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Pharmacovigilance

It has been estimated that 6.5% of hospital admissions are related to adverse drug reactions (ADRs) and that at least 60% of ADRs are preventable.[1,2]

The process of preventing and detecting adverse effects from medicines is termed *pharmacovigilance* and is a key part of effective drug regulation systems, clinical practice, and public health programmes. Pharmacovigilance is becoming increasingly important in light of shorter approval times for new drugs and greater use of over-the-counter (OTC) and herbal medicines.

In the UK, the bedrock of pharmacovigilance is spontaneous reporting of ADRs via the Yellow Card Scheme, which is run by the Medicines and Healthcare products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM). The Yellow Card Scheme acts as an early warning system for identifying previously unrecognised adverse reactions and has proved to be successful in the early detection of several important safety issues with medicines (see Table 1).

The Yellow Card Scheme provides invaluable information. However, it relies on voluntary reporting of suspected ADRs by healthcare professionals and patients, and its usefulness can be limited by the problem of under-reporting. It is thought that only 10% of serious suspected reactions and 2 to 4% of non-serious suspected reactions are reported.[3]

Over the last few years, there has been a decrease in Yellow Card reports from most groups of healthcare professionals, and from patients.[4] Reports from GPs in Wales have declined markedly during the last decade, from almost 1000 reports in 2001 to fewer than 200 in 2011.[5]

A recent campaign by the MHRA to raise awareness of the Yellow Card Scheme aims to ensure that health professionals recognise their responsibilities in reporting adverse reactions and to increase public awareness of the scheme.[6] To encourage good practice, ADR reporting via the Yellow Card Scheme has been identified by the All Wales Prescribing Advisory Group (AWPAG) as a local comparator for 2013 – 14.

Several factors, related to the knowledge and attitudes of health professionals, have been found to be associated with under-reporting of suspected ADRs.[7,8] These include lack of knowledge about the functioning of spontaneous ADR reporting; diffidence about reporting a mere suspicion; lack of confidence in diagnosing ADRs; and complacency that only safe medicines are marketed.

This bulletin discusses how to identify and report suspected ADRs effectively and efficiently, and how this can improve patient safety and benefit public health. Several factors associated with under-reporting of suspected ADRs are considered.

Table 1. Examples of safety issues that Yellow Card reports have helped to identify.[9]

Year	Medicine	Adverse reaction	Resulting action or advice
2012	Dabigatran	Serious haemorrhages	Contraindications clarified and reminder to monitor renal function.
2011	Citalopram/ escitalopram	QT interval prolongation	New maximum daily dose restrictions, contraindications, and warnings.
2009	Antiepileptics	Adverse effects on bone	Vitamin D supplementation should be considered for at-risk patients.
2001	Bupropion	Seizures	Improved warnings and revised dosing instructions.
2000	Cisapride	Serious cardiovascular reactions	Use suspended in the UK.

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Adverse Drug Reactions

An ADR is a response to a medicinal product which is noxious and unintended. ADRs may arise from the use of a product within or outside the terms of the marketing authorisation, e.g. from off-label use, medication errors, overdose, or misuse.[10]

ADRs may be broadly classified as type A (augmented) or type B (bizarre) reactions (see Figure 1). This simple system of classification is still widely used, but has been expanded to take into account other types of reactions such as type C (continuing), e.g. osteonecrosis of the jaw with bisphosphonates; type D (delayed), e.g. leucopenia with lomustine; and type E (end of use), e.g. withdrawal reactions with opioids.[11] A system of classification has also been proposed based on dose-relatedness, time course, and susceptibility – this is known as DoTS.[12]

Figure 1. Characteristics of Type A and Type B ADRs.[13,14]

Type A ('augmented') reactions	Type B ('bizarre') reactions
An exaggeration of the normal pharmacological actions of a drug when given at the usual therapeutic dose. ▪ Common ▪ Usually dose dependent ▪ Low mortality, high morbidity ▪ Responds to dose reduction e.g. low blood pressure with antihypertensives or low blood sugar with insulin.	Unusual responses that are not expected from the known pharmacological actions of the drug. ▪ Less common ▪ Rarely dose dependent ▪ High mortality ▪ Responds to drug withdrawal e.g. anaphylaxis with penicillin, skin rashes with antibiotics, or angioedema with ACE inhibitors.

How do I identify an ADR?

It is important to listen to the patient's own concerns regarding their therapy; they may tell you about symptoms they have experienced since taking a new medicine. However, some adverse reactions may not be apparent to the patient, and clinicians should be alert to this. It may be helpful to consider the following criteria, in addition to clinical judgement, to aid the differentiation of disease from the possible occurrence of an ADR. In this way a 'prescribing cascade', whereby one medicine is prescribed to treat the adverse effects of another, may be avoided.

Possibility of a reaction – a reaction that might be predicted from the known pharmacology of a medicine is relatively easy to diagnose. However, identifying type B reactions can be difficult unless there have been previous reports of similar reactions;[15] this emphasises the importance of reporting your suspicions (see pages 3 – 4).

Timing of reaction – anaphylaxis usually develops within a few minutes of parenteral drug administration but reactions can develop days, weeks, months, or years after the administration of a medicine and may be related to a cumulative effect, or, rarely, may occur in the patient's offspring.[16]

Relationship to dose – ADRs can be dose related and may be minimised by reducing the dose. If symptoms disappear when the medicine is stopped, although possibly coincidental, it suggests that they are associated with the medicine. A recurrence of symptoms on reintroduction of the medicine strongly suggests an association. However, deliberate rechallenge may be associated with the risk of a severe ADR and may therefore be inappropriate.[16]

Nature of reaction – some clinical events are frequently caused by medicines. For example, if your patient develops one of the following conditions, you should consider the possibility of an ADR:

- neuroleptic malignant syndrome
- blood dyscrasia
- acute dystonia
- skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis.[16]

Consider other possible causes – a suspected reaction may be a manifestation of an underlying illness, may be caused by another medicine, including OTC products or herbal remedies, or by an interaction between two or more medicines.[16]

Aren't medicines proven to be safe before they are licensed?

At the point of marketing, when a medicine leaves the protected scientific environment of clinical trials and is taken by the general population, most will have been tested for a limited duration in a relatively small number (rarely more than 5 000) of carefully selected individuals. This group usually excludes specific populations such as pregnant women, children, and older people.

This means that rarer ADRs, occurring in only a small percentage of patients, or after long periods of use, or when the drug interacts with particular combinations of other medicines or conditions, may not be detected during pre-approval clinical trials. It is essential to continue monitoring the effectiveness and safety of medicines after marketing, under 'real-life' conditions. Assessment of the risks and benefits of medicines applies throughout their life cycle – from pre-approval stage to use by patients.[1]

There are many ways in which information can be collected and used for pharmacovigilance, including pharmacoepidemiological studies (such as prescription event monitoring),[17] published medical literature, longitudinal patient databases, and spontaneous reporting schemes (such as the Yellow Card Scheme).

How does the Yellow Card Scheme work?

The scheme was introduced in 1964, following the thalidomide tragedy. Initially, only doctors could submit reports. However, this has gradually been extended to include many other health professionals, and patients. The MHRA also receives ADR reports from pharmaceutical companies, which have a statutory obligation to report them.

Yellow Cards should be submitted directly to the MHRA. The resulting data are used to detect 'signals' of emerging drug safety problems. At the MHRA, pharmacovigilance scientists and physicians assess the causal relationship between the drug and reported reactions, and identify possible risk factors. To do this, they must also consider what is already known about the drug, taking into account data from other sources such as pre-approval trials, epidemiological studies, case reports in the literature, and data from other drug regulatory authorities.[3]

When should I report an ADR?

Many professionals wrongly believe that the sole aim of spontaneous reporting is to detect serious ADRs. However, all types of reaction are relevant to a medicine's safety profile. ADRs arising from widely-used medicines such as oral anticoagulants, NSAIDs, and diuretics are responsible for a large proportion of hospital admissions, even though their effects are well known.[2]

> You should not refrain from reporting simply because you are not certain about cause and effect.

You should report cases where you have a suspicion that there is a relationship between the medicinal product taken and the suspected reaction experienced. Remember, you are reporting a possible association, not a certainty, and if you are in doubt about causality you should report anyway. The report will be looked at in the context of other information held and can add to the knowledge and understanding of an ADR.

ADRs resulting from prescription, OTC, and herbal medicines should all be reported. It is also worth noting that you should report suspected ADRs that arise as a result of error, misuse, or off-label use.

You should complete a Yellow Card for:

All suspected reactions to 'black triangle' medicines irrespective of the severity of reaction. A black triangle (▼) denotes a medicine that is included in the EU-wide additional monitoring scheme.

Serious reactions to other medicines, including prescription, OTC, and herbal medicines, vaccines, x-ray contrast media, blood products, and dental or surgical materials.

Serious reactions are those that are medically significant; are fatal or life-threatening; are disabling or incapacitating; or those that result in, or prolong hospitalisation. A congenital abnormality would also be considered a serious reaction.

All reactions in children under 18, regardless of whether the medicine is licensed for use in children.

Delayed drug effects, which may appear months or even years after exposure, e.g. withdrawal effects or cancers.

Congenital abnormalities, adverse foetal effects in newborn or miscarriage, which are suspected to be drug related.

Why should I report serious suspected ADRs to long-established medicines?

Rare or delayed adverse effects may still be identified when a medicine has been available for many years. Even when ADRs have been identified, they need to be investigated in more detail to establish risk factors such as age or concurrent disease. If sufficient information about recognised reactions is gathered, medicines in the same therapeutic class may be compared to investigate their relative safety. For example, Yellow Card data contributed to the evidence that among NSAIDs, standard-dose ibuprofen is associated with the lowest risk of gastrointestinal reactions.

Who should report suspected ADRs?

Healthcare professionals (including doctors, dentists, pharmacists, nurses, midwives, health visitors, radiographers, and optometrists) have a responsibility to submit a Yellow Card report where they suspect an ADR has occurred. It should not be assumed that someone else will have submitted a report. The MHRA can detect duplicate reports and information from different professionals can give different data on the same ADR, creating a fuller picture of the reaction that has taken place. Likewise, patient reporting was not introduced to replace healthcare professional reporting, but to enrich the data held by the MHRA with patient experiences of ADRs.

How should I report the ADR?

Yellow Cards can be submitted online at www.mhra.gov.uk/yellowcard. This is the quickest and easiest way to submit and you can track any reports that you send. Alternatively, you can mail a report; Yellow Cards are available in the BNF, or can be downloaded from the above website.

Yellow Card Centre Wales (YCC Wales)

YCC Wales is one of five regional centres acting locally on behalf of the MHRA and CHM. It is jointly co-ordinated by clinical pharmacologists at the All Wales Toxicology and Therapeutics Centre (AWTTC) and pharmacists at the Welsh Medicines Information Centre (WMIC).

The primary role of YCC Wales is to encourage reporting of suspected ADRs via the Yellow Card Scheme amongst local healthcare professionals and patients, by providing support and education.

For further information visit **www.yellowcardwales.org**

Why should I submit a Yellow Card report?

The use of any medicine is an acceptance that harm may be caused to an individual patient even if the desired effect is more likely, and good prescribing practice includes monitoring ADRs at the clinical level and reporting when appropriate. The importance of reporting ADRs is recognised by the General Medical Council (GMC) in their core guidance *Good Medical Practice.*[18]

Identifying a new risk associated with a medicine could have a major impact on the clinical management of patients.[6] Although single reports are rarely conclusive, recurring, similar reports can generate a signal that warrants further investigation.

The value of the Yellow Card Scheme in identifying important safety issues has been demonstrated (see Table 1). Timely reporting of suspected ADRs is fundamental to the scheme's continuing success. In this way, a single vigilant health professional or patient can make a significant contribution to public health and patient safety.

Where can I find up-to-date information on ADRs?

Drug Safety Update (MHRA)	The MHRA's monthly drug safety bulletin is available on the MHRA website, where you can also search previous issues and receive free monthly updates by email. This publication often gives the first warning of safety advice changes. **www.mhra.gov.uk/DrugSafetyUpdate**
'Dear Health Professional' letters	Sent out by pharmaceutical companies to clinicians, containing information, typically approved by the regulatory authorities, on newly identified risks and how they can be managed. **www.mhra.gov.uk/mhra/HealthcareProfessionalLetters**
British National Formulary (BNF)	The paper edition is released twice a year, so the current edition may not reflect the newest safety information. However, the BNF now updated monthly online and via the NICE mobile app. **www.bnf.org**
Drug Analysis Prints	This is a record of all suspected reactions submitted using a Yellow Card. Although it can be useful, the data have limitations, which should be fully understood before interpretation and use. **www.mhra.gov.uk/daps**

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