

ADVERS DRUG REACTION

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Abstract: Despite the implementation of ADR prevention strategies and regulation measures, ADRs constitute still one of the significant issues in contemporary healthcare, primarily with regards to the augmentation of medical treatments' varieties, the ageing population, and growing levels of multimorbidity. This paper portrays some of the facts about ADRs and also discusses some extents of aspects on prevention, diagnosis, reporting and management in the present day practice.

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

Key points

- Survey of different studies indicates that ADRs – undesirable effects in relation to a medicinal product – happen as a reason for, and during, a considerable portion of UHAs.
- Combining a medication history helps the prescriber not only get an overall idea of the patient's past experience with drug treatment but also to detect previous ADRs which might bar the patient from future use of that medication again.
- Preventing ADRs relies on not administering the treatment in populations that are more vulnerable to develop an ADR or administering the treatment following a therapeutic plan that has a reduced risk of the ADR (e. g two drugs interact, blood results to check the kidney function).
- Pharmacovigilance based on the spontaneous reporting using the Yellow Card Scheme in the United Kingdom based on a suspicion of an ADR is equally a critical component of clinical reality, however, overall there is a worrying level of ADR under-reporting in acute, primary care, and community care settings as well across health care sectors. It is always advisable to submit a report if one is in doubt as to how the set objectives were met.

INTRODUCTION

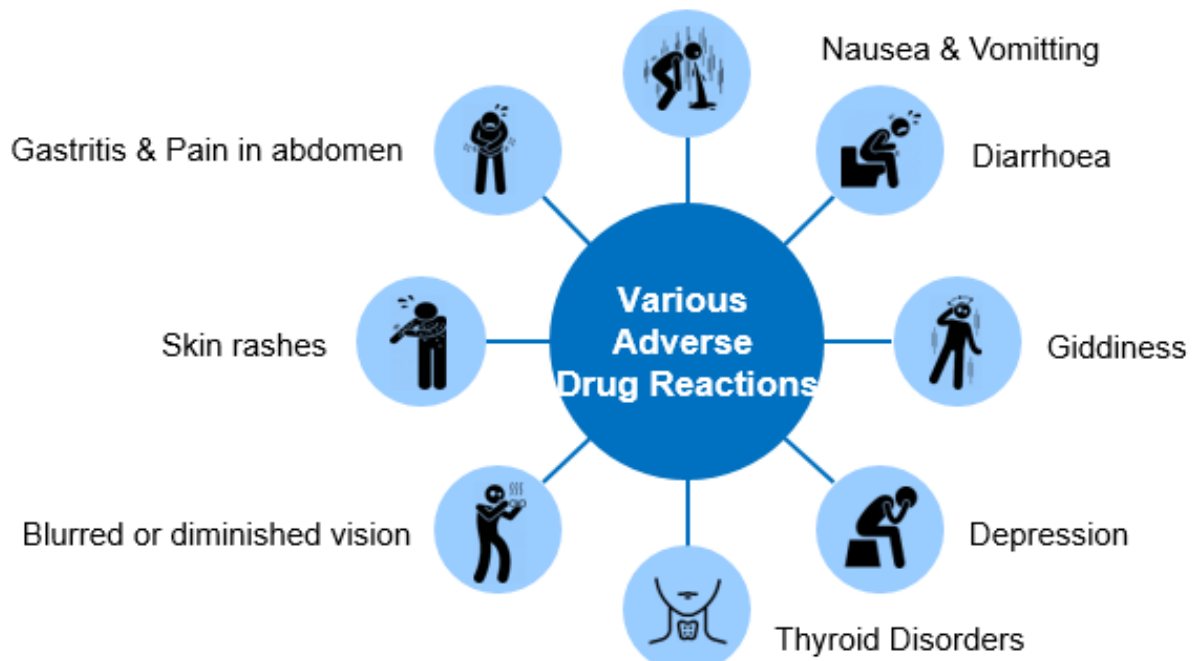
Every time a patient is exposed to a medical substance, there are certain circumstances involved, therefore we can never be sure what will happen. A notable illustration of this is The thalidomide disaster of the late 1950s and early 1960s. Many of the babies born to thousands of pregnant mothers who received Thalidomide as a safe hypnotic had a severe form of limb deformity called as phocomelia. This momentous occasion set the stage for the creation of contemporary drug regulations that seek to detect, validate, and measure adverse medication reactions. Any unwanted pharmacological effect that occurs during clinical usage that goes beyond expected therapeutic effects is referred to as an adverse drug reaction (ADR) (pirmohamed etal 1998). For this reason, each medical practitioner who counsels patients must be aware of the frequency.

Basics of adverse drug reactions.

Adverse drug reaction (ADR) is defined as 'an unfavorable response which is caused by drugs and is detrimental to patient's health; it is also known as side effect and it is a reaction which should be prevented or requires intervention', the definition underlines the fact that ADRs are clinically important events. 1 Such definition has been in place since 2012 and includes reactions that are as a consequence of an error, misuse or abuse, and all they regard them as adverse reactions to data medicines even if for uses of a medicinal product that are unlicensed or off-label, in addition to the authorised use of the product at normal doses. 2 Though this change may introduce a shift in the reporting and surveillance done by the manufactures of medicines and medicines regulators this shift in clinical practice should not change how ADRs should be handled in practice.

Numerous studies conducted in the late twentieth and early twenty-first centuries in the USA and in the UK provided evidence of the high prevalence of ADRs in clinical practices including as a cause of admit-from-home and inpatient cases, developing during hospital stay, and after its termination. 3–6 It has been established that the rate of reporting of ADRs has not changed much, and different studies estimate an overall average, a frequency of 5 to 10 %, of patients experiencing an ADR at admission or during admission or at the time of discharge despite measures that were in place to prevent the occurrence of ADRs. As it would become clear, many of these ADR events are related to the frequency that is identified by the specific method employed in such cases and that most of the ADRs are not more villainous enough to make serious systemic impacts. However, this potential harm occurs with these frequency and for this reason the following points should be taken into consideration because the morbidity and mortality associated with it is preventable; the costs which can be incurred due to it are again avoidable; and it does not have a good impact on the prescriber-patient relationship either.

Some of the medicines that this study found to be associated with ADRs resulting in hospitalisation are antiplatelet, anticoagulant, cytotoxic, immunosuppressant, diuretic, antidiabetic and antibiotics. When fatal ADRs are reported, hemorrhage is more frequently cited as the expected outcome and, among the specific medications that are suspected of sparking the event, antithrombotic/anticoagulant ranks as the most commonly mentioned.

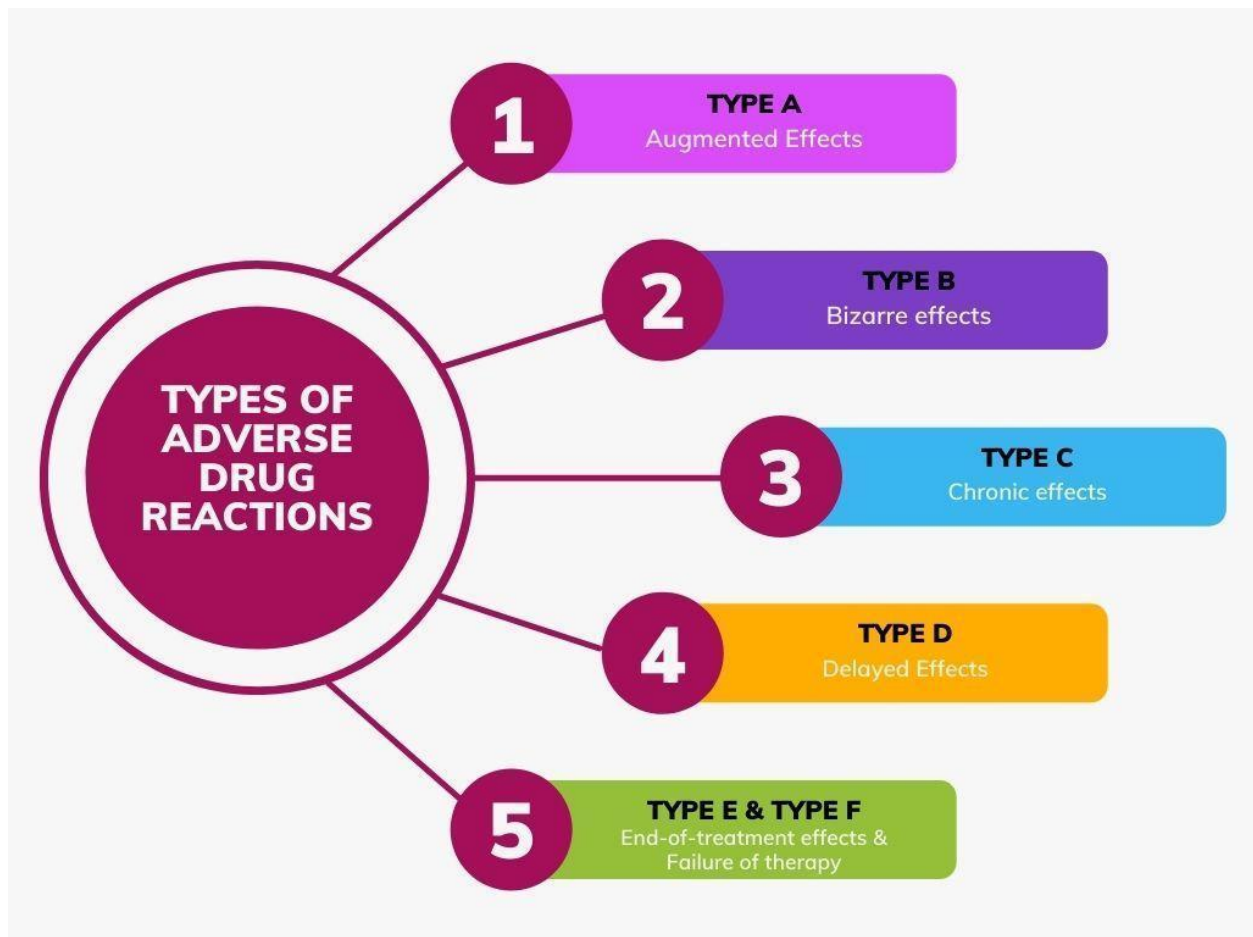


Types of adverse drug reactions

Type A reactions – often described as augmented reactions – that are explained on the basis of the pharmacology of the doses taken

Type B reactions – the so called psychotic reactions – which can be side effects but are not expected from the pharmacology. 8

Although this classification is still often cited and informative, it does not fit every ADR, especially when an ADR has a delayed temporal relationship to drugs, including chronic adverse effects resulting from drug accumulation (for instance, osteoporosis due to long-term corticosteroids), or withdrawal reactions (for instance, rebound hypertension when patients stop taking central-acting antihypertensive agents). An alternative and possibly more extensive taxonomy is the 'DoTS'; this categorises reactions based on the Dose of the drug, the Time to reaction and Susceptibility factors (genetic, disease or other) to the reaction. It has the advantage over DoTS classification that is useful to think about the diagnosis and prevention of ADRs in practice.



Preventing adverse drug reactions

While some ADRs are as unexpected as anaphylaxis developing in a patient after one prior uneventful course of a penicillin-containing antibiotic – many are avoidable should there be sufficient anticipation and watchfulness. Most of the time, it defines the situation when the drug treatment plan does not conform with the best known practice or is physically impossible to achieve in light of certain facts. 10 Some 30%-50% of ADRs are (potentially) preventable, but ‘preventability’ is much easier to judge after the event. Nevertheless, measures to prevent the likelihood of an ADR may be one of the strategies to prevent harm to the patient.

Find out which patients can potentially develop the adverse effect and make changes to treatment plan on that basis.

Make sure the treatment plan eliminates any adverse effects where they exist.

Identifying susceptibility

Knowing the patient susceptibilities will help you manage his case and possibly avoid some of the ADR. A patient’s medication history will reveal any prior ADRs and thus avoid ‘re-challenge’ with the drug. For other types of ADRs, factors such as age, gender, pregnancy and ethnicity can be used in identifying the probability of developing the adverse effect. For instance, National Institute for Health and Care Excellence has recommended African or Caribbean origin patients should be offered an angiotensin-II receptor blocker instead of an ACE inhibitor for the hypertension management due to the possibility of developing ACE inhibitor-induced angioedema. Pharmacogenetics is gradually providing more individual options on medication with more chances of having a certain ADR (Table 1).

Table 1.

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

Drug/drug class	Pharmacogenetic marker	Additional factors	susceptibility	Example of clinical context
Carbamazepine	<i>HLA B*15:02</i> (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

Integrated point of care CDSS can notify the practitioners of any patient-specific caution to certain treatment or subsequent requirement for increased vigilance to prevent harm. A further discussion on this is, however, beyond the scope of this paper; but it is notable that practitioners cannot solely rely on decision support as it ranges from the lack of the relevant alert to the presence of too many to create what is known as alert fatigue.

Treatment plan

Safe and rational prescribing is the most effective solution to prevent both occasional and cumulative measures that lead to ADRs. Contingency measures need to be taken while formulation of treatment plans to counter almost all possible side effects. For instance, folic acid combined with methotrexate administration will decrease the impact of the side effects arising from folate deficiency; checking the levels of potassium and kidney function while using potassium-sparing diuretics or other renally active drugs. All of these can potentially mitigate treatment-emergent adverse effects although several may be limited since most monitoring recommendations are insufficient or vaguely defined. It is vital to understand that safer use of medications might also exclude a drug and the treatment program should always have non-drug or minimalism in mind.

Thus, a systems approach is needed that encompasses many strategies and, more importantly, encompasses the patient and all the healthcare professionals to minimize the risk of an ADR and thus negate those 'avoidable' reactions seen in practice.

Diagnosing adverse drug reactions

ADRs are one of the great mimics in the health care setting, a mimic of the so-called 'traditional diseases' with the ability to affect all body systems. Drug-related incidents manifest in various forms; weakness or drowsiness, biochemical and haematological complications like AKI, electrolyte imbalance, anaemia, bleeding, gastrointestinal complications, hypoglycaemia, healthcare acquired infection such as *Clostridium difficile*. However, atypical

presentations – for instance, systemic lupus erythematosus induced by a drug, fixed drug eruptions, drug-induced hepatitis or angioedema – should make a clinician sit up and look hard for a culprit drug. A medication history is paramount to assessing any relationship between a complaint on presentation or an unrelated clinical discovery and an ADR; and more importantly, to avoiding subsequent ADRs. There exists different criteria that can be used to ascribe causality to a particular drug (see Table 2).

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

By contrast, particular studies could help in the diagnosis of an ADR because they document the reaction and demonstrate that it was precipitated by a drug. For example, organ-specific damage witnessed with intracellular tissue deposition of the drug or a metabolite, for instance, Indinavir and urinary crystalluria and nephropathy.

Pharmacovigilance

Pharmacovigilance has been described as 'the science and activities associated with the identification, evaluation, understanding and mitigating of risks attributed to medicinal products or other drug related issues'.

In the European Union, new legislation was proposed in 2012 to set the standards of good vigilance practice for pharmaceutical companies and the medicines regulators. This new guidance is quite specific in defining the roles and responsibilities of all the parties concerned with drug safety. Notably the guidance has proposed a programme of 'super' sixty monitoring for the new pharmacological agents and biological agents having black triangle status. One of the foundational assumptions is that the strategies of risk management policy are pro-active and do not incorporate the previously used re-active strategies.

Adverse Drug Reactions (ADRs)

The most important approach to identifying potential ADRs for the past half century has been the application of spontaneous reporting system like the Yellow Card Scheme in UK administrated by MHRA and CHM. It was established in 1964 as a result of thalidomide tragedy that occurred in the late 1950s. The scheme also covers suspected ADRs reporting on all licensed and unlicensed medicines and vaccines offered on prescription, and those available for purchase over the counter. For a report to be valid, only four items of information are required: patient, reaction, suspected medicinal product and reporter. However, it is also suggested that reporters supply as much detail as possible

or, in other words, to supply further data and clinical background information for assessors. The UK scheme currently receives around 25,000 reports per annum and affords the medicine regulators some understanding of the presence of ADRs. However, reporting continues to be a difficulty as fewer than 5% of all ADRs are believed to be reported in real life. This hampers the ability of systems to provide the incidence of the disease as shown below. In 2014, NHS England and the MHRA issued a joint alert: By enhancing the reporting and learning system of the medication error incidents. So too, any ADRs emerging from medication errors filed in the National Reporting and Learning System (NRLS) will be automatically reported to the Yellow Card Scheme.

This is a case that patients are now more involved in managing their own illnesses, and given that a pilot study carried out concerning the patient Yellow Card reporting demonstrated the effectiveness of this approach,¹⁶ all patients are urged to report ADRs. Writing up on the original yellow cards has to a great extent been replaced by online reporting or use of Yellow Card application. Integrated reporting to central agencies used in electronic health records available in general practices and some hospitals also helps in sending data on ADRs directly to various databases including national and international ones.

Despite its popularity in pharmacovigilance, SRS is most useful only in investigating ADRs which are idiosyncratic or occur in less than 1% of patients receiving the drug and if the event relates mainly to the condition induced by the drug such as erythema multiforme. Their use is more proscribed in raising the suspicion of a small difference in the frequency of mundane occurrences like myocardial infarction or stroke. This is why current drugs safety scandal including thiazolidinedione-induced and rofecoxib-induced cardiovascular events developed unnoticed though these agents were widely used.

However, outside the purview of this article, a current source of signals can identify even potential signs of harm and inform the practitioner of new therapeutic possibilities. The usual complex statistical data-mining algorithms are performed repeatedly to identify these signals but often necessitate a deeper review prior to execution. The analysis of drug exposure and possible adverse events in the audiences including the CPRD – the longitudinal database containing anonymised UK primary care records – can strengthen or refute the possibility of signals.

There are many others methods and data that are used in pharmacovigilance that include formal drug safety studies, published data, pharmaceutical companies data derived from the PSURs and more so the International data. But, regulators and scientists are also aiming at signals originating from other ‘big data’ platforms including the social media; this is still a promising and underexplored area.

Managing adverse drug reactions

Changing the dose or temporarily stopping a drug that is thought to be the cause of the ADR remain two of the most frequent strategies for dealing with ADRs in clinical practice. However the approach adopted to practice an ADR is clearly expected to differ from one clinician to the other. According to the EU legislation, all new medicines entering the market are required to be approved along with a proper risk management plan from the holder of marketing authorisation, which may include formation of individual treatment protocols for specific ADRs alongside other constant safety trials. This has been evident with focal therapies for direct oral anticoagulant induced bleeding. Some of the specific approaches for the management of particular ADRs and other potential solutions described above are presented in Table 3.

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 overdose with opioids in a non-medical setting and reversal of postoperative respiratory depression

Specific treatments	Drug/drug class causing ADR	Clinical effect of treatment	Clinical context
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 resultin

Conclusion

In this article we have reviewed the identification, management and reporting of ADRs. We have discussed how using modern technology, it is possible predict, prevent, detect and manage ADRs and that we remain working on how to enhance these procedures with new methods and technologies. Individualised therapy is gradually becoming a reality and not just pharmacogenetics but other phenotypic factors can be incorporated to derive patient specific recommendation to prescribers. Such regulatory science on both national and international basis can be helpful in maintaining a positive benefit risk throughout the life cycle of a medicinal product. Therapies should remain the best for individual clinicians since eradicating or protecting against ADR risks still endeavors our clinical practice.

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