typical of the muscular pain which is induced by statins. The incidence of mild muscle pain with statins is between 2% and 7% in clinical trials. The onset varies from a few weeks to over 2 years after starting treatment, the incidence is dose-related and the severity ranges from mild aches to severe pain, causing reduced mobility. Older people, who may have reduced renal function or liver function, are at greater risk of statin-induced myopathy.

Diltiazem can inhibit the metabolism of simvastatin due to its actions on cytochrome P450 isoenzyme CYP3A4, thereby increasing the risk of myopathy.

Statin-induced myopathy ranges from mild myopathies and myalgias, to myositis, to rare cases of potentially life-threatening rhabdomyolysis, in which muscle cell walls are disrupted and the

contents leak into the systemic circulation. Muscle pain in patients taking statins should, therefore, always be taken seriously.

2. The problem is associated with all drugs in the class. Although simvastatin and atorvastatin, the most widely prescribed, are both lipophilic and metabolised by cytochrome P450 3A4 and, therefore, may be most likely to cause muscle pain, there is no reliable comparative data on different statins.

3. Creatinine kinase (CK) levels should have been measured before initiating statin therapy, but regardless of whether or not this was done, a CK level should be measured now, plus liver function tests. Mr KM's primary care doctor should be contacted to inform him about the suspected ADR and the patient encouraged to report the ADR via the Yellow Card Scheme. It may be appropriate to discontinue or reduce the dose of the simvastatin, depending on the result of the CK level and the severity of the symptoms. The problem may not resolve immediately on discontinuation. Grapefruit juice can increase blood levels of simvastatin and high alcohol intake increases the risk of myopathy, so the pharmacist should also warn Mr KL about avoiding these.

Case 5.2

A 39-year-old male taking varenicline for smoking cessation reports that he has been suffering from vivid dreams and has become increasingly aggressive towards his family. Last night he had a major argument with his wife. His wife mentioned he hadn't been the same since he started the varenicline and he would like to know if this was a possible cause.

Questions

1. Is varenicline a possible cause of his vivid dreams and aggression?
2. Is this a reportable adverse drug reaction?

Answers

1. Varenicline has been associated with neuropsychiatric ADRs, including depression, suicidal thoughts, suicidal behaviour and aggression. Vivid dreams and other sleep disorders have also been reported. Prescribers have been warned that such reactions have been reported. Assessing the cause of this reaction is difficult, since smoking cessation itself is associated with exacerbations of underlying psychiatric illness and the risk of symptoms of depression. As varenicline dosing starts 1–2 weeks before stopping smoking, a key question is how long the patient has been taking the drug, and if the symptoms appeared before the smoking cessation date.

2. If a health professional considers that a patient's symptoms are a possible ADR to a newer drug, then they should be reported to regulatory authorities (in the UK, this would be through the MHRA's Yellow Card Scheme). Only a suspicion is necessary to report a reaction, not proven causality. In the case of intensively monitored medicines (identified by an inverted black triangle in the BNF), any reaction, no matter how trivial should be reported. Patients can also report directly to regulatory authorities in some countries, including the UK. Neuropsychiatric reactions such as this are commonly reported by patients.

Case 5.3

A 65-year-old man with heart failure is admitted to hospital with a potassium level of 7.1 mmol/L. Already stabilised on lisinopril 20 mg daily, he had recently been started on spironolactone 25 mg daily. He had a serum creatinine of 160 μmol/L.

Questions

1. What is the mechanism of any possible adverse drug reaction?
2. How should future episodes of hyperkalaemia be avoided?

Answers

1. Spironolactone, an aldosterone receptor antagonist, has a beneficial effect on mortality and hospital admission in patients with heart failure. However, spironolactone can increase potassium serum levels due to its effect on aldosterone. When used in combination with ACE inhibitors, serious hyperkalaemia can occur.

Although clinical trials of spironolactone showed no risk, cases have been reported in the literature and other epidemiological studies have indicated that in real-world clinical situations, the incidence of hyperkalaemia is increased.

2. Care should be taken when prescribing spironolactone outside of trial criteria, particularly with regard to renal function. Other susceptibilities for the development of hyperkalaemia include diabetes and the elderly due to reduced aldosterone production. Changes in other therapy should be monitored, as well as episodes of acute illness. Those with mildly increased serum potassium should have a reduced dose of spironolactone. More intensive monitoring of potassium levels at the commencement of therapy might be useful, although the hyperkalaemia can occur months after initiation.

Case 5.4

A 55-year-old woman attending a warfarin out-patient clinic has a raised INR. On questioning it is discovered that she has recently started taking glucosamine for muscle aches for the last 2 weeks.

Questions

1. What is the likelihood that glucosamine was responsible for the rise in the INR?
2. Should this reaction be reported to regulatory authorities?

Answers

1. Glucosamine is a popular supplement purchased for 'joint health'. It is commonly used by older patients. Spontaneous reports of interactions between warfarin and glucosamine have been submitted to UK, Australian and US regulators. Additional cases have been reported in the literature. While there is no known mechanism and no formal interaction studies, the published cases and spontaneous reports are sufficient evidence to suggest a potential interaction. Given the wide use of glucosamine, the interaction may be rare, although under-reporting is common.

Assessment of this individual case requires further questioning to eliminate other confounding factors such as changes in diet or adherence issues.

2. Interactions with, or adverse reactions to, complementary and alternative remedies can be reported to spontaneous reporting schemes, such as the Yellow Card Scheme. Collation of such reports allows regulators to gather further information on the suspected reaction, and any susceptibilities that may in time provide useful information to other users.

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