Adverse drug reaction

Right drug, wrong reaction

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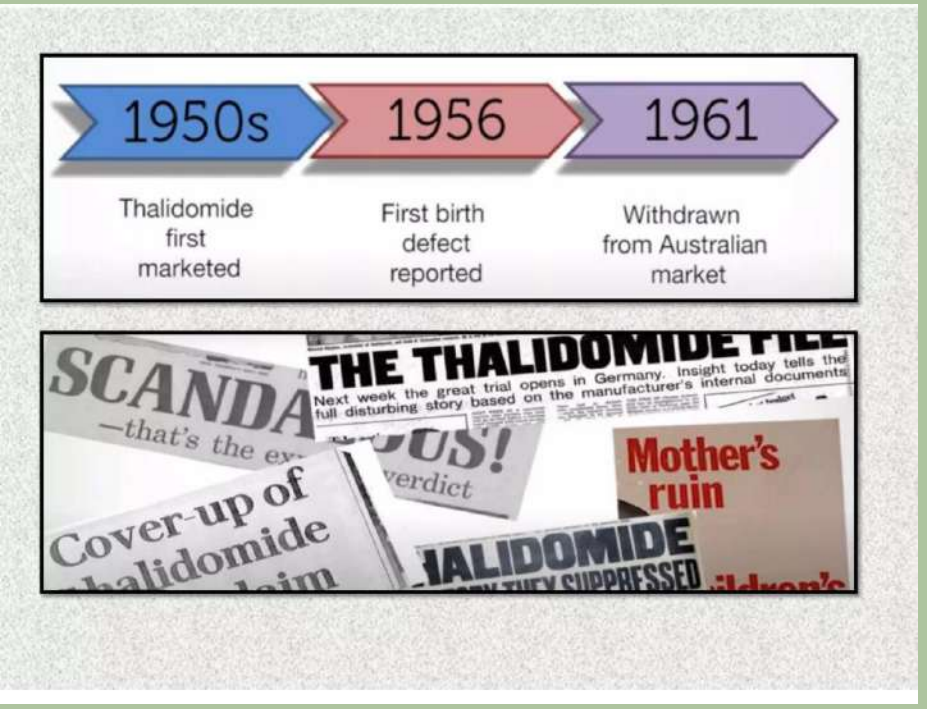
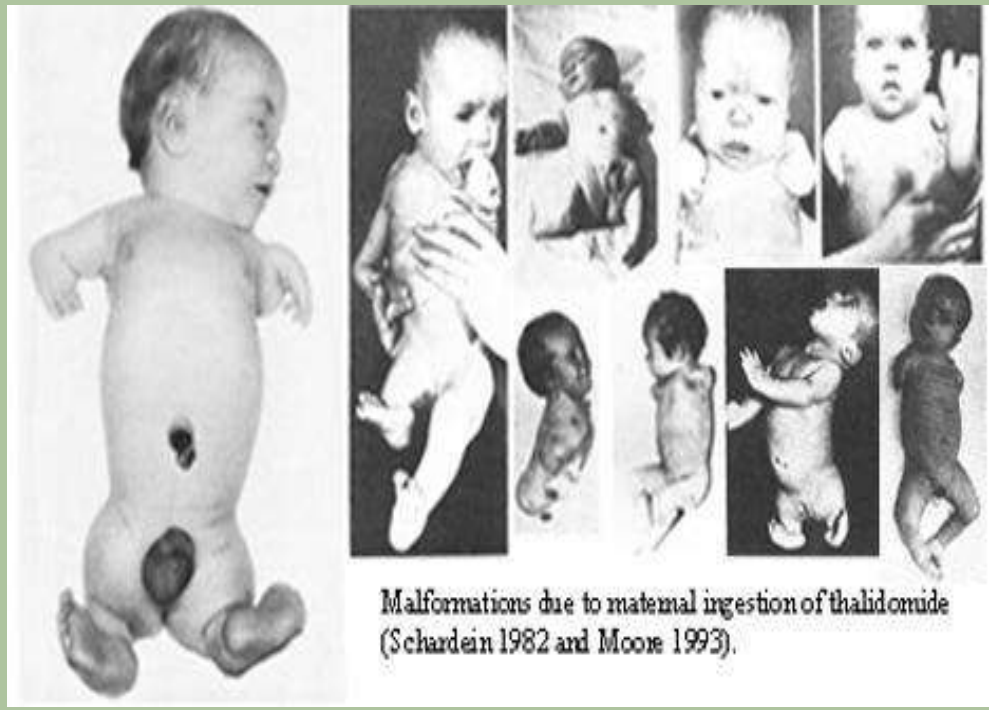
History of adverse drug reaction

- Thalidomide tragedy (1950- 1961)





Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

History of adverse drug reaction

- Rofecoxib (Vioxx, Merck)- was voluntarily recalled in 2004
- increased the risk of cardiovascular event.
- approved in 1999 for the treatment of arthrits

History of adverse drug reaction

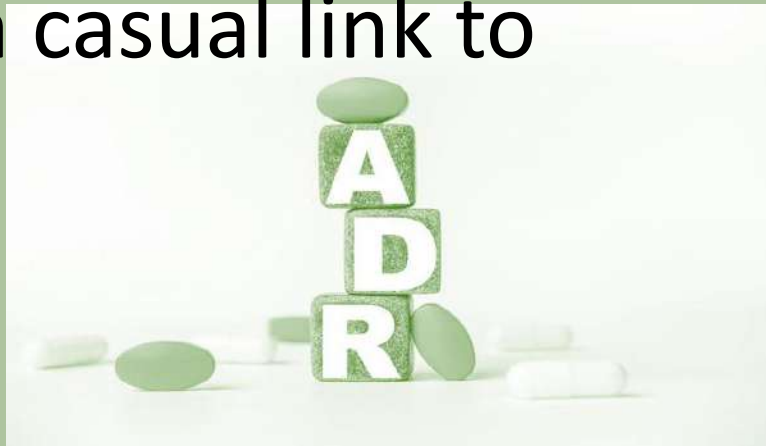
- In 2005, here have been reports of fatal toxic epidermal necrolysis (TEN) cases in Bangladesh associated with levofloxacin use.

- Medicines can produce unwanted or adverse effects (Edward and Aronson, 2000).

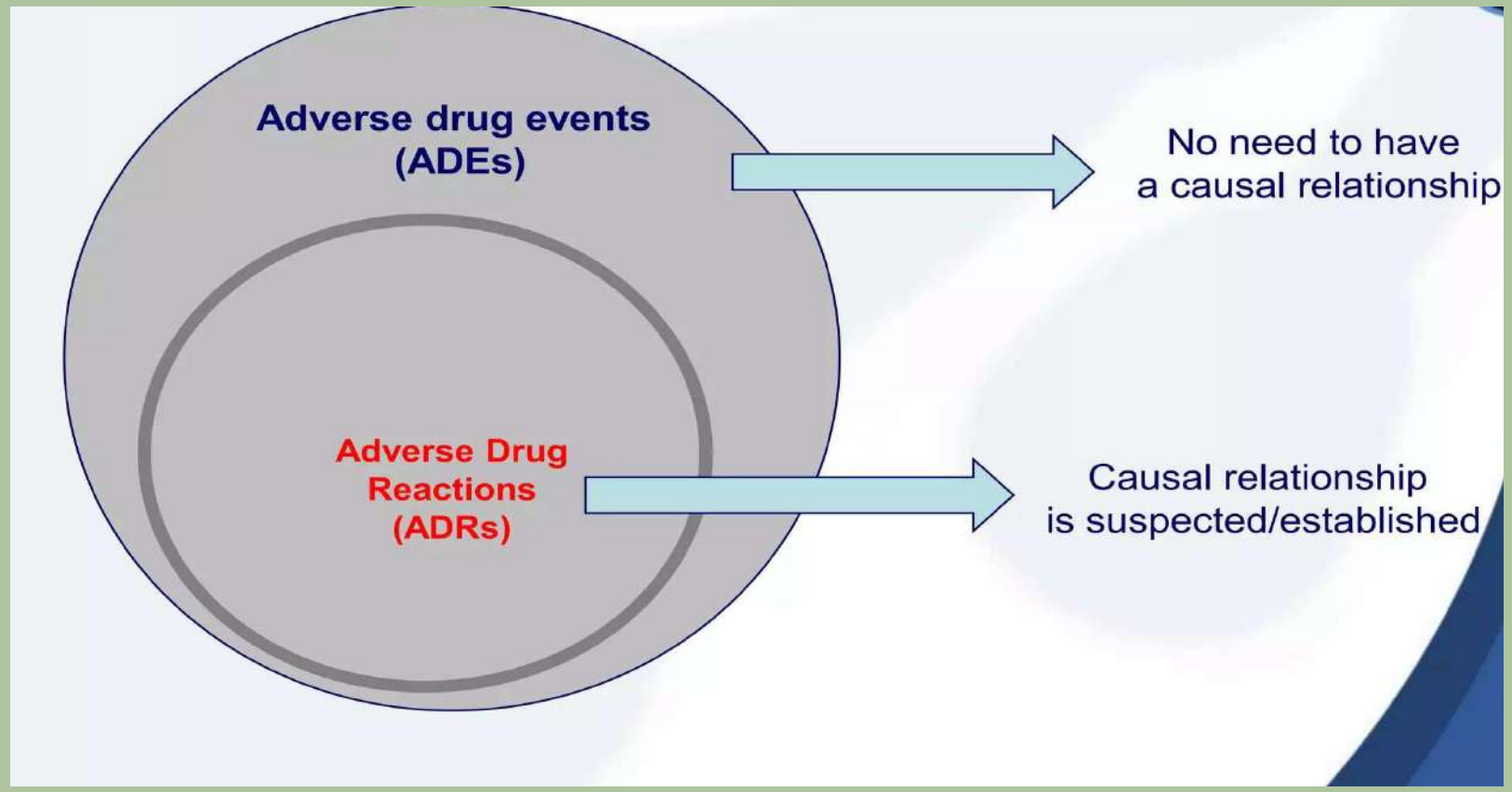
- The safety of medicines has been a major concern (Helali et al., 2014).

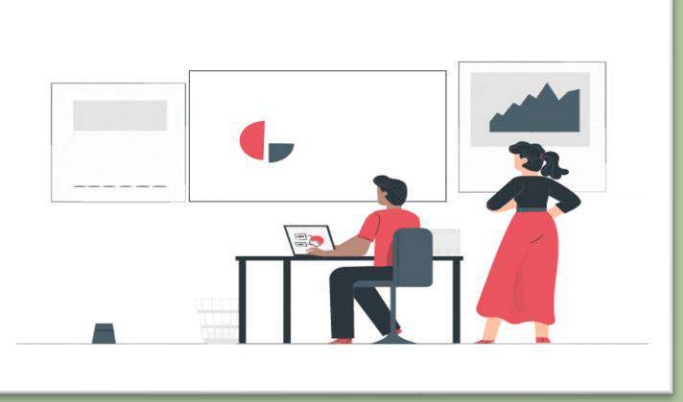
Adverse events & Adverse drug reaction

- Adverse Event: Any untoward medical occurrence which does not necessarily have a casual relationship with this treatment
- Adverse Drug Reaction: Any noxious change which is suspected to be due to a drug, occurs at doses normally used
- Therefore an adverse drug reaction is a casual link to a drug



Adverse events & Adverse drug reaction





Statistics

- USA estimated that 11.4-35.5% of emergency department visits are due to drug-related causes (Budnitz et al., 2007)
- ADRs appear to be between the fourth and sixth leading cause of death in USA (Lazarou et al., 1998)
- ADR costs up to 30.1 billion dollars annually (Sultana et al., 2013)

DEFINITION

- According to WHO – Any response to a drug which is noxious or unintended & which occurs at doses used in man for prophylaxis, diagnosis or treatment.
- Or, harmful or serious unpleasant effects occurring at doses intended for therapeutic use.

What to do

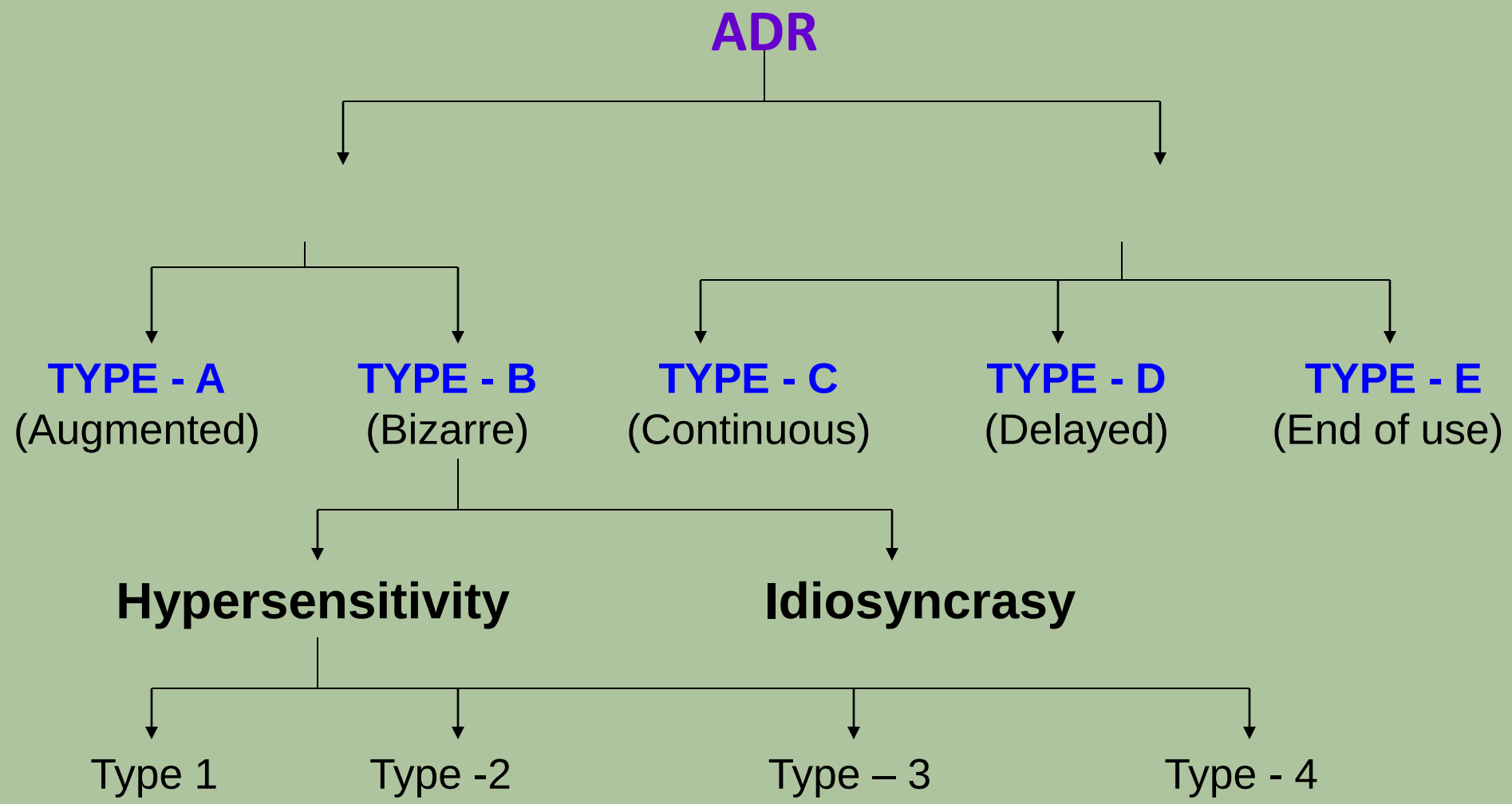
- Reduction of doses
- Withdrawal of drugs
- Forecast hazards from future administration
- Should be informed to drug administration authority.

Classification of ADRs

Depending of

- Onset of events: Acute(< 60 minutes),Sub acute(1-24hrs), Latent (> 2days)
- Severity: Minor, Moderate, Severe, Lethal ADRs

CLASSIFICATION:



TYPE A (AUGMENTED)

- Occurs from direct extension of pharmacological effects
- Dose related
- Predictable
- Relatively common
- Usually not fatal
- Skilled management reduces the effects

TYPE A (AUGMENTED)

EXAMPLE:

- Hypoglycemia – Insulin
- Hemorrhage - Anticoagulants
- Sedation – BDZ
- Postural hypotension – α blockers
- Hyperkalaemia - K+ sparing diuretics

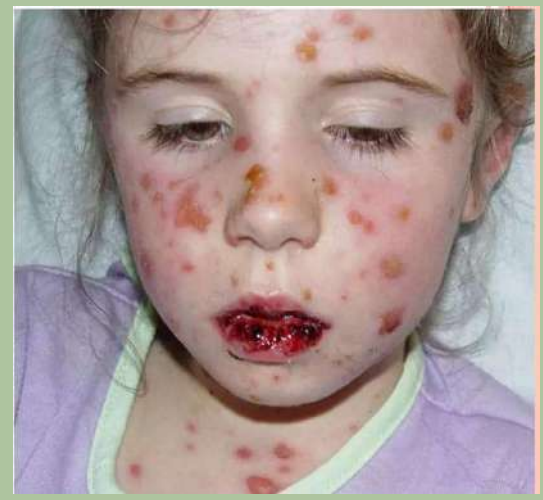
TYPE B (BIZZARE)

- Unpredictable
- Not the extension of pharmacological effects
- Not dose related
- Uncommon
- Occurs only in some people
- High rate of morbidity & mortality

TYPE B (BIZZARE)

- Includes:
- Idiosyncrasy - Inherited abnormal response to drugs
- Allergy or Hypersensitivity - Occurs due to antigen & antibody reaction.
- Chief target organs:

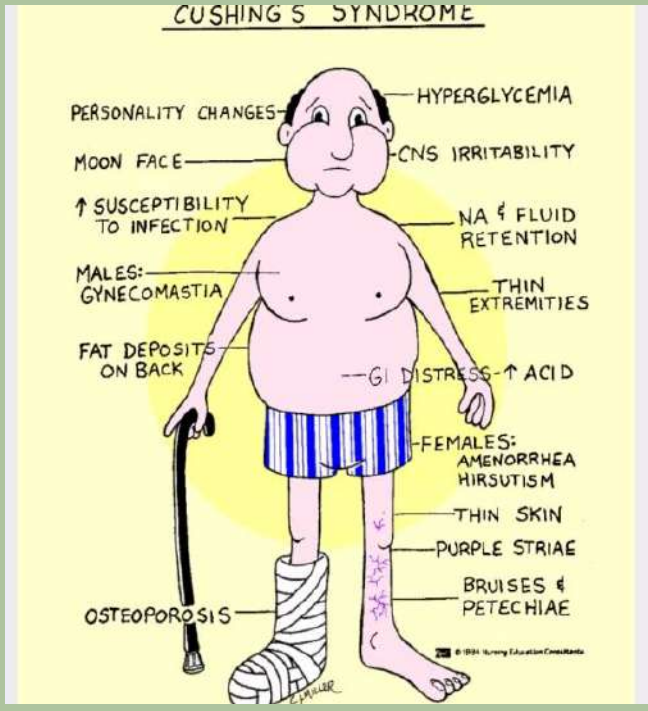
Skin, Respiratory tract, Blood, GIT, Blood vessel



TYPE – C (Chronic)

- Reactions occur due to long term exposure
- **EXAMPLE:**

1. Paracetamal – Analgesic nephropathy
2. Glucocorticoids - Cushing syndrome
3. Levodopa - Dyskinesia
4. Chloroquine - Retinopathy



TYPE – D (Delayed)

- Effects occur following prolonged exposure
- **EXAMPLE:**

1. Secondary Carcinoma - (hodgkins treated with alkylating agents)
2. Teratogenicity - Teratogenic drugs

TYPE – E (End of use)

- Occurs when there is abrupt withdrawal of drugs after discontinuation of chronic therapy.

TYPE – E (End of use)

- **EXAMPLE :**

1. Glucocorticoids – Adrenocortical insufficiency
2. β blockers – cardiac arrhythmias & unstable angina (after sudden withdrawal)
3. Morphine, Pethidine, Heroin – Withdrawal syndrome.

Type – F (Failure of therapy)

- **EXAMPLE:**

1. Oral contraceptives
2. Antihypertensives
3. Antiepileptics
4. Insulin

TERATOGENIC DRUGS

A. DIRECT EFFECTS ON FOETUS AND EMBRYO:

- Thalidomide
- Cytotoxic drugs
- Antithyroid drugs
- Isotretinoin
- Any drugs affecting cell division, enzymes, protein synthesis & DNA synthesis - Many antimicrobials

B. EARLY PREGNANCY (DURING PERIOD OF EMBRYOGENESIS UPTO 56 DAYS):

- Cytotoxic drugs
- Warfarin
- Alcohol
- Lithium
- Phenytoin
- Valproate
- Adrenocorticosteroids
- Isotretinoin
- Thalidomide

C. LATE PREGNANCY :

- Hormones – Androgens, Progesterone
- Iodides
- Antithyroids
- Lithium
- Tetracycline
- ACE inhibitors
- NSAIDS
- Chloroquine
- Chlorpromazine
- Anticoagulants

Side Effects

- Unwanted but often unavoidable,
- Predicted
- Known
- Examples: Atropine → dryness of mouth, Promethazine→ sedation, Estrogen→ nausea

Side Effects

- Drug discovery
- Occasionally ,’adverse” effects may be exploited to develop an entirely new indication for a drug
- Example: Unwanted hair growth during minoxidil.
- Sulfonamides produced hypoglycemia and acidosis→ hypoglycemic sulfonylureas and Acetazolamide

Toxic effects

- Results of excessive pharmacological action of the drug due to over dosage or prolonged use
- Barbiturates→ coma, Digoxin→ complete A-V block
- Atropine→ Delirium
- Paracetamol → hepatic necrosis

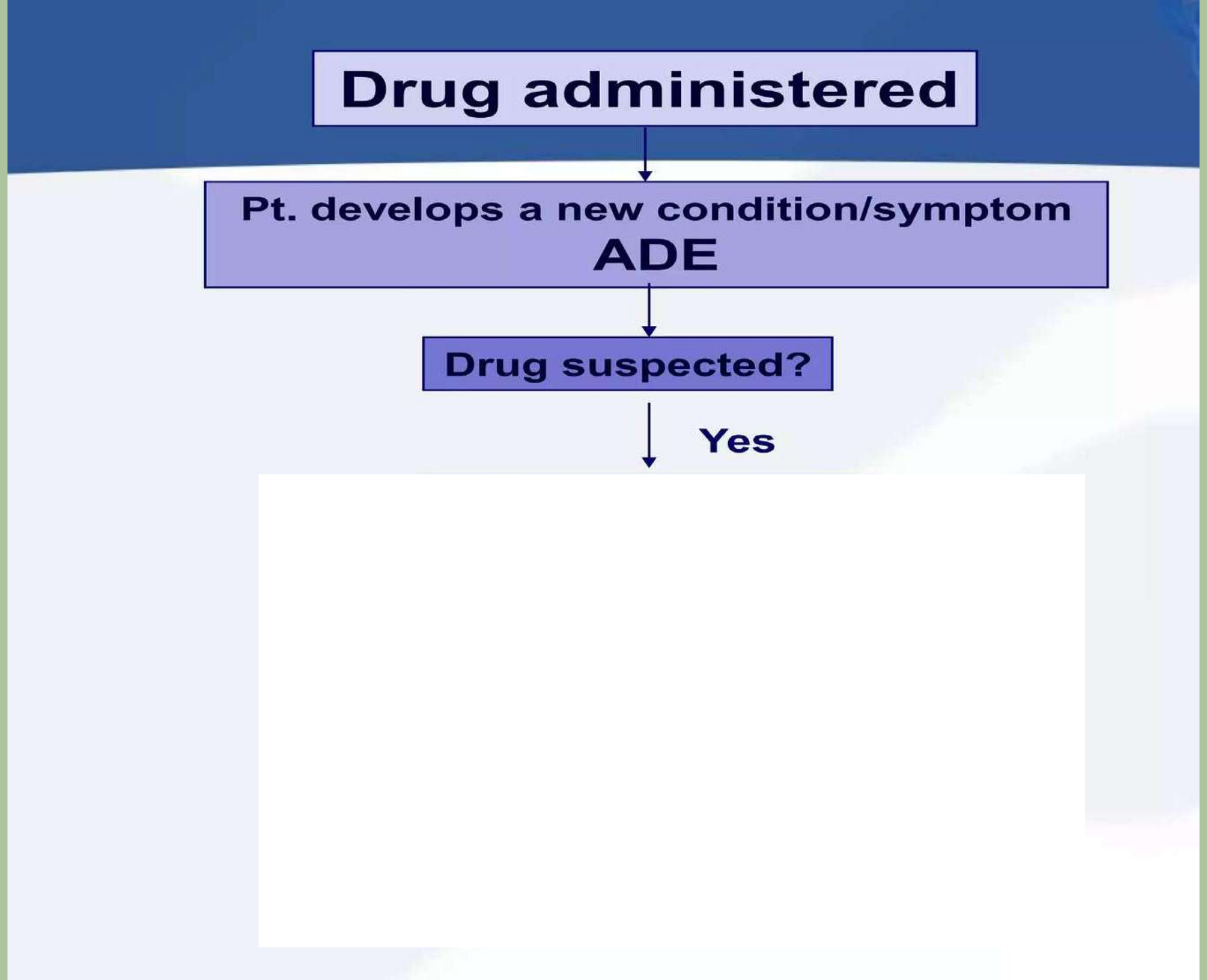
Intolerance

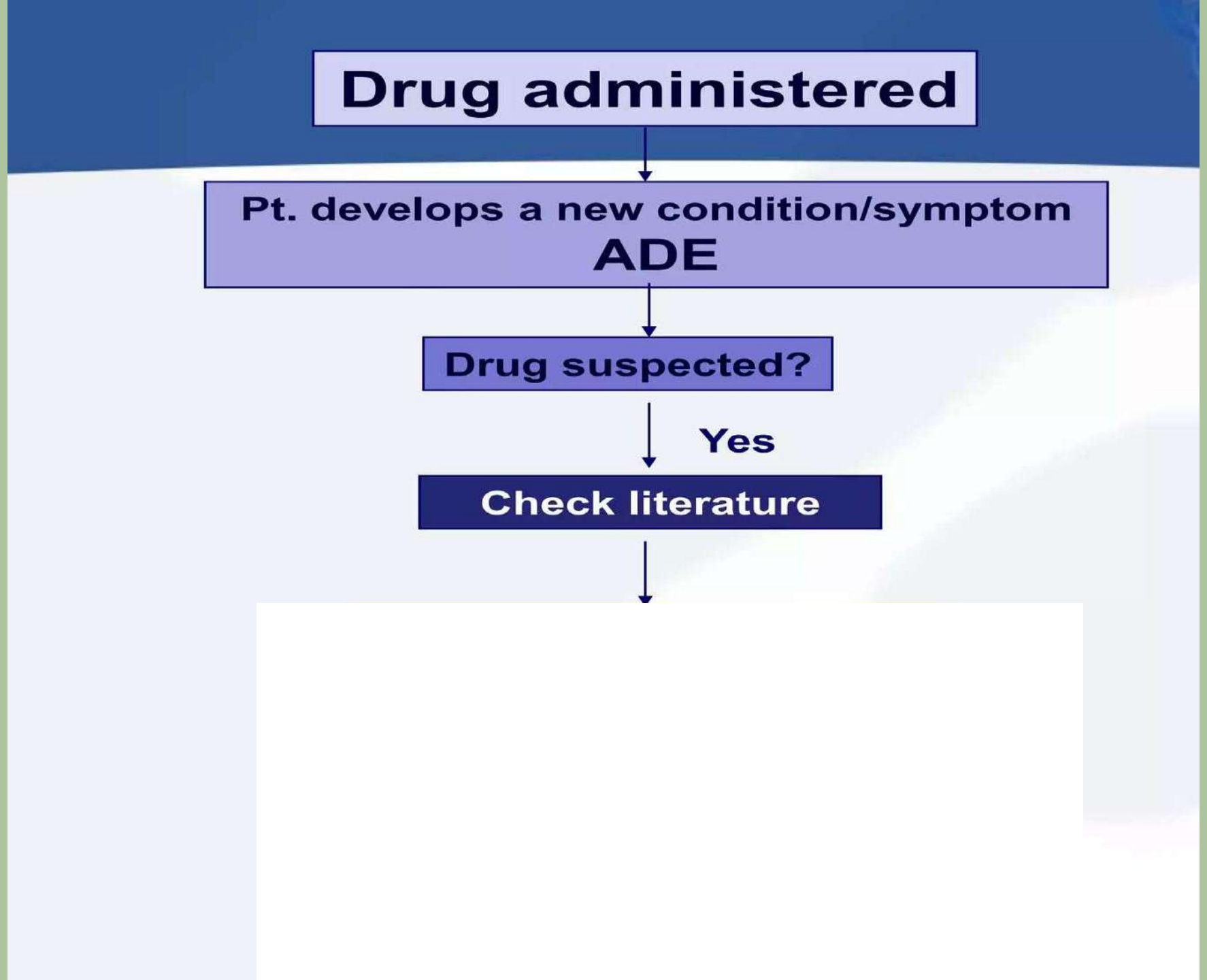
- Toxic effects of a drug in an individual at the therapeutic doses
- low threshold of the individual
- Carbamazepine (few doses)→ ataxia in some individuals
- Chloroquine (single Tablet)→ vomiting and abdominal pain

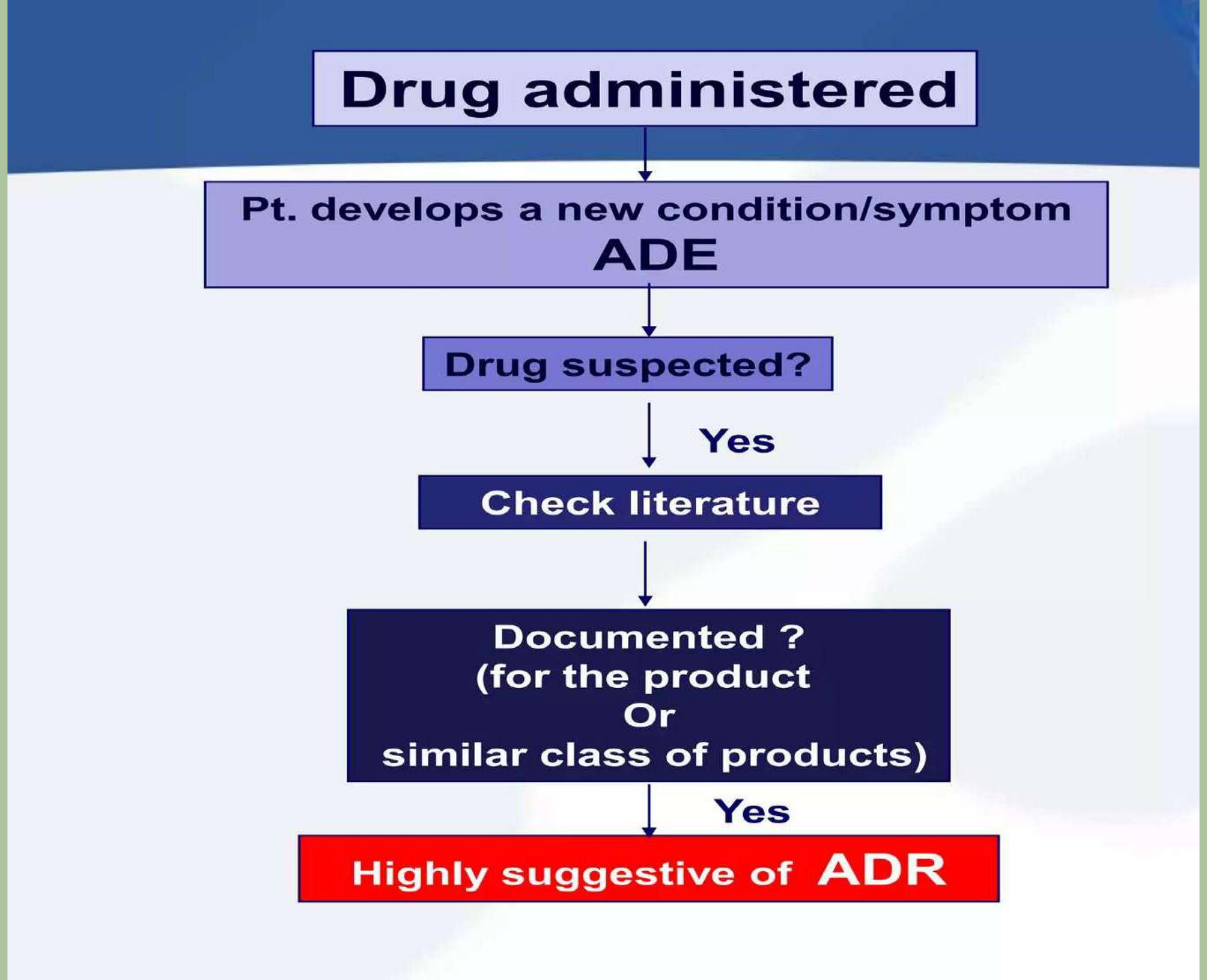
Idiosyncrasy

- Genetically determined abnormal reactivity to a chemical
- Succinylcholine apnea
- Chloramphenicol→ aplastic anemia in rare individuals


Drug administered
Pt. develops a new condition/symptom
ADE

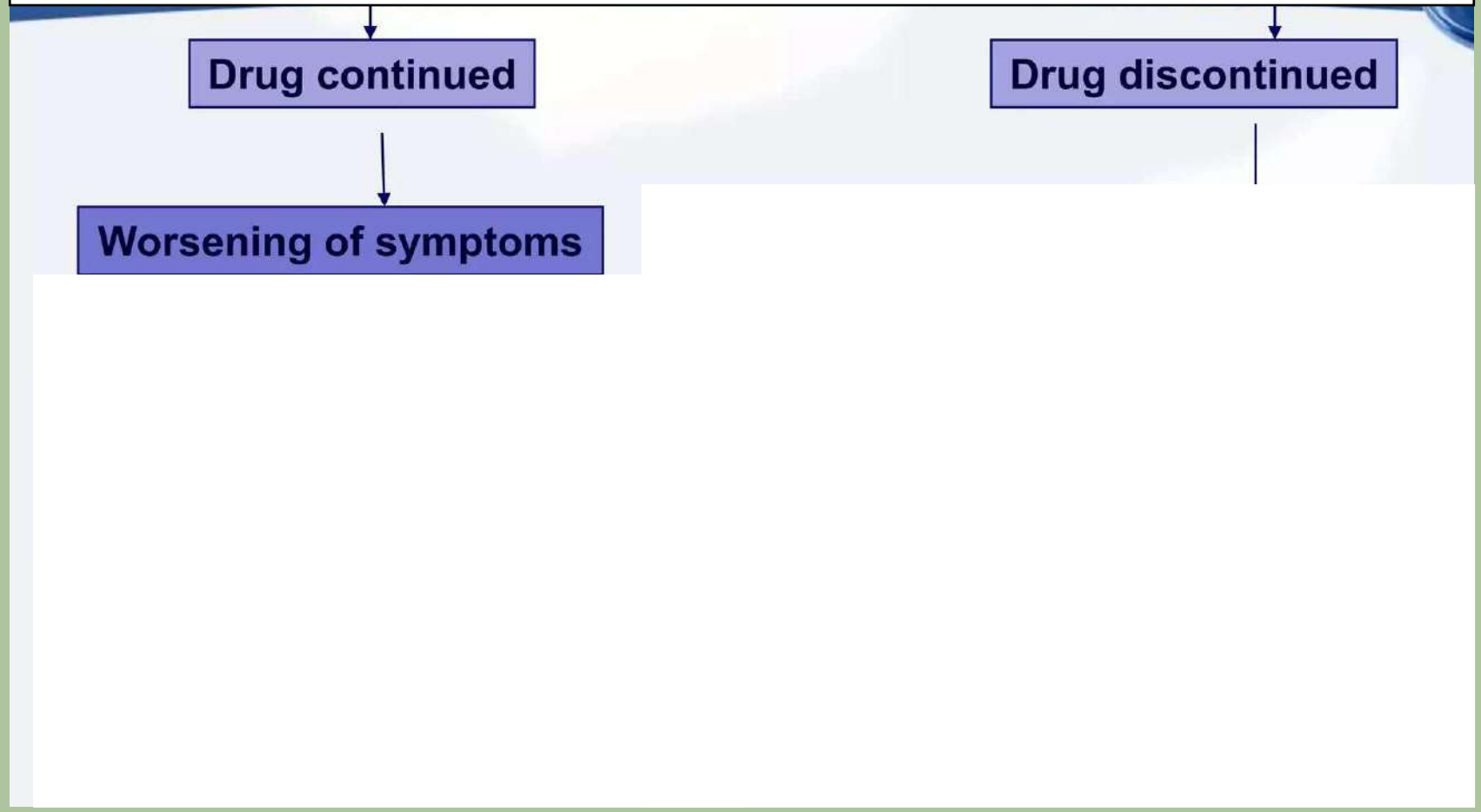

Drug administered
Pt. develops a new condition/symptom
ADE
Drug suspected?
Yes


Drug administered
Pt. develops a new condition/symptom
ADE
Drug suspected?
Yes
Check literature

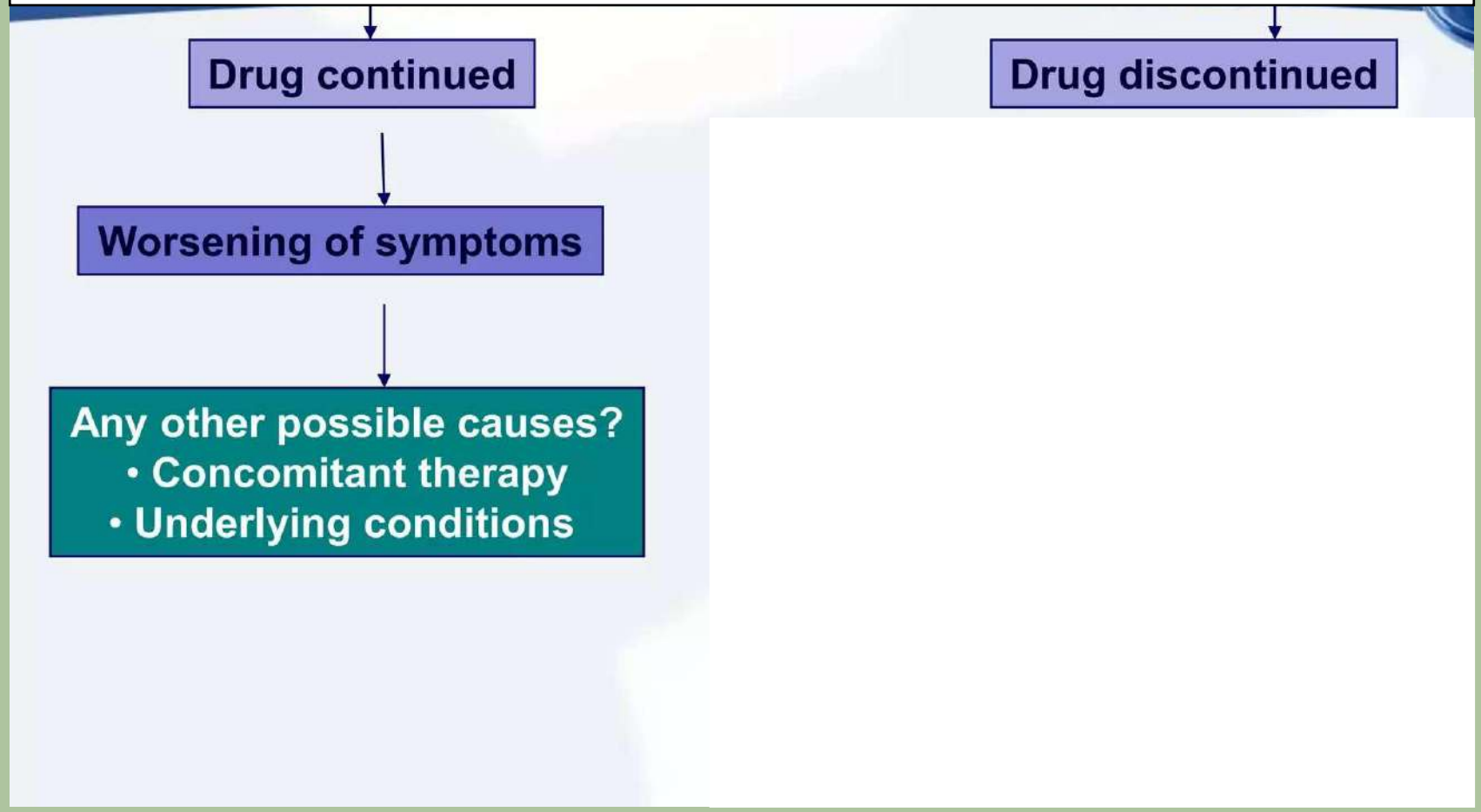

Drug administered
Pt. develops a new condition/symptom
ADE
Drug suspected?
Yes
Check literature
Documented ?
(for the product
Or
similar class of products)
Yes
Highly suggestive of ADR

Not documented in literature

Not documented in literature



Not documented in literature



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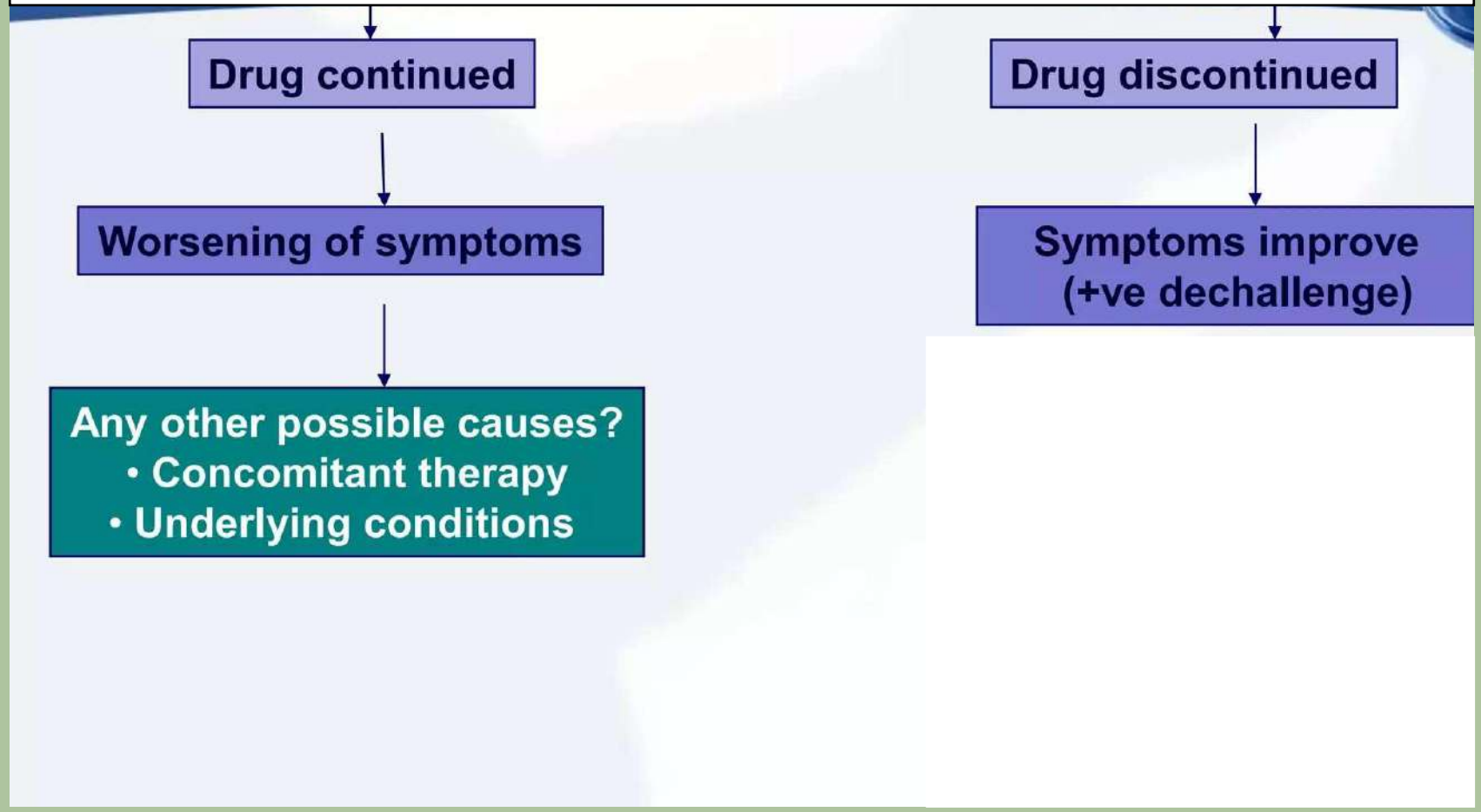

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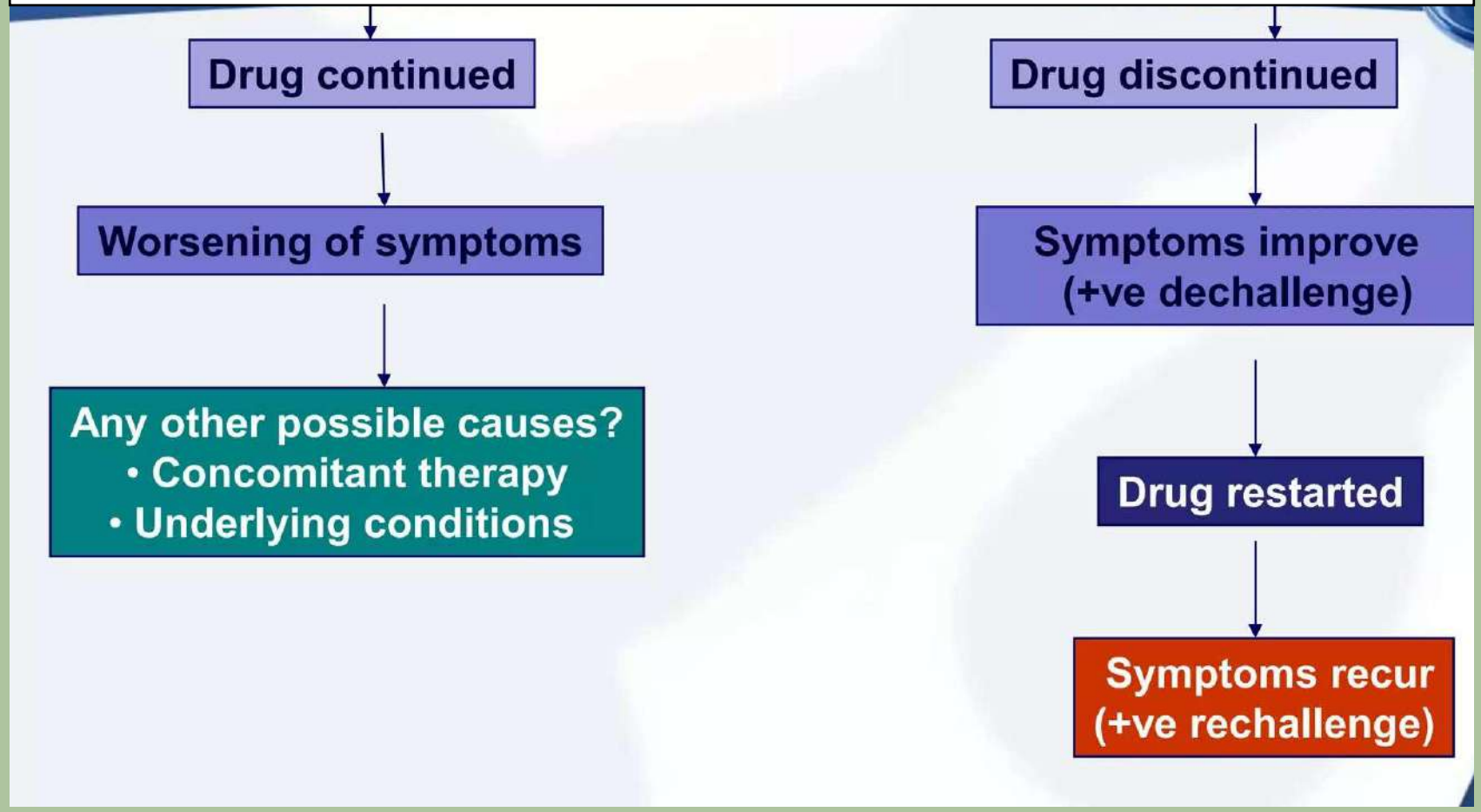
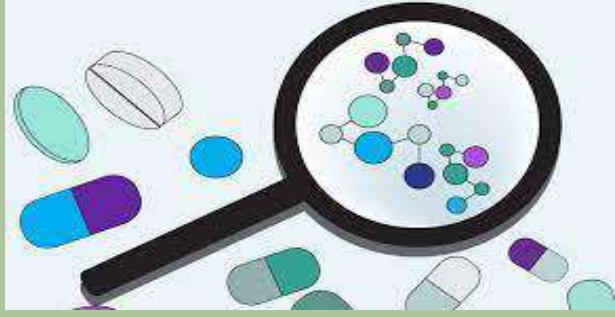
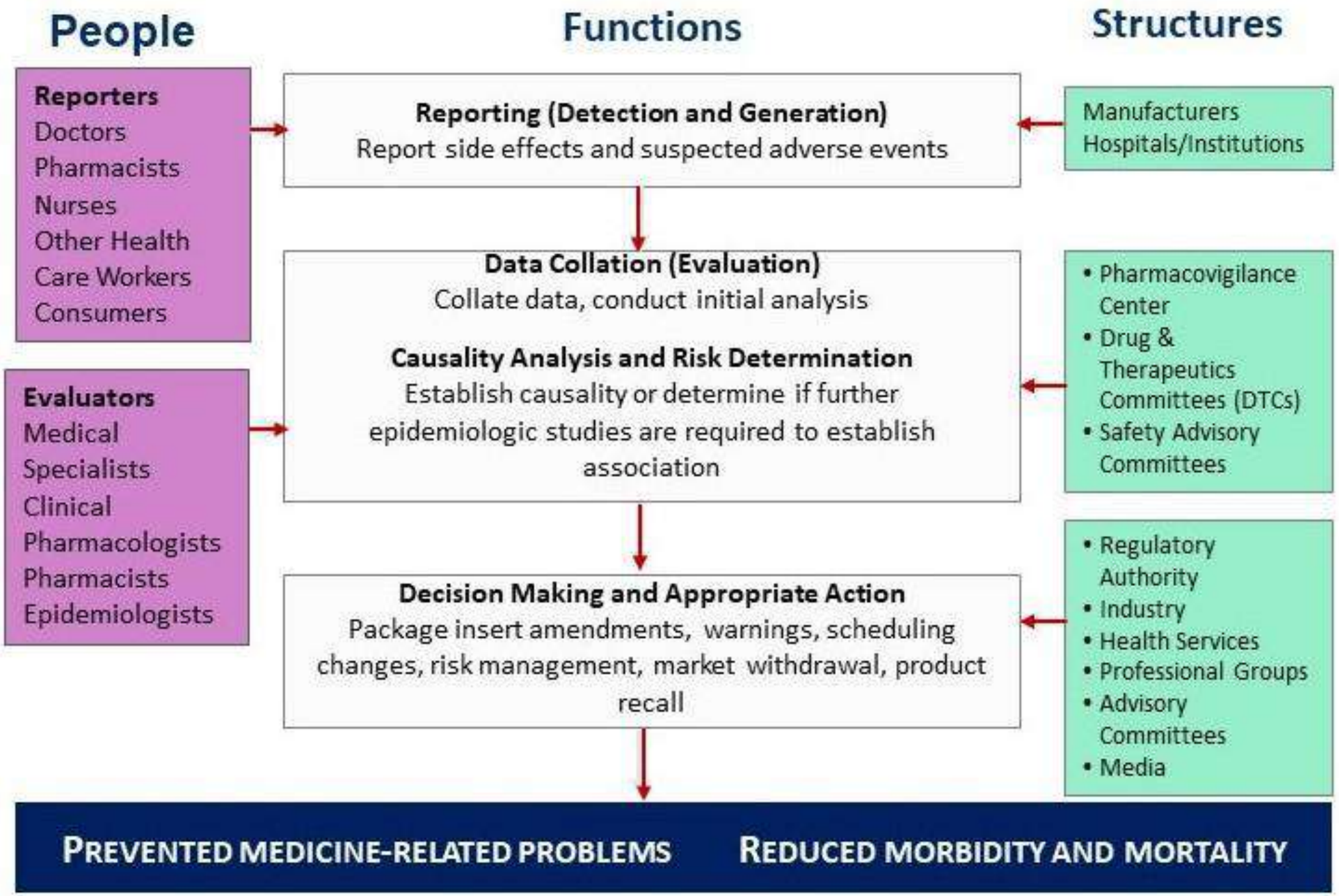


- When a medicine is first launched into the market, it is estimated that half of the risks are known and recorded
- The remaining risks are detected in the next 10-15 years through Phase-1V clinical trials during post-marketing surveillance (Amran, 2021; Johora et al., 2020).

Pharmacovigilance



- Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem


People
Functions
Structures
Reporters
Doctors
Pharmacists
Nurses
Other Health Care Workers
Consumers
Evaluators
Medical Specialists
Clinical Pharmacologists
Pharmacists
Epidemiologists
Reporting (Detection and Generation)
Report side effects and suspected adverse events
Data Collation (Evaluation)
Collate data, conduct initial analysis
Causality Analysis and Risk Determination
Establish causality or determine if further epidemiologic studies are required to establish association
Decision Making and Appropriate Action
Package insert amendments, warnings, scheduling changes, risk management, market withdrawal, product recall
Manufacturers
Hospitals/Institutions
• Pharmacovigilance Center
• Drug & Therapeutics Committees (DTCs)
• Safety Advisory Committees
• Regulatory Authority
• Industry
• Health Services
• Professional Groups
• Advisory Committees
• Media
PREVENTED MEDICINE-RELATED PROBLEMS
REDUCED MORBIDITY AND MORTALITY


Uppsala
Monitoring
Centre

- Uppsala Monitoring Centre, located in Sweden, is the Centre for International Drug Monitoring
- Bangladesh became the 120th member country of the WHO pharmacovigilance program in December 2014 (UMC, 2014)
- VigiBase, WHO’s database of reported potential side effects of medicinal products

- Access information on global ADR reports at www.vigiaccess.org
- VigiAccess™
- is a public gateway that allows anyone to access information on reported cases of adverse events

ADR reporters

Physicians

Pharmacists

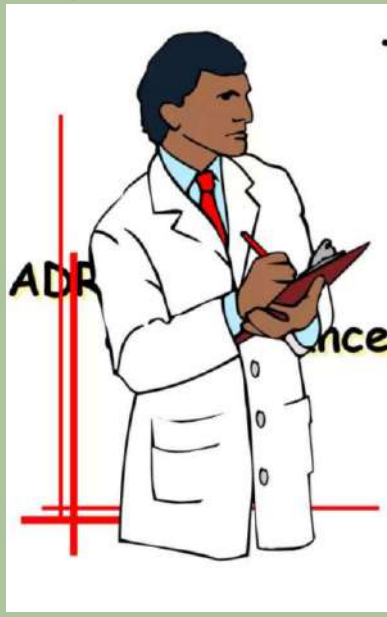
Nurses

Health care Professionals

Patients

How do we report ADRs

- Step 1- Generally the physicians themselves act as reporters, completing the reporting form
- Step 2- keeping a record and sending them to the ADRM Cell, Directorate General of Drug Administration



How do we report ADRs

- Step 3- After evaluation of ADRs report by the Adverse Drug Reactions Advisory Committee (ADRAC)
- Step 4- the ADRM Cell of DGDA→ ADRs data to WHO collaborating center for International Drug Monitoring & Exchange of Drug Information

Yellow Card

SUSPECTED ADVERSE EVENT REPORTING FORM

Identities of reporter, patient, institution, and product trade name(s) will remain confidential

* Mandatory Information

FOR OFFICE USE ONLY

AE report number _____ Data received _____

A. PATIENT INFORMATION

Name/Initial:
Address:

* Contact number

*Age--------- Weight(Kg)------- *Gender ☐Male ☐Female ☐Other

Pregnant : ☐ Yes ☐ No ☐Unknown ☐Not applicable

B. SUSPECTED ADVERSE EVENT INFORMATION

Type of event:

☐ Adverse drug reaction/AEFI
☐ Product quality problem
☐ Medication error
☐ Others (Please specify)

***Describe event including relevant tests and laboratory results:**

☐ Others (Please specify)

***Event start Date** _____
***Event stopped Date** _____

Was the adverse event treated? ☐ **Yes** ☐ **No**
If yes, please specify:

Action taken after reaction:
☐Dose stopped
☐Dose reduced
☐No action taken

Did reaction subside after stopping / reducing the dose of the suspected product? ☐ Yes ☐ No ☐ Not applicable
Did reaction appear after reintroducing the suspected product?
☐ Yes ☐ No ☐ Not applicable

Seriousness of the adverse event:
☐ Non serious
☐ Serious

***Outcomes attributed to the adverse event:**
☐ Recovered

Other relevant history: (pre-existing medical history)
☐ Hypersensitivity ☐ Allergies ☐ Hypertension ☐ Liver or kidney problems ☐ Smoking ☐ Alcohol ☐ Diabetes
☐ Others (Please specify):

C. SUSPECTED DRUG/VACCINE INFORMATION

Brand/Trade name _____ *Generic name with strength _____

*Indication _____

*Medication Start Date/Vaccination Date _____ End Date/Vaccination Time _____

Dosage Form _____ *Frequency (Daily Dose) _____ Batch/Lot number _____

Manufacturer _____ Diluent Information for vaccine _____

CONCOMITANT MEDICINE/VACCINE INFORMATION

Brand/Trade name	Generic name	Indication	Dosage form	Strength & Frequency

WHY REPORT ADRS?

- To prevent drug-induced human suffering
- To avoid financial risks associated with unexpected risks

Underreporting of ADR

- Despite the immense benefits of reporting ADR,under-reporting remains as a major obstacle (Wu et al., 2010)
- 6% of all ADRs are reported in the USA (Alatawi & Hansen, 2017

Underreporting of ADR

- ADRs account for 4.2-30% of hospital admissions in th USA and Canada
- 5.7-18.8% of admissions in Australia and
- 2.5-10.6% of admissions in Europe.

- Member country to send annually over 200 reports per million inhabitants (Rosli et al., 2016)

- Bangladesh has population around 170 million, so Bangladesh should send at least 170×200=34,000 reports/year

Consequences of under-reporting ADR

- Prolongation of hospital stay.
- The mean hospital stay from a mean of 8 days in patients without ADRs to 20 days in patients with ADRs

PREVENTION OF ADR

1. Avoid all inappropriate use of drugs.
2. Use of appropriate dose , route & frequency of drug administration.
3. Elicit & take into consideration previous history of drug reactions.
4. Elicit h/o allergic diseases & exercise caution.
5. Rule out possibility of drug interaction.
6. Adopt correct drug administration technique.
7. Carry out appropriate laboratory investigation.
8. Be aware of interactions with certain foods, alcohol and even with household chemicals.

Management of ADR

Discontinue the offending agent if -

- It can be safely stopped
- The event is life-threatening or intolerable
- There is a reasonable alternative
- Continuing the medication will further exacerbate the patient's condition

Continue the medication (modified as needed) if -

- It is medically necessary
- There is no reasonable alternative
- The problem is mild and will resolve with time

- Discontinue non-essential medications
- Administer appropriate treatment -
  e.g., atropine,protamine sulfate ,digibind antibodies, flumazenil.
- Provide supportive or palliative care -
  e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics
- Consider rechallenge or desensitization

Take home message

- Every drug as an adverse effects
- One of the primary causes of morbidity and mortality
- ADEs; raise the expense of healthcare in general
- For rationale use of drug not only it’s clinical indications are important to be remembered equally important is remembering adverse effects
- Early detection of adverse effects and proper management can be life saving in many situations


Thank
You