Fourth: Side effects & Adverse Drug Reactions

A) Classifications and Definitions

1) Definitions

- **A side-effect** is any effect caused by a drug other than the intended therapeutic effect, whether beneficial, neutral or harmful. The term 'side-effect' is often used interchangeably with 'ADR' although the former usually implies an effect that is less harmful, predictable and may not even require discontinuation of therapy (e.g. ankle oedema with vasodilators).

- **An adverse drug outcome** is an unwanted or harmful reaction experienced following the administration of a drug or combination of drugs under normal conditions of use. **Adverse effect** is seen from the point of view of the drug, whereas an **Adverse reaction** is seen from the point of view of the patient. While both can be attributed to some action of a drug, the **Adverse event** is an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it.

- **Drug toxicity** describes adverse effects of a drug that occur because the dose or plasma concentration has risen above the therapeutic range, either unintentionally or intentionally (drug overdose).

- **Drug abuse** is the misuse of recreational or therapeutic drugs that may lead to addiction or dependence, serious physiological injury (such as damage to kidneys, liver, heart), psychological harm (abnormal behavior patterns, hallucinations, memory loss), or death.

2) Side effects classification based on prevalence and incidence

- Very common: more than 1 in 10 people are affected
- Common: between 1 in 10 and 1 in 100 people are affected
- Uncommon: between 1 in 100 and 1 in 1,000 people are affected
- Rare: between 1 in 1,000 and 1 in 10,000 people are affected
- Very rare: fewer than 1 in 10,000 people are affected

3) Standard & Classical classification of Adverse Drug Reactions

They are classified as Type A (intrinsic) or Type B (idiosyncratic).

Type A are predictable, dose-related toxicities, often identified in preclinical or clinical trials, and usually occur in overdose settings or with pre-existing hepatic impairment.

Type B are not clearly related to increasing dose and are associated with drug-specific and patient-specific characteristics and environmental risks. Rare Type B reactions are often identified postmarketing.

4) Adverse Drug reaction according Merck Manual for professionals

Dose-related ADRs are particularly a concern when drugs have a narrow therapeutic index (eg, hemorrhage with oral anticoagulants). ADRs may result from decreased drug clearance in patients with impaired renal or hepatic function or from drug-drug interactions.

Allergic ADRs are not dose-related and require prior exposure. Allergies develop when a drug acts as an antigen or allergen. After a patient is sensitized, subsequent exposure to the drug produces one of several different types of allergic reaction. Clinical history and appropriate skin tests can sometimes help predict allergic ADRs.

Idiosyncratic ADRs are unexpected ADRs that are not dose-related or allergic. They occur in a small percentage of patients given a drug.

Idiosyncrasy (idios, own, synkrasis, mixing together) is an imprecise term that has been defined as a genetically determined abnormal response to a drug, but not all idiosyncratic reactions have a pharmacogenetic cause. The term may become obsolete as specific mechanisms of ADRs become known.

Adverse Drug Reactions Classification

Characteristics	Type A	Type B
Dose dependency	Dose Related	Dose Relationship is unclearly defined
Frequency of Occurrence	Common	Uncommon
Severity of Reaction	Variable but usually mild	Variable, but proportionately more severe
Host factors	Genetic factors might be important	Dependent on host factors
Animal models	Usually reproducible in animals	Unknown in animal models
Percentage proportion of adverse drug reaction	80%	20%
Predictable from known pharmacology	Yes	Not usually
First detection (Clinical Trials)	Phase I - III	Phase IV, occasionally phase III
Clinical burden	High morbidity & Low Mortality	High morbidity & High mortality

5) Classification based on severity of Adverse Drug Reactions (ADRs)

Severity	Description	Example
Mild	No antidote or treatment is required; hospitalization is not prolonged.	Antihistamines (some): Drowsiness, Opioids: Constipation
Moderate	A change in treatment (eg, modified dosage, addition of a drug), but not necessarily discontinuation of the drug, is required; hospitalization may be prolonged, or specific treatment may be required.	Hormonal contraceptives: Venous thrombosis NSAIDs: Hypertension and edema
Severe	An ADR is potentially life threatening and requires discontinuation of the drug and specific treatment of the ADR.	ACE inhibitors: Angioedema Phenothiazines: Abnormal heart rhythm
Lethal	An ADR directly or indirectly contributes to a patient's death.	Acetaminophen overdosage: Liver failure Anticoagulants: Hemorrhage

6) Immunologic and Nonimmunologic Drug Reactions

TYPE	EXAMPLE
Immunologic	
Type I reaction (IgE-mediated)	Anaphylaxis from β-lactam antibiotic
Type II reaction (cytotoxic)	Hemolytic anemia from penicillin
Type III reaction (immune complex)	Serum sickness from anti-thymocyte globulin
Type IV reaction (delayed, cell-mediated)	Contact dermatitis from topical antihistamine
Specific T-cell activation	Morbilliform rash from sulfonamides
Fas/Fas ligand-induced apoptosis	Stevens-Johnson syndrome (Anti-gout medications, such as allopurinol)
	Toxic epidermal necrolysis
Other	Drug-induced, lupus-like syndrome (hydralazine (rate roughly 20%), procainamide (rate roughly 20%, 5-8% if taken for 1 y), quinidine, isoniazid, and minocycline.
Nonimmunologic	
Predictable	
Pharmacologic side effect	Dry mouth from antihistamines
Secondary pharmacologic side effect	Thrush while taking antibiotics
Drug toxicity	Hepatotoxicity from methotrexate
Drug-drug interactions	Seizure from theophylline while taking erythromycin
Drug overdose	Seizure from excessive lidocaine (Xylocaine)
Unpredictable	

TYPE	*EXAMPLE*
Pseudoallergic	Anaphylactoid reaction after radiocontrast media
Idiosyncratic	Hemolytic anemia in a patient with G6PD deficiency after primaquine therapy
Intolerance	Tinnitus after a single, small dose of aspirin

G6PD = glucose-6-phosphate dehydrogenase.

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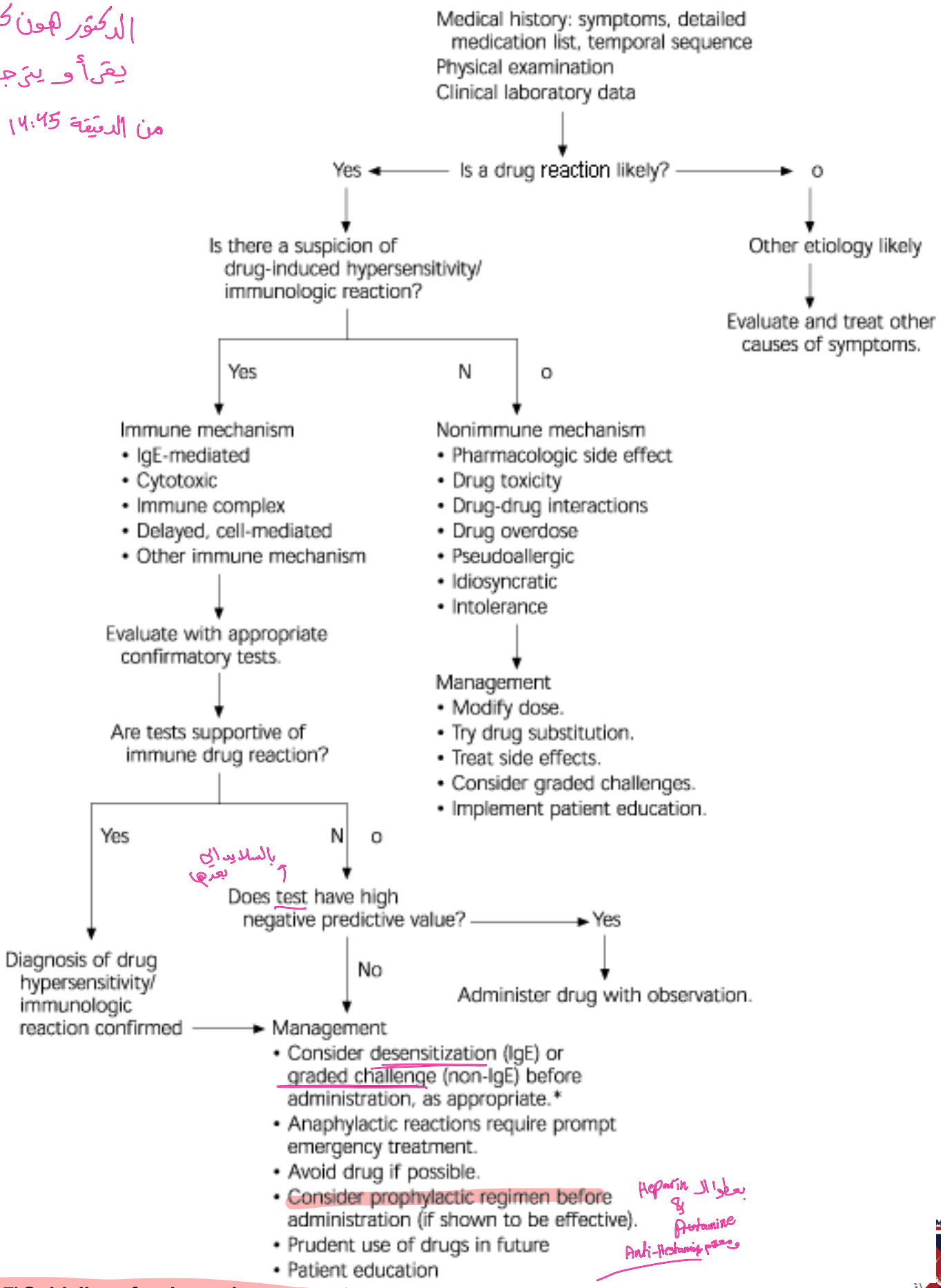


7)Guidelines for drug adverse event

8) Diagnostic Testing and Therapy for Drug Hypersensitivity

IMMUNE REACTION	*LABORATORY TESTS*	*THERAPEUTIC CONSIDERATIONS*
Type I (IgE-mediated)	Skin testing	Discontinue drug.
	RAST	Consider epinephrine, antihistamines, systemic corticosteroids, bronchodilators.
	Serum tryptase	Inpatient monitoring, if severe
Type II (cytotoxic)	Direct or indirect Coombs' test	Discontinue drug.
		Consider systemic corticosteroids.
		Transfusion in severe cases
Type III (immune complex)	ESR	Discontinue drug.
	C-reactive protein	Consider NSAIDs, antihistamines, or systemic corticosteroids; or plasmapheresis if severe.[18]
	Immune complexes	
	Complement studies	
	Antinuclear antibody, antihistone antibody	
	Tissue biopsy for immunofluorescence studies	
Type IV (delayed, cell-mediated)	Patch testing	Discontinue drug.
	Lymphocyte proliferation assay	Consider topical corticosteroids, antihistamines, or systemic corticosteroids if severe.

RAST = radioallergosorbent test; ESR = erythrocyte sedimentation rate

9) Adverse Drug Reactions(ADRs) and Drugs that cause them

Drugs in Jordan The new way to think about Side Effects

Symptoms : What are drugs that their Side effects are related to this symptoms

10) Further reading

Toxic epidermal necrolysis (TEN) is a potentially life-threatening dermatologic disorder characterized by widespread erythema, necrosis, and bullous detachment of the epidermis and mucous membranes, resulting in exfoliation and possible sepsis and/or death. TEN can be induced by drugs or infection or can be idiopathic. Medications are the major precipitating cause. Numerous medications have been implicated

Antibacterial drugs associated with TEN include the following:

• Sulfonamides (4.5 cases per million users per week)

• Chloramphenicol • Macrolides (eg, erythromycin) • Penicillins • Quinolones (eg, ciprofloxacin, trovafloxacin)

Anticonvulsants associated with TEN include the following:

• Phenobarbital • Phenytoin • Carbamazepine • Valproic acid • Lamotrigine

TEN in patients taking anticonvulsants has most often been reported within 2 months of starting the drug. However, some cases associated with long-term use have been reported.

NSAIDs associated with TEN include the following:

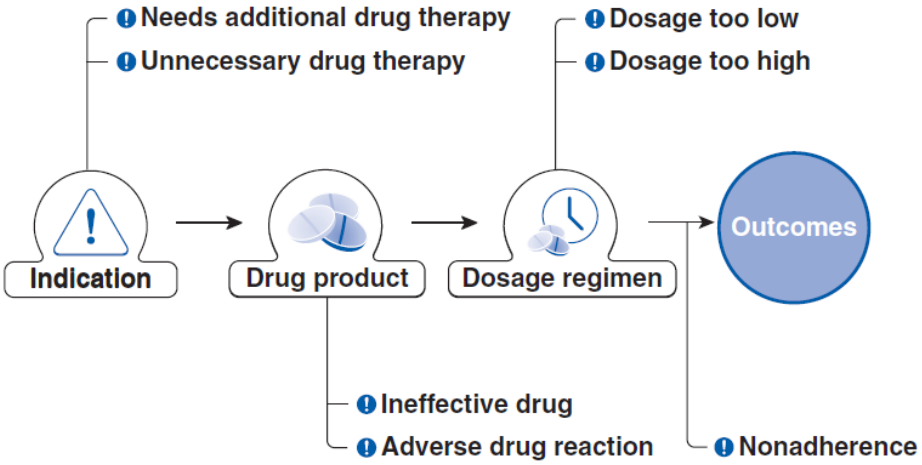
• Phenylbutazone and oxybutazone • Ibuprofen • Indomethacin

• Oxicams (eg, piroxicam, tenoxicam) - Implicated more often than other NSAIDs

With allopurinol, risk is not constant over time. Patients have a 5.5 relative risk. However, during the first 2 months of therapy, the relative risk is 52, and the long-term therapy risk is 0.5.

No laboratory test is able to confirm a specific drug etiology. A causal link is suggested when TEN occurs during the first 4 weeks of medication therapy, usually between 1 and 3 weeks. Drugs with longer half-lives and those with circulating active metabolites may result in more fulminant disease.

11) Some Additional Notes on the Adverse Drug reactions and Medication Related Problems



Top 10 of drugs causing fatal adverse reactions	Top 20 of drugs causing hospitalizations, prolonged hospitalizations, life-threatening condition, and disability

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Drug top 10	Drug top 20
Methotrexate	Methotrexate
Warfarin	Theophylline
Opioids	NSAID
Digoxin	Opioids
Theophylline	Digoxin
Other anticoagulants	Acetylic salicylic acid
Acetylic salicylic acid	Diuretics
NSAID	Antiepileptics
Beta-blockers	Beta-blockers
Antibiotics	Warfarin
	Other anticoagulants
	Potassium-sparing diuretics
	Antibiotics
	Sulfonylureas
	ACE inhibitors
	Glucocorticoids
	Antipsychotics
	Calcium-channel blockers
	Insulin
	Antidepressants

Reference:
Eva A. Saedder & Birgitte Brock & Lars Peter Nielsen & Dorthe K. Bonnerup & Marianne Lisby. Eur J Clin Pharmacol (2014) 70:637–645. DOI 10.1007/s00228-014-1668-z