

Adverse Drug Reactions

Adverse Drug Reactions

Definitions:

- The WHO defines an adverse drug reaction (ADR) as “ a response to a drug that is **noxious** and **unintended** and occurs **at doses normally used in man** for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”.

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- The use of the phrase **'at doses normally used in man'** distinguishes the noxious effect during normal medical use **from** the **toxic effect caused by poisoning** (over dose).
- There is no need to prove a pharmacological mechanism for any noxious response to be termed as ADR.

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- The term “side effect” is distinct from ADR.
- A side effect is an unintended effect of a drug related to its pharmacological properties and can include unexpected benefits of treatment.

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- The WHO definition has been criticized for **excluding** the potential for **contamination** of the product (dosage form) and ADRs associated with pharmacologically inactive **excipients** in the product.
- The use of the term drug also **excluded the use of complementary and alternative treatments such as herbal products.**

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- In an attempt to overcome these issues, the following definition of ADR was proposed:
“A harmful or unpleasant reaction, resulting from the intervention **related to the use of a medicinal product**, which:
 1. predicts hazard for future administration.
 2. warrants prevention or specific treatment.
 3. requires alteration of dosage regime.
 4. requires withdrawal of the product.

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- It is also important to avoid confusion with the term **“adverse drug event (ADE)”**.
- **ADE is an adverse outcome that occurs after the use of the drug, but which may or may not be linked to this use.**
- **Therefore, all ADRs are ADEs, but not all ADEs will be ADRs.**

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- ADE can be used when it is NOT possible to suggest a causal link between a drug treatment and an adverse outcome.
- The suspicion of a causal relationship between the drug and the adverse effect is central to the definition of an ADR.

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Epidemiology of ADRs:

1. ADRs are responsible for 2.6% - 6.5% of admissions to hospitals.
2. 3.5-14.7% of inpatients develop ADRs.
3. 2.3% of patients die as a result of ADRs.
4. In primary care, estimates of the incidence of ADRs range from 25-30%.
5. ADRs are the 4th - 6th leading cause of death in USA.

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- **Stay in hospital for patients having ADR was ~ 20 days compared to ~ 8 days without ADRs, leading to escalation of cost.**

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Classification of ADRs:

- Are useful for avoidance and management of ADRs.

A. Rawlins-Thompson classification: defined by the properties of the drug and the ADR.

1. **Type A: normal but exaggerated (augmented) pharmacological effects of the drug. Predictable, dose-dependent, common (80% of all ADRs), preventable.**

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- 2. Type B: abnormal (bizzare) effects not related to the pharmacological effects of the drug, such as hepatotoxicity of isoniazid, and allergic reactions. More serious, could be fatal, often discovered after marketing of the drug. Unpredictable.**
- 3. Other types: see table.**

Table 5.1 Extended Rawlins–Thompson classification of adverse drug reactions

Type of reaction	Features	Examples
<i>Type A:</i> Augmented pharmacological effect	Common Predictable effect Dose-dependent Low morbidity Low mortality	Bradycardia associated with a beta-adrenergic receptor antagonist
<i>Type B:</i> Bizarre effects not related to pharmacological effect	Uncommon Unpredictable Not dose-dependent High morbidity High mortality	Anaphylaxis associated with a penicillin antibiotic
<i>Type C:</i> Dose-related and time-related	Uncommon Related to the cumulative dose	Hypothalamic pituitary–adrenal axis suppression by corticosteroids
<i>Type D:</i> Time-related	Uncommon Usually dose-related Occurs or becomes apparent some time after use of the drug	Carcinogenesis
<i>Type E:</i> Withdrawal	Uncommon Occurs soon after withdrawal of the drug	Opiate withdrawal syndrome
<i>Type F:</i> Unexpected failure of therapy	Common Dose-related Often cause by drug interactions	Failure of oral contraceptive in presence of enzyme inducer

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- B. The DoTS system:** It is based on **D**ose relatedness, **T**iming and patient **S**usceptibility:
- Examines the various factors that both describe the reaction and influence an individual patient susceptibility.
 - It first considers the dose of the drug (ADRs are dose-related).
 - Reactions are divided into:

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1. **Toxic effects:** Effects related to the use of the drug outside their usual therapeutic dosage.
2. **Collateral effects:** Effects occurring within the normal therapeutic use of the drug. They include reactions not related to the expected pharmacological effect of the drug or off-target reactions of the expected therapeutic effect in other body systems.

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- 3. Hyper-susceptibility reactions: Reactions occurring in sub-therapeutic doses in susceptible patients.**
 - The time course of a drug's presence at the site of action can influence the occurrence of ADR.**
 - a. Rapid infusion of furosemide is associated with transient hearing loss and tinnitus.**
 - b. A constant low dose of methotrexate is more toxic than equivalent intermittent bolus doses.**

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- **DoTS categorizes ADRs as:**
 - 1. Time-dependent reactions. Range from rapid and immediate reactions, to those that can be delayed.**
 - 2. Time-independent reactions. Occur at any time within the treatment period, regardless of the length of course.**
- **The last factor in DoTS is susceptibility which include factors like genetic predisposition, age, sex, altered physiology, disease, and drug interactions.**

Table 5.2 DoTS system of ADR classification

Dose relatedness	Time relatedness	Susceptibility
<p><i>Toxic effects:</i> ADRs that occur at doses higher than the usual therapeutic dose</p>	<p><i>Time-independent reactions:</i> ADRs that occur at any time during treatment.</p>	<p>Raised susceptibility may be present in some individuals, but not others.</p>
<p><i>Collateral effects:</i> ADRs that occur at standard therapeutic doses</p>	<p><i>Time-dependent reactions: Rapid reactions</i> occur when a drug is administered too rapidly.</p>	<p>Alternatively, susceptibility may follow a continuous distribution – increasing susceptibility with impaired renal function.</p>
<p><i>Hypersusceptibility reactions:</i> ADRs that occur at sub-therapeutic doses in susceptible patients</p>	<p><i>Early reactions</i> occur early in treatment then abate with continuing treatment (tolerance).</p>	<p><i>Factors include:</i> genetic variation, age, sex, altered physiology, exogenous factors (interactions) and disease.</p>
	<p><i>Intermediate reactions</i> occur after some delay, but if reaction does not occur after a certain time, little or no risk exists.</p>	
	<p><i>Late reactions</i> risk of ADR increases with continued-to-repeated exposure, including withdrawal reactions.</p>	
	<p><i>Delayed reactions</i> occur some time after exposure, even if the drug is withdrawn before the ADR occurs.</p>	

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Factors affecting susceptibility to ADRs:

1. Age:

Elderly patients:

- are more prone to ADRs because of age-related decline in both metabolism and elimination of drugs from the body. They also have multiple co-morbidities and thus more prescribed drugs.

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Children:

- 1. Differ from adults in drug response.**
- 2. Neonatal differences in body composition, metabolism, and other physiological parameters increase the risk of specific ADRs.**
- 3. Higher body water content can increase the volume of distribution of water soluble drugs.**
- 4. Reduced albumin may be associated of high free concentrations of highly protein-bound drugs.**

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5. **Immature blood-brain barrier can increase sensitivity to morphine and other drugs.**
 - **Differences in drug metabolism and elimination and end-organ responses can increase risk.**
 - **Chloramphenicol, digoxin, and ototoxic antibiotics have higher risks of toxicity in the first weeks of life.**

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Older children and young adults:

- are more susceptible to some ADRs:
 1. Increased risk of extrapyramidal effects associated with metoclopramide.
 2. Use of aspirin is restricted under age of 12 ys because of association with Reye's syndrome.
 3. Heightened probability of dosing errors and the relative lack of evidence for both safety and efficacy put children at high risk.

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2. Gender:

- **Women may be more susceptible to ADRs.**
- **Some ADRs are more common in women than men:**
 - 1) **Impairment of concentration and psychiatric adverse events associated with anti-malarial agent mefloquine.**
 - 2) **Drug-induced *torsade de pointes*, may be because of their longer QTc interval compared to men.**

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3. Co-morbidities and concomitant drug use:

- Reduction in hepatic and renal functions increase the risk of ADRs.
- Co-morbidities such as congestive heart failure, diabetes, and peripheral vascular, chronic pulmonary, rheumatological, hepatic, renal, and malignant diseases were strong predictors of readmissions for ADRs.
- This might be due to pharmacokinetic or pharmacodynamic changes in these diseases, or drug interactions due to multiple therapy.

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4. Ethnicity:

- This is related to ADRs due to inherited traits of metabolism, and environmental factors.
- There is increased risk of angioedema with the use of ACE-inhibitors in Africans.
- Increased susceptibility of whites and blacks to CNS adverse effects of mefloquine compared to Chinese and Japanese.
- Increased risk of myopathy after rosuvastatin in Asians.

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5. Pharmacogenetics:

- discussed before.
- Read it again – **Required.**

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Immunological Reactions:

- The immune system is able to recognize drugs as foreign leading to allergic reactions.
- Small molecules can bind to proteins to trigger an immune response, and larger molecules can trigger an immune response directly.
- The immune response is not related to the pharmacological action of the drug.
- Prior exposure to the drug is required.

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- **Allergic reactions range from rashes, serum sickness and angioedema to life-threatening bronchospasm and anaphylaxis.**
- **Patients with a history of atopic or allergic disorders are at higher risk.**
- **Types of immunological reaction: see following table.**

Table 5.3 Classification of immunological (hypersensitivity) reactions

Classification	Mechanism	Symptoms/signs and examples
Type I (immediate)	Drug/IgE complex to mast cells release of histamine and leukotrienes.	Pruritis, urticaria, bronchoconstriction, angioedema, hypotension, shock, for example, penicillin anaphylaxis.
Type II (cytotoxic)	IgG and complement binding to (usually) red blood cell. Cytotoxic T-cells lyse the cell.	Haemolytic anaemia and thrombocytopenia, for example, associated with cephalosporins, penicillins and rifampicin.
Type III (immune complex)	Drug antigen and IgG or IgM form immune complex, attracting macrophages and complement activation.	Cutaneous vasculitis, serum sickness, for example, associated with chlorpromazine and sulphonamides.
Type IV (delayed type)	Antigen presentation with major histocompatibility complex protein to T-cells and cytokine and inflammatory mediator release.	Usually occur after 7–20 days. Macular rashes and organ failure, including Stevens–Johnson syndrome and toxic epidermal necrolysis, for example, associated with neomycin and sulphonamides.

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Formulation Issues Contributing to ADRs.

- Rare.
- In 2006, cough medicines made using glycerin contaminated with diethylene glycol, (from China), were responsible for deaths in Panama due to diethylene glycol poisoning.
- Episodes of diethylene glycol poisoning have been reported in Nigeria, India, Argentina and Haiti.

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- **Osmosin was a slow-release preparation of indomethacin which uses an osmotic pump to deliver the drug. It caused 36 fatal cases of gastrointestinal bleedings, caused by tablets lodged against the mucosa of GIT, exposing it to high local concentrations of indomethacin.**
- **Change of the excipient in a phenytoin formulation lead to development of severe ADR including coma in previously stable patients.**

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- **In that case, calcium phosphate dihydrate was replaced with lactose. The first slows phenytoin absorption, while lactose increased it.**
- **Although excipients are considered inert substances, serious adverse reactions such as anaphylaxis and angioedema have been reported.**
- **Sweeteners, flavours, coloring agents, and preservatives have all been associated with ADRs.**

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Pharmacovigilance and Methods of ADR

Detection:

- Pharmacovigilance is **defined** as “the study of the safety of marketed drugs under the practical conditions of clinical use in large communities”.

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- **Pharmacovigilance is concerned with the detection, assessment and prevention of ADRs and other drug-related problems, in order to achieve rational and safe therapeutic decisions in clinical practice.**

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Spontaneous reporting:

- Is one of the main method to collect data about ADRs, by people who make a connection between a drug and a suspected drug-induced event.
- It requires only a suspicion of a causal link between the drug the adverse event.
- Spontaneous reports should contain variable levels of information. Because re-challenge with the drug is un-ethical, few reports contain such information.

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Causality Assessment:

- **Causality is very difficult to prove in pharmacovigilance and a high degree of suspicion is all that is needed for “Regulatory Authority” action.**
- **The most common method of causality assessment in use is ‘unstructured clinical assessment’ called ‘global introspection’.**
- **Studies have shown marked disagreement between experts.**

Table 5.4 WHO causality categories for ADRs

Category	Description
Certain	Pharmacologically definitive, with re-challenge if necessary
Probably/likely	Reasonable temporal relationship, unlikely to be attributed to disease processes or other drugs, with reasonable dechallenge response
Possible	Reasonable temporal relationship, but could be explained by concurrent disease or drugs. No information on withdrawal
Unlikely	Temporal relationship improbable, concurrent disease or drugs provide plausible explanation
Conditional/unclassified	An event which requires more data for assessment
Unassessable/ unclassifiable	An event that cannot be judged because of insufficient/contradictory information which cannot be supplemented or verified

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- A more standardized objective method to assess causality that reduce assessor bias is the **“Naranjo algorithm”**.
- It uses a questionnaire, and points are added or subtracted based on responses to each question.
- The total score is then used to place assessment as: definite, probable, possible or doubtful.

Table 1-2. Naranjo ADR Probability Scale

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event appear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that, on their own, could have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

Total Score ADR Probability Classification

9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

Adapted with permission from: Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

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Roles of Health Professionals:

- Health professionals in this context are those who prescribe, supply, administer, monitor or advise on drug use.
1. Their fundamental role is ensuring drugs are used safely.
- All patient factors that predispose to ADRs should be taken into consideration, which include co-morbidities, concomitant drugs, renal and liver functions, and genetic predisposition.

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2. It is invaluable to have information about **patient's history of ADRs**, to avoid inappropriate re-use of drugs which previously have caused ADRs.
3. Documentation of identified ADRs.

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Identifying and assessing ADRs in Clinical Practice:

- **Must take into account the factors listed in the box of the next slide.**

Box 5.1 Factors that may raise or suppress suspicion of a drug-induced event (Shakir, 2004)

The *temporal relationship* between the exposure to the drug and the subsequent event

The *clinical and pathological characteristics of the event* – events which are known to be related to drug use, rather than disease processes

The *pharmacological plausibility* – based on the observer's knowledge of pharmacology

Existing information in published drug information sources – whether or not the event has been noted by others

Concomitant medication – which may be considered the cause of an event

Underlying and concurrent illnesses – may alter the event or be considered the cause of the event

De-challenge – disappearance of symptoms after dose reduction or cessation of therapy

Re-challenge – reappearance of symptoms after dose increases or recommencement of therapy

Patient characteristics and previous medical history – past history of the patient may colour the view of the event

The potential for *drug interactions*

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Preventing ADRs:

- The majority of ADRs are preventable, thus reducing cost and even death. (How?)
 1. Checking previous ADR history.
 2. Minimizing the use of drugs with high risk to develop ADRs.
 3. Tailoring drug selection to individuals based on factors that predispose to ADRs.

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4. Rational prescribing.
5. Improved sharing of information about patients between health-care providers.
6. Monitoring Therapy:
 - Monitoring the effect of drugs by measurement of serum concentration or by measurement of physiological markers is another method of reducing the risk of ADRs.

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- **It has been estimated that 25% of preventable drug-related hospital admissions are caused by failure to monitor renal function and electrolytes.**
- **Clozapine used for management of treatment – resistant schizophrenia is associated of significant risk of agranulocytosis, that can be eliminated by mandatory monitoring of white blood cells.**

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- Advice on monitoring should be clear, provide an **evidence-based frequency of monitoring**, and acceptable outcomes or values.
- 7. Explaining risks to patients:
 - Patients have the right to receive **understandable** information about the potential for ADR, to enable them to make an informed decision

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Definition of serious adverse event:

1. Results in death.
2. Is life-threatening (places the subject at immediate risk of death from the event as it occurred).
3. Results in inpatient hospitalization or prolongation of existing hospitalization.
4. Results in a persistent or significant disability/incapacity.
5. Results in a congenital anomaly/birth defect.

Adverse Events Severity Classification

Rank	Definition
Mild	Causing no limitation of usual activities, the participant may experience slight discomfort
Moderate	Causing some limitation of usual activities, the participant may experience annoying discomfort
Severe	Causing inability to carry out usual activities, the participant may experience intolerable discomfort or pain

Adverse Effect Prevalence

Very common	More than 1/10 of subjects. >10%
Common	More than 1/100 to less than 1/10. >1% - <10%
Uncommon	More than 1/1000 to less than 1/100. >0.1% - <1%
Rare	Less than 1/1000. < 0.1%