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ADVERSE REACTIONS TO MEDICINES

- **Adverse reactions to medicines, also known as adverse drug reactions (ADRs), are an important cause of morbidity and mortality**
- **Many ADRs that occur are considered to be potentially preventable**
- **Patient risk factors for ADRs include extremes of age, polypharmacy, co-morbidity, female gender and genetics**
- **Medicinal products that have an inverted black triangle "▼" in their prescribing information are subject to additional monitoring**

INTRODUCTION

All medicines, in addition to their therapeutic effects have the potential to cause unwanted effects or adverse reactions (i.e. adverse drug reactions [ADRs]).[1] There are various international definitions of an ADR;[1-3] since 2012 the European Medicines Agency (EMA) defines an ADR as "*a response to a medicinal product which is noxious and unintended*".[4] This definition extends beyond the licensed use of a drug and includes adverse reactions occurring from off-label use, overdose, misuse, abuse and medication errors.[4] A serious ADR is defined as that which: 1) results in death, 2) is life-threatening, 3) results in hospitalisation or prolongs hospitalisation, 4) results in persistent or significant disability or incapacity or 5) is a congenital anomaly/birth defect.[4,5]

ADRs occur in approximately 5% of patients who are taking a medicine.[6] Many ADRs result in minor symptoms, however **ADRs are an important cause of morbidity and mortality.[6-9]** Globally, ADRs are an important cause of hospital admission (ranging from 3 to 15%) or prolonged hospitalisation.[6,7,10-18] An Irish study (2014) found that 8.8% of patients had an ADR-related hospital admission of which 57% were considered potentially avoidable.[19] **The types of ADRs that frequently result in hospitalisation include gastrointestinal (GI) bleeding with antithrombotics, bradycardia/hypotension with cardiovascular (CV) drugs and neutropenic fever with cytotoxics.[12,20,21]** ADRs result in an estimated in-hospital mortality of up to 4.5%; the greatest risk is in those aged ≥75 years.[8,10,12,20,22] ADRs constitute a significant economic burden from both direct and indirect costs.[6,8,11,23] There are ongoing global efforts to reduce the number of preventable ADRs.[16] This bulletin will provide an overview of ADRs.

CLASSIFICATION OF ADVERSE DRUG REACTIONS

ADRs can be classified into 2 main types: Type A reactions – which are dose-dependent and considered predictable based on the pharmacology of the drug, and Type B reactions which are idiosyncratic and not predictable on the basis of their pharmacology.[6,7] **Up to 80% of ADRs resulting in hospitalisation or occurring in hospital are Type A;[6,8,10,11,13,24]** many of these ADRs are considered potentially preventable.[6,11] It is not always possible to assign an ADR to Type A or Type B; the classification has been extended to include other types of ADRs (see table 1).[1]

Table 1: Classification of adverse drug reactions[1]

Type of reaction	Mnemonic	Features	Examples
A: Dose-related	Augmented	Common; related to the pharmacological action of the drug; predictable; low mortality	Digoxin toxicity; serotonin syndrome with SSRIs; anticholinergic effects of TCAs
B: Non dose-related	Bizarre	Uncommon; not related to pharmacological action of the drug; unpredictable; high mortality	Penicillin hypersensitivity, acute porphyria, malignant hyperthermia with general anaesthetics
C: Dose-related and time-related	Chronic	Uncommon; related to the cumulative dose	Osteonecrosis of the jaw (bisphosphonates); adrenal suppression (corticosteroids)
D: Time-related	Delayed	Uncommon; usually dose-related; occurs some time after the use of the drug	Teratogenesis, carcinogenesis
E: Withdrawal	End of use	Uncommon; occurs soon after withdrawal of the drug	Withdrawal symptoms with opiates or benzodiazepines; myocardial ischaemia (beta blocker withdrawal)
F: Unexpected failure of therapy	Failure	Common; dose-related; often caused by drug interactions	Reduced efficacy of contraceptives when used with enzyme inducers

SSRIs – selective serotonin reuptake inhibitors; TCAs – tricyclic antidepressants

An alternative three dimensional classification scheme has been proposed which describes ADRs according to the **D**ose of the drug at which they usually occur, the **T**ime course over which they occur and patient **S**usceptibility factors (**"DoTS"**) (see table 2).[2,25-27] This classification can be used to help clinicians to understand, predict and prevent ADRs from occurring in practice.[7,27]

Table 2: DoTS classification scheme of adverse drug reactions[25-27]

Relation of adverse drug reaction to dose • Toxic reactions – reactions that occur at supratherapeutic doses • Collateral reactions – reactions that occur at standard therapeutic doses • Hypersusceptibility reactions – reactions that occur at subtherapeutic doses in susceptible patients
Time course • Time-independent reactions – reactions that occur at any time during a course of therapy • Time-dependent reactions – reactions may occur immediately, are delayed or occur following withdrawal
Susceptibility factors • Genetic, age, sex, physiological variation (e.g. weight, pregnancy), exogenous factors (e.g. polypharmacy, food, weather) and diseases (e.g. renal and hepatic impairment)

RISK FACTORS FOR ADVERSE DRUG REACTIONS

Patient risk factors: While **any individual can experience an ADR,** there are some populations at greater risk. Patient risks or susceptibility factors include age, polypharmacy, genetics, gender and co-morbidities (e.g. renal impairment).[11,16,17]

Older patients: There is an increased prevalence of ADRs (especially Type A ADRs) in older people (aged >65 years);[6,9,12,17,28] it is estimated that up to 50% of ADRs occurring in the elderly are potentially avoidable.[12] Older people are more at risk of ADRs for reasons including 1) pharmacokinetic (PK) changes, 2) increased pharmacodynamic (PD) sensitivity, 3) polypharmacy, 4) co-morbidities (e.g. renal impairment, heart failure), 5) cognitive problems (resulting in non-adherence) and 6) frailty.[2,6,17,22,27] **An Irish study (2014) found that 80% of community dwelling older patients had experienced at least one ADR in the previous 6 months.[21]**

Paediatric patients are at increased risk of experiencing ADRs.[6,29,30] Reasons for this include the off-label use of drugs (occurs in 80 to 90% of neonates and infants), immature organ function, polypharmacy, co-morbidities and inappropriate formulations.[6,27,29,30] Drug classes most often linked to ADR-related hospital admission in paediatrics include cytotoxics, corticosteroids, vaccines, immunosuppressants and non-steroidal anti-inflammatory drugs (NSAIDs).[6]

Genetic factors can determine the PD and PK of drugs and play a role in specific ADRs. They may contribute in particular to those ADRs classified as idiosyncratic e.g. drug-induced liver injury and drug-induced long QT syndrome.[22]

Gender: Some studies suggest that there is an increased prevalence of ADRs in females.[9,22,27,31] The reason behind this remains unclear, but it has been hypothesised that it may be due to gender differences in immunological and hormonal physiology, which influence PD and PK response.[9,22,27]

Renal and hepatic impairment: Most drugs are metabolised by the liver and excreted by the kidneys.[6] Impairment or failure of either of these organs can affect the PK profile of a drug leading to an increased risk of an ADR.[6] Monitoring laboratory values and adjusting the doses of drugs metabolised and excreted by these pathways may prevent an ADR.[6,22]

Drug risk factors: While medicines that have a narrow therapeutic index (e.g. antiarrhythmics, anti-epileptics, cytotoxics and oral anticoagulants) are of concern particularly in the elderly, **any medicine can potentially cause an ADR**. The most common medicines resulting in hospitalisations due to ADRs include low dose aspirin, warfarin, NSAIDs, diuretics, psychotropics, and cytotoxics.[6,7,10,13,19] **Fatal ADRs are often attributable to haemorrhage, the most common cause being an NSAID co-administered with an anticoagulant.[7]** In the elderly, certain drugs are associated with specific ADRs, e.g. hypnotics, benzodiazepines, neuroleptics, antidepressants and antihypertensives are strongly associated with falls.[27,28]

Polypharmacy (the concomitant use of ≥5 drugs) is consistently found to be a risk factor for ADRs.[2,6,13] **The risk of ADRs increases from 13% in a person taking 2 drugs, to 58% when taking 5 drugs, and to 82% when taking ≥7 drugs.[32]** Polypharmacy is increasing; an Irish study (2019) found that the proportion of patients aged 45 to 54 years on polypharmacy was 38.6%, which increased to 82.6% in those aged ≥75 years.[33] The highest rate of polypharmacy occurs in nursing home residents, who have the highest prevalence of ADRs.[22] **Drug interactions are a common cause of ADRs leading to hospitalisation**; examples include aspirin with warfarin causing GI bleeding, aspirin with other NSAIDs leading to GI effects and renal failure associated with combinations of diuretics or the concomitant use of diuretics and angiotensin converting enzyme (ACE) inhibitors.[10] **Information on potential PD and PK interactions that can occur between drugs is available in the Summary of Product Characteristics (SmPC).**

PREVENTION OF ADVERSE DRUG REACTIONS

Many ADRs are preventable, especially those that are dose-dependent.[2,7,12,24,27] **More than 50% of ADR-related hospital admissions are considered potentially preventable**, most being attributable to NSAIDs, antiplatelets, anticoagulants, diuretics and antidiabetic drugs.[22]

Measures to prevent ADRs include good communication between healthcare professionals, regular review of the patient's diagnoses, medication and previous history of ADRs, the setting of clear therapeutic goals, the avoidance of polypharmacy if possible, explaining the benefits and risks to the patients and the monitoring of the effects of treatment.[2,7,22,24,28] ADR risk factors should be identified in an individual patient and the most effective drug at an appropriate dose for that patient should be chosen.[2,7,22] For some drugs it is practice to establish the patient's phenotype or genotype before treatment (e.g. HLA-B*5701 screening for abacavir hypersensitivity), while other drugs may need baseline laboratory assessment (e.g. renal, haematological).[6] While

polypharmacy may represent appropriate prescribing (e.g. in secondary cardiovascular prevention), unnecessary polypharmacy is associated with increased risks and should be avoided.[22,24]

Gradual dose up-titration of a drug should be considered especially in the elderly; if possible, only one new medication should be commenced at any one time.[22,24] In older people, drugs with a narrow therapeutic index should be avoided if possible and the use of antipsychotics, antihistamines, benzodiazepines, anticholinergics and hypnotics should be limited to reduce the risk of falls.[22,24] Prescribing indicators can be used to define and detect potentially inappropriate medicines (PIM) in older people (e.g. STOPP/START criteria [Screening Tool of Older Person's Prescriptions/Screening Tool to Alert doctors to Right Treatment]).[6,22,28] There is evidence that use of STOPP/START criteria, by identifying PIM, improves the quality of prescribing in clinical settings.[22,28]

The SmPC in addition to providing information on indications, dosing and precautions for use of a medicine also includes detailed information on the known ADRs associated with the medicine. **Supplemental educational materials that focus on specific medicine safety concerns are additional risk minimisation measures** that are produced by a pharmaceutical company and approved by a regulatory authority.[5] They are intended to promote the safe and effective use of medicines; examples of educational materials for healthcare professionals (HCPs) include dosing and administration guides, prescriber checklists and monitoring charts, and those for patients include patient alert cards, patient guides and reminder cards.

DIAGNOSIS OF AN ADVERSE DRUG REACTION

An ADR should be considered in any patient presenting with symptoms who is taking a drug (including OTC and recreational drugs).[1,2,22] In particular, **ADRs should be included in the differential diagnosis, if an unexpected change occurs in a patient's clinical condition leading to transfer to a higher level of care (e.g. hospitalisation), and in all older patients who develop new symptoms after starting, or having had dose adjustment of, a drug.[6,22]** ADRs may be undiagnosed as patients may not associate the symptoms they are experiencing with the drugs they are taking, however a comprehensive medication history should help to establish the diagnosis.[2,22] Failure to recognise an ADR may result in a **"prescribing cascade", when a new drug is given to alleviate symptoms caused by a drug(s) already prescribed;[2,6]** this puts the patient at a further increased risk of experiencing an ADR from the new drug.[22]

It can be difficult to reliably diagnose ADRs or determine causality in clinical practice, especially in older patients who often present with nonspecific symptoms (e.g. falls, fatigue, cognitive decline) and who may have multiple contributory factors.[6,22] ADRs present in many different ways, including weakness or drowsiness, biochemical or haematological abnormalities (e.g. acute kidney injury or electrolyte imbalance), bleeding, GI disturbances and hypoglycaemia.[7] A causality assessment should be performed for each potential ADR, which should include a medication history, the symptom pattern of the event, the temporal association to use of the drug, previous similar symptoms with the drug, background frequency of the event and relevant laboratory tests.[1,6] **There are various algorithms that can be used to help determine ADR causality**, of which the Naranjo ADR Probability Scale is one of the most frequently cited (see table 3).[6,7,22,34]

Table 3: Naranjo ADR Probability Scale[34]

Question	Yes	No	Do not know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
Are there alternative causes (other than the drug) that could solely have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in the blood (or other fluids) in a concentration known to be toxic?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by objective evidence?	+1	0	0
Total Score - ADR Probability Classification 9 - Highly probably; 5-8 – Probable; 1-4 – Possible; 0 - Doubtful			

MANAGEMENT OF ADVERSE DRUG REACTIONS

Management depends on the type of ADR; clinical judgement, assessing the benefit-risk of the medicine (with the help of investigations) and the severity of the reaction, is required to determine whether a drug needs to be stopped (consider alternative treatments that could be used instead) or the dose regimen adjusted.[1,7] Immediate

withdrawal of the drug may be required and emergency treatment given (e.g. naloxone for opioid toxicity, idarucizumab for dabigatran), with cautious reintroduction of the drug if appropriate.[1] If the patient cannot stop the drug that has caused the ADR, consider symptomatic relief e.g. anti-emetics for vomiting in patients receiving anticancer drugs.[1]

PHARMACOVIGILANCE

All medicinal products that receive a marketing authorisation (MA) or licence, do so on the basis of a positive benefit-risk profile of the drug at the time of authorisation. Prior to the granting of a MA, information on the safety and efficacy of drugs is limited to clinical trials, where there are a relatively small number of selected patients who are followed up closely under controlled conditions.[4] After authorisation, the drug may be used in a large number of patients in less controlled circumstances and new, less common ADRs may emerge. Therefore **it is essential that the safety of all drugs is monitored throughout their period of usage in clinical practice.[4]**

Pharmacovigilance is the study of the safety of marketed drugs;[5,35] it includes all activities related to the detection, assessment, understanding and prevention of adverse events and other possible drug-related problems.[4-7] Revised EU pharmacovigilance legislation was implemented in 2012, with activities co-ordinated by the EMA.[4] This introduced a number of changes including the additional monitoring of medicines after authorisation and specific changes related to ADR reporting including the provision for direct patient reporting of ADRs.[3,5] **The additional monitoring status of a medicine is indicated by the presence of an inverted black triangle symbol** "▼", accompanied by an explanatory statement encouraging the reporting of ADRs, in the SmPC and the Package Leaflet.[3,5] An Irish study (2018) found that >85% of pharmacists were aware of the black triangle "▼" compared to 35% of hospital doctors and GPs.[36] In Ireland, the Health Products Regulatory Authority (HPRA) is responsible for the monitoring of medicine safety. [5]

Reporting of adverse drug reactions: Following the thalidomide disaster in the late 1950s, spontaneous ADR reporting systems were introduced in many countries in the 1960s (Ireland in 1968).[3,5,7] The WHO established an international database of ADRs in 1971, using information derived from its member countries which had spontaneous ADR reporting systems.[2,6,7,16] The WHO Collaborating Centre for International Drug Monitoring, based at the Uppsala Monitoring Centre (UMC) is responsible for this database (now called Vigibase), which currently contains three million ADR reports originating from 130 member countries, including Ireland.[3,5,37] The data from Vigibase is analysed to generate hypotheses and signals about potential hazards of drugs that require further investigation.[5,37] The EMA which is responsible for EudraVigilance (a database of suspected ADRs from the EU) collaborates with the WHO and the US Food and Drug Administration.[4]

Healthcare professionals (HCPs) play a critical role in pharmacovigilance by reporting suspected ADRs to a regulatory authority (e.g. HPRA) or pharmaceutical company. **Only 4 items of information are required for a suspected ADR report to be valid: 1) an identifiable patient, 2) a reaction, 3) a suspected medicinal product and 4) and an identifiable reporter;** reporters are encouraged to provide additional relevant information if possible.[5] By reporting known or suspected ADRs, HCPs and patients can assist in identifying signals, which may alter the benefit-risk profile of a medicine, potentially leading to restrictions (e.g. dose alteration in specific populations) or even withdrawal of a medicine.[6] Spontaneous ADR reports are particularly useful in identifying rare and uncommon or delayed ADRs.[5,35]

Under-reporting however is a major challenge; it is estimated that <5% of all ADRs are reported in practice.[6,7,35,36,38,39] Reasons for HCPs not reporting suspected ADRs include 1) lack of awareness of the importance of reporting, 2) unavailability of training programmes for HCPs on ADR detection, 3) fear of the ramifications of reporting and 4) the time-consuming nature of submitting the reports.[6] An Irish study from 2018 found that 43% of hospital doctors and 35% of GPs had never reported a suspected ADR.[36] The study found that those with >10 years' experience were significantly more likely to report than those with <10 years' experience.[35]

The HPRA encourages HCPs to report suspected ADRs observed in their practice, particularly those ADRs highlighted in table 4.[5]

Table 4: Adverse drug reactions to report to the HPRA[5]

In particular the following adverse drug reactions should be reported to the HPRA:

- all suspected reactions to newly authorised medicinal products
- serious reactions to established medicinal products
- suspected reactions to medicinal products undergoing additional monitoring (e.g. those with ▼ on the SmPC)
- suspected reactions to vaccines
- suspected reactions to medicines used in pregnancy

Suspected ADRs can be reported to the HPRA (www.hpra.ie) via an online form or by downloading an ADR report form and emailing it to medsafety@hpra.ie. Alternatively the ADR report form can be printed from the HPRA website and posted by freepost.

SUMMARY

ADRs are an important cause of mortality and morbidity, and occur in up to 5% of patients taking drugs. Risk factors for ADRs include extremes of age, polypharmacy, co-morbidity, gender and genetics. The majority of ADRs that occur are considered potentially preventable.

List of references available on NMIC website. Date of preparation: Oct 2019

Adverse drug reactions – references

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