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ADVERSE DRUG REACTION

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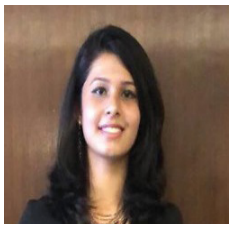

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Introduction

Every occasion when a patient is exposed to a medical product, is a unique situation and we can never be certain about what might happen. A good example for this is thalidomide tragedy in late 1950s and 1960s. Thalidomide prescribed as a safe hypnotic to many thousands of pregnant women caused severe form of limb abnormality known as phocomelia in many of the babies born to those women. It was a seminal event that led to the development of modern drug regulations aimed to identify, confirm and

An adverse drug reaction (ADR) may be defined as '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 regimen, or withdrawal of the product'. By the time a drug is marketed, only about 1500–3000 patients may have been exposed to the drug. Thus, only those adverse reactions occurring at a frequency of greater than 1 in 500–1000 will have been identified at the time of licensing. Assessment of ADRs therefore is likely to represent an important aspect of drug therapy for many years to come, and indeed, with the development of new biotechnology compounds, it is likely that the pattern of these reactions will change. Furthermore, using gene and protein screening technologies, many new targets will be discovered.

As new drugs are developed to modulate the function of these targets, it is very unlikely that we will fully understand the biology of the new target molecule(s), and this will lead to unforeseen adverse reactions.

For example, adverse effects such as the exacerbation of multiple sclerosis, systemic lupus erythematosus (SLE) and blood dyscrasias that have been reported with anti-tumour necrosis factor (anti-TNF) therapies or cardiovascular events with cyclo-oxygenase-II (COX-II) inhibitors may not have been reasonably expected given the known pharmacology of these therapies.

Hence every health care professional who give advice to patients need to know the frequency and magnitude of the risks involved in medical treatment along with its beneficial effects. Recent epidemiological studies estimated that ADRs are fourth to sixth leading cause of death. It has been estimated that approximately 2.9-5% of all hospital admission are caused by ADRs and as many as 35% of hospitalised patients experience an ADR during their hospital stay. An incidence of fatal ADRs is 0.23%-0.4%. Although many of the ADRs are relatively mild and disappear when drug is stopped or dose is reduced, others are more serious and last longer. Therefore there is a little doubt that ADRs increase not only morbidity and mortality but also add to the overall health care cost. 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. 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).

IMPORTANCE OF ADVERSE DRUG REACTION

1. Adverse drug reactions are a major clinical problem. A meta-analysis suggested that ADRs were between the fourth and sixth commonest cause of death in the United States in 1994.
2. A large prospective study in the United Kingdom has shown that ADRs were responsible for 6.5% of all hospital admission.
3. Adverse drug events are associated with an increased length of stay in hospital of 2 days and an increased cost of approximately $2500 per patient.
4. ADRs can also have many other indirect effects , which in total, highlight the overall importance of ADRs in modern medicine.

CLASSIFICATION OF ADVERSE DRUG REACTION

TYPE A (augmented)

TYPE B (Bizzare)

TYPE C (Chemical)

TYPE D (Delayed)

TYPE E (Exit/ End of treatment)

TYPE F (Familial)

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TYPE G (Genotoxicity)
TYPE H (Hypersensitivity)
TYPE U (Un classified)

CLASSIFICATION OF ADRs DEPENDING ON SEVERITY

1. There are many different classifications of ADRs. We will use the original classification proposed by Rawlins and Thompson (1991), which divided adverse drug reactions into two types, type A (pharmacological) and type B (idiosyncratic)

CHARACTERISTICS OF TYPE A AND B ADR's

CHARACTERISTIC	TYPE A	TYPE B
Dose dependency	Usually shows a good relationship	No simple relationship
Predictable from known pharmacology	Yes	Not usually
Host factors	Genetic factors may be important	Dependent on (usually uncharacterized) host factors
Frequency	Common	Uncommon
Severity	Variable but usually mild	Variable, proportionately more severe than type A
Morbidity	High	High
Mortality	Low	High
Overall proportion of ADRs	80%	20%
First detection	Phases I–III	Usually phase IV, occasionally phase III
Mechanism	Usually because of parent drug or stable metabolite	May be because of parent drug or stable metabolite, but CRMs also implicated
Animal models	Usually reproducible in animals	Very few reproducible animal models

highlights the need for continued development of appropriate in vivo and, bridging, in vitro test systems for the prediction of secondary pharmacological adverse effects in humans.

5. Factors predisposing to pharmacological adverse reactions include dose, pharmaceutical variation in drug formulation, pharmacokinetic or pharmacodynamic abnormalities and drug–drug interactions.

6. In essence, type A reactions occur when the drug concentration in plasma or tissue exceeds the perceived therapeutic window.

7. Alternatively, the drug concentration may be within the normal range defined for the population, but because of increased sensitivity of the target in the individual, an adverse reaction results.

8. There are many examples of drugs (e.g. captopril) that had been introduced into clinical practice at a dose that was subsequently shown to be associated with an unacceptable frequency of ADRs, and for which a lower dose was found to be both safe and effective.

9. In general, however, the individual affected by a type A adverse reaction will have impairment of clearance or increased sensitivity because of the normal process of ageing, disease, concomitant drugs or genetic variation or a combination of these factor.

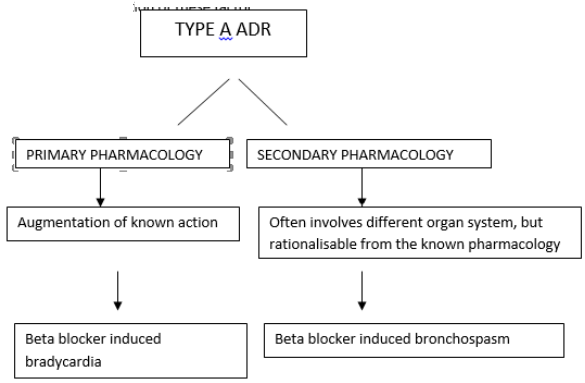
TYPE A ADVERSE DRUG REACTION

1. Pharmacological (type A) ADRs are the most common forms of drug toxicity.

2. They can occur because of the primary and secondary pharmacological characteristics of the drug.

3. More emphasis is now placed on the secondary pharmacology of new drugs during preclinical evaluation, to anticipate and thus avoid problems that might arise once the drug is introduced into humans.

4. The experience with fialuridine, an experimental drug for hepatitis B,



GENETIC POLYMORPHISMS AND TYPE A ADVERSE DRUG REACTIONS

1. A gene can be defined as exhibiting genetic polymorphisms if the variant allele exists in the normal population at a frequency of at least 1%.

2. In relation to type A ADRs, polymorphisms in both pharmacokinetic and pharmacodynamic parameters can act as predisposing factors.

FACTORS PREDISPOSING TO PHARMACOLOGICAL TYPE A ADR's

TYPE	EXAMPLE	TOXICITY	MECHANISM
Pharmaceutical	Phenytoin	Phenytoin toxicity (ataxia, nystagmus, etc.)	Increase in bioavailability because of a change in formulation
Pharmacokinetic (can involve absorption, distribution, metabolism and excretion)	Digoxin	Digoxin toxicity (nausea, arrhythmias, etc.)	Decreased elimination if renal function is impaired
Pharmacodynamic	Indomethacin	Left ventricular failure	Water and sodium retention
Genetic	Nortriptyline	Confusion	Reduced hepatic elimination because of a deficiency of CYP2D6
Drug–drug interactions (can involve any of the above processes	Lithium and non-steroidal anti-inflammatory drugs	Lithium toxicity	Inhibition of excretion of lithium

3. A drug metabolised by this pathway will show reduced elimination from the body with a consequent increase in half-life. This will lead to dose-dependent toxicity; a typical example is neutropenia with azathioprine in patients deficient in the enzyme thiopurine methyltransferase.

DRUG INTERACTIONS AND ADR

1. Patients on polytherapy are more likely to have type A reactions. The likelihood of developing an adverse interaction increases with the number of drugs prescribed.

2. An Australian study showed that 4.4% of all ADRs resulting in hospital admission were because of drug interactions (Stanton et al., 1994), whereas a study in the United Kingdom showed that one in six of all adverse reactions causing hospital admission were because of interactions.

3. Drug interactions due to effects on metabolic pathways may be because of either enzyme induction or enzyme inhibition.

4. Enzyme inhibition on the contrary is more likely to lead to type A ADRs because the clearance of the affected drug is reduced; this is particularly likely when the affected drug has a narrow therapeutic index.

TYPE B OR IDIOSYNCRATIC ADVERSE DRUG REACTIONS

1. Idiosyncratic adverse reactions are less common than the pharmacological adverse reactions but are as important, if not more so, because they are often more serious and account for many drug-induced deaths.

ORGAN SYSTEM	TYPE OF REACTION	DRUG EXAMPLES
Generalised reaction	Anaphylaxis	Penicillins
Generalised reaction	Hypersensitivity	Temafloxacin
Skin	Toxic epidermal necrolysis	Non-steroidal anti-inflammatory drugs
Liver Haematological system	Hepatitis Aplastic anaemia, Agranulocytosis, Haemolysis	Halothane Remoxipride, Clozapine, Nomifensine
Central nervous system	Guillain–Barré syndrome	Zimeldine
Kidney	Interstitial nephritis	Penicillins
Lung	Pneumonitis	Dapsone
Heart	Cardiomyopathy	Tacrolimus
Reproductive toxicity	Etretinate	Various foetal abnormalities

2. Type B ADRs have been characterised as being dose-independent or rather there is no simple relationship between dose and the occurrence of toxicity.

3. Many type B ADRs are thought to be mediated by the formation of chemically reactive metabolites (CRMs) through metabolism by P450 enzymes (a process termed ‘bioactivation’) perhaps a relationship exists with the ‘internal dose’, i.e. the concentration of the toxic metabolite formed in the body.

THE ROLE OF DRUG METABOLISM IN TYPE B ADVERSE DRUG REACTION

1. In general, drug metabolism can be considered to be a detoxication process in that it converts therapeutically active compounds to inactive metabolites, which can then be excreted harmlessly from the body.

2. Indeed, it is possible that most therapeutically used drugs undergo some degree of bioactivation but do not cause toxicity because the amount of toxic metabolite formed is below a ‘toxic’ threshold or it is promptly detoxified.

3. According to the conventional definition of ADRs, paracetamol hepatotoxicity should not be classified as an ADR, because the hepatic injury occurs when the drug is used inappropriately.

4. However, it is important to note that the occurrence of liver damage with paracetamol and its severity is a function not only of the dose but also of various host factors.

5. Alcoholics show increased susceptibility to paracetamol overdosage because excess alcohol consumption results in the depletion of glutathione.

ROLE OF THE IMMUNE SYSTEM IN TYPE B ADVERSE DRUG REACTION

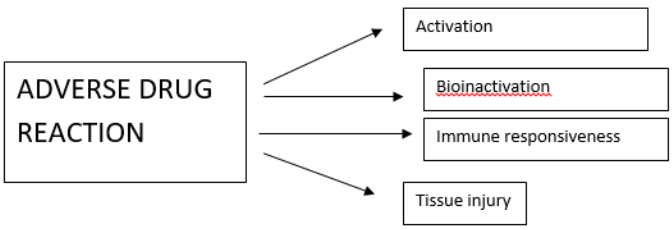
1. Based on clinical criteria, it has been postulated that many idiosyncratic ADRs are immune mediated.

2. The mechanism by which a drug leads to an immune-mediated adverse reaction is explained by the hapten hypothesis.

3. Central to the hapten hypothesis is the assumption that small molecules such as drugs macromolecular carrier such as a protein.

4. The best understood reactions are the type I hypersensitivity reactions induced by penicillins and cephalosporins and mediated by immunoglobulin E (IgE) antibodies directed against a drug hapten conjugated to protein.

5. The fundamental concept that protein conjugation is an obligatory step in the process of immune recognition of drugs has however recently been challenged by the observation that T-cell clones from patients hypersensitive to many drugs undergo proliferation in an antigen-processing–independent [but major histocompatibility complex (MHC)-restricted] manner.



Adverse drug reaction (ADR) monitoring involves following steps:

I. Identifying adverse drug reaction (ADR

II. Assessing causality between drug and suspected reaction

III. Documentation of ADR in patient's medical records

IV. Reporting serious ADRs to pharmacovigilance centres /ADR regulating authorities

Identifying adverse drug reaction (ADR)

Several definitions of ADRs exists, including those of WHO, FDA, Karch and Lasanga.The WHO definition is internationally accepted and most widely used. WHO technical report no 498(1972) defines ADR as "A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the modification of physiological function". This definition excludes therapeutic failures, intentional and accidental poisonings and drug abuse. Also this does not include adverse events due to errors in drug administration or noncompliance (taking more or less of a drug than prescribed amount).

ADRs are mainly identified in the pre-marketing studies and in the post-marketing surveillance studies. Disadvantages of the pre-marketing studies are that they lack sufficient knowledge to extrapolate information collected from animal studies directly into risks in humans and very few number of subjects (not more than 4000) are exposed to the new drug prior to the general release of product into market. Another major disadvantage is that clinical trials can not be done in rare group of subjects like children, elderly and pregnant women. For cost reasons clinical trials often have short duration which means they can not generate information about long term adverse effects. As a consequence of the above reasons, only type A adverse reactions are known at the time of general marketing of a new drug. So, all other types of ADRs can only be identified in post marketing surveillance.

Post marketing surveillance can be done by different methods:

1. Anecdotal reporting: The majority of the first reports of ADR come through anecdotal reports from individual doctors when a patient has suffered some peculiar effect. Such anecdotal reports need to be verified by further studies and these sometimes fail to confirm problem.

2. Intensive monitoring studies: These studies provide systematic and detailed collection of data from well defined groups of inpatients .The surveillance was done by specially trained health care professionals who devote their full time efforts towards recording all the drugs administered and all the events, which might conceivably be drug induced. Subsequently, statistical screening for drug-event association may lead to special studies. Popular example for this methodology is Boston collaborative drug surveillance program.

Strengths:

a. Derives incidence rates

b. Analyses factors which may contribute to reactions

c. Identifies drug interactions d. Generates and tests hypothesis e. Under reporting can be minimized

Weakness

a. They need great expense of resources

b. The relatively short period of observation resulting in non identification of delayed reaction

c. Relatively small proportion of population size resulting in non identification of rare reactions d. The lack of follow up and outcome information

3. Spontaneous reporting system (SRS): It is the principal method used for monitoring the safety of marketed drugs. In UK, USA, India and Australia, the ADR monitoring programs in use are based on spontaneous reporting systems. In this system, clinicians are encouraged to report any or all reactions that believe may be associated with drug use. Usually, attention is focused on new drugs and serious ADRs. The rationale for SRS is to generate signals of potential drug problems, to identify rare ADRs and theoretically to monitor continuously all drug used in a variety of real conditions from the time they are first marketed.

Strengths

a. Simple, effective, inexpensive and continuous

b. The entire population comprising extremes of age, people in hospital and community may be included

c. ADRs that are too rare to be demonstrated by other methods may be detected

d. Drugs that are uncommonly used may be monitored

Weakness:

a. Under reporting is almost universal

b. Absence of reliable numerator or denominator precludes the provision of quantitative information

c. Numerous other reporting biases include the novelty factor of new drug and the effect of publicity

d. Reporting rates for each agent or group of agents may vary with time

e. Clinical information supplied is often limited.

4. Cohort studies (Prospective studies): In these studies, patients taking a particular drug are identified and events are then recorded. The weakness of this method is relatively small number patients likely to be studied, and the lack of suitable control group to assess the background incidence of any adverse events. Such studies are expensive and it would be difficult to justify and organize such a study for every newly marketed drug.

5. Case control studies (retrospective studies): In these studies, patients who present with symptoms or an illness that could be due to an adverse drug reaction are screened to see if they have taken the drug. The prevalence of drug taking in this group is then compared with the prevalence in a reference population who do not have the symptoms or illness. The case control study is thus suitable for determining whether the drug causes a given adverse event once there is some initial indication that it might. However, it is not a method for detecting completely new adverse reactions.

6. Case cohort studies: The case cohort study is a hybrid of prospective cohort study and retrospective case control study, Patients who present with symptoms or an illness that could be due to an adverse drug reaction are screened to see if they have taken the drug. The results are then compared with the incidence of the symptoms or illness in a prospective cohort of patients who are taking the drug.

7. Record linkage: The idea here is to bring together a variety of patient

records like general practice records of illness events and general records of prescriptions. In this way it may be possible to match illness events with drugs prescribed. A specific example of the use of record linkage is the so called prescription event monitoring scheme in which all the prescriptions issued by selected parishioners for a particular drug are obtained from the prescription pricing authority. The prescribers are then asked to inform those running scheme of any events in the patients taking the drugs. This scheme is less expensive and time consuming than other surveillance methods.

8. Meta analysis: Meta analysis is a quantitative analysis of 2 or more independent studies for the purpose of determining an overall effect and of describing reasons for variation in study results, is another potential tool for identifying ADRs and assessing drug safety.

9. Use of population statistics: Birth defect registers and cancer registers can be used If drug induced event is highly remarkable or very frequent. If suspicions are aroused then case control and observational cohort studies will be initiated.

II. Assessing causality between drug and suspected reaction:

Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. There are three approaches to asses' causality.

These include: a) Opinion of an individual expert

b) Opinion of a panel of experts

c) Formal algorithms

In the first approach, an individual who is an expert in the area of ADRs would evaluate the case. In the process of evaluation, he or she may consider and critically evaluate all the data obtained to assess whether the drug has caused the particular reaction. A panel of experts adopts a similar procedure to arrive at a collective opinion. Using formal algorithms, collected data is subjected and critically assessed by using one or more standard algorithms.

Some of the important algorithms used are Naranjo, WHO, European ABO system, Kramer, Bayesian, Karch and lasanga and French imputation method. There is no gold standard for causality assessment. The categorisation of causal relationship between a drug and suspected adverse reactions varies with the scale adopted. WHO scale categorises the causality relationship into certain, probable, possible, unassessible/ unclassifiable, unlikely, conditional /unclassifiable. The Naranjo's scale categorises the reaction as definite, probable, possible or unlikely.

In general the following four different basic points can be considered in attributing a clinical adverse event to the drug

1. Temporal time relationship between suspected reaction and drug.

2. Dechallenge (cessation of drug)

3. Rechallenge (re introducing drugs)

4. Likelihood of other possible causes

III. Documentation of ADRs in patient's medical records

This aids as reference for alerting clinicians and other health care professionals to the possibility of a particular drug causing suspected reaction.

IV. Reporting serious ADRs to pharmacovigilance centers / ADR regulating authorities

According to FDA, a serious reaction is classified as one which is fatal, life threatening, prolonging hospitalisation, causing a significant persistent disability, resulting in a congenital anomaly and requiring intervention to prevent permanent damage or resulting in death.

Hatwig SC, Seigel J and Schneider PJ categorised ADRs into seven levels as per their severity. Level 1&2 fall under mild category whereas level 3 & 4 under moderate and level 5, 6 & 7 fall under severe category. Karch and Lasanga classify severity into minor, moderate, severe and lethal. In minor severity, there is no need of antidote, therapy or prolongation of hospitalisation. To classify as moderate severity, a change in drug therapy, specific treatment or an increase in hospitalization by at least one day is required. Severe class includes all potentially life threatening reactions causing permanent damage or requiring intensive medical care. Lethal reactions are the one which directly or indirectly contributes to death of the patient.

Different ADR regulatory authorities are - Committee on safety of medicine (CSM), Adverse drug reaction advisory committee (ADRAC), MEDWATCH, Vaccine Adverse Event Reporting System. WHO-UMC international database maintains all the data of ADRs. In India, national pharmacovigilance programme was officially inaugurated on 23rd November 2004. It has one national pharmacovigilance center located at CDSCO in Delhi, two zonal, five regional and twenty four peripheral centers. National pharmcovigillance center communicates all the reported ADR data to WHO - UMC international database.

PREVENTING ADVERSE DRUG REACTIONS

There are two basic steps that can be followed 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

1. 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.

2. In other cases, susceptibility factors such as age, gender, pregnancy status and ethnicity can help predict the risk of an ADR occurring.

3. 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.

TREATMENT PLAN

1. Prudent, safe prescribing is key to reducing errors that can contribute to ADRs. Treatment plans should consider and mitigate for any possible adverse effects.

2. 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.

3. 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.

DIAGNOSING ADR

1. ADRs are one of the great mimics in healthcare, often emulating 'traditional diseases' and manifesting in all systems of the body.

2. 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*

3. 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.

4. 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.

QUESTION	CLINICAL RELEVANE
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 hyper susceptibility reactions less likely
Did anything else change around the time of possible ADR other than suspected drug (eg other treatments, over the counter medicines, disease progression)	Examination of whether there are alternative causes (other than suscepted drug) that could either 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 drug following an ADR	An ADR occurring on re-exposure to a drug increases the probability of a causal relationship

REPORTING OF AN ADR

1. 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).

2. The scheme was founded in 1964 following the thalidomide disaster in the late 1950s. Through spontaneous reporting, the scheme collects data on suspected ADRs related to all licensed and unlicensed medicines and vaccines, including those issued on prescription or purchased over the counter.

3. 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.

4. 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.

5. 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 erythema multiforme).

Their use is more limited in identifying 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.

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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.