"Adverse Drug Effect"

- ADR vs. Side effect ⟹ Both are unintended but noxious ADR related to its pharmacological properties
  - Side effect – Beneficial
- ADR vs. overdose — toxic effect caused by poisoning.
- ADR vs. ADE
  all ADRs are ADEs but not all ADEs are ADRs.

Adverse Drug Reactions

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- Idiosyncratic reactions
  Examples
  - chloramphinecol ⟶ AA (Aplastic Anemia) / Grey baby syndrome (failure of metabolism)
  - Aspirin in <12yo ⟶ Reye's syndrome
  - Isoniazid ⟶ Hepatotoxicity.

Adverse Drug Reactions

There's a problem in this definitions; it didn't talk about:
1- contaminations + exciepients in dosage form
2- complementary and alternatives such as herbs

ADR ? what about ?

Definitions:

"A harmful or unpleasant reaction, resulting from the intervention related to the use of a medicinal product, which:

- **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".**

Adverse Drug Reactions vs. overdose

- 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.

Adverse Drug Reactions

- 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.

+ not necessarily noxious

Adverse Drug Reactions

- 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.

Adverse Drug Reactions

- **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 regimen.**
4. **requires withdrawal of the product.**

Adverse Drug Reactions

- 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.

Adverse Drug Reactions

- **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.**

↑ deaths.
↑ Stays in hospital.

Adverse Drug Reactions

sig. problem!

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.
   death = event.
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.

Adverse Drug Reactions

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

Double and half

Adverse Drug Reactions

A - F

Classification of ADRs:

Study the next slide's table.

- 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.

Low morbidity + mortality. By modifying the dose and monitoring your patient.

↓HR → Bradycardia
↑GI motility → diarrhea
Diuretic → Dehydration

Table 5.1 Extended Rawlins–Thompson classification of adverse drug reactions

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

Adverse Drug Reactions

- Immune rxns. /- idiosyncratic rxns.
- allergies
hemolytic anemia

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.

anti mycobacterium.

# of patients before marketing is ↓↓↓

↑ morbidity and mortality.

uncommon, not-dose dependant

3. Other types: see table.

* Age.
* Gender.
* Comorbidities + drugs #
* Ethnicity..
* pharmacogenetics.

Adverse Drug Reactions

Factors affecting susceptibility to ADRs:

1. **Age:** "Extremities".

Elderly patients: ↑ Doses > Requirements. because of

- 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.

1

2

Adverse Drug Reactions

Children: 1 – 17 y.o

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.**

Adverse Drug Reactions

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.**

Abx for: typhoid fever, cholera, plague, meningitis, eye ointment to treat conjunctivitis

causes Aplastic Anemia (Idiosyncratic)

* Grey baby syndrome → failure of metabolism of chloramphenicol in neonates.

Adverse Drug Reactions

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 years 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.**

Adverse Drug Reactions

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.

polymorphic ventricular tachycardia → V. fib.

could lead to dangerous arrhythmias.

QT interval longer in ♀ > ♂

Adverse Drug Reactions

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.**

Adverse Drug Reactions

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.**

1
2
impaired concentration + psychiatric adverse events.
3
◦ north africa + middle east = Caucasians

Adverse Drug Reactions

5. **Pharmacogenetics:** Genetic reasons affecting drugs actions and ADRs.

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

* whole lecture later on.
+ 3rd topic

Start

Adverse Drug Reactions

Immunological Reactions:

Type B - Bizzarre.

- The immune system is able to recognize drugs as foreign leading to allergic reactions.
- Small molecules can bind (Hapten) 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.

Adverse Drug Reactions

- 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.

All types of immunological reaction may occur with drug use: type I (immediate), type II (cytotoxic), type III (immune complex) and type IV (delayed).

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 thrombocytopaenia, 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.

Adverse Drug Reactions

ADRs related to the drug or not?

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.**

Adverse Drug Reactions

- A more standardized objective method to assess causality that reduce assessor bias is the "Naranjo algorithm". Questionnaire.
- 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.

it's just if there's a pharmacological explanation. ↑ GI motility → Diarrhea

* highly probable

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.

Adverse Drug Reactions

Preventing ADRs:

- **The majority of ADRs are preventable, thus reducing cost and even death. (How?)**

Type A.

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.**

someone that's susciptible to ADR → don't use.

Adverse Drug Reactions

4. **Rational prescribing.** Based on evidence-based medicine.
5. **Improved sharing of information about patients between health-care providers.**
6. **Monitoring Therapy:** * clinical signs and symptoms. + serum conc. + markers. } Differs from one drug to another.

- **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.**

Adverse Drug Reactions

- **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.**

Adverse Drug Reactions

- Advice on monitoring should be clear, provide an evidence-based frequency of monitoring, and acceptable outcomes or values.

7. Explaining risks to patients: ← Yes

- Patients have the right to receive understandable information about the potential for ADR, to enable them to make an informed decision

Adverse Drug Reactions

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.**

even if no death.

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% 1.1 One patient out of 100 patients had the ADR *common
Uncommon	More than 1/1000 to less than 1/100. >0.1% - <1%
Rare	Less than 1/1000. < 0.1%