Basic principles of drug interactions

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Drug interaction

A drug interaction occurs when:

- **the amount or**
- **action of a drug**

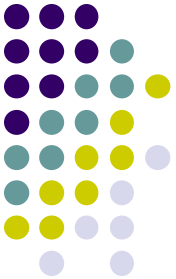
in the body is altered
– usually ⇑ or ⇓ –
by the presence of another drug or multiple drugs

- Drug interactions **contribute to the cost of healthcare**

(because of the costs that are required to treat problems caused by):

- changes in effectiveness
- or side effects

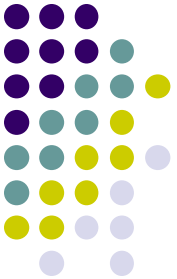
Drug interactions
Statistics



- interactions are responsible for only about 3.8 % of emergency department visits
- however, many of these cases are serious
- in 1994 - 106,000 Americans died of adverse drug reactions (ADRs)
- a 1998 article in the JAMA estimated that:

"ADRs may rank from the fourth to the sixth leading cause of death"

Drug interactions
Additional data



- at least 25% of patients over age 65 take 3 or more medications daily
- in many cases - prescribed by different doctors
- any time 2 or more are taken at the same time, there is the risk of a

drug interaction

Increasing risk
Drug interactions

- further ⇑ the risk, about 40%

  of patient adults regularly take herbal supplements or vitamins

- often in combination with prescription or OTC medications

- usually without the knowledge of their doctors or pharmacists

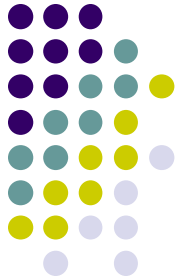
Drug interactions
Category

- **wanted – to therapeutic effect or toxicity treatment**

  (hypertension, asthma, infection, cancer therapy)

- **unwanted – usually result in side effects or therapy failure**

Drug interaction categories



- **drug-drug interactions** occur when two or more drugs react with each other

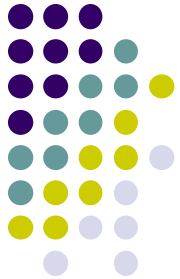
  (sedative & antihistamine)

- **drug-food/beverage interactions** result from drugs reacting with foods or beverages (alcohol & sedative)

- **drug-condition interactions** may occur when an existing medical condition makes certain drugs potentially harmful

  (high BP & nasal decongestant)

Drug interaction levels



- **pharmaceutical level** occurs when two or more drugs or vehicles react with each other on the basis of their chemistry

- **pharmacological level** should be divided:

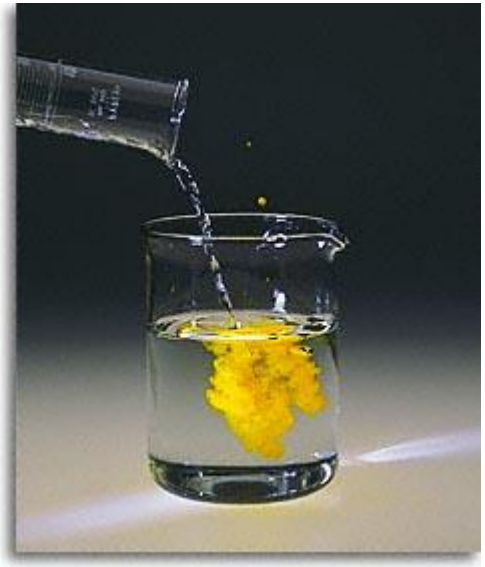
  - **pharmacokinetic level** (one drug affects the **absorption, distribution, metabolism,** or **excretion** of another)

  - **pharmacodynamic level** (alteration of the **sensitivity** or the **responsiveness** of the tissues to one drug by another)

Chemical drug interactions
Pharmaceutic

- ***phenytoin*** precipitates in ***dextrose***
- ***amphotericin*** precipitates in ***saline***
- ***gentamycin*** is incompatible (chemically)

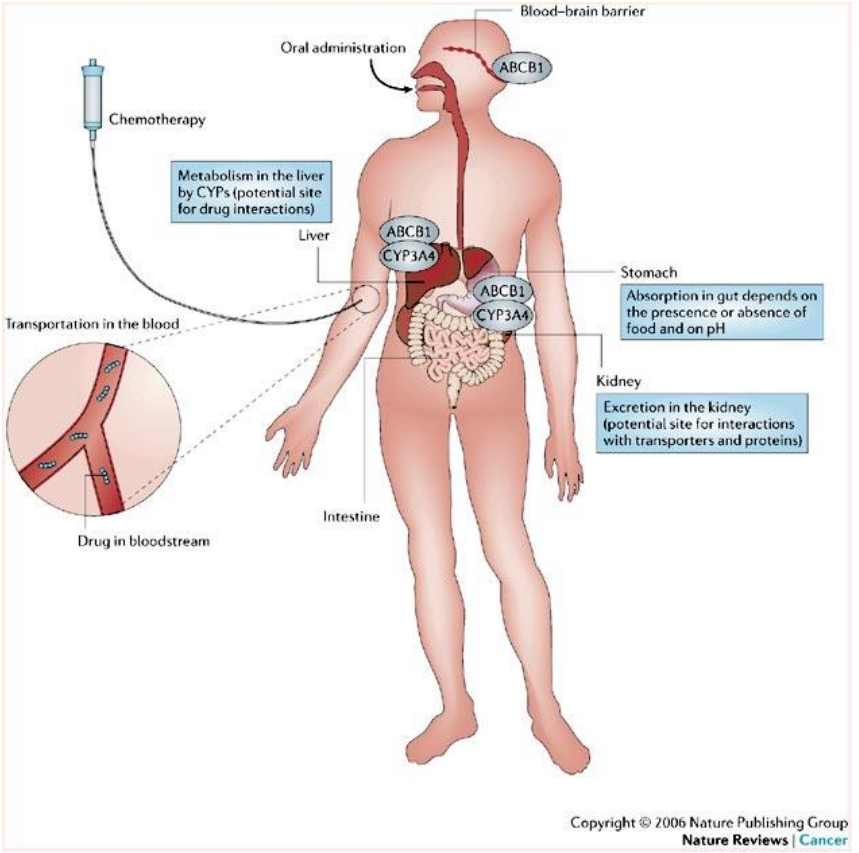
  with ***β-lactamames***



http://resources.educ.queensu.ca/science/main/concept/gen/g09/N.%20Sabet/Qualitative%20Analysis%20-%20Lab.html

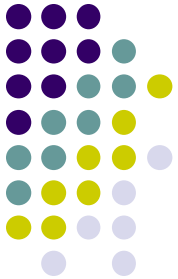
Pharmacokinetic drug interactions

- **absorption** of a drug into the body
- **plasma protein binding & distribution** of the drug within the body
- **metabolism** - alterations made to the drug by the body
- **excretion** of the drug from the body



http://www.nature.com/nrc/journal/v6/n7/fig_tab/nrc1887_F1.html

Pharmacokinetic interactions
Absorption



- ***metoclopramide***

⇑ gastric emptying - ⇑ paracetamol absorption

Chelation/complex formation

- ***cholestyramine***

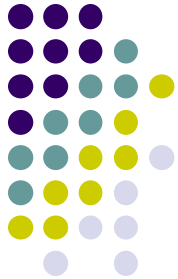
complexes with acidic drugs - ⇓ warfarin absorption

- ***TTC***

complexes with Ca^{2+}, Al^{3+}.. - ⇓ TTC absorption

Drug absorption interactions

Stomach pH change & GI passage



- **stomach pH change**

example:

- **H_2 - *antihistamines* + *ketoconazole***

result: ⇓ *ketoconazole* solubility *&* absorption

- **GI passage**

examples:

- ***anticholinergics* + *paracetamol***

result: delayed *paracetamol* absorption

- ***metoclopramide* + *paracetamol***

result: ⇓ *paracetamol* absorption

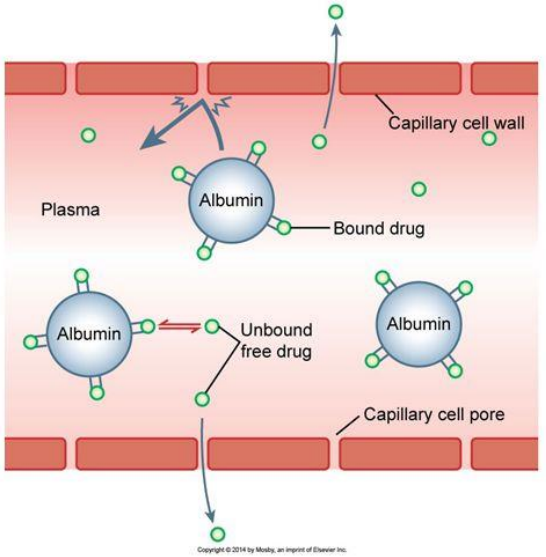
Drug distribution interactions

Plasma protein binding

- **identical binding site**
- **high binding affinity** (Ba)
- **small volume of distribution** (Vd)

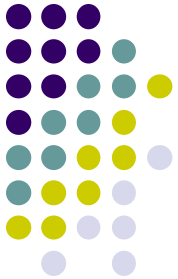
result: **unpredictible, usually ⇑ effect & toxicity**

Protein Binding of Drugs



Pharmacokinetic interactions

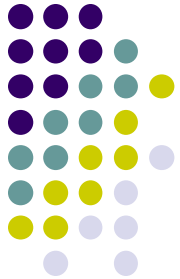
Protein binding



- **target drug → high protein binding**
  → low volume of distribution
  - *warfarin* (99%, 9 l)
  - *phenytoin* (90%, 35 l)
  - *tolbutamide* (96%, 10 l)

- **interaction with each other or with:**
  - salicylates
  - NSAIDs
  - sulphonamides

Pharmacokinetic interactions
Distribution



- ***rifampicin***

⇓ *warfarin* uptake by hepatocytes → ⇓ its effect

- ***clonidine***

⇓ active *methyl-dopa* transport in sympathetic nerve endings

Pharmacokinetic interactions

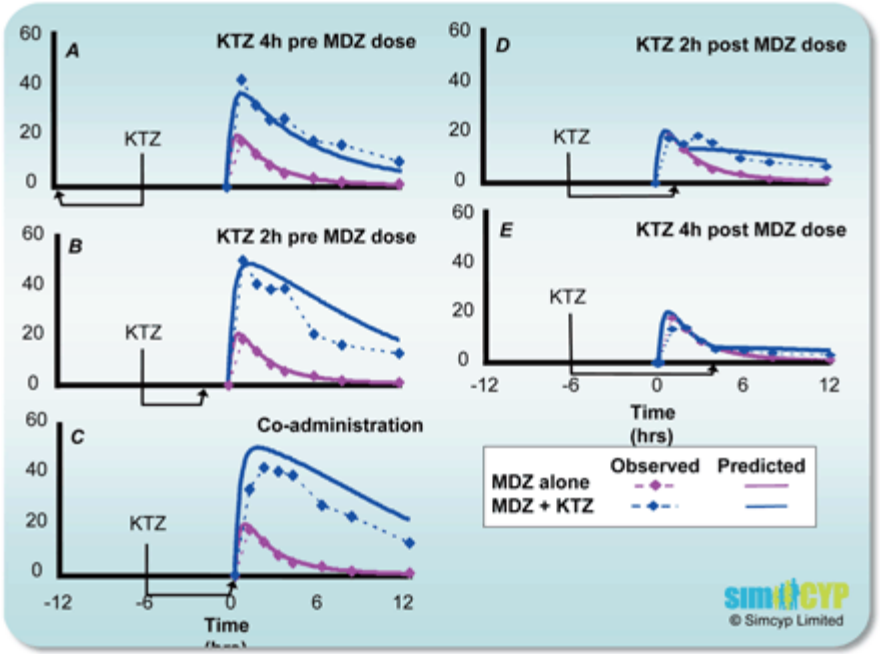
Metabolism

example:

- plasma ***midazolam*** *(MDZ)* after **metabolism inhibition** by ***ketoconazole*** (*KTZ* - CYP 450 inhibitor)

result:

- ⇑ **concentration**
- prolonged **effect** of ***MDZ***

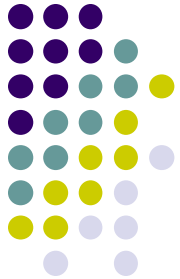


Plasma MDZ concentration-time profiles when the relative timing of the administration of the 2 drugs is varied

http://www.simcyp.com/ResearchDevelopment/SimcypScience/Predictionofdrugdrug/enzymeinhibition/

Drug metabolism interactions

Enzyme inhibition



Metabolic enzyme inhibition

allopurinol → ⇓ *6-mercaptopurine, azathioprine*

cimetidine → ⇓ benzodiazepine, *propranolol*

MAO inhib. → ⇓ tyramine, noradrenaline

disulphiram → ⇓ ethanol

Pharmacokinetic interactions

Metabolism

example:

- ***warfarin***

  after **metabolism induction** by

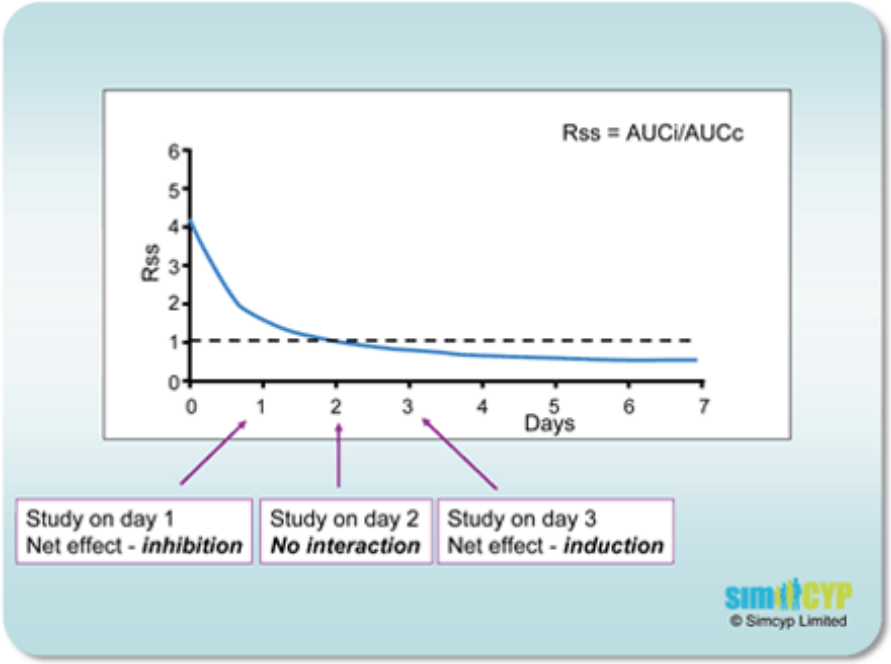
  barbiturates (CYP 450 inducers)

result:

- ⇑ plasma disappearance
- hypoprothrombinemic

  ⇓ effect
- ⇓ anticoagulant activity of

  warfarin

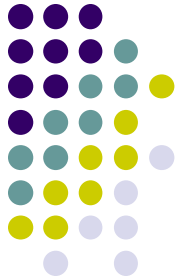


Simulation of the change in systemic exposure to a drug over time when co-administered with another compound that is both an inhibitor and an inducer of CYP450. The extent of drug interaction varies with time, as indicated by the change in Rss (the ratio of AUC in the absence and presence of the inhibitor/inducer).

http://www.simcyp.com/ResearchDevelopment/SimcypScience/Predictionofdrugdrug/enzymeinduction/

Drug metabolism interactions

Enzyme induction



Metabolic enzyme induction

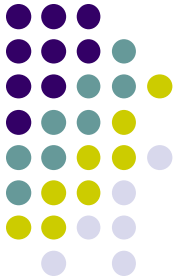
ethanol → ⇑ *phenytoin, tolbutamide, warfarin*

barbiturate → ⇑ *digoxin, phenytoin, warfarin*

phenytoin → ⇑ *steroids, warfarin*

antihistamins → ⇑ *progesterone*

Substrates, inhibitors, & inducers for specific CYP enzymes



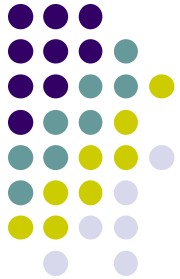
CYP	Substrate	Inhibitor	Inducer
1A2	*theophylline, caffeine*	*fluvoxamine*	*smokers/non-smokers*
2B6	*efavirenz*		*rifampin*
2C8	*repaglinide,rosiglitazone*	*gemfibrozil*	*rifampin*
2C9	*warfarin, tolbutamide*	*fluconazole, amiodarone*	*rifampin, phenobarbital*
2C19	*omeprazole, lansoprazole, pantoprazole*	*omeprazole, fluvoxamine, moclobemide*	*rifampin*
2D6	*desipramine, dextromethorphan*	*paroxetine, quinidine, fluoxetine*	*none identified*
2E1	*chlorzoxazone*	*disulfiram*	*ethanol*
3A4/ 3A5	*midazolam, buspirone, felodipine, lovastatin, sildenafil, triazolam*	*atazanavir, clarithromycin, indinavir, ketoconazole, ritonavir*	*rifampin, carbamazepine*

Examples of *in vivo* substrate, inhibitor & inducer for specific CYP enzymes
(oral administration)

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm081177.htm#4

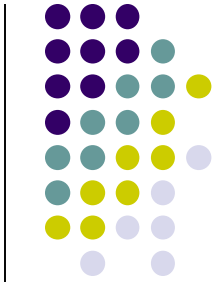
Pharmacokinetic interactions

Excretion



- ***probenecid*** → ⇓ **clearance** *(penicilline, indomethacine....)*
- ***verapamil*** → ⇓ **tubular secretion** of *digoxin...*
- ***salicylates*** → ⇓ **active secretion** of *metothrexate...*

Pharmacodynamic drug interactions



- drugs with **opposing** pharmacologic effects
  (antagonistic)

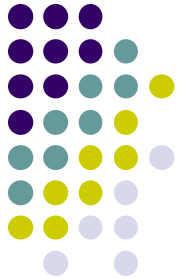
- drugs with **similar** pharmacologic effects
  (additive)

- interactions at **receptor sites**

  (antagonistic or additive)

Pharmacological level

Pharmacodynamic interactions



- **identical site synergism** – neuromuscular junction
  (myorelaxants – aminoglycosides)
- **different sites synergism -** β-receptor/Ca^{2+} channel (β-blockers - calcium channel blockers)
- **identical site antagonism** - β-receptor

  (adrenaline - β-blockers)

- **different sites antagonism -**

  COX inhibition/antihypertensive effect

  (NSAIDs - β-blockers & ACEi)

Striatal muscle relaxation

Identical site synergism

- sometimes **aminoglycosides** (*gentamicine*) **may be** applied along with **myorelaxants**

  (*atracurium, succinylcholine*) during surgery

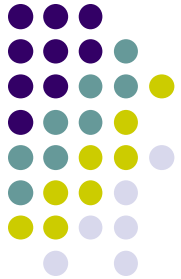
↓

- the combination can trigger in some individuals prolonged myorelaxation

  (longer assisted ventilation)

Heart & BP medications

Different sites synergism



- sometimes **β-blockers** *(atenolol, propranolol)* **may be** prescribed along with

  calcium channel blockers *(amlodipine, diltiazem, verapamil)*

- the combination **usually works well**

- in some individuals, however, the interaction can:
  - **make angina worse**
  - **slow the heart beat**
  - **lead to a rhythm disturbance**

Heart & BP medications

Different sites synergism

- several deaths have been recorded as a result of the combination of ***sildenafil* & nitrates**

- ***warfarin & aspirin*** or other **NSAIDs** (*ibuprofen*) or ***vitamin E*** (in daily doses greater than 400 IU) create the **risk of internal bleeding**

NSAIDs- D#D interactions

Analgesic	Drug	Potential Interaction	Management/ Prevention measures
Salicylates	Uricosoric agents	↓uricosoric effect, ↑uric acid	Avoid concurrent use, avoid all NSAID in patients with gout, hyperurecemia
NSAIDs	Alcohol	↑GI bleeding risk	Minimise alcohol intake while using NSAIDs
NSAIDs	Warfarin	↑risk of bleeding	Avoid concurrent use

Consequences of drug interactions

Examples of additive effects

- ***antianxiety agents, antipsychotic agents, antihistamines*** (other drugs having depressant effects)

+

alcoholic beverages

⇒ ⬆ **CNS-depressant effect**

#

- ***β-blockers*** *(atenolol, propranolol)*

+

calcium channels blockers
(*amlodipine*)

⇒ ⬆ **antihypertensive effect**
(bradycardia, dysrhythmia, AV block)

- **2 different products** (not knowing that they contain the same drug):

arthritic patient ⇒ ***ibuprofen***
may purchase an OTC ***ibuprofen***
for pain or discomfort not associated with the arthritis

⇒ ⬆ **risk of adverse effects**

Consequences of drug interactions

Interactions at receptor sites - additive

- ***MAO inhibitors*** *(isocarboxazid, phenelzine, tranylcypromine, pargyline)*

+

indirectly acting sympathomimetics *(ephedrine, phenylephrine)*

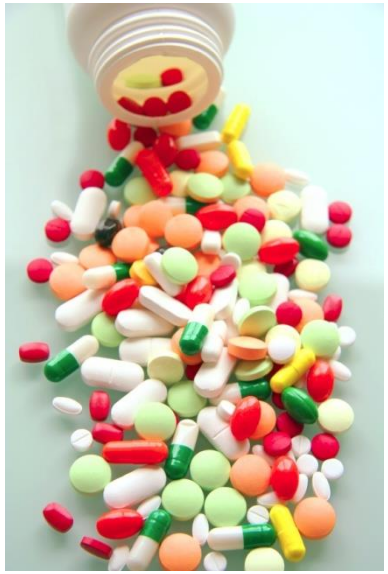
in many OTC (cold, allergy, diet remedies)

or

- ***MAO inhibitors***

+

foods & beverages with high ***tyramine*** content



$\Rightarrow \Uparrow$ **risk of adverse effects**

(headache, hypertension, hypertensive crisis, cardiac arrhythmias)

Heart, metabolism…

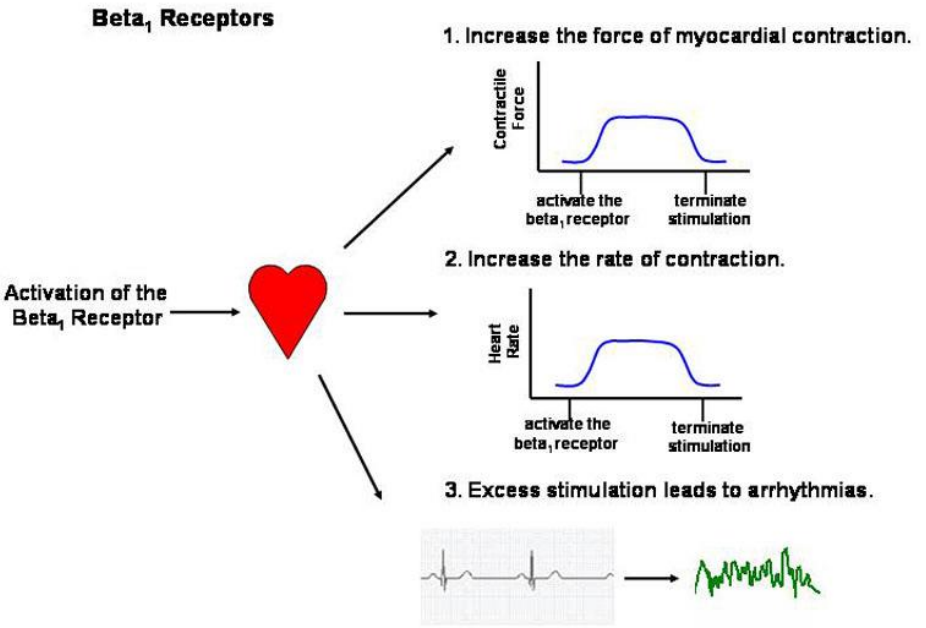
Identical site antagonism

- ***adrenaline*** is a physiological cardiovascular & metabolic stress regulatory mediator

↓

- **β-blockers** antagonize its effects by direct binding to β-receptors

(resulting in positive as well as commonly known side effects)



Heart & BP medications

Different sites antagonism

- **NSAIDs** can interfere with the action of

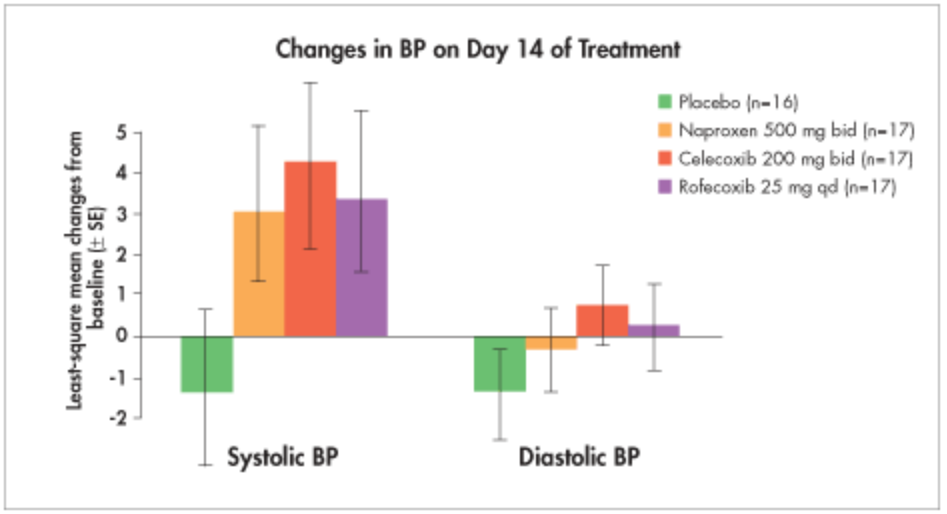
  β- blockers & ACEi

  (captopril, enalapril)

- **it's important to inform the patient to monitor BP** closely

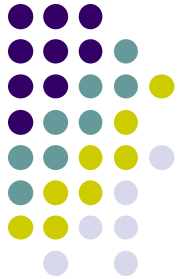
  (when taking these OTC drugs for inflammation or pain relief)

FIGURE 6. **Effect of naproxen and coxibs on systolic blood pressure in the elderly.**
Data from Schwartz et al. EULAR 2001; Abstract SAT0055.



Consequences of drug interactions

Examples of antagonistic effects



- ***thiazides*** (certain other diuretics)

  may elevate blood glucose levels

  +

  insulin (or an oral hypoglycemic agent)

  ↓

  hypoglycemic action

- ***NSAIDs*** (including OTC drugs)

  inhibit COX →

  ⇓ vasodilating effect of PGs

  +

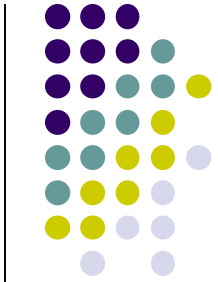
  β-blockers* or *ACE-I

  ↓

  ⇓ **antihypertensive effect**

Consequences of drug interactions

Interactions at receptor sites - antagonistic



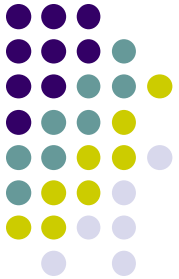
- ***adrenaline*** **-** regulator of cardiovascular function, metabolic & other processes

+

β-blockers – antagonize its effect by direct binding to β-receptors

(it can result in **wanted** as well as **unwanted** effects)

Most frequent drug interactions



Drugs	Interaction/drug
Anticoagulants	**43**
Antidiabetics	**16**
MAO-inhibitors	**16**
Phenothiazines	**10**
Anticonvulsives	**10**
Antidepressives (tricyclic)	**6**
Cardioglycosides	**6**
Antiarrhythmics	**6**
Salicylates	**4**

Drug – food interactions

- ***theophylline, β_2-agonists*** **+ coffee, tee, chocolate** (methylxanthines – CNS stimulation)
- ***K^+ sparing duretics*** **+ banana, green vegetable, oranges** (high K^+ content)
- ***warfarin*** **+ brocolli, cauliflower, spinach** (high vitamine K content)
- ***TTC*** **+ milk** (milk products - chelation)
- ***MAO-I*** **+ cheese, beer, smoked meat, chicken liver** (adrenergic stimulation)
- ***CNS depressants*** **+ alcohol** (CNS depression)

Grapefruit – drug interactions
CYP 3A4 inhibition

example:

- **grapefruit** (grapefruit juice)

+

amiodarone, statins, budesonide, buspirone, cisapride, colchicine, etoposide, quinidine, sildenafil, terfenadine

↓

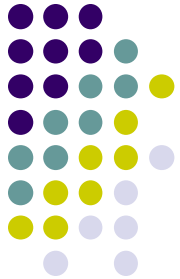
furanocoumarins in grapefruit **inhibit** **CYP3A4**

result: ⇓ **metabolism – ⇑ effect**

Phytotherapeutics - drug interactions

Ginkgo biloba	*aspirin, warfarin, ticlopidine, clopidogrel, dipyridamol* **bleeding**
Hypericum perforatum	*antidepressants* ⇓ **in plasma levels**
Ephedra	*caffeine, decongestants* ⇑ **CNS stimulation**

Drug - disease interactions



- **appear when the drug worsens existing disease symptoms**

- ***calcium channel blockers* & chronic heart failure**
- ***β-blockers* & diabetes**
- ***β-blockers* & peripheral vein diseases**
- ***β-blockers* & COPD**
- ***NSAIDs* & GI ulcer, hypertension**
- ***decongestants* & hypertension**
- ***corticosteroids* & diabetes, ulcer, osteoporosis**
- ***aminoglycosides* & myasthenia gravis**

Nothing is intrinsically good or evil,
but its manner of usage may make it so

St. Thomas Aquinas