

Variation in drug responses & Drug-Drug Interactions

Properties of an Ideal Drug

Effective

Safety

Selective

Reversible Action

Predictable

Freedom from drug interactions

Low cost

Chemically stable

Sources of Variability in Therapeutic Responses

Similar drugs usually produce similar qualities of responses in patients, but might produce different intensities and duration of effects.

- **Dose, Dosage schedule, and Route of administration.**
- **Diurnal variation "Chronopharmacology".**
- **Age and sex of the patient.**
- **Drug reactions.**
- **Drug interactions: other drugs, diet, and environment.**
- **Placebo effect.**
- **Intercurrent illnesses.**
- **Tolerance.**
- **Genetic or racial factors, "Pharmacogenetics".**

Causes of Variability in Drug Response

Those related to the biological system

1. Body weight and size
2. Age and Sex
3. Genetics - pharmacogenetics
4. Condition of health
5. Placebo effect

Causes of Variability in Drug Response

- **Those related to the conditions of administration**
 - 1. Dose, formulation, route of administration.**
 - 2. Resulting from repeated administration of drug:**
 - drug resistance; drug tolerance-tachyphylaxis; drug allergy
 - 3. Drug interactions:**
 - chemical or physical;
 - GI absorption;
 - protein binding/distribution;
 - metabolism (stimulation/inhibition);
 - excretion (pH/transport processes);
 - receptor (potentiation/antagonism);
 - changes in pH or electrolytes.

Pharmacogenomics:

The relation between the individual's genetic makeup to his/her response to specific drugs (entire genome).

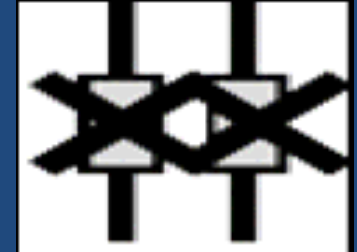
Pharmacogenetics:

Interindividual variation in drug response that is due to genetic influences (specific gene).

Phenotypes of CYP450

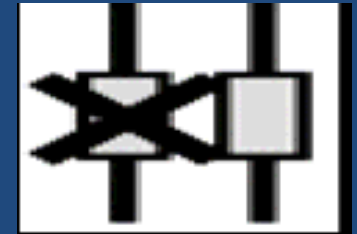
1. Poor metabolizer (PM)

- has low metabolic capacity
- has two mutant alleles



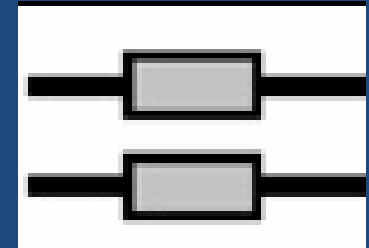
2. Intermediate metabolizer (IM)

- has metabolic capacity between PM and EM
- has one reduced activity allele and one null



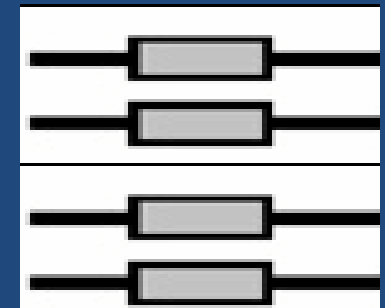
3. Extensive metabolizer (EM)

- has regular metabolic capacity
- has at least one and no more than two normal functioning alleles



4. Ultrarapid metabolizer (UM)

- has higher metabolic capacity than EM
- has multiple copies of functional alleles



Drug-drug interaction

- When two drugs taken together, there is a possibility that the drugs will interact with each other to cause unanticipated effect. Usually increase or decrease in the desired therapeutic effect.
- Drug-drug interaction can occur in the following sites
 1. at the site of absorption, tetracycline is not absorbed from the GI tract if calcium product present in the stomach.
 2. during biotransformation (CYP 450).
 3. At the site of action, drug antagonism.

Drug-drug interaction

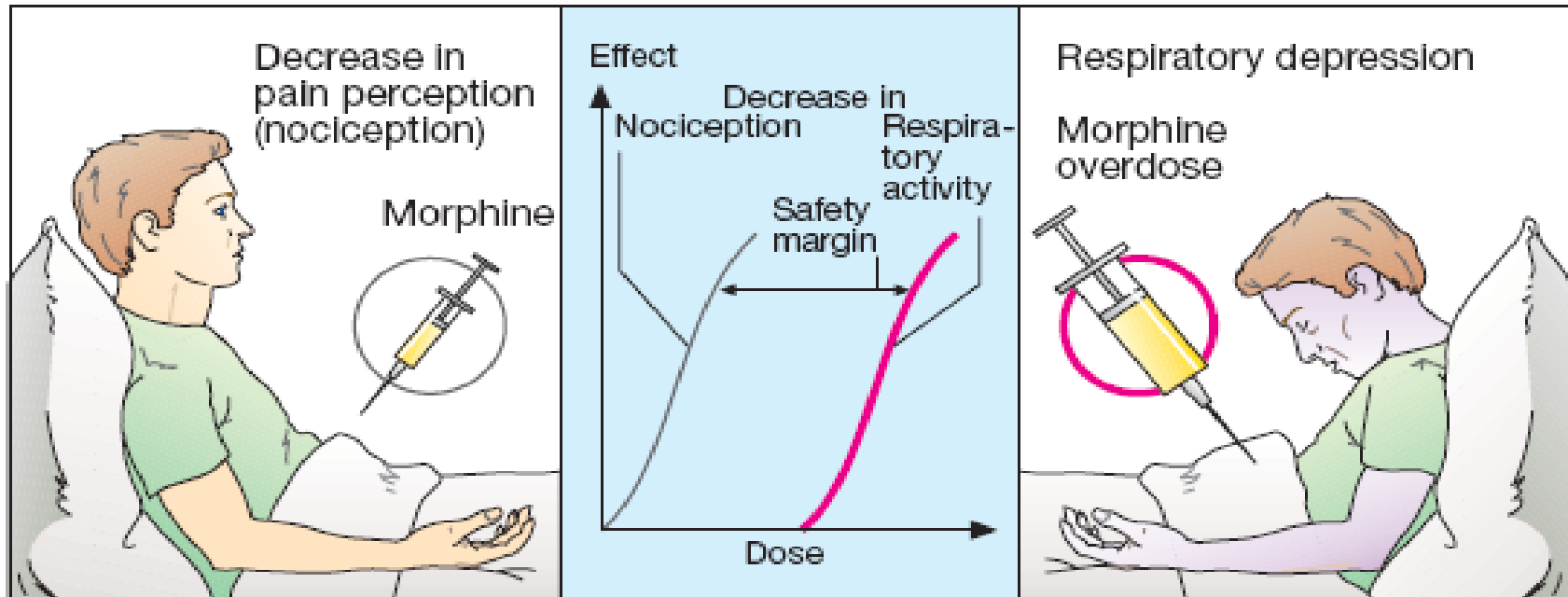
3. During excretion, digoxin and quinidine are both excreted from the same sites in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin.
4. During distribution, aspirin competes with methotrexate for protein binding sites, and because aspirin is more competitive for the sites, resulting in increased release of methotrexate and so increase toxicity to tissues.

Adverse effect

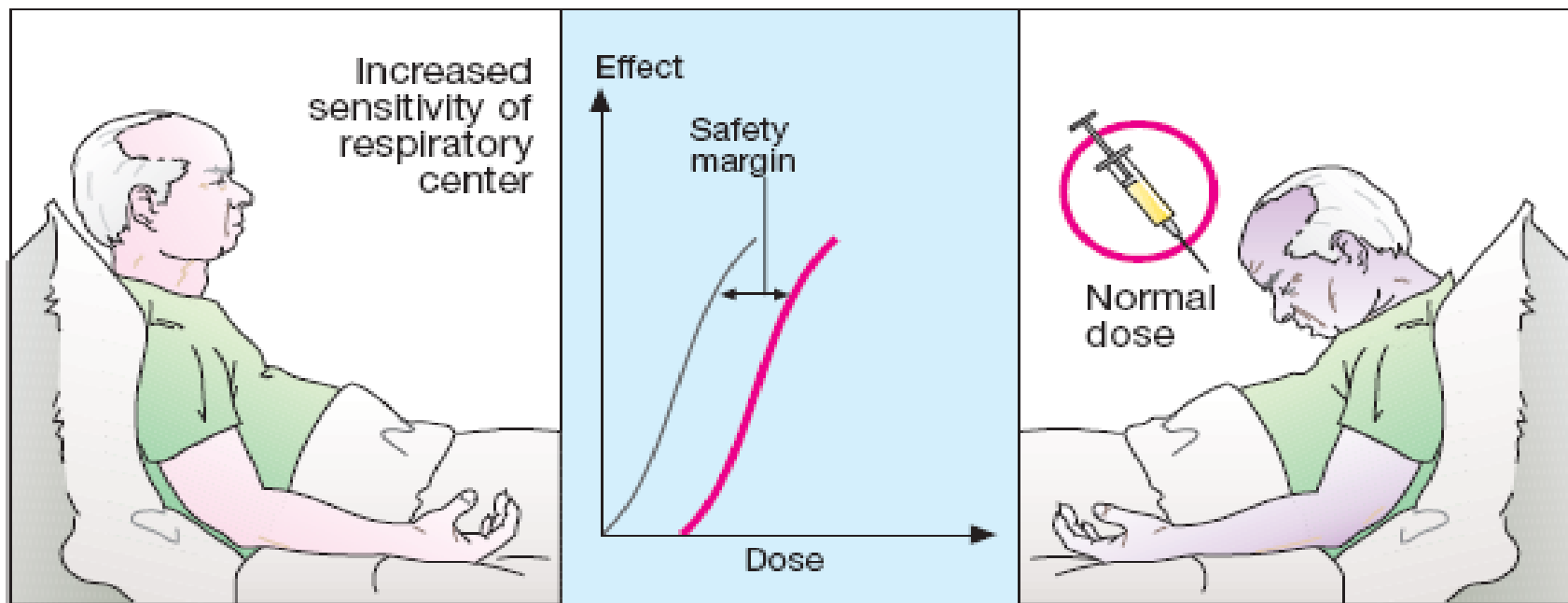
- Adverse effect are undesired effect that may be unpleasant or even dangerous they can occur for many reasons:
 1. The drug may have other effects on the body besides the therapeutic effect.
 2. The patient is sensitive to the drug.
 3. The patient is taking too much or too little of the drug.
- the nurse, as the most frequently administers medications, must be constantly alert for sign of drug reactions of various types.

Remember !!!

- With every drug use, unwanted effects must be taken into account.
- Before prescribing a drug, the physician should therefore assess the **risk: benefit ratio**.
- In this, knowledge of principal and adverse effects is a prerequisite.



A. Adverse drug effect: overdosing



B. Adverse drug effect: increased sensitivity

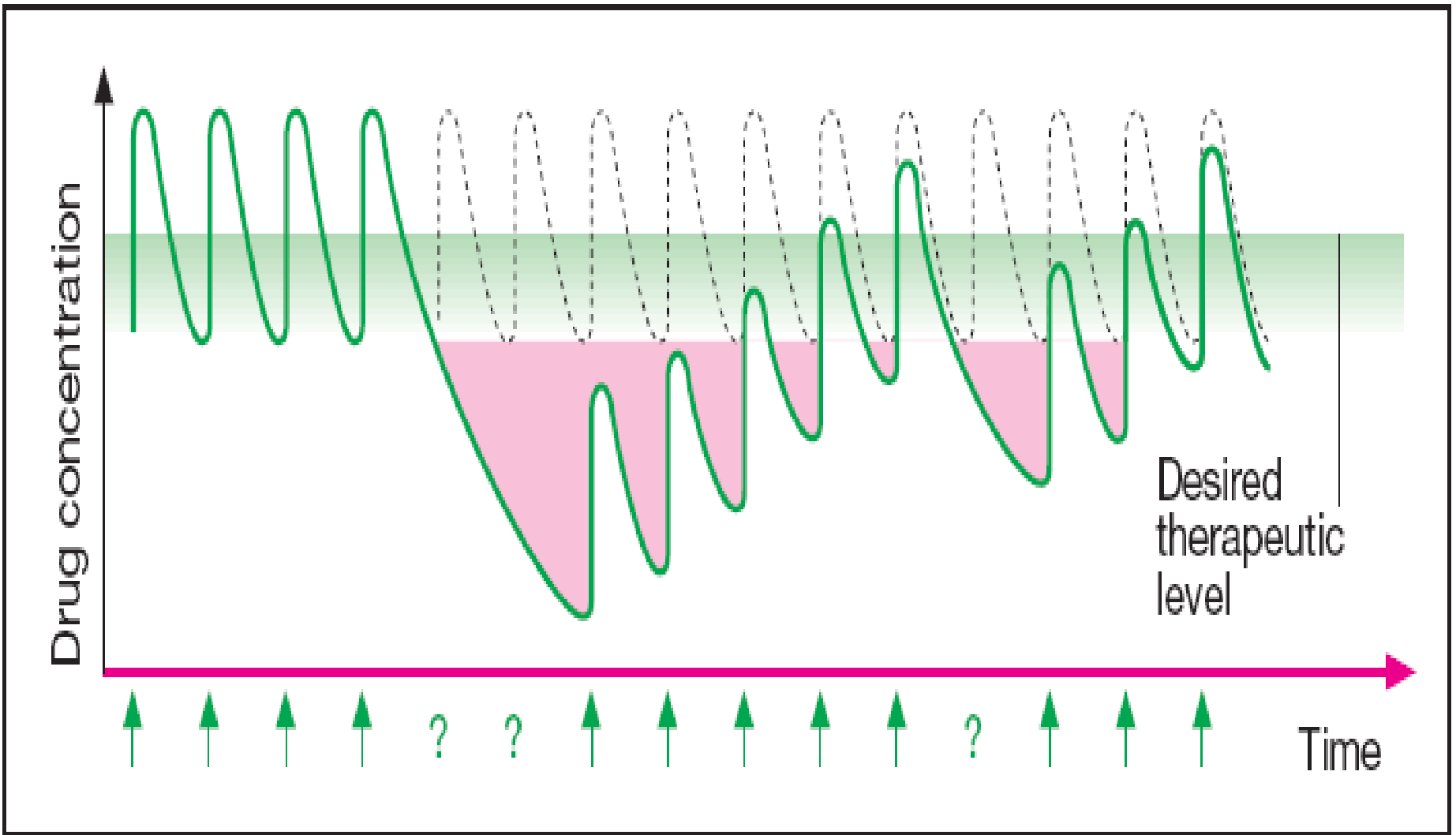
Adverse Drug Reaction

- Adverse drug reactions are classified as predictable or unpredictable.
- A predictable drug reaction is related to the pharmacological actions of the drug.
- An unpredictable reaction is related to immunological response (hypersensitivity reactions) or non-immunological response

Drug Allergy

- It is defined as an adverse reaction to a drug by a specific immune response either directly to the drug or one or more of its metabolites alone, or to a drug bound to a body protein such as albumin, (*Hapten*).
- Such binding alters the structure of the drug/protein complex, rendering it antigenic.

Compliance



Time course of drug concentration with irregular intake

Adults >65 years old

- growing population
- 20% of hospitalizations for those >65 are due to medications they're taking

Pharmacokinetics

- Decrease in total body water (due to decrease in muscle mass) and increase in total body fat affects volume of distribution
- Water soluble drugs: lithium, aminoglycosides, alcohol, digoxin
 - Serum levels may go up due to decreased volume of distribution
- Fat soluble: diazepam, thiopental, trazadone
 - Half life increased with increase in body fat

- Oxidative metabolism through cytochrome P450 system does decrease with aging, resulting in a decreased clearance of drugs

Pharmacokinetics: Excretion and Elimination

- GFR generally declines with aging, but is extremely variable
 - 30% have little change
 - 30% have moderate decrease
 - 30% have severe decrease
- Serum creatinine is an unreliable marker
- If accuracy needed, do Cr Cl

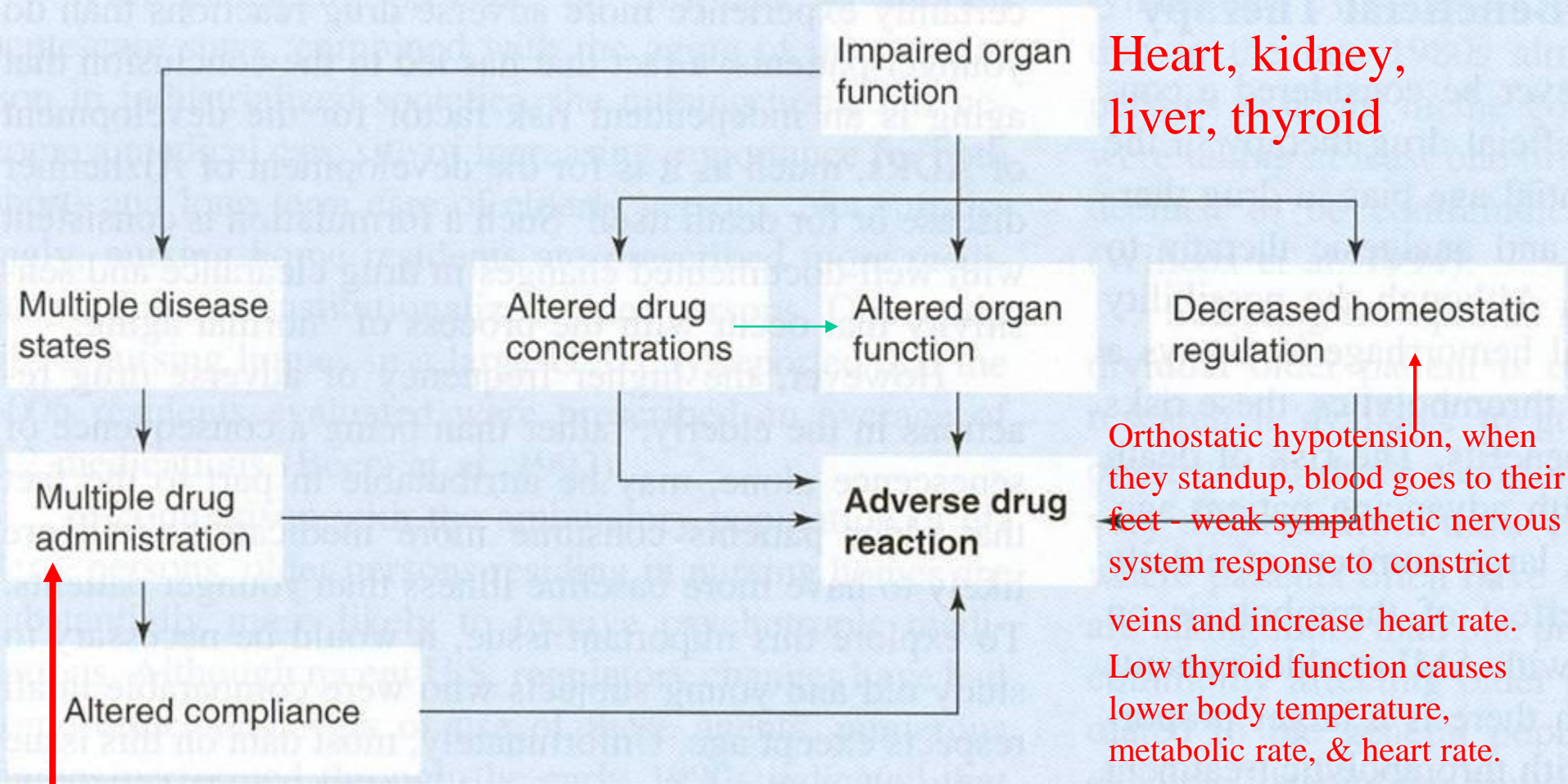
Example: Creatinine Clearance vs. Age

<u>Age</u>	<u>Scr</u>	<u>CrCl</u>
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

Pharmacodynamics (PD)

- Definition: the time course and intensity of pharmacologic effect of a drug
- Age-related changes:
 - ∇ sensitivity to sedation and psychomotor impairment with benzodiazepines
 - ∇ level and duration of pain relief with narcotic agents
 - ∇ drowsiness and lateral sway with alcohol
 - ©HR response to beta-blockers
 - ∇ sensitivity to anti-cholinergic agents
 - ∇ cardiac sensitivity to digoxin

Factors contributing to adverse drug reactions in elderly patients



Heart, kidney, liver, thyroid

Orthostatic hypotension, when they stand up, blood goes to their feet - weak sympathetic nervous system response to constrict veins and increase heart rate. Low thyroid function causes lower body temperature, metabolic rate, & heart rate.

Polypharmacy

How many prescription medications are too many? >4 or >6
Many elderly people receive 12 medications per day

Pediatric Patients

- Higher proportion of water
- Lower plasma protein levels
 - More available drug
- Immature liver/kidneys
 - Liver often metabolizes more slowly
 - Kidneys may excrete more slowly

Pediatric Dosing

Traditionally, for less frequently used drugs, extrapolation is done from adult dose on a weight or surface area basis

Problems

- Absorption may be more or less than adult
- Clearance of some drugs in children is affected by maturation, as well as size
 - Cytochrome P450 enzyme system matures over time
 - Glomerular filtration changes over time
- Drug targets may vary with age

CYP Enzymes

- CYP isoforms vary with age
- For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1.2 ml/min/kg to 9 ml/min/kg over first few months of life
- Carbamazepine (3A4) clearance faster in children than adults – requires higher doses

- “Children are not Small Adults”

Questions ??????