

ADVERSE DRUG REACTIONS & PHARMACOVIGILANCE

*Cur'd yesterday of my disease
I died last night of my physician*

Matthew Prior (1664-1721): remedy worse than the disease.

ADVERSE DRUG REACTIONS (ADRs)

- Def. : “ any harmful or seriously unpleasant effects occurring at doses intended for therapeutic (incl. prophylactic/ diagnostic) effect and which requires reduction of dose or withdrawal of drug & /or forecasts hazard from future administration.”

Defn...

- S/E
- TOXICITY
- SECONDARY EFFECTS
- INTOLERANCE
- IDIOSYNCRACY
- ADVERSE EVENT

Table 1. Definition of ADEs and ADRs

Adverse Drug Event

- Unfavorable and unintended response to a drug, whether or not considered related to the product (i.e., no causality implied)
- Includes medical errors (miscalculations, misadministrations, difficulty in interpreting handwritten orders, misunderstanding of verbal orders, name confusion of drugs, and packaging or labeling of drugs are thus not included in this definition) and adverse drug reactions

Adverse Drug Reaction

- Noxious and unintended response to a medicinal product if a medicine properly prescribed (normal dose, route, etc.) and administered
- Causal relationship between medicinal product and adverse event cannot be ruled out
- Medical errors are not included in this definition

*ADEs: adverse drug events; ADRs: adverse drug reactions.
Source: Reference 1.*

- Adverse drug reactions caused by immune and nonimmune mechanisms are a major cause of morbidity and mortality worldwide. They are the most common iatrogenic illness, complicating 5 to 15 percent of therapeutic drug courses.
- In the United States, more than 100,000 deaths are attributed annually to serious ADRs.
- Three to 6 percent of all hospital admissions are because of ADRs, and 6 to 15 percent of hospitalized patients (2.2 million persons in the United States in 1994) experience a serious adverse drug reaction.

Classification of ADRs

- **Type A** : Augmented eg S/E
- **Type B** : Bizzare eg drug allergy , idiosyncrasy
- **Type C** : Continuous : d/t long term use
- **Type D** : Delayed : duration or critical time exposure
eg teratogenesis
- **Type E**: End of use eg acute adrenal insuff d/t abrupt
steroid cessation

Causes

- **PATIENT:** age, gender , genetic predisposition, allergic diathesis , disease, personality,
- **DRUG:** eg anticancer drugs are cytotoxic, digoxin has steep DRC-type a rxn , AMAs –type B rxns
- **PRESCRIBER:**ADR may occur if drug used for inappropriately long time (Type C), at a critical phase in gestation (Type D) or is abruptly d/c (Type E) or given with other drugs (Drug-drug interactions)

Patient Risk Factors for Adverse Drug Reactions

Female gender

Serious illness

Renal insufficiency

Liver disease

Polypharmacy

HIV infection

Herpes infection

Alcoholism

Genetics(P'genetics)



Allergy in response to drugs :

Gell and Coombs Classification of Drug Hypersensitivity Reactions

- 1. Immune reaction 2. Mechanism
- 3. Clinical manifestations 4. Timing of reaction
- **Type I (IgE-mediated)**
- Drug-IgE complex binding to mast cells with release of histamine, inflammatory mediators
- Urticaria, angioedema, bronchospasm, pruritus, vomiting, diarrhea, **anaphylaxis**
- Minutes to hours after drug exposure
- **Type II (cytotoxic)**
- Specific IgG or IgM antibodies directed at drug-hapten coated cells
- Hemolytic anemia, neutropenia, thrombocytopenia
- Variable

Allergy in response to drugs....

- **Type III (immune complex)**
- Tissue deposition of drug-antibody complexes with complement activation and inflammation
- Serum sickness, fever, rash, arthralgias, lymphadenopathy, urticaria, glomerulonephritis, vasculitis
- 1 to 3 weeks after drug exposure
- **Type IV (delayed, cell-mediated)**
- MHC presentation of drug molecules to T cells with cytokine and inflammatory mediator release
- Allergic contact dermatitis, maculopapular drug rash*
- 2 to 7 days after cutaneous drug exposure
- MHC = major histocompatibility complex.
- *—Suspected Type IV reaction, mechanism not fully elucidated

Cutaneous symptoms of Drug Hypersensitivity Reactions (M. common)

- Exanthematous or morbilliform eruption originating on trunk
- Urticaria
- Purpura
- Maculopapular lesions with distribution on the fingers, toes, or soles
- Blistering lesions with mucous membrane involvement
- Eczematous rash in sun-exposed areas
- Solitary circumscribed erythematous raised lesion
- Papulovesicular, scaly lesion

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.
	Immune complexes	
	Complement studies	
	Antinuclear antibody, antihistone antibody	
Tissue biopsy for immunofluorescence studies		

- Distinctive features of allergic rxns
- Diagnosis and treatment of allergic drug reactions
- Adrenaline 0.3-0.5 ml of 1:1000 IM, rpted 3-5 min if reqd----life saving ,
- Others Antihisaminics-CPM , Corticosteroids,

Pseudoallergic rxns

- Mimic allergic rxns BUT have no immunological basis ,are largely genetically determined. Are d/t release of endogenous mediators like histamine, LTs . PAR mimicking Type 1 rxn- anaphylactoid rxn eg aspirin, nsaids
- PAR mimicking type 2 rxn eg hemolysis d/t antimalarials, sulphones in G6PD def pt.

ADRs on prolonged use – Type C , D

- **EYE**- cataract d/t: chloro, corticosteroids,
- Corneal opacities :phenothiazines
- Retinal injury : thioridazine, chloro, indo
- **CNS** : Tardive dyskinesia- neuroleptics,
- Polyneuritis- metronidazole
- Optic neuritis- ETM
- **LUNG**: pulm fibrosis- amiodarone, busulphan,
- **KIDNEYS**: nephropathy-gold salts, NSAIDs
- **LIVER**: fibrosis, failure-MTX, alcohol, PZA

Carcinogenesis

- Takes months to years 3-5 yrs
- Mech:1.Alteration of DNA (mutagenicity)-
chemicals/metab-
- 2.Immunosuppression:
- 3.Hormonal- long term use of ERT –
endometrial Ca, DES exp in-utero –vaginal
adenoCa in females

Adverse effect on reproduction

- Drugs may act on embryo & fetus-directly eg teratogens ; indirectly eg on uterus – vasoconstrictors; on mother’s hormonal balance.
- **Early pregnancy:** m.vulnerable pd- 2-8 weeks (10-56 days) of IU life –organogenesis
- Teratogenesis (teratos-monster)
- Teratogens: **thalidomide**, cytotoxics, warfarin, alcohol, lithium, valproate, phenytoin, methotrexate, isotretinoin, ACE inhb..... ..

Phocomelia due to Thalidomide



Teratogenic drugs...

- Definitive list not practical- depends on dose taken, and at what stage of pregnancy. VV cautious use of drugs during pregnancy
- **Late pregnancy:** eg I and antithyroid drugs- fetal goitre, tetracyclines - , Ace inhib.-, NSAIDs,
- **During labour-** opioid anagesics, diazepam--

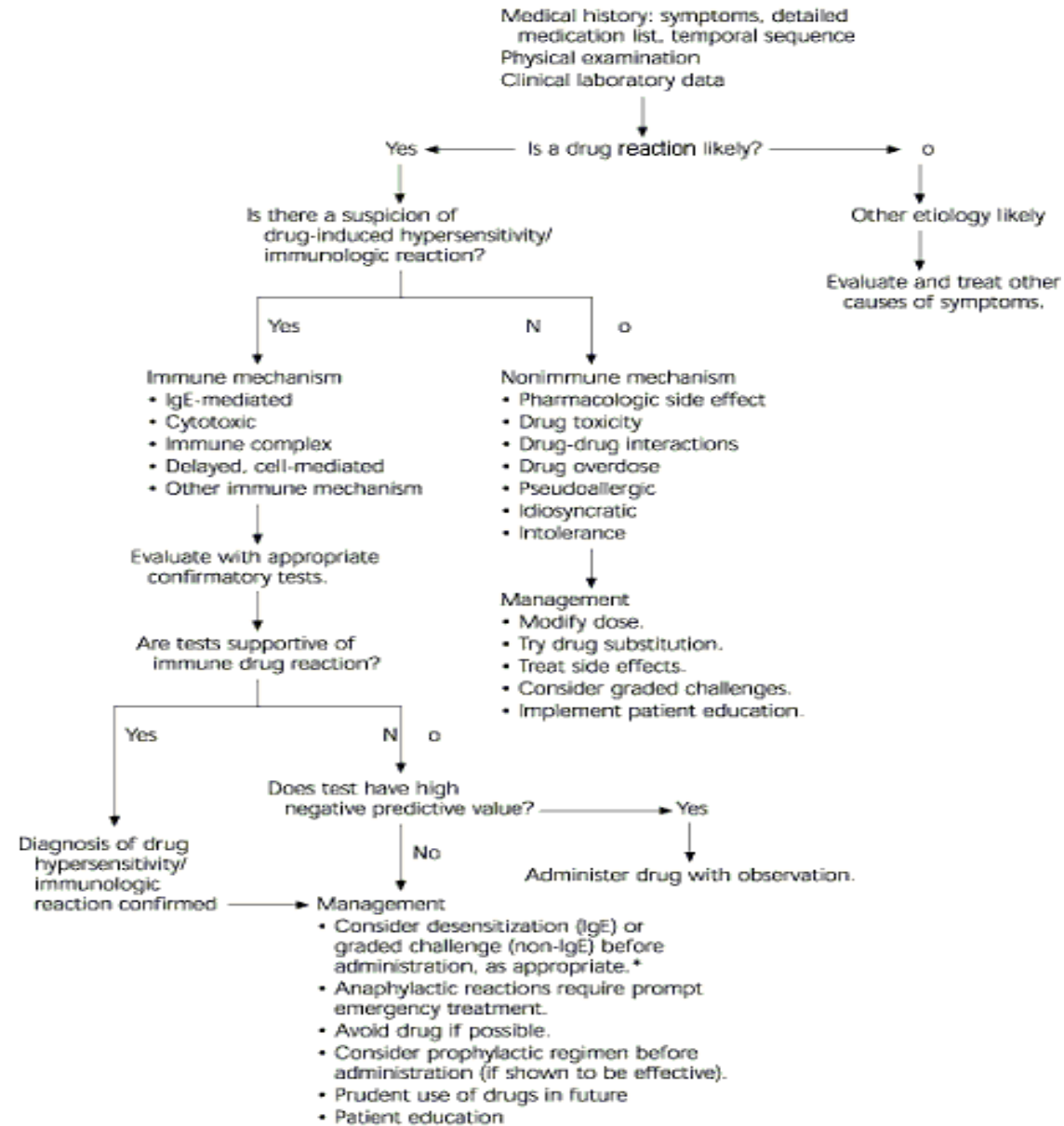
Adverse effects on Male reproductive system

- **Impotence** :ANS drugs eg beta blockers, thiazides
- **Decreased spermatogenesis** : sulfasalazine, cytotoxic anticancer drugs, nitrofurantoin
- Iatrogenic diseases

General Criteria for Drug Hypersensitivity Reactions

- The patient's symptomatology is consistent with an immunologic drug reaction.
- The patient was administered a drug known to cause such symptoms.
- The temporal sequence of drug administration and appearance of symptoms is consistent with a drug reaction.
- Other causes of the symptomatology are effectively excluded.
- Laboratory data are supportive of an immunologic mechanism to explain the drug reaction (not present or available in all cases).

Evaluation and Management of Drug Reaction



Pharmacovigilance

- Refers to the process of continuous monitoring for unwanted effects and other safety related aspects of marketed drugs. It is the science and application of detection , assessment ,understanding and prevention of adverse drug reactions.
- Post marketing surveillance/ phase 4 trials
- PSURs
- Severe ADRs:

Naranjo ADR probability scale

Score >9=definite, 5-8=probable,1-4=possible,0=doubtful

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

WHO –Uppsala
Causality term

Assessment criteria (all points should be reasonably complied)

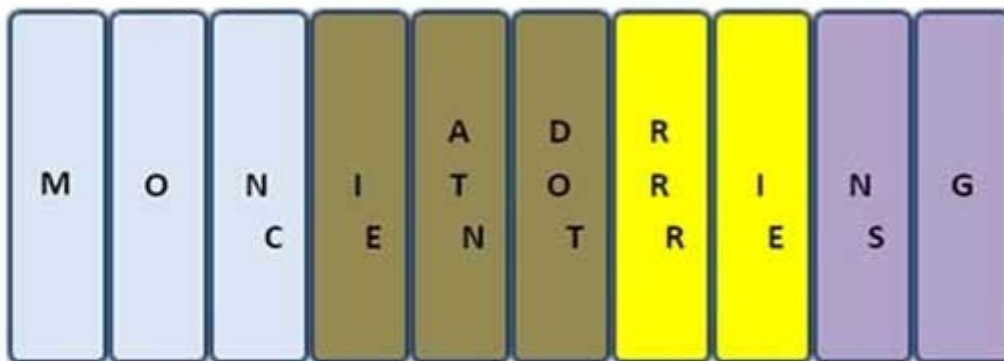
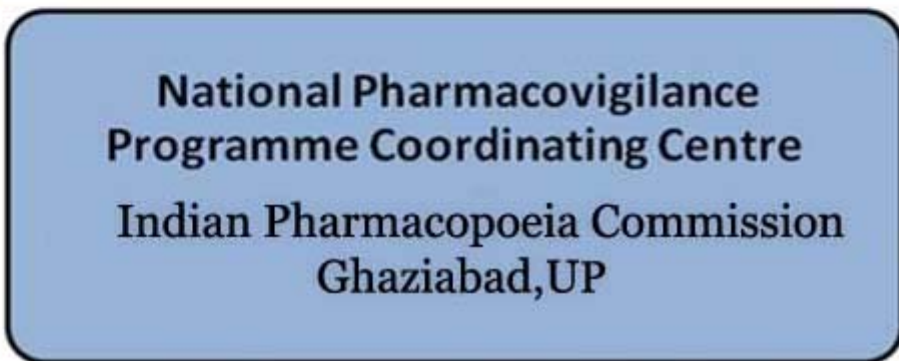
Certain	<ul style="list-style-type: none">•Event or laboratory test abnormality, with plausible time relationship to drug intake•Cannot be explained by disease or other drugs•Response to withdrawal plausible (pharmacologically, pathologically)•Event definitive pharmacologically or phenomenologically (ie, an objective and specific medical disorder or a recognized pharmacologic phenomenon)•Rechallenge satisfactory, if necessary
Probable/likely	<ul style="list-style-type: none">•Event or laboratory test abnormality, with reasonable time relationship to drug intake•Unlikely to be attributed to disease or other drugs•Response to withdrawal clinically reasonable•Rechallenge not required
Possible	<ul style="list-style-type: none">•Event or laboratory test abnormality, with reasonable time relationship to drug intake•Could also be explained by disease or other drugs•Information on drug withdrawal may be lacking or unclear
Unlikely	<ul style="list-style-type: none">•Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)•Disease or other drugs provide plausible explanation
Conditional/unclassified	<ul style="list-style-type: none">•Event or laboratory test abnormality•More data for proper assessment needed, or•Additional data under examination
Unassessable/unclassifiable	<ul style="list-style-type: none">•Report suggesting an adverse reaction•Cannot be judged because information is insufficient or contradictory•Data cannot be supplemented or verified



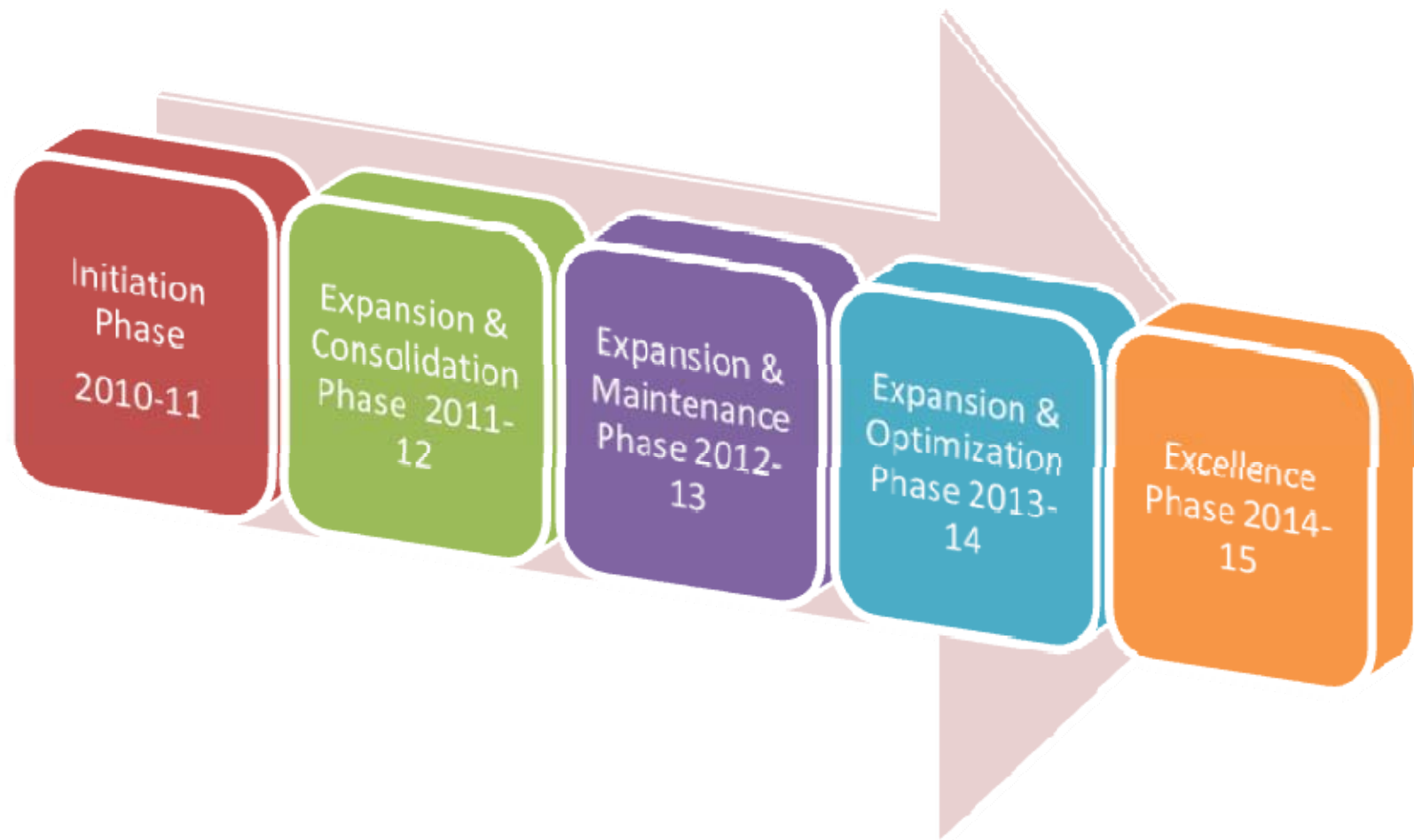
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Pharmacovigilance Programme of India(PvPI)

- **Objectives**
- To monitor Adverse Drug Reactions (ADRs) in Indian population
- To create awareness amongst health care professionals about the importance of ADR reporting in India
- To monitor benefit-risk profile of medicines
- Generate independent, evidence based recommendations on the safety of medicines
- Support the CDSCO for formulating safety related regulatory decisions for medicines
- Communicate findings with all key stakeholders
- Create a national centre of excellence at par with global drug safety monitoring standards



- MCI Approved Medical Colleges & Hospitals
- Private Hospitals
- Public Health Programmes
- Autonomous Institutes (ICMR etc)



TARGETS FOR THE FIVE PHASES OF PHARMACOVIGILANCE PROGRAMME OF INDIA

FY 2010-11

- Developing systems & procedures
- Enroll 40 Medical Colleges
- Start Data Collection from AEFI(Adverse Event Following Immunization)
- Development & establishment of training centers
- Training of Pharmacovigilance human resource
- Linkage with Uppsala monitoring Center, Sweden, WHO
- Initiate software development for National Drug Safety database
- Zonal workshop for Public awareness of drug safety
- Publication of Drug Safety Newsletter

FY 2011-12

- Enroll additional 60 Medical Colleges
- Training of Pharmacovigilance human resource
- Identify gaps & address through appropriate training
- Training in Pharmacovigilance software provided by Uppsala Monitoring Center Sweden, WHO (Vigiflow)
- Software Development and Validation
- Zonal Workshop for Public awareness of drug safety
- Publication of drug safety newsletter

FY 2012-13

- Enroll additional 100 medical colleges
- Training of Pharmacovigilance Human Resource
- Zonal Workshop for Public awareness of drug safety
- Publication of drug safety newsletter

FY 2013-14

- Enroll additional 100 medical colleges
- Interaction with international Pharmacovigilance bodies
- Training of Pharmacovigilance Human Resource
- Publication of drug safety newsletter

FY 2014-15

- Create Center of excellence for Pharmacovigilance in Asia Pacific