Toxicological aspects of medicine

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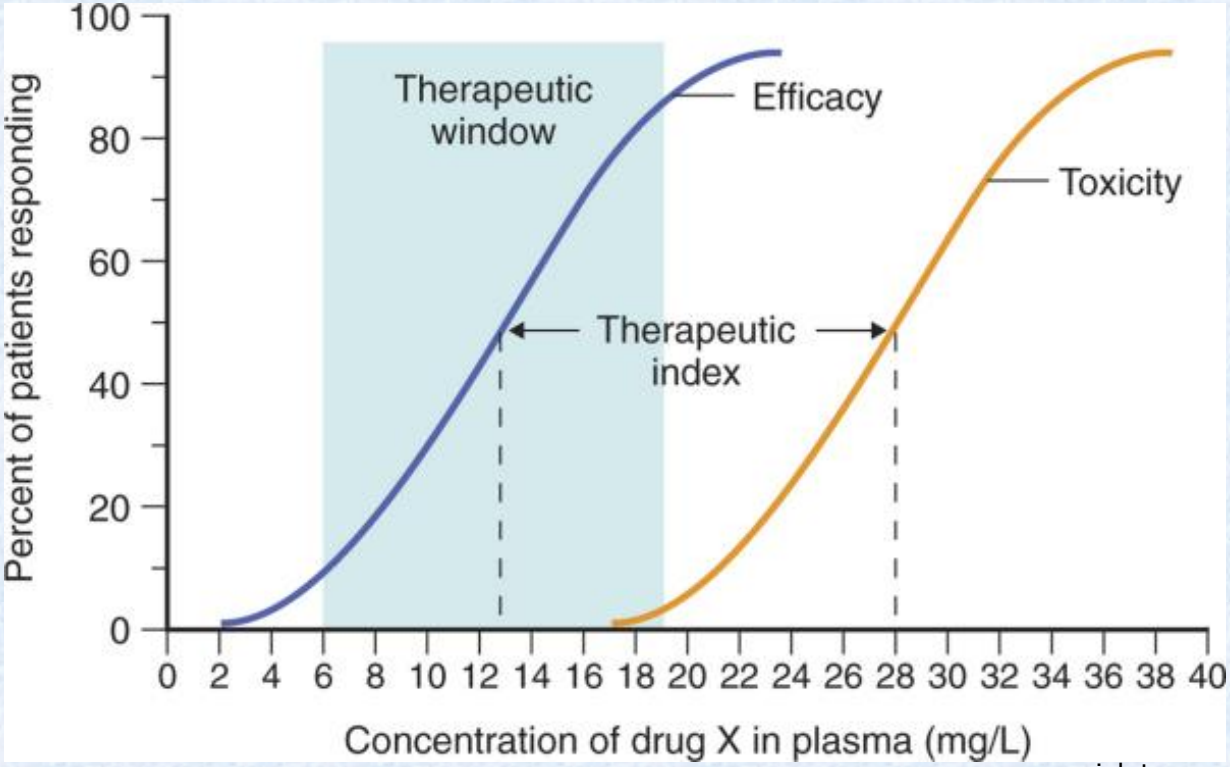
Pharmacology and toxicology

"The dose makes the poison." (Paracelsus)

Gilbert, 2005

Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493-1541)



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Alle Ding' sind Gift und nichts ohn' Gift; allein die Dosis macht, das ein Ding kein Gift ist."

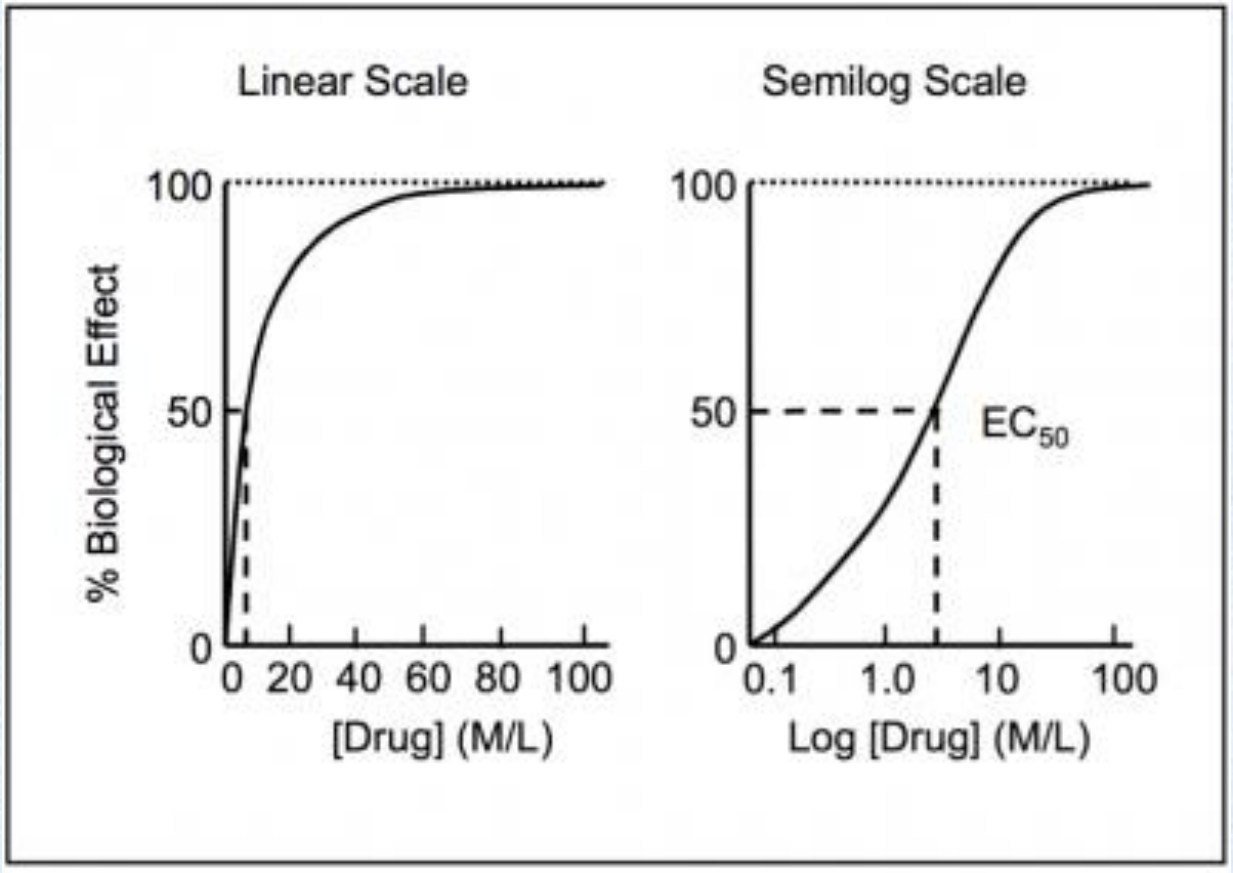
„All things are poison and nothing is without poison, only the dosage makes a thing not poison.."

Dose-response relationship

$$[AR] = \frac{[R_O][A]}{K_D + [A]}$$

A: agonist, R: receptor,

KD: dissociation constant

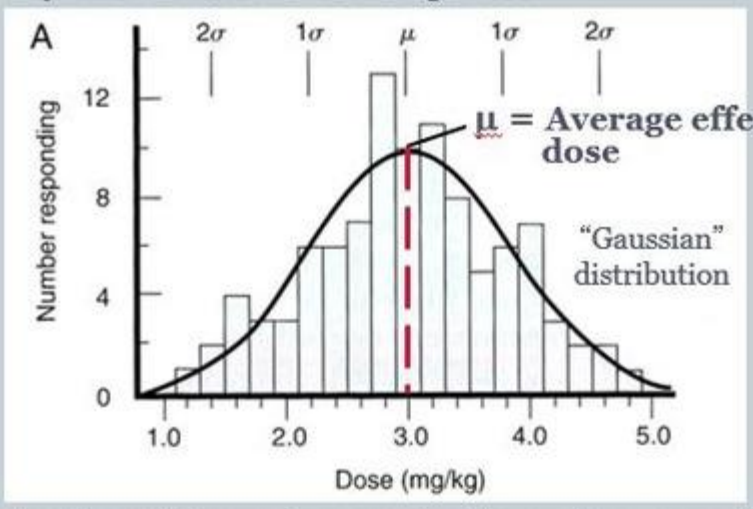


tmedweb.tulane.edu

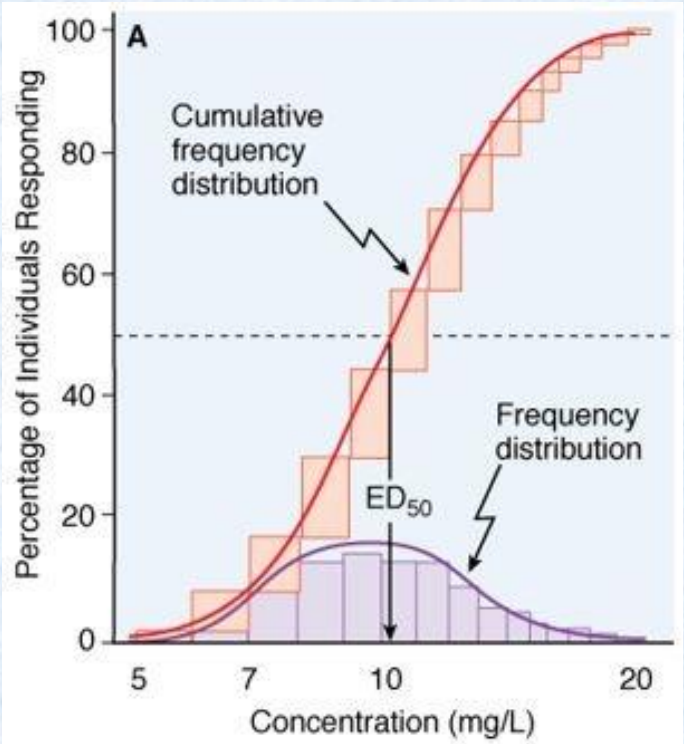
Quantal vs. cumulative dose-response curves

Responsiveness/sensitivity of individuals is variable, follows normal distribution.

Frequency distribution curve of drug doses



Determine the minimum dose required to produce a specified effect for each member of the population



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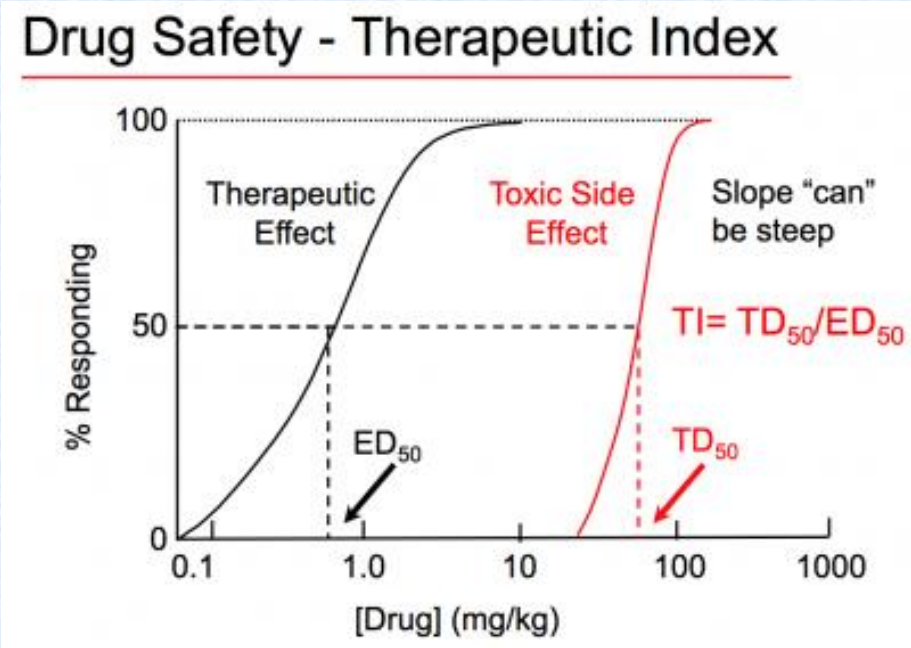
Pharmacology and toxicology

Therapeutic window: concentration range within which the drug exerts the wanted therapeutic effect, without toxic side effects.

Therapeutic index: median toxic dose/median therapeutic dose



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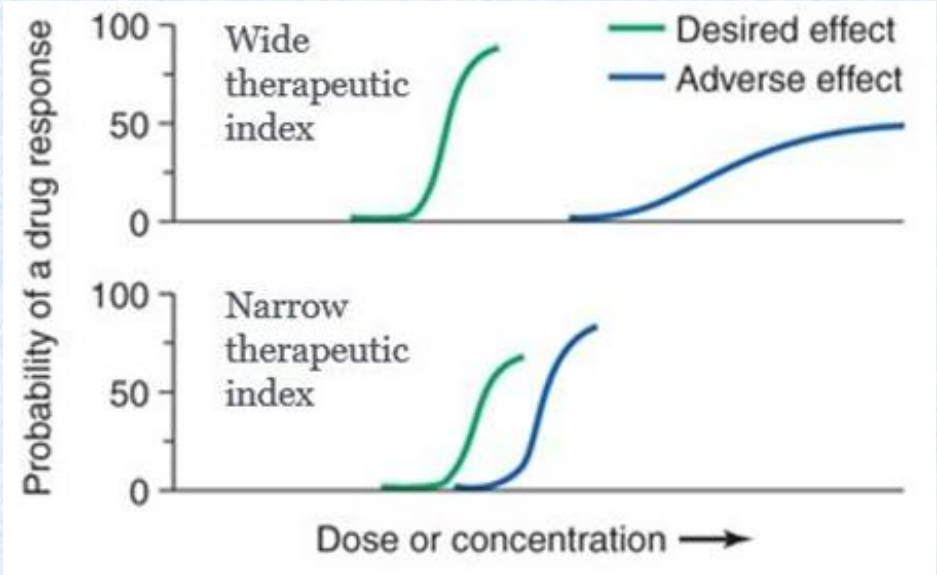

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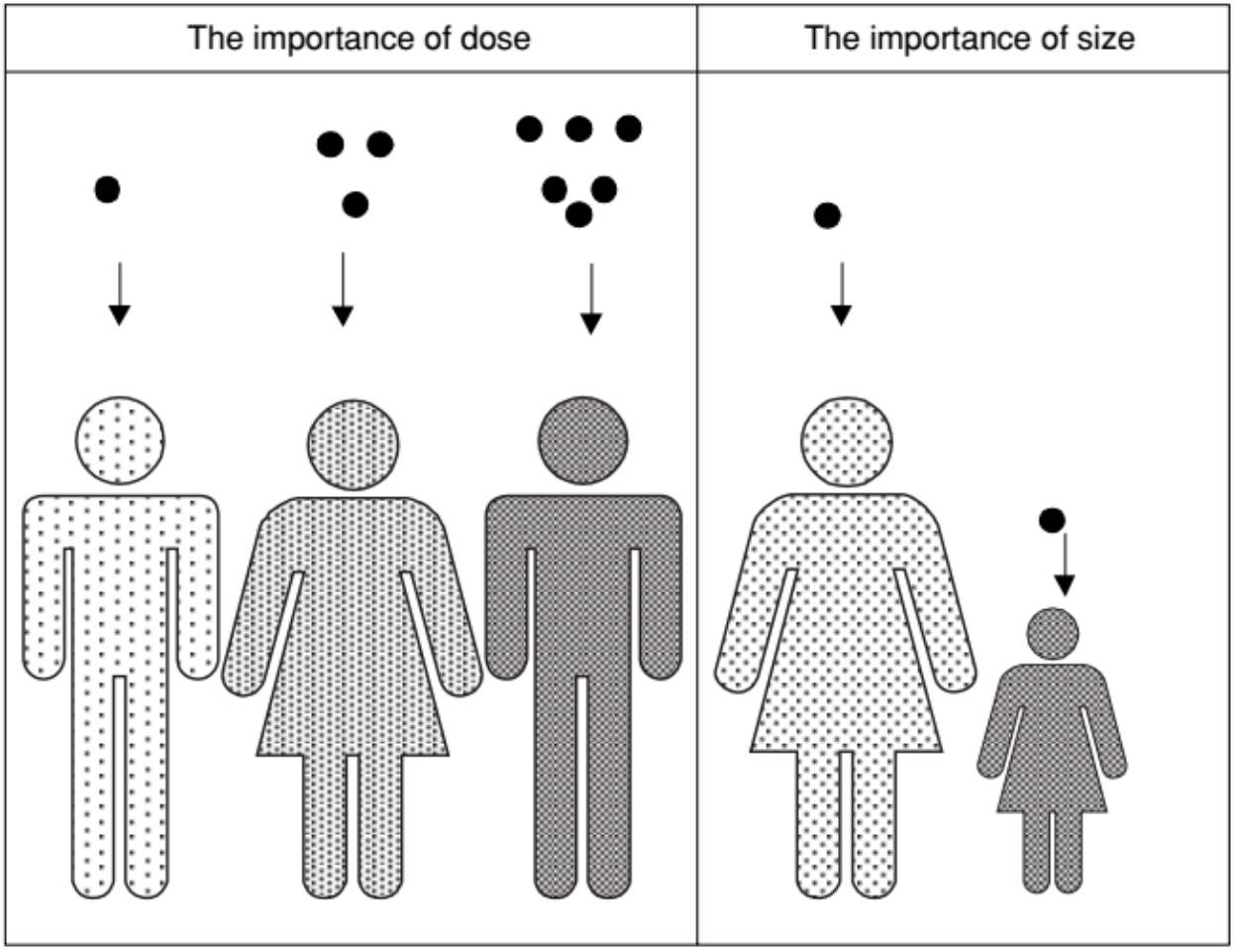
Dose-response relationship



Gilbert, 2005

Harris & Goonetilleke, 2004

Adverse drug effects

Incidence of adverse drug effects in normal population 0,5-1%

Incidence in hospitalised patients ≈ 15%!

Causes of adverse drug effects:

- Interactions between drugs
- Different metabolic rate
- Special sensitivity – foetus, neonate, elderly, chronic disease…
- Allergy/hypersensitivity
- Addiction (CNS drugs, anxiolytics, stimulants…)

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inadequate dosing

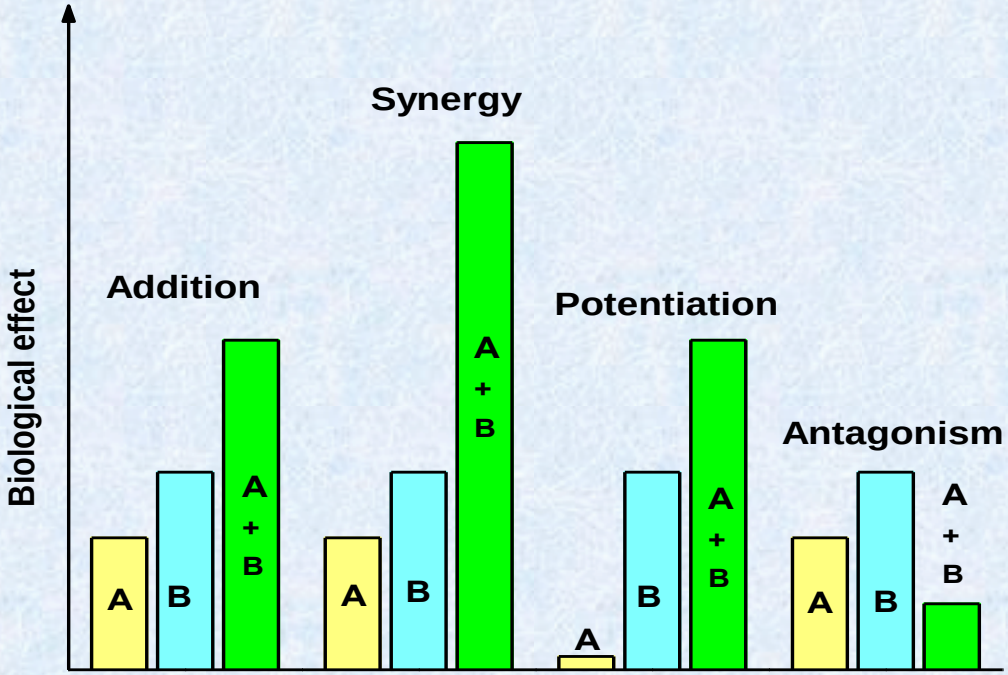
(mostly overdose)

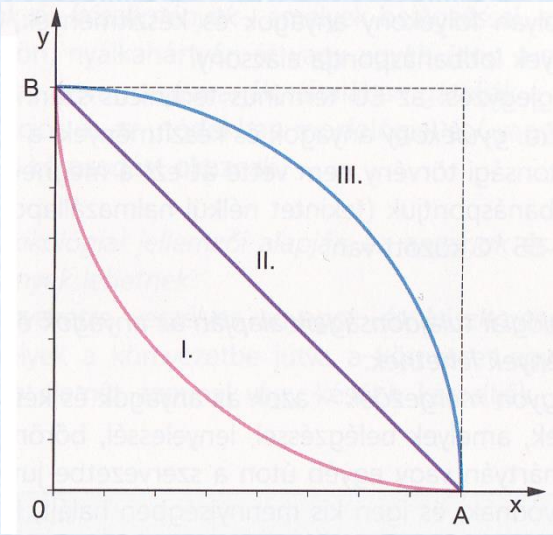
Interactions

Addition

Synergy ≈ Potentiation

Antagonism





Fürst, 2007

Isobolograms of drugs A and B

I: synergy

II: addition

III: antagonism

Interactions

Background mechanisms of drug interactions

Pharmacokinetic interactions

Competition for plasma protein binding, specific transporters

Metabolism, enzyme induction

Elimination – competition for transporters in kidney

Pharmacodynamic interactions

Same system as target for multiple drugs

Factors affecting metabolism

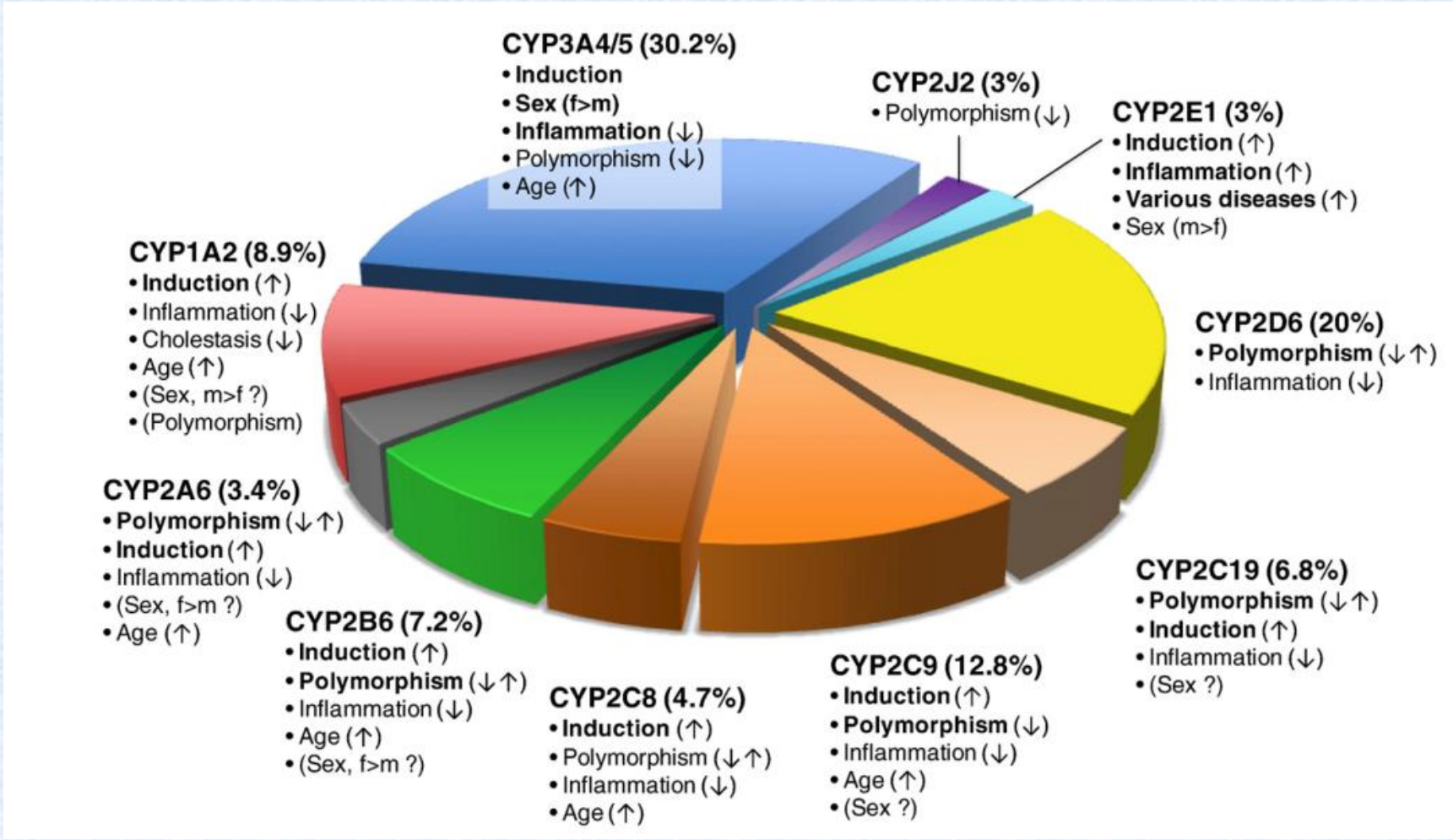
- <u>Enzyme induction/inhibition</u>

- occurs for phase I and phase II enzymes
- mechanism: “xenobiotic sensors” (transcription factors, steroid receptor-like receptors) → transcription of enzymes ↑
- induction: carbamazepine (antiepileptic) → halflife decreases dramatically in a few weeks → increasing dose
- chronic alcohol induces enzyme responsible for production of toxic paracetamol metabolite
- inhibition: erythromycin
- basis for drug interaction!

Factors affecting metabolism

- Genetic variability, enzyme polymorphisms - isoforms
- Species (animal studies!)
- Diseases (liver, kidney, gastrointestinal, infection)
- Sex (female slower metabolism for certain drugs)
- Age – in babies, liver metabolism is much slower than in adults (caffeine half-life: days, in adults: 4 hours), elderly also slower
- Environmental pollutants (heavy metals, PAH), nutrition (grapefruit juice cytochrome inhibitor)

Factors affecting metabolism



Zanger & Schwab, 2013

Genetic variability in CYP

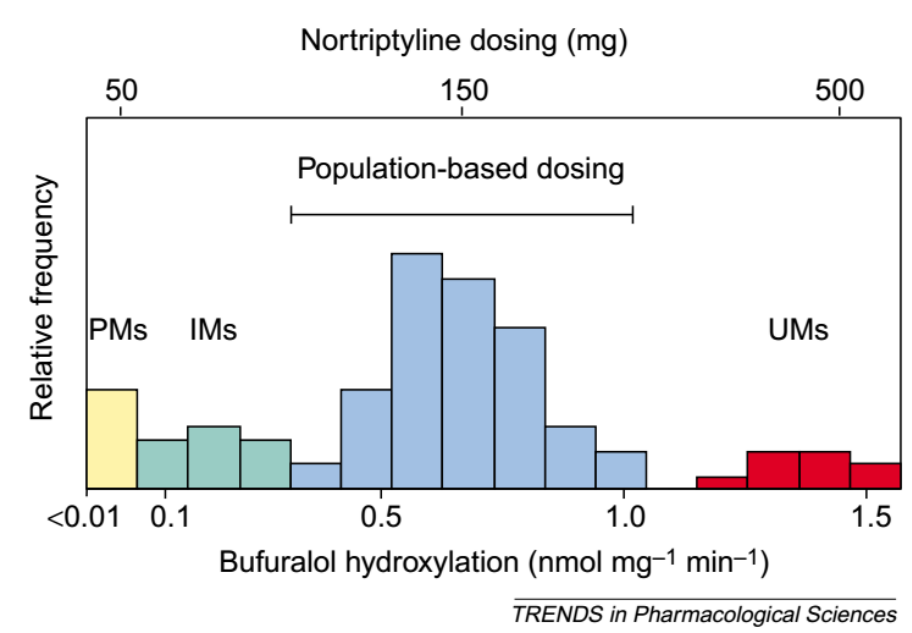
Clinically relevant enzyme polymorphisms – CYP2C, CYP2D

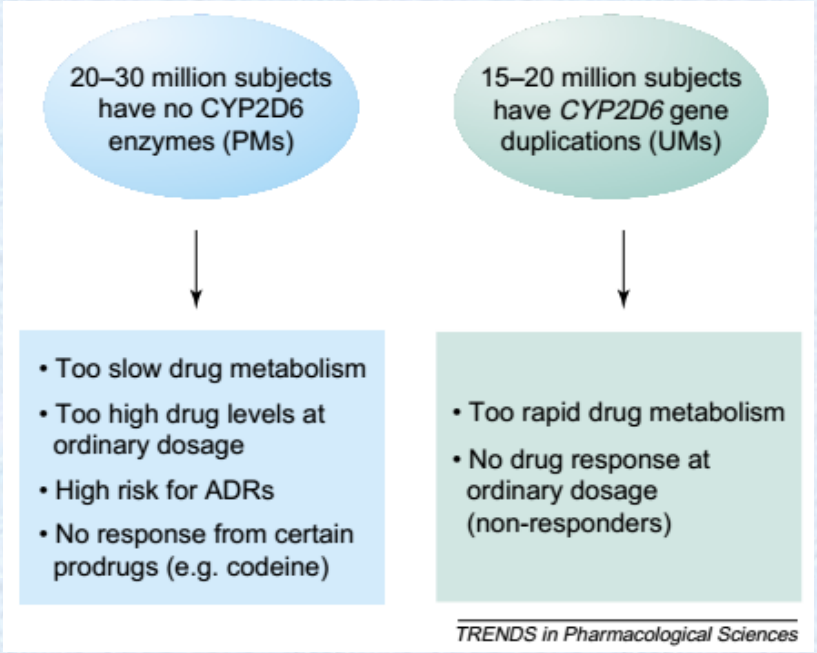
Poor, intermediary, extensive and ultra-rapid metabolisers

ADR: adverse drug response ↔ non-responders

Antidepressants, antipsychotics, antitumour agents, immunosuppressants, antiepileptics…

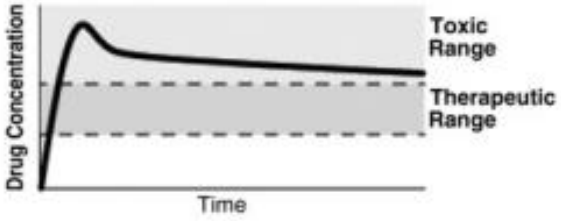
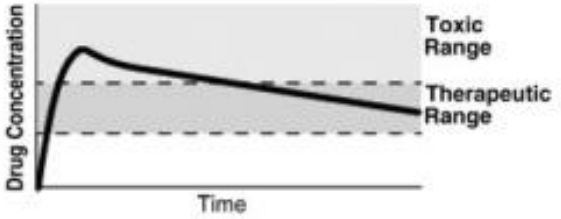
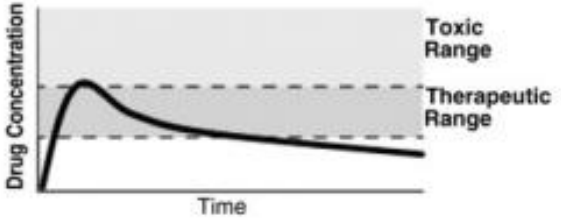
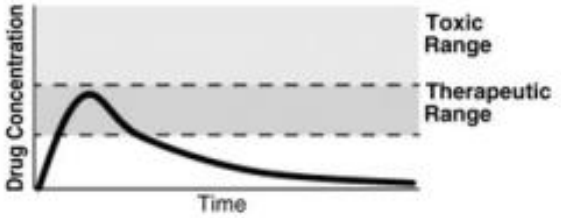
Pharmacogenetics, personalized therapy





Ingelman-Sundberg, 2004

Genetic variability in CYP

Phenotype	Genetic Mechanisms	Pharmacokinetic Effects
Poor Metabolizer (PM)	2 inactive alleles	
Intermidiate Metabolizer (IM)	2 decreased-activity alleles OR one active allele *and* one inactive allele OR one decreased-activity allele *and* one inactive allele	
Extensive Metabolizer (EM)	2 functional alleles (wild type)	
Ultrarapid Metabolizer (UM)	Gene duplication in the absence of inactive or decreased alleles	

Genetic mechanisms for CYP450 metabolic phenotypes and their pharmacokinetic implications (van der Weide et al., 2005)

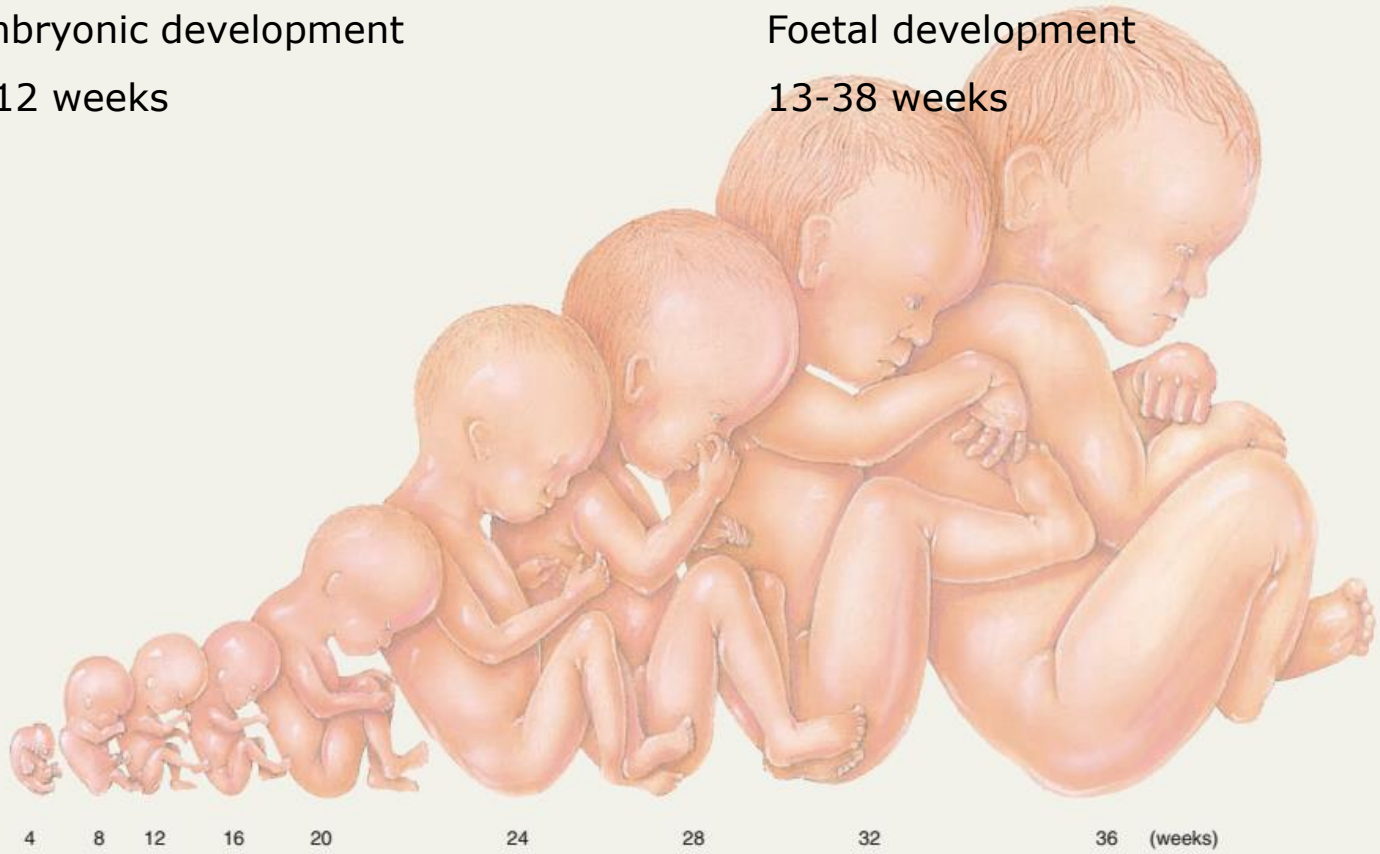
Teratogenic effects

Embryonic development

1-12 weeks

Foetal development

13-38 weeks



Organogenesis

↓

Severe teratogenesis

Differentiation (maturation), growth

↓

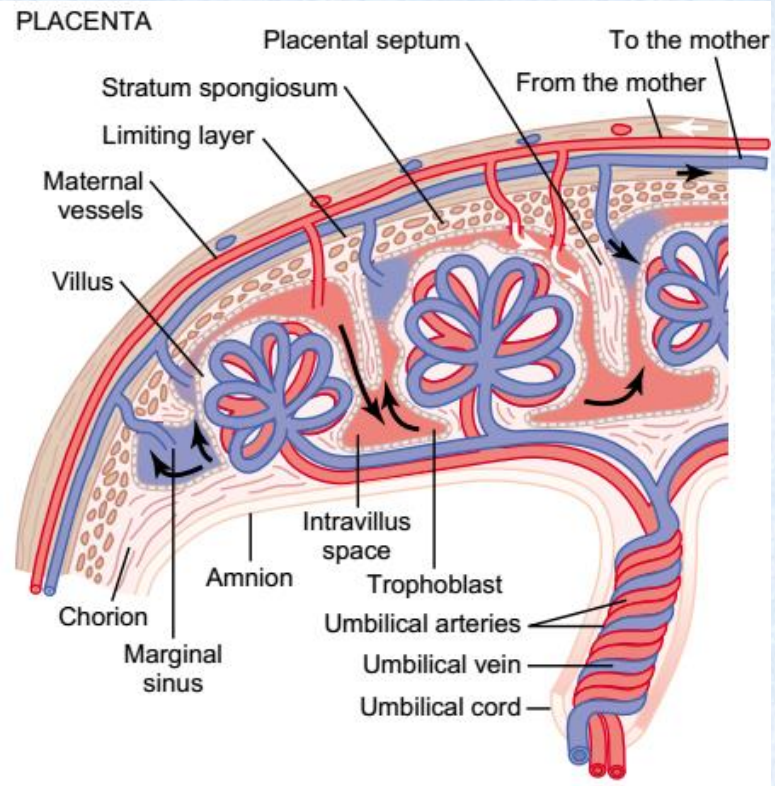
Milder, delayed teratogenic effects

Tortora & Derrickson, 2012

Exposition in utero

- Placental barrier
- Small, lipophilic molecules cross (drugs!)
- Foetal metabolism limited
- Foetal blood-brain barrier not developed (human neonatal period)

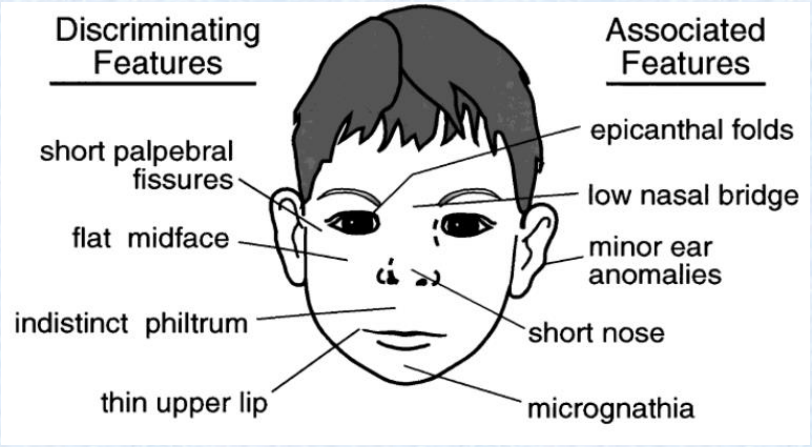
Teratogenic agents: disrupt developmental processes

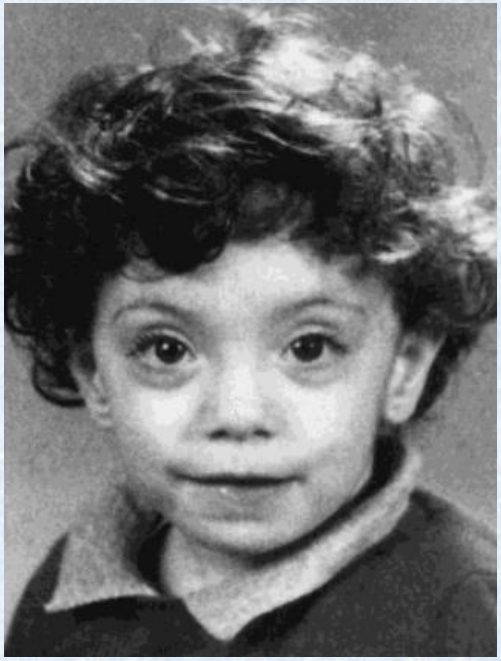


Guyton, 2006

Ethanol – foetal alcohol syndrome

- Limb malformations, heart defects, slow prenatal + postnatal growth, structural brain abnormalities
- Neurological deficits: hearing loss, poor fine motor skills, eye-hand coordination
- Mental retardation, behavioural problems
- Characteristic facial features in childhood, no other marker
- Estimated incidence: 3-4/1000





Sampson et al., 1997

Teratogenic effects

Other teratogens

- Irradiation – first trimester
- Illegal drugs – cocaine
- Antibiotics
- Anticoagulants, antitumor agents, antiepileptics, thyroid drugs….
- Cigarette smoking – low weight, higher risk of infant mortality, heart and respiratory problems

Many drugs can pass into mother's milk and can harm the baby during nursing!

Thalidomide (Contergan®)

Marketed in 1957

Sedative, anxiolytic, antiemetic agent for pregnant women

>10000 malformations worldwide until withdrawal in 1961

Largest drug disaster ever → stricter protocols in pharmacological toxicology

Now prescribed against leprosy, certain cancer types

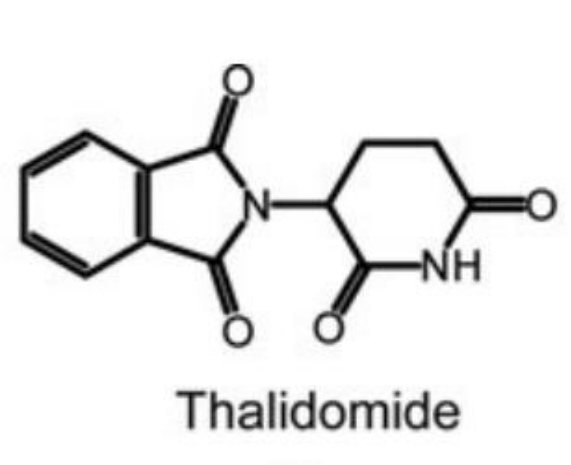
www.toxipedia.org

helix.northwestern.edu

Thalidomide (Contergan®)

Mechanism of effect still not clear

- ROS (reactive oxygen species) generation
- Inhibits formation of blood vessels
- DNA damage of S-stereoisomer (R-S conversion)
- differences in metabolism
- Rodents – resistant, rabbit, chicken, zebrafish – sensitive
- Rodent cell/tissue cultures sensitive! (ROS, blood vessel effect)

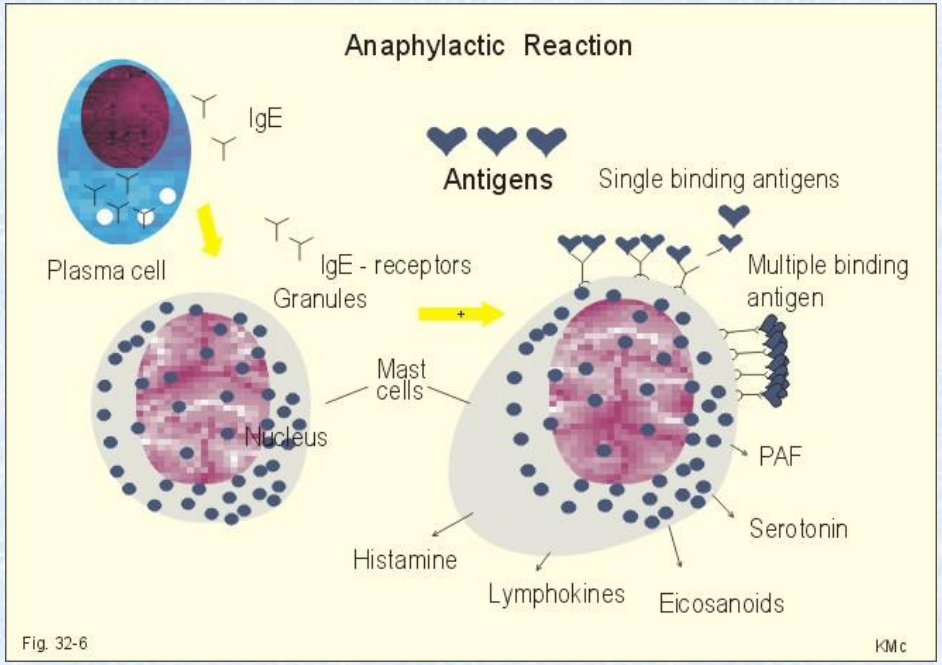


Thalidomide

Ito, 2011

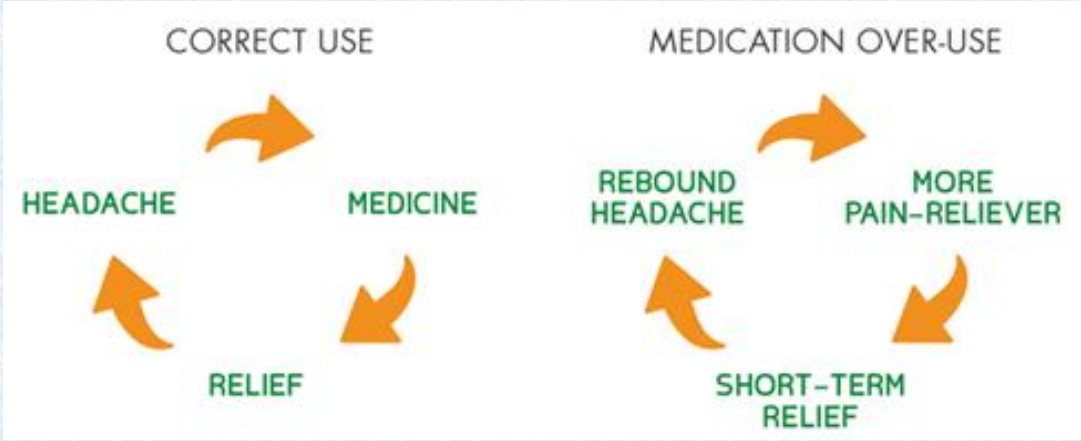
Medication allergies

- Hypersensitivity reaction, drug behaves as antigen, antibodies produced
- Symptoms: skin rash, itching → → anaphylactic shock
- Most common: penicillin allergy (10-15% of patients, but 80-90% may not be truly allergic!)
- Desensitisation, resensitisation may occur, skin test
- Cross-allergy: derivatives, similar compounds (amoxicillin, cephalosporins) – matter of debate



Headache

- 8% of headache patients may suffer due to medication!
- headache is a frequent side effect of many drugs: drugs acting on blood vessels, antidiabetics, anti-inflammatory drugs, antidepressants, antiepileptics, hormonal drugs…
- "medication overuse headache" or "rebound headache"
  pain killers taken on a daily basis for years → chronic headache may develop, especially in migraine-prone patients

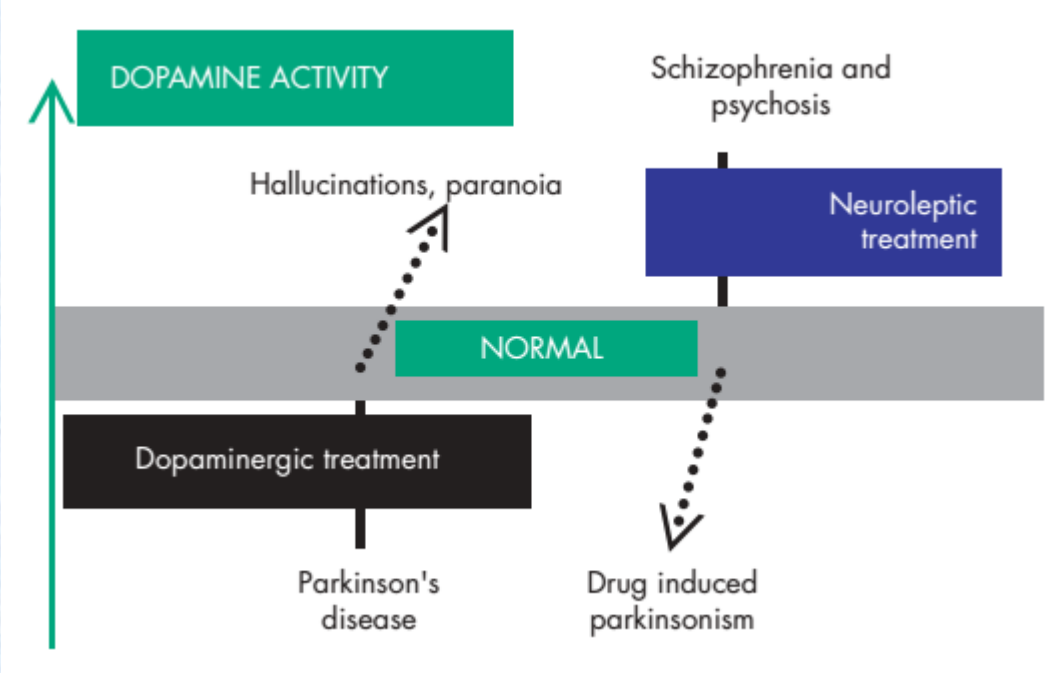


www.rbforhealth.co.uk

Neurological symptoms

Movement disorders

- 1/3 of Parkinson cases is caused by medicines!
- Neuroleptics, antidepressants, antiepileptics
- Parkinson medication – mostly levodopa



Grosset & Grosset, 2004

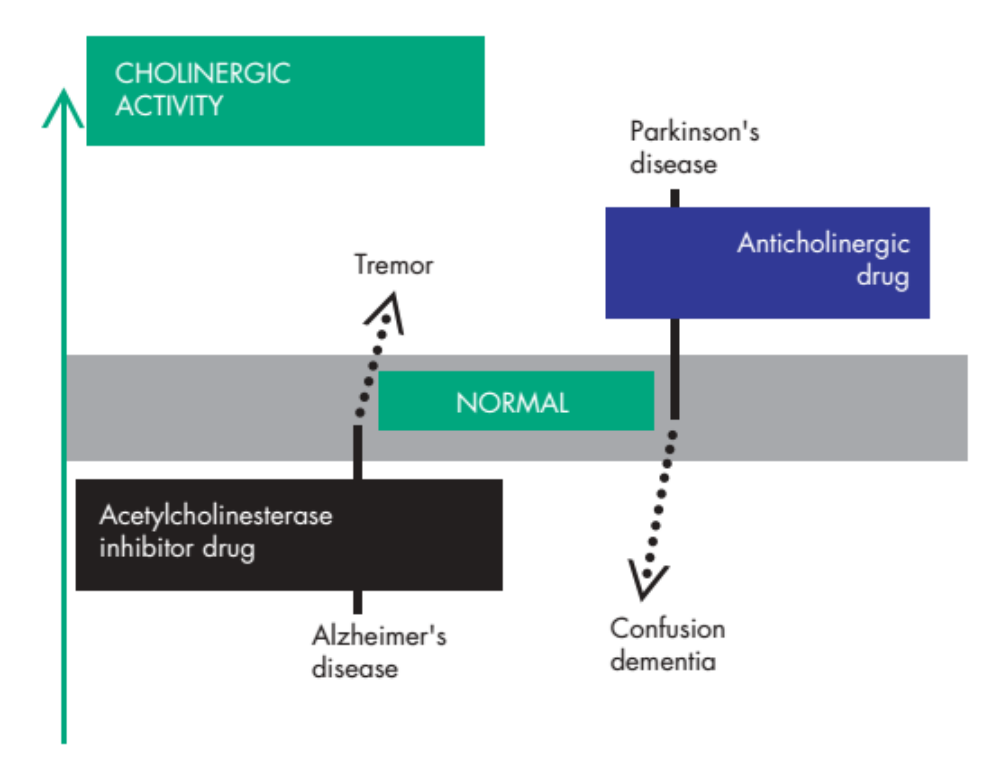
Neurological symptoms

Cognitive deficits

- anticholinergic drugs (Parkinson medication)

Tremor, hyperexcitation

- drug causing cholinergic excess (Alzheimer medication)



Grosset & Grosset, 2004