Objectives

- Explain how to predict, identify and characterise an adverse drug reaction including an allergic drug reaction.
- Explain how to respond to an adverse drug reaction including an allergic reaction.
- Explain the frequency of adverse drug reactions and their impact on public health.
- Discuss the importance of and the prescriber’s responsibility in pharmacovigilance.

Clinical scenario Unexplained loss of consciousness

An 87 year old NZ European woman is brought to the Emergency Department by ambulance. Her CT scan shows a large intracerebral haemorrhage.

It transpires that she is taking warfarin (a blood thinning agent). It seems likely that the haemorrhage is due to an interaction between warfarin and a medicine she has recently started.

Is this a side effect of her medicine? A medication error? An adverse drug reaction? How would you describe the severity?
**WHO definition of an adverse drug reaction (ADR)**

“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 modifications of physiological function.”


**American Society of Health-System Pharmacists definition**

Any unexpected, unintended, undesired, or excessive response to a medicine that:
- requires discontinuing the medicine
- requires changing the medication therapy
- requires modifying the dose (except for minor dosage adjustments)
- necessitates admission to the hospital
- prolongs stay in a healthcare facility
- necessitates supportive treatment
- significantly complicates diagnosis
- negatively affects prognosis
- results in temporary or permanent harm, disability, or death


**How do “medication errors” relate to ADRs?**

Medication errors are mishaps that occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring a drug. Medication errors are more common than adverse drug events, but result in harm less than 1% of the time.

An adverse drug event is “an injury resulting from the use of a drug including harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy). Adverse drug events may result from medication errors (about 25%) but most do not.”

What about “allergies” and “side effects”?

An allergy is an adverse drug reaction mediated by an immune response (e.g., rash, hives).

A side effect is an expected and known effect of a drug that is not the intended therapeutic outcome; ie an adverse drug reaction.

Most ADRs are MILD, some are MODERATE; SEVERE ADRs are rare.

Disabling, life-threatening, requires hospital admission; congenital anomaly.

Classification of ADRs - ABC

Type A (Augmented pharmacologic effect)
• Extension of pharmacologic effect
• Often predictable and dose dependent
• Responsible for at least 2/3 ADRs

Type B (Bizarre)
• Idiosyncratic or immunologic (drug allergy)
• Rare and unpredictable
• Dose independent

Type C (Chronic effects)
• Associated with long-term use
• Accumulation of dose/damage

Type D (Delayed)
• Carcinogenicity
• Teratogenicity

Type E (End of treatment)

Type F (Failure of treatment)

Type A (augmented) e.g. Anticholinergic effects with tricyclic antidepressants
Type B (bizarre) e.g. Malignant hyperpyrexia in anaesthesia
Type C (Chronic effects) e.g. Analgesic nephropathy
Type D (Delayed)
Type E (End of treatment) e.g. Seizures after stopping phenytoin
Type F (Failure of treatment) e.g. Inadequate dosage of an oral contraceptive, particularly when used with specific enzyme inducers
Drug Allergies

Immediate
occur within one hour
Type I
Anaphylactic

Delayed
occur after one hour (most after six hours and typically after days)
Type II
Cytotoxic
Type III
Immune complex
Type IV
Cell mediated

Type I (immediate, anaphylactic): mediated by IgE and mast cells and/or basophils
Type II (cytotoxic): caused by IgG and IgM antibody and complement mediated cell destruction
Type III (immune complex): caused by IgG:drug immune complexes and complement activation
Type IV (cell mediated): T cell-mediated

Classification of ADRs - DoTS

Dose
- Supratherapeutic (toxic effects)
- Standard therapeutic doses (collateral effects)
- Subtherapeutic doses in susceptible patients (hypersusceptibility reactions)

Timing
- Time independent reactions
- Time dependent reactions
  - Rapid reactions
  - First dose reactions
  - Early reactions
  - Intermediate reactions
  - Late reactions
  - Delayed reactions

Susceptibility
- Reasons for hypersensitivity include genetic variation, age, sex, physiological variation, exogenous factors, and disease

Rapid reactions occur only when a drug is administered too rapidly (e.g. the red man syndrome with vancomycin)

First dose reactions occur after the first dose of a course of treatment and not necessarily thereafter (e.g. hypotension after the first dose of an angiotensin converting enzyme inhibitor)

Early reactions occur early in treatment then abate with continuing treatment (patients develop tolerance (e.g. nitrate induced headache))

Intermediate reactions occur after some delay; however, if a reaction has not occurred after a certain time, there is little or no risk that it will occur later (e.g. increased risk of neutropenia with carbimazole)

Late reactions occur rarely or not at all at the beginning of treatment, but the risk increases with continued or repeated exposure (e.g. adverse effects of corticosteroids). Withdrawal reactions are late reactions that occur when a drug is withdrawn or its dose is reduced after prolonged treatment.

Delayed reactions are observed sometime after exposure, even if the drug is withdrawn before the reaction appears (e.g. carcinogenesis)
Why do ADRs matter?

Death and serious harm

Hospital admission or prolonged stay

Cost

In the US the annual incidence of severe ADRs was 6.7%.
The fatality rate was 0.32% making ADRs the 4th leading cause of death in the US.
Bond et al. Pharmacotherapy 2006

6.5% of UK hospital admissions were found to be medication-related.
Pirmohamed et al. BMJ 2004

5% of hospitalized patients in the EU will experience an ADR causing 197,000 deaths annually throughout the EU.
European Commission 2008

Hospital-acquired ADRs cost £380 million per year in the UK.
Wiffen et al Bandolier Extra 2002

The overall cost of hospitalized patient with an ADR was $2,461 per patient in the US equivalent to 19.86% additional increase in the cost of total care.
Bond et al. Pharmacotherapy 2006

35-46% of ADRs are preventable
Kahn European Journal of Clinical Pharmacology 2013

The NZQHS reported that 12.9% of public hospital admissions were associated with an adverse event, a rate that is similar to those recorded for Australia (16.6%) and the United Kingdom (10.8%) in comparable studies. Half of the events in this New Zealand study were shown to be preventable and occurred inside hospital, and, of these, 7.5% were associated with pharmacological treatment and 10.7% with therapy-related incidents.

Clinical scenario: Unexplained loss of consciousness

An 87 year old NZ European woman suffers an intracerebral haemorrhage as an adverse effect of warfarin.

What aspects of this case made an ADR more likely?

How could this have been prevented?


Certain drugs are more common causes of ADRs


Drug Classes
Cardiovascular
ticlopidine
Adrenal corticosteroids
Aminoglycosides and aminoglycoside antibiotics
Opioids and related narcotics
Anticoagulants
Cardiovascular, heart disease
Cardiac drugs (other)
Diphenoxylate
Antihypertensive
Congestive heart failure
Cardiac Drugs
Volume depletion disorder
Adrenocortical, heart disease
Captopril
Dipyridamole
Hyponatremia
Hypersensitivity, leucopenia
Carbohydrate disorder (other)
Respiratory failure

Figure 1: Drug classes and diagnosis associated with a high risk of adverse drug reactions.

Three of the most commonly implicated drug classes in ADR are anticoagulants, opioids, and insulin.
Certain patients are at higher risk:

- Younger children, older adults
- Individuals with multiple comorbidities (particularly renal impairment)
- Polypharmacy
- Women
- Race and genetic polymorphism

Children are at higher risk because of the need to tailor doses to age, weight, or body mass index.

Older adult patients are vulnerable due to their multiple comorbidities, diminished physiologic reserve, and more frequent use of multiple drugs.

Patients with impaired renal or hepatic function are at substantially increased risk of developing ADRs to drugs metabolized and eliminated by these organs.

The incidence of ADRs has been known to increase sharply with the number of drugs taken.

Women in comparison to men have lower bodyweight and organ size, more body fat.

Inherited factors that affect the pharmacokinetics of drugs can also predispose to an individual’s risk of ADRs. E.g. increased incidence of ADRs due to isoniazid and other cytochrome P450 metabolized drugs in poor metabolizers.

How can we prevent ADRs?

Doctor-based strategies

- Avoid and be vigilant of high-risk drugs
- Discontinue unnecessary drugs
- Consider drugs as a cause of any new symptom
- Avoid treating side effects with another drug
- Avoid drug-drug interactions
- Adjust dosing based on age and creatinine clearance

Systems based strategies

- Computerised order entry
- Electronic medication administration record
- Bar coding
- Smart pumps
- Pharmacist interventions
- Medication reconciliation
- Educational programs (modest effect)
- Accurate allergy list (stored in one place)

Computerized physician order entry — Computerised physician order entry (CPOE) refers to a variety of computer-based systems that facilitate the medication ordering process:

- Providing a means for standardization of practice
- Improving the completeness and legibility of orders
- Alerting clinicians to drug allergies, drug-drug interactions, and cumulative dose-limits
- Updating clinicians with the most current medication information
- Providing dosage adjustment calculations based on patient characteristics
- Timely communication of critical changes in a patient’s condition, in turn facilitating appropriate adjustments

Medication reconciliation — Medication reconciliation is a process that identifies medication discrepancies, informs prescribing decisions, and prevents medication errors that could harm patients. The process of medication reconciliation has three steps:

- Verification — reviewing the patient’s medication use history and developing an accurate list of medications
- Clarification — ensuring that the medications and doses are appropriate and using the current list when writing medication orders
• Reconciliation — identifying any discrepancies between medication ordered for patients and those on the list, making appropriate changes to the orders, documenting any changes, and communicating the updated list to the next provider within or outside the hospital.

Clinical scenario Obesity

A 42 year old NZ European woman comes for a follow-up GP visit because she recently had blood tests that have shown abnormal liver function. She is obese and complains of irregular periods and fatigue for a few months. She feels her mood is low. Her blood pressure is 156/94 mmHg and there is glucose in her urine.

It has previously been recommended that she take metformin, but she is worried about side-effects and asks you whether they are likely to be a problem.

How would you find out?
Knowledge of ADRs comes from:

- Drug development and clinical studies
  - Phase 1 - 4 clinical studies
  - Case reports and series, case-control studies
- Surveillance
  - Post-marketing surveillance
  - Prescription event monitoring

Post-marketing surveillance, also known as pharmacovigilance, is the process of identifying, reporting, and responding to risk-benefit issues arising with marketed medicines.
A note of caution…

- A NZ study found that:
  - Too many ADRs were listed (median 50 per drug)
  - The number of ADRs varied between source
  - There was a substantial overlap between commonly experienced symptoms and frequently listed ADRs

- They recommended:
  - an emphasis on data from randomised trials
  - provision of estimates of absolute risk
  - discussion of the nocebo phenomenon,
  - positive framing of information

A 30 year old NZ European man comes in to the Emergency Department with a widespread itchy rash that has been present for several days. This morning he also woke up with swollen eyelids and lips.

He tells you that he recently injured his knee and his GP prescribed Diclofenac. He started taking this a few days ago.

How can you tell if this is an ADR? What should you do?

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Clinical scenario facial swelling and itchy rash

- Always consider the possibility that a drug may be associated with worsening of a patient’s condition or with a new medical problem.
- Investigate whether that particular drug is known to cause such a reaction
- Rule out alternative explanations
- Establish a temporal link between the onset of the reaction and drug administration
- If unsure, you can use a probability assessment tool, such as the Naranjo probability scale

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Table: The Naranjo Algorithm

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Was the adverse event present before the suspected drug was administered?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>2</td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>2</td>
</tr>
<tr>
<td>3. Did the adverse event improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>1</td>
</tr>
<tr>
<td>4. Did the adverse event improve when a specific antagonist was administered?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>1</td>
</tr>
<tr>
<td>5. Are there alternative causes other than the drug that could be that can have caused the reaction?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>1</td>
</tr>
<tr>
<td>6. Did the reaction improve when a specific antagonist was given?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>1</td>
</tr>
<tr>
<td>7. Was the drug detected in the blood or other fluids or concentrations lower at the time?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>1</td>
</tr>
<tr>
<td>8. Was the adverse event observed by any objective examiner?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>1</td>
</tr>
<tr>
<td>9. Was the reaction worsened when the dose was increased, unless the dose was increased?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>1</td>
</tr>
<tr>
<td>10. Did the patient have a similar reaction to the same or similar drugs in the previous exposure?</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>1</td>
</tr>
</tbody>
</table>

What to do when you suspect an ADR

- Withdraw the trigger medicine
- Record the suspected ADR in the drug chart
- Inform the patient, care giver and family doctor
- Complete a CARM adverse drug reactions form.

CARM Reporting

- Adverse drug reaction only has to be suspected
- You do not need to have evidence of association or cause

- Health professionals
- Pharmaceutical companies
- Consumers (but where possible an attempt is made to involve the patient’s practitioner)

- Record patient details, details of medicine and of the event
- Yellow form on ward
- Download from both the CARM and Medsafe web sites
- Return by email, post or fax.

https://nzhvc.otago.ac.nz/carm
Some strategies for avoiding ADRs

- Do not give a drug unless absolutely indicated.
- Whenever possible use a familiar drug. Look out for possible adverse reactions when prescribing new medication.
- Prescribe as few drugs as possible and give very clear instructions on taking it.
- Assess if the patient is already taking any other medication, including OTC, herbal medication and supplements.
- Ask if the patient has had previous reactions before prescribing any medication.
- Age, renal and hepatic disease may alter drug metabolism, so that smaller doses are required.
- Warn the patient of common side effects of a medication, and potential ADRs.