MODULE 2

Recognising Adverse Drug Reactions (ADRs) in Clinical Practice

This is a joined presentation between
NPC and SAHPRA

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health
Department:
Health
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SAHPRA
South African
Health Products
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Objectives

- Explain the different ways in which ADRs can be classified
- Explain how to recognize an ADR in a patient
- Identify special situations where there maybe increased or unique risk of ADRs
- How to prevent ADRs!
- Know your role as healthcare professionals in pharmacovigilance

Why do ADRs occur?

- The effects of any medical intervention cannot be predicted with absolute certainty.
- There is no medicine or medical intervention that will not have some negative and undesirable effect on someone, somewhere at some time.
- Medicines by their chemical nature produce pharmacological effects and induce physiological changes.
- People respond differently to medicine due to inter-individual variation (idiosyncrasy).

Objective 1

- Explain the different ways in which ADRs can be classified

Classification of ADRs

1. By the organ or part of the body affected
   e.g., skin rash or kidney failure
2. By the seriousness of the reaction
   e.g., hospitalization, death, disability, congenital anomaly, etc.
3. By level of severity
   e.g., mild, moderate or severe headache
4. By the mechanism of the reaction
   e.g., overdose, withdrawal, allergic predisposition, etc.
5. By whether or not the ADR was preventable
   e.g., medication errors

Now – we will go into a bit more detail about some of these ….

1. Classification by Organ System

- Most product information and patient information leaflets list adverse effects by the organ system that is affected
  - e.g. Central Nervous System, Respiratory, Gastrointestinal etc.
- These effects are categorized by how frequently they may occur based on available evidence

Term	Rate	Percentage
Very common (Very Frequent)	>1 in 10	>=10%
Common (Frequent)	1 in 10 – 1 in 100	1 – 10%
Uncommon (Less Frequent)	1 in 100 – 1 in 1000	0.1% to 1%
Rare	1 in 1000 – 1 in 10 000	0.01% to 0.1%
Very rare	<1 in 10 000	< 0.01%

- Some ADRs present as a group of signs and symptoms affecting >1 organ system
  - e.g. serotonin syndrome reported with some antidepressants presents with high blood pressure, agitation, muscle rigidity and fever

1. Classification by Organ System

Organ System

Frequency of side effects

SIDE-EFFECTS:

The following side-effects may occur with the use of [redacted]

Infections and infestations:
Less frequent: Oropharyngeal candidiasis.

Immune system disorders:
Less frequent: Immediate or delayed hypersensitivity reactions, such as angioedema.

Respiratory, thoracic and mediastinal disorders:
Less frequent: Paradoxical bronchospasm (immediately after dosing), cough after inhalation, hoarseness.

Gastrointestinal disorders:
Less frequent: Unpleasant (bad) taste.

Skin and subcutaneous tissue disorders:
Less frequent: Eczema and rash.

General disorders and administrative site conditions:
Less frequent: Application site reactions, including inflammation, irritation, burning and application site dryness.

[redacted] may cause systemic corticosteroid effects, especially when used at [redacted] for extended periods (see "WARNINGS AND SPECIAL

2. Classification by seriousness of the reaction

A serious adverse event or adverse drug reaction is any untoward medical occurrence associated with the use of a medical product in a patient that at any dose, the patient outcome is one of the following:

Death

Life threatening

Hospitalization / prolongation of existing hospitalization

Persistent or significant disability

Congenital anomaly/ birth defects

Medically important event or reaction

e.g., seizure

Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. EMA 1995

3. Classification by severity of the reaction

- The term “severe’’ is used to describe the intensity (severity) of a specific ADR (as in mild, moderate or severe);
- The ADR itself, however, may be of relatively minor medical significance
  - A severe headache can be non-serious
  - A mild heart attack is serious

4. Classification by mechanism of the reaction

- Type A – Dose related
  - E.g., Peripheral neuropathy with isoniazid
- Type B – Non dose related
  - E.g., Ototoxicity from aminoglycoside
- Type C – Dose & time related (cumulative)
  - Myelosuppression caused by linezolid
- Type D – Time related (onset is late)
  - E.g., Optic neuritis by ethambutol/linezolid
- Type E – Withdrawal
  - E.g., Anxiety/insomnia on benzodiazepine
- Type F - Unexpected failure of therapy
  - E.g., Virological failure/bacterial resistance

4. Classification by mechanism of the reaction cont'd…

Type A (Augmented) Predictable

- Expected based on the pharmacology of the drug
- Dose-related
- More common
- More preventable
- Includes toxic effects, long term effects and withdrawal effects
- e.g., Hypotension with BP medicine

Type B (Bizarre) Unpredictable

- Unexpected
- Non-dose-related
- Less common, genetic predisposition
- Less preventable
- May be more serious – require withdrawal
- Includes allergic reactions
- e.g., Rash with antibiotics

Examples of events on classification by mechanism

- Anaphylactic shock an hours after penicillin administration
  - Type B
- Osteoporosis with corticosteroids use
  - Type A
- Angioedema with enalapril
  - Type B
- Kidney failure following long exposure to Ibuprofen use
  - Type A
- Opioid addiction with Codeine
  - Type A

5. Classification by preventability of the reaction

Preventable ADRs are also referred to “Medication Errors”

- Prescribing errors
  - e.g., Inappropriate medicine for patient’s condition, age, weight, etc.
  - Previous allergy or contraindication
  - Known antidote or treatment not given
- Dispensing errors
  - Dispensing wrong medication, dosage strength or dosage form
  - Dose miscalculation
  - Failure to identify drug-interactions and contraindications
  - Poor counselling on ways to avoid or minimize ADR
- Medicine preparation errors
  - Not diluting or incorrect diluent used
- Administration error
  - Poor adherence
  - Given with interacting medicine or food
  - Wrong route of administration. (e.g., IV instead of SC)
- Monitoring errors
  - Not performing relevant monitoring where required

NOTE: Not all Medication errors may result in an ADR! However, all medication errors, should be reported.

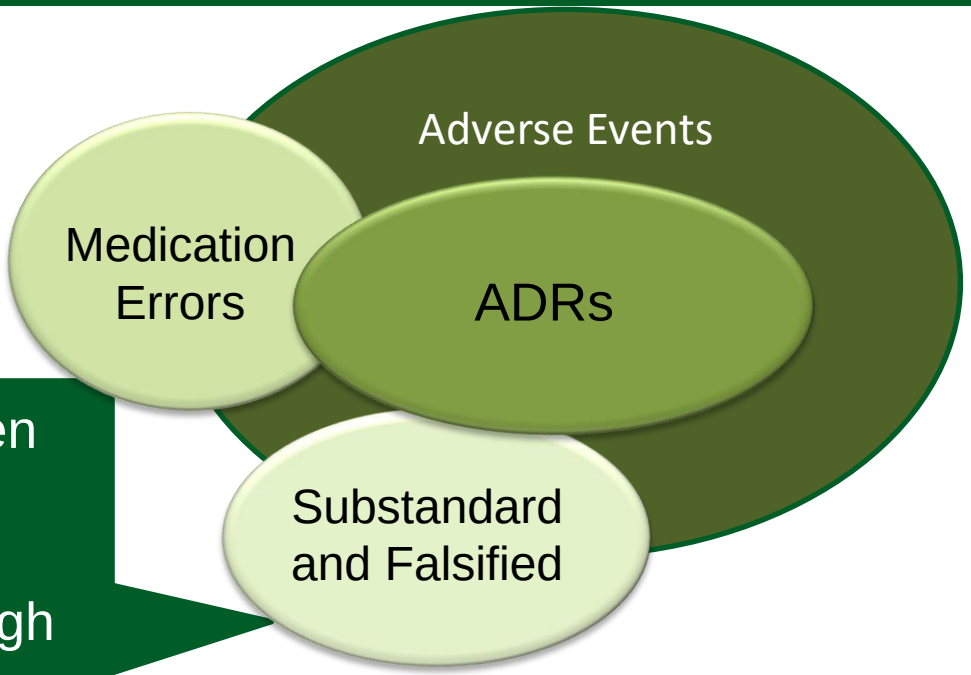
Examples of events on preventability

- Hypoglycemia with insulin
  - **Preventable – inadequate monitoring**
- Fatal liver failure with paracetamol
  - **Preventable – overdose, delayed access to antidote (n-acetyl-cysteine)**
- Bleeding in patient on warfarin and alcohol
  - **Preventable – interaction, monitoring of INR**
- Anaphylaxis with Amoxicillin without prior exposure to B-Lactam antibiotics
  - **Not preventable**
- Pregnancy with oral contraceptives and rifampicin
  - **Preventable – drug interaction**

Product Quality and Formulation Issues

- A medicine is considered to be poor quality when it **does not meet established standards** in terms of **identity**, **purity**, **bioavailability** of the active pharmaceutical ingredient and **appropriate packaging** and **labeling** of the finished product.
- **'substandard'** medical products – authorised medicines that fail to meet their quality standards or specifications
- **'falsified'** medical products – products deliberately/fraudulently misrepresent their identity, composition or source
- Switching between different product brands can also affect the risk of an ADR - especially medicines with a narrow therapeutic index (e.g., warfarin)

Relation between Product Quality Issues, ADRs & Medication Errors



2022: 70 children died in The Gambia from adulterated cough mixture

Objective 2

Explain how to recognize an ADR in a patient

Steps to recognise ADRs!

- Verify that the suspected medicine was actually consumed.
- Verify that the onset of the suspected ADR was after the medicine was taken.
- Consider whether the event is pharmacologically plausible.
- Evaluate the suspected ADR after discontinuing/reducing the dose of the suspected medicine.
- Consider the possibility of a drug interaction with contraceptives, herbal/traditional medicines, drugs of abuse, alcohol, long term medicines, polypharmacy, etc.
- Consider alternative factors e.g. comorbidies, concomitant medicines, etc.
- Use relevant up-to-date literature and personal experience on medicines and their ADRs.

How to recognise ADRs?

- Listen carefully to patient complaints of new signs or symptoms.
- Ask the patient questions pertaining to their treatment and how they feel.
- Assess adherence to treatment (non-adherence may be due to intolerance to ADR or errors).
- Consider possibility of a medicine-related cause if there is new signs and symptoms, new medicines added or changed treatment.
- Obtain a complete medical history and do proper examination of the patient
  - new signs and symptoms.
  - new treatments including over-the-counter and Complementary, African and Traditional Medicines (CATM).

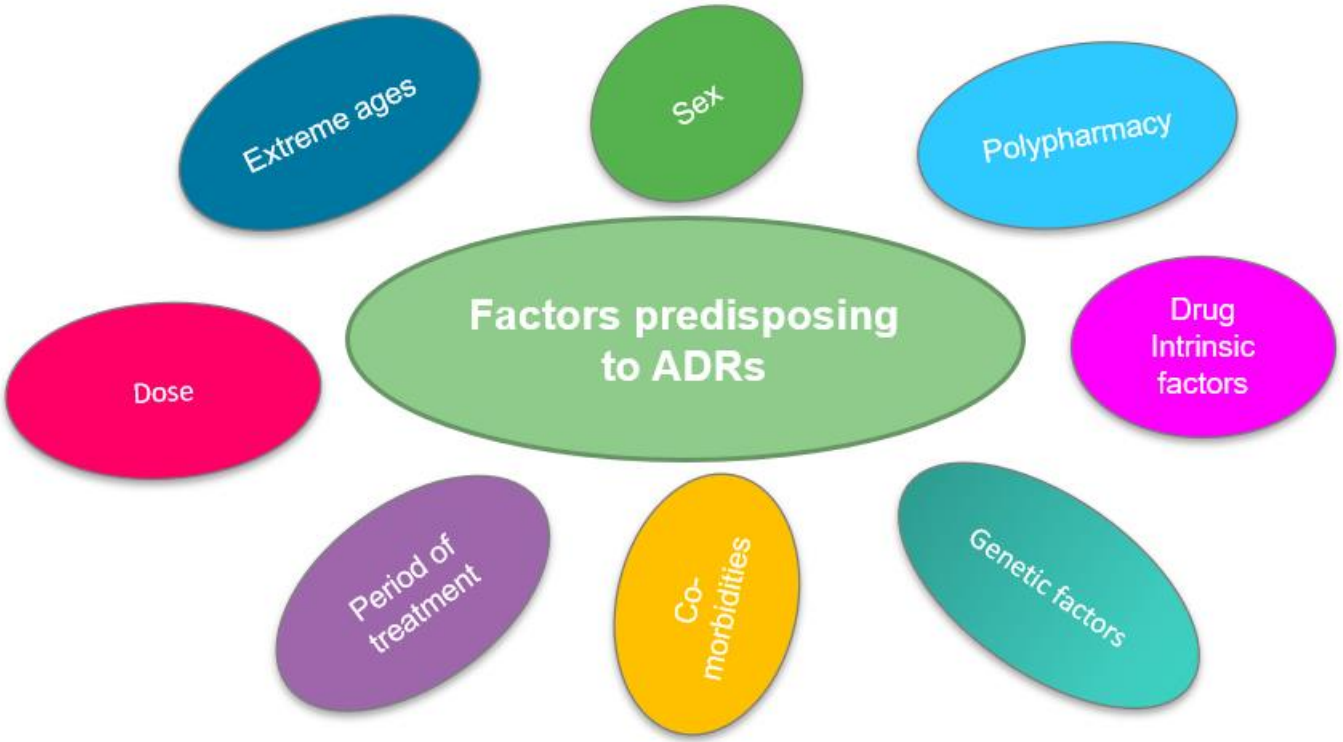
Points to remember about recognising ADRs

- ADRs may present as:
  - A new sign or symptom
  - Abnormal laboratory test finding
  - Abnormality detected on imaging (e.g., CT scans, MRI,…),
  - Abnormal clinical measurements (e.g., temperature, pulse, BP, blood glucose, body weight).
- Not all ADRs may be adequately reflected in the product information and Patient Information Leaflet!

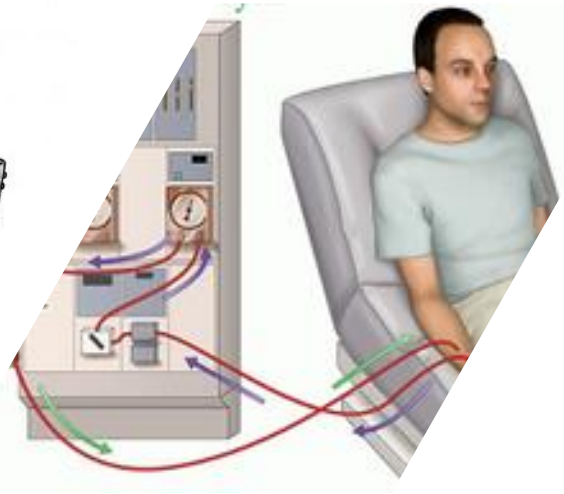
Objective 3

- Identify special situations where there maybe increased or unique risk of ADRs

Major factors predisposing to ADRs



Increased vigilance in special population



Some patient groups need special attention

1) Pregnant and breastfeeding women
2) Children
3) Elderly
4) Immune compromised people e.g, HIV, tuberculosis and/or cancer
5) Patients with compromised organ function
6) Patients with impaired cognition

Why the need for enhanced monitoring in special populations?

- Data on safety from clinical trials may be more limited in these groups.
- Use in practice may differ compared to general population
  - E.g., polypharmacy, inadvertent exposures or off label use
- May be more susceptible to risk of harm.
- Normally require specialised dosing, formulation and preparation.
- Perception and tolerability of risk may differ from general population.

Objective 4

How to prevent ADRs!

Preventability of ADRs

- Good prescribing practice
- Good dispensing practice
- Education and training of healthcare professionals
- Monitoring and reporting of ADRs

Preventability of ADRs

- Good prescribing practice
  - Be clear about the reasons for prescribing
  - Take into account the patient's medication history before prescribing
  - Take into account other factors that might alter the benefits and risks of treatment
  - Write unambiguous legal prescriptions
  - Monitor the beneficial and adverse effects of medicines
  - Adhere to national guidelines & local formularies where appropriate
  - Prescribe within the limitations of your knowledge, skills and experience.
  - Communicate and document prescribing decisions and reasons

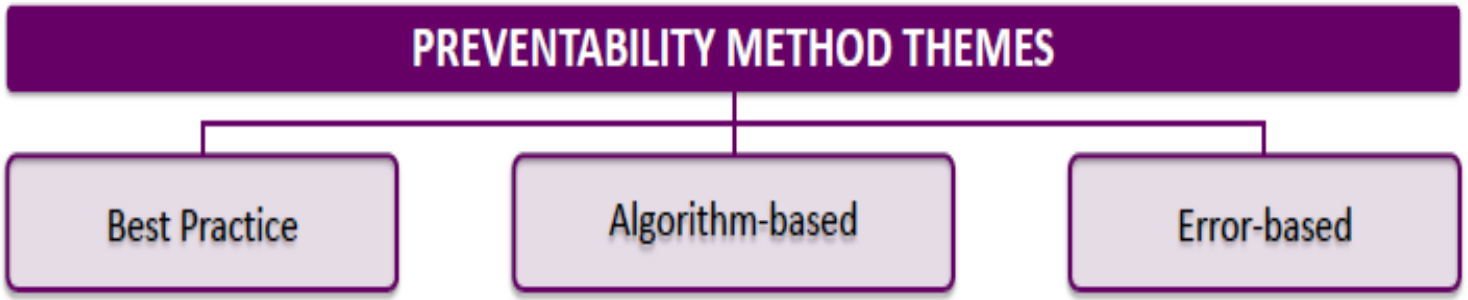
Preventability of ADRs

- Good dispensing practice
  - Delivery of the right medicines of desired quality to the right patient with the right dose, strength, frequency, dosage form and quality.
  - 3 phases of dispensing
    - Receive and validate a prescription
    - Filling a prescription
    - Issuing & counselling
- Education and training of healthcare professionals
- Monitoring and reporting of ADRs

Preventability Assessment

Assessment of the likelihood that an adverse event may have been prevented based on the appropriateness of therapy

✓Right patient ✓Right drug ✓Right dose ✓Right route ✓Right time



Preventability Assessment

ALGORITHM-BASED: SCHUMOCK & THORNTON SCALE

Answering "YES" to any question suggests that the ADR may have been preventable

Assessment Criteria	Preventable?	
1. Was there a history of allergy or previous reactions to the drug?	YES	No /?
2. Was the drug involved in the ADR inappropriate for the patient's clinical condition?	YES	No /?
3. Was the dose, route and frequency of administration not appropriate for the patient's age, weight and disease state?	YES	No /?
4. Was there a known treatment for the adverse drug reaction?	YES	No /?
5. Was a drug interaction involved in the ADR?	YES	No /?
6. Was a toxic serum drug level (or laboratory monitoring test) documented?	YES	No /?
7. Was required therapeutic drug monitoring or other necessary laboratory test(s) not performed?	YES	No /?

Source: Shajahan J, Parathoduvil AA, Purushothaman S. Int J Basic Clin Pharmacol, 7(12), 2433-2438.
Reference: Schumock GT, Thornton JP. Hosp Pharm. 1992 Jun;27(6):538.

Objective 5

Know your role as healthcare professionals in pharmacovigilance

The Role of HCPs in Pharmacovigilance

- Detection
- Assessment
- Understanding
- Prevention

The role HCPs in pharmacovigilance?

- Recognise ADRs
- Understanding medicines benefits and their risk of ADRs (or where to find this information)
- Counsel and support patients
  - on self-limiting ADRs to expect
  - when to seek help when a new ADR occurs
  - How to take medicines and monitor health outcomes to avoid certain ADRs
- Report suspected ADRs to SAHPRA
- Monitor patients for possible or increased risk of ADRs
- Rational and careful prescribing, preparation, dispensing and administration to avoid ADRs
- Manage or refer patients when ADR occurs

Any Questions?