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AUTHOR QUERIES

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1. Check all names and affiliations are listed correctly.
2. 'Their use if more limited to identify a small increase in the rate of common events such as myocardial infarction or stroke' – please clarify this sentence, it seems incomplete.
3. Define TPMT in Table 1.

Adverse drug reactions

Authors: Jamie J Coleman[A] and Sarah K Pontefract[B]

ABSTRACT

Adverse drug reactions (ADRs) remain a challenge in modern healthcare, particularly given the increasing complexity of therapeutics, an ageing population and rising multimorbidity. This article summarises some of the key facts about ADRs and explores aspects relating to their prevention, diagnosis, reporting and management in current clinical practice.

Basics of adverse drug reactions

An adverse drug reaction (ADR) can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product; adverse effects usually predict hazard from future administration and warrant prevention, or specific treatment, or alteration of the dosage regimen, or withdrawal of the product'.[1] Since 2012, the definition has included reactions occurring as a result of error, misuse or abuse, and to suspected reactions to medicines that are unlicensed or being used off-label in addition to the authorised use of a medicinal product in normal doses.[2] While this change potentially alters the reporting and surveillance carried out by manufactures and medicines regulators, in clinical practice it should not affect our approach to managing ADRs.

Seminal research undertaken in the late 20th and early 21st century in the USA and the UK demonstrated that ADRs are a common manifestation in clinical practice, including as a cause of unscheduled hospital admissions, occurring during hospital admission and manifesting after discharge.[3–6] The incidence of ADRs has remained relatively unchanged over time, with research suggesting that between 5 and 10% of patients may suffer from an ADR at admission, during admission or at discharge, despite various preventative efforts. Inevitably, the event frequency is associated with the method used to identify such events and the majority of ADRs do not cause serious systemic manifestations. Nevertheless, this frequency of potential harm needs to be considered carefully because it has associated morbidity and mortality, can be financially costly and has a potentially negative effect on the prescriber-patient relationship.

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Medicines that have been particularly implicated in ADR-related hospital admissions include antiplatelets, anticoagulants, cytotoxics, immunosuppressants, diuretics, antidiabetics and antibiotics. Fatal ADRs, when they occur, are often attributable to haemorrhage, the most common suspected cause being an antithrombotic/anticoagulant co-administered with a non-steroidal anti-inflammatory drug (NSAID).[7]

Classification of adverse drug reactions

Traditionally ADRs have been classified into two types:

1 Type A reactions – sometimes referred to as augmented reactions – which are 'dose-dependent' and predictable on the basis of the pharmacology of the drug
2 Type B reactions – bizarre reactions – which are idiosyncratic and not predictable on the basis of the pharmacology.[8]

Key points

Adverse drug reactions (ADRs) – unintended, harmful events attributed to the use of medicines – occur as a cause of and during a significant proportion of unscheduled hospital admissions.

A careful medication history can assist a prescriber in understanding the patient's previous experiences with drug treatment particularly in identifying previous ADRs that may preclude re-exposure to the drug.

Preventing ADRs depends on avoiding treatment in cohorts of patients who are at increased susceptibility or providing treatment under a therapeutic plan that reduces the risk of an adverse effect (eg co-administration of other drugs, monitoring blood test results).

Spontaneous reporting (using the Yellow Card Scheme in the UK) based on the suspicion of an ADR is an important part of pharmacovigilance but, overall, ADRs are vastly underreported across healthcare settings and sectors. If in doubt, it is best to submit a report.

KEYWORDS: Adverse drug reactions, clinical pharmacology, drug-related side effects and adverse reactions, pharmacovigilance, adverse drug reaction reporting systems ■

Although still widely quoted, this basic classification does not work for all ADRs, such as with chronic adverse effects associated with cumulative drug exposure (eg osteoporosis with long-term corticosteroid treatment) or withdrawal reactions (eg rebound hypertension with centrally-acting antihypertensive cessation). An alternative and perhaps more comprehensive classification scheme is 'DoTS', which classifies reactions dependent on the **Do**se of the drug, the **T**ime course of the reaction and relevant **S**usceptibility factors (such as genetic, pathological and other biological differences).[9] As well as classifying reactions, DoTS has the advantage of being helpful to consider the diagnosis and prevention of ADRs in practice.

Preventing adverse drug reactions

While some ADRs are unpredictable – such as anaphylaxis in a patient after one previous uneventful exposure to a penicillin-containing antibiotic – many are preventable with adequate foresight and monitoring. Preventability (or avoidability) usually refers to when the drug treatment plan is inconsistent with current evidence-based practice or is unrealistic when taking known circumstances into account.[10] Epidemiological studies tend to find that between a third and a half of ADRs are (at least potentially) preventable although preventability is much easier to diagnose in hindsight. However, interventions that reduce the probability of an ADR occurring can be an important way to reduce the risk of patient harm.

There are two basic steps that can be following to prevent an ADR occurring:

1 identify the subgroup of patients who are likely to be susceptible to the adverse effect and modify the treatment choice accordingly
2 ensure the treatment plan mitigates any possible adverse effects.

Identifying susceptibility

Knowledge of patient susceptibilities can inform your prescribing decision and reduce the risk of an ADR. A patient's medication history will identify any previous ADRs and therefore preclude re-exposure to the drug. In other cases, susceptibility factors such as age, gender, pregnancy status and ethnicity can help predict the risk of an ADR occurring. For example, National Institute for Health and Care Excellence guidance has suggested that patients of African or Caribbean descent should be prescribed an angiotensin-II receptor blocker in favour of an angiotensin converting enzyme (ACE) inhibitor for hypertension because of the risk of ACE inhibitor-induced angioedema. Pharmacogenetics is starting to yield more personalised medicine choices by predicting who is more susceptible to suffer a specific ADR (Table 1).

Clinical decision support systems available at the point of care can inform practitioners of any patient specific cautions to treatment or additional monitoring requirements to reduce the risk of harm. A detailed discussion is beyond the remit of this paper, but practitioners should not rely on decision support as systems vary widely in their provision of information from absence of relevant alerts to information overload leading to alert fatigue.

Treatment plan

Prudent, safe prescribing is key to reducing errors that can contribute to ADRs. Treatment plans should consider and mitigate for any possible adverse effects.[11] For example, co-prescription of folic acid with methotrexate will reduce the incidence of adverse effects associated with folate deficiency; and monitoring electrolytes and renal function when treating with renally active drugs or diuretics. These examples can all prevent treatment-emergent adverse effects although may be limited because monitoring recommendations are often inadequate or ambiguous. It is important to remember that prudent prescribing may also avoid the use of drugs altogether and the treatment plan should always consider non-pharmacological or conservative options.

Overall a systems approach, involving multiple strategies and including the patient and all healthcare professionals, is required to reduce the risk of an ADR and prevent those 'avoidable' reactions occurring in practice.[12]

Table 1. Examples of pharmacogenetic susceptibility for drug-specific adverse drug reactions.

Drug/drug class	Pharmacogenetic marker	Additional susceptibility factors	Example of clinical context
Carbamazepine	*HLA-B*15:02* (in the populations listed)	Han-Chinese, Thai and Malaysian populations	Marker for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis
Simvastatin	SLCO1B1 (solute carrier organic anion transporter 1B1)	Advanced age, untreated hypothyroidism, excess physical activity, concomitant medications (eg fibrates)	Statin-induced rhabdomyolysis (rare) whose risk is four times greater with single defective allele, 16 times greater with two defective alleles
Abacavir	HLA-B*57:01	Higher CD8 cell count at start of therapy	Marker for abacavir-induced hypersensitivity reactions with fever, rash, lethargy and abdominal and acute respiratory symptoms
Thiopurines (Azathioprine and mercaptopurine)	Thiopurine Methyl Transferase Activity	N/A	1 in 10 individuals are heterozygous (50% normal TPMT activity) and 1 in 300 have completely deficient activity. Thiopurine-induced myelosuppression is associated with TPMT activity.

N/A = not applicable; TPMT = XXX

Diagnosing adverse drug reactions

ADRs are one of the great mimics in healthcare, often emulating 'traditional diseases' and manifesting in all systems of the body. Drug-related problems in patients admitted to hospital may present in many different ways, including weakness or drowsiness, biochemical or haematological derangements (such as acute kidney injury, electrolyte imbalance or anaemia), bleeding, gastrointestinal disturbances, hypoglycaemia or healthcare-associated infections such as *Clostridium difficile*. However, rarer manifestations – such as drug-induced lupus, fixed drug eruptions, drug-induced eosinophilia or angioedema – require a level of vigilance and suspicion on behalf of the clinician who should look very hard to identify a causative agent. A comprehensive medication history is fundamental in identifying any possible connection between a presenting complaint or subsequent finding and an ADR, as well as preventing future ADRs. Various criteria can help in attributing causality to a particular drug (Table 2).[13]

In some cases, specific investigations can assist in the diagnosis of an ADR by providing objective evidence of the reaction and confirming a drug-induced disease. For example, organ-specific damage accompanied by intracellular tissue deposition of the drug or a metabolite (eg indinavir crystalluria and nephropathy).[14]

Table 2. Medication history elements that may assist clinical assessment of adverse drug reaction (ADR) probability.

Question	Clinical relevance
Have you taken the medication before without adverse effects?	Prior drug exposure doesn't entirely rule out an ADR, although tolerating treatment previously may make hypersusceptibility reactions less likely
Did anything else change around the time of possible ADR other than the suspected drug (eg other treatments, over-the-counter medicines, disease progression)	Examination of whether there are alternative causes (other than the suspected drug) that could on their own have caused the reaction
Did the reaction occur only after the drug was started?	While not all ADRs occur immediately or early in therapy (ie on drug challenge), an effect occurring before drug exposure is good counter evidence
Did the reaction resolve when the drug was stopped (or when a specific treatment was given)?	Effects that disappear when treatment is stopped (de-challenge) may increase suspicion of an ADR unless an irreversible reaction
Was there ever intentional or accidental use of the drug following an ADR?	An ADR occurring on re-exposure to a drug increases the probability of a causal relationship

Based on original criteria described by Naranjo *et al* (1981).[12]

Pharmacovigilance

Pharmacovigilance is defined as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other drug-related problem'.[15]

New legislation was introduced in the European Union in 2012 to ensure good vigilance practice for pharmaceutical companies and the medicines regulators. This new guidance clearly identifies the roles and responsibilities of relevant stakeholders in terms of drug safety. Notably, the guidance has introduced a programme of more intensive surveillance for new pharmacological agents and biological agents with black triangle status (ie those requiring additional monitoring). One of the guiding principles is that the pro-active strategies of the risk management policy replace the previous reactive strategies.

Reporting of adverse drug reactions

The mainstay of detecting potential ADRs over the last half a century has been spontaneous reporting systems such as the Yellow Card Scheme in the UK, operated by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM). The scheme was founded in 1964 following the thalidomide disaster in the late 1950s. Through spontaneous reporting, the scheme collects data of suspected ADRs related to all licensed and unlicensed medicines and vaccines, including those issued on prescription or purchased over-the-counter. For a report to be valid, only four items of information are required: an identifiable patient, a reaction, a suspected medicinal product and an identifiable reporter. However, reporters are encouraged to provide as much information as possible, ie to provide additional data and clinical context for assessors. The UK scheme continues to receive in the region of 25,000 reports per year and provides the medicine regulators an insight into the occurrence of ADRs. Unfortunately, underreporting remains a key challenge, with fewer than 5% of all ADRs estimated as being reported in practice. This limits the ability of systems to give accurate incidence data. In 2014, NHS England and the MHRA issued a joint alert: *Improving medication error incident reporting and learning*. As part of this, ADRs occurring as a result of medication errors reported to the National Reporting and Learning System (NRLS) will automatically be reported to the Yellow Card Scheme.

Patients are increasingly involved in their own therapeutic management and, because an early assessment of patient Yellow Card reporting proved the value of this approach,[16] all patients are now actively encouraged to report ADRs. Paper reports (on the original yellow cards) have largely been superseded by online reporting systems or use of the Yellow Card app. Electronic health records used in general practice and in some hospitals can also include integrated reporting that sends data on ADRs directly to central agencies for processing before entry into national and international databases.

Spontaneous reporting systems, while widely adopted for pharmacovigilance, are most effective when the adverse events are rare and uncommon (less than 1% of treated patients) and when the event is typical of a drug-induced condition (eg

Table 3. Examples of agents used in the management of specific adverse drug reactions.

Specific treatments	Drug/drug class causing ADR	Clinical effect of treatment	Clinical context
Naloxone	Opioids	Antidote for opioid toxicity	Widely used for treatment of overdosage with opioids in a non-medical setting and reversal of postoperative respiratory depression
Icatibant	ACE inhibitors	Treatment for life-threatening angioedema affecting airway/ head and neck	This selective bradykinin B2 receptor antagonist has proven to reduce the time to complete resolution of angioedema
Idarucizumab	Dabigatran	Antidote for the reversal of direct oral thrombin inhibitor	Novel humanised monoclonal antibody fragment developed as specific reversal agent, promptly restoring dabigatran-prolonged coagulation parameters to baseline values
Intravenous lipid emulsion (Intralipid®)	Local Anaesthetics (eg lidocaine)	Treatment for systemic toxicity from local anaesthetic agents (eg severe cardiotoxic effects)	Reduce adverse effects resulting from inadvertent local anaesthetic overdoses, intravascular injections, or rapid absorption effects from injections in highly vascular sites

ACE = angiotensin-converting enzyme; ADR = adverse drug reaction

erythema multiforme). The case if more limited to identify a small increase in the rate of common events such as myocardial infarction or stroke. This is the reason why recent drug safety scandals, such as thiazolidinedione-induced and rofecoxib-induced cardiovascular events, remained undetected despite widespread use of these agents.

While beyond the scope of this article, modern signal generation can detect early potential signals of harm and alert clinicians to potential new therapeutic risks. Complex statistical data-mining algorithms are run routinely to detect such signals but usually require further assessment before being actioned. The ability to examine drug exposure and potential adverse events in databases such as the Clinical Practice Research Datalink (CPRD) – the database of anonymised longitudinal UK primary care records – can support or refute the existence of potential signals.

There are many other methods and data streams used in pharmacovigilance, including formal drug safety studies, published data, pharmaceutical company data from periodic safety update reports (PSURs) and shared international data. However, regulators and scientists are also looking at the ability of other 'big data' sources, such as social media, to detect early signals; this remains an exciting and largely unexplored area of research.

Managing adverse drug reactions

Altering a dosage regimen or withdrawing a medicine suspected of causing an ADR are common methods of managing ADRs in practice. However, the course taken to manage an ADR is likely to vary from clinician to clinician. Under EU legislation, the approval of all new medicines onto the market must now be accompanied by a robust risk management plan from the marketing authorisation holder, which – as well as ongoing safety trials – may involve the development of specific treatments for managing specific ADRs. Such has been the case with antidotes for direct oral anticoagulant-induced bleeding. This and other notable examples of approaches for the management of specific ADRs are shown in Table 3.

Conclusion

Herein we have discussed the identification, management and reporting of ADRs. We have described how modern technology is changing the way that ADRs are predicted, prevented, detected and managed, and how we continue to try and improve these processes with technological advances. Individualised therapy is becoming more of a possibility as not just pharmacogenetics but other phenotypic information can be combined to generate patient-specific advice to prescribers. Such regulatory science at national and international level can help achieve a positive benefit-to-harm ratio throughout the lifecycle of a medicinal product. For individual clinicians, achieving the best outcomes from therapies remains a key goal because avoiding or mitigating the risk of ADRs continues to challenge our everyday clinical practice. ■

Conflicts of interest

JJC is a member of the Pharmacovigilance Expert Advisory Group of the Medicines and Healthcare Products Regulatory Agency (MHRA) and an honorary consultant at the West Midlands Centre for Adverse Drug Reactions, which receives funding from the MHRA through the Yellow Card Centre.

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