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Drug Interactions

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Agenda

- Drug interactions (DDI) - terminology
- Pharmacokinetic DDI – examples
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Pharmacodynamic DDI - examples
- Pharmaceutical DDI - examples
- Drug interactions with food, beverages, herbs
- Recommendation
- Summary

Definitions and Terms

Drug Interactions: “The pharmacologic or clinical response to the administration of a drug combination different from that anticipated from the known effects of the two agents when given alone ”

1Tatro DS (Ed.) Drug Interaction Facts. J.B. Lippincott Co. St. Louis 1992.

Positive?

Negative?

Clinically significant

Definition of drug-drug interaction

- **Interactions of two or more different drugs that affect the action and effects of at least one of them**
  - **One-sided**
    - combination of levodopa and carbidopa
    - combination of 5-fluorouracil and leucovorin
    - combination of glucocorticoids and setrons
  - **Double-sided**
    - combination of sulfamethoxazole and trimethoprim

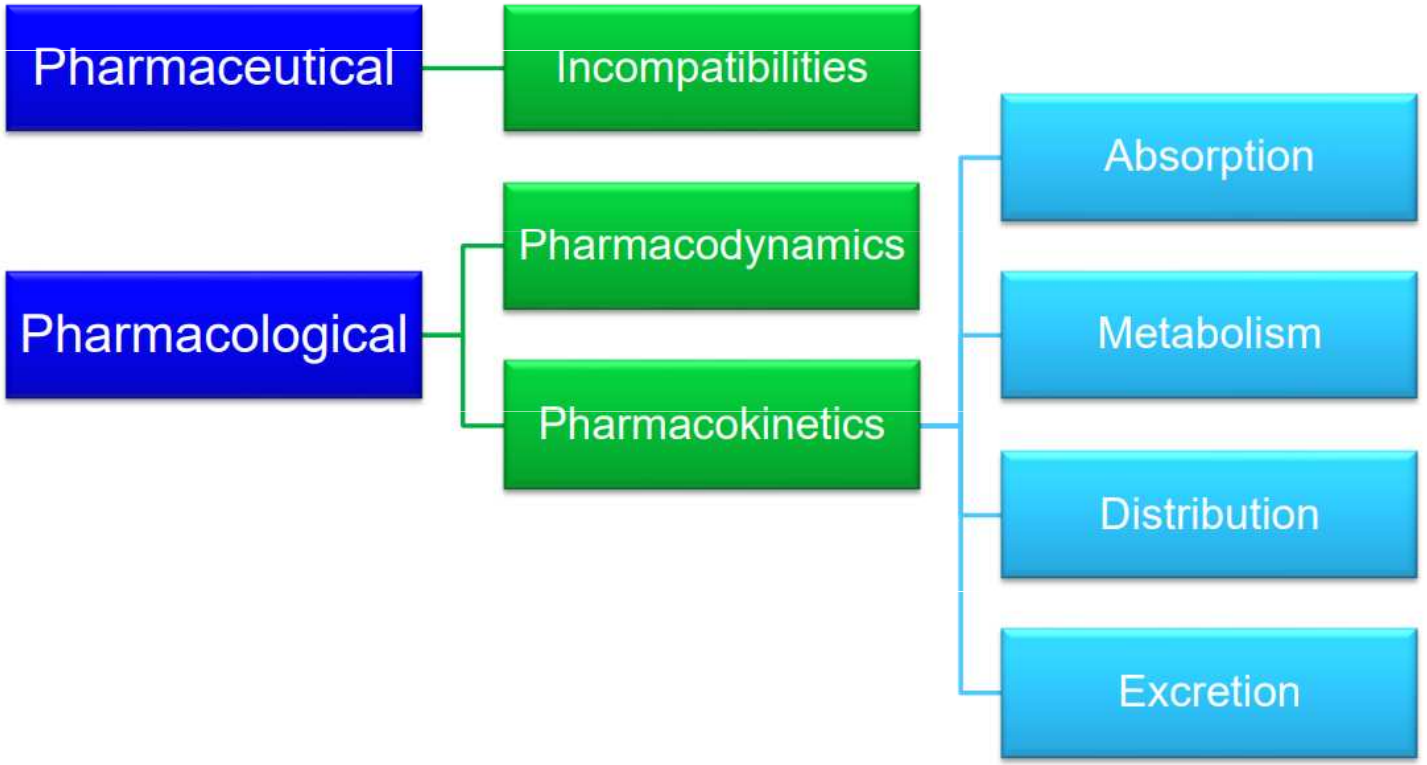
Definition of drug-drug interaction

- **Antagonism** is the opposite effect of two or more drugs administered (NSAIDs and ACEIs, methotrexate and leucovorin, heparine and protamine)

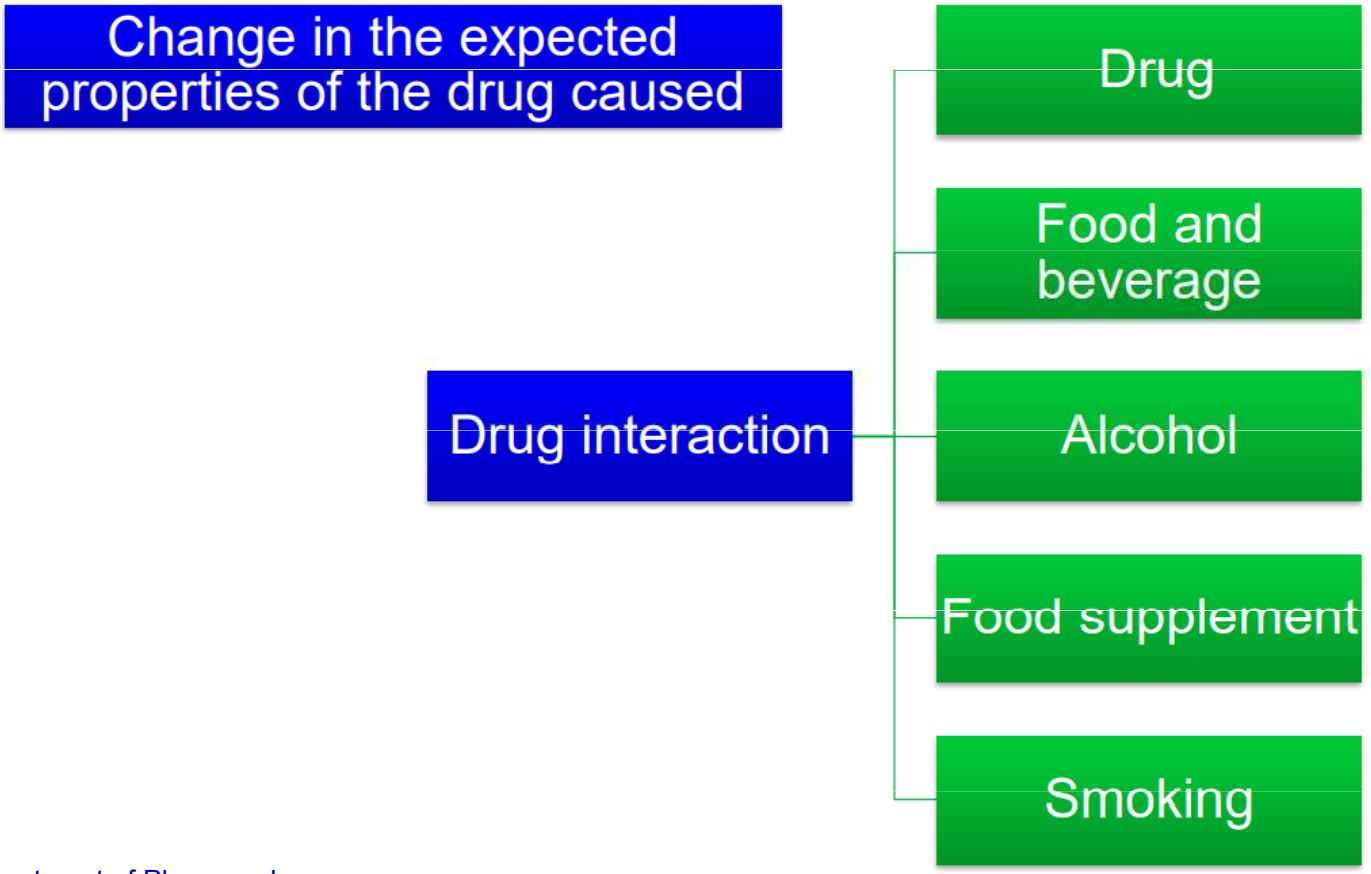
- **Receptor antagonism** - naloxone with fentanyl

- **Synergism** - The effects are magnified many times over (opioids and benzodiazepines, sulfamethoxazole with trimethoprim, amoxiciline and gentamicine)
- **Addition** - the resulting effect corresponds to the sum of the effects of both substances (summation) (amoxicillin and clavulanic acid)
- **Potentiation** – one drug has an effect, the other one not, but enhances effect of the first one (probenecid + penicillin).

Drug interactions



Drug interactions



Why are the drug interactions so important?

- The side effects of the drugs are 4.-6. the most common cause of death (analysis of national registers of ARs, Lazaru J., JAMA, 1998)
- Two-thirds of side effects are caused by drug interactions (US National Register Analysis, Philips KA, JAMA, 2001)
- Behind most serious interactions is the background of polymorphism in the metabolism of several dozen "problematic" drugs (analysis of serious emergencies, McNamara, Circulation, 2001)

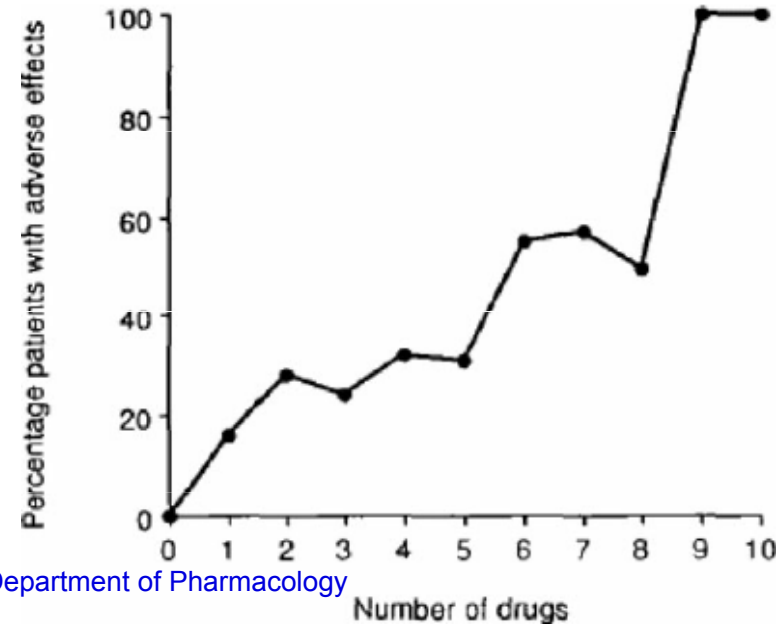
- The risk of drug interactions increases with the number of drugs

- Frequent polypharmacy in gerontological practice

The risk of polypharmacy

– Polypharmacy - unjustified and irrational overuse of pharmacotherapy

Drugs with a narrow therapeutic index and therapeutic range. Drugs that are metabolised via CYP3A4



Cresswell, Kathrin & Fernando, Bernard & Mckinstry, Brian & Sheikh, Aziz. (2007). Adverse drug event in the elderly. British medical bulletin. 83. 259-74. 10.1093/bmb/ldm016.

Classifying drug interactions

	Risk rating	Description	Action
Non-relevant	A	Data have not demonstrated either pharmacodynamic or pharmacokinetic interactions between the specified agents	No interaction
Minor	B	Data demonstrate that the specific agents may interact which each other, but there is little to no evidence of clinical concern resulting from their concomitant use	No action needed
Moderate (use with caution)	C	Data demonstrate that the specific agents may interact which each other in a clinically significant manner. The benefits of concomitant use of these two medications usually outweigh the risk	Monitor therapy
Major (should be avoided)	D	A patient-specific assessment must be conducted to determine whether the benefits of concomitant therapy outweigh the risks	Modify regimen
Contraindicated (prohibited)	X	The risks associated with concomitant use of these agents usually outweigh the benefits	Avoid combination

Significance of drug interactions

- **Desirable** (beneficial for the patient) drug combination

potentiating drug effect and decreasing the toxicity

- combination of:
  - cytostatics
  - analgesics
  - antihypertensives
  - ATBs
  - drugs for asthma…

Significance of drug interactions

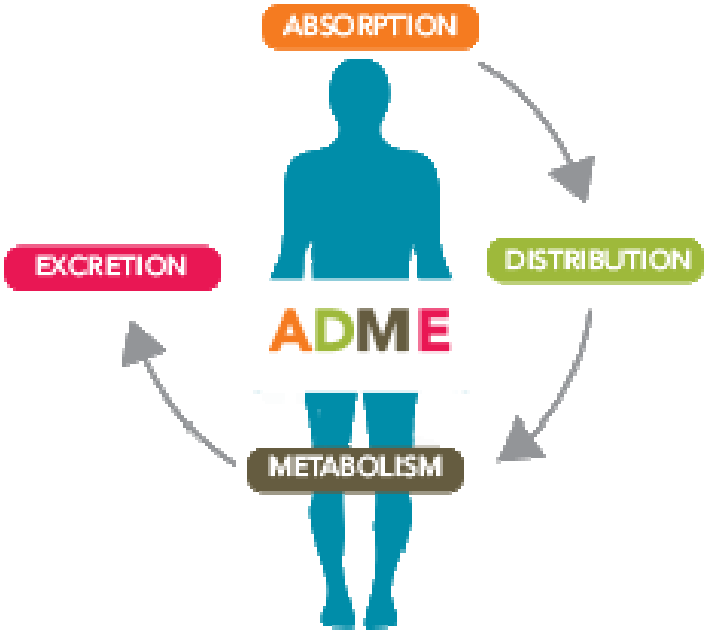
– **Desirable** (beneficial for the patient) - combination of the active substance suppressing/inhibiting the effect of another drug in the **treatment of intoxication/poisoning** organism

Significance of drug interactions

- **Undesirable** (for the patient harmful, potentially dangerous)
- This may result in:
  - increase or decrease (loss) effect
  - increasing or reducing the incidence of side effects
  - other changes in effect
  - injury or even death

Always evaluate clinical significance

2. Pharmacokinetic DDIs



Pharmacokinetic interactions - Absorption

1. altered pH
2. altered bacterial flora
3. formation of drug chelates or complexes
4. drug induced mucosal damage
5. altered GIT motility

1. Altered pH

– The non-ionized form of a drug is more lipid soluble and more readily absorbed from GIT than the ionized form does.

Antacids
H2 antagonists (acidic)
PPI

→ Decrease the tablet dissolution of p.o. azole antimycotics (e.g. Ketoconazole)

↓ Therefore, these drugs must be separated by at least 2h in the time of administration of both.

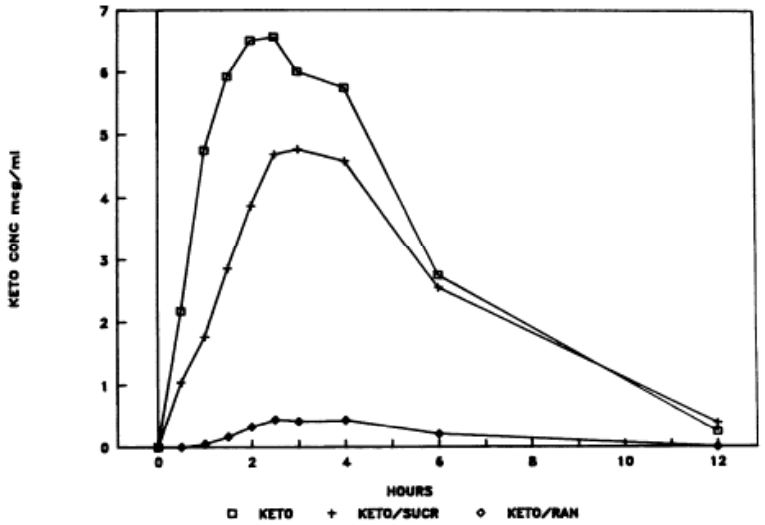
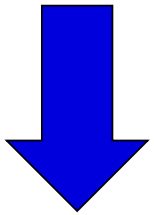


FIG. 1. Mean ketoconazole serum concentration for each study phase.

Effects of ranitidine and sucralfate on ketoconazole bioavailability. Piscitelli S., Antimicrob Agents Chemother. 1991 Sep; 35(9): 1765–1771.

2. Altered intestinal bacterial flora

– 40 % or more of the administered **digoxin** dose is under physiological conditions metabolized by the intestinal flora. **Antibiotics** kill a large number of the normal flora of the intestine



Increase digoxin concentration and increase its toxicity

3. Formation of drug chelates or complexes

DDIs Can Occur in the GI Tract

- Sucralfate, some milk products, antacids, and oral iron preparations → Block absorption of quinolones, tetracycline, and azithromycin
- Medical coal (charcoal) → Reduces absorption of p.o. drugs (e.g. Metoprolole, delavirdine…)
- Didanosine (given as a buffered tablet) → Reduces ketoconazole absorption
- Cholestyramine → Binds raloxifene, thyroid hormone, and digoxin

Complexation or chelation

– **Tetracyclines, Quinolones** interact with **iron, calcium, magnesium, aluminium preparations** (antacid - aluminum or magnesium hydroxide)

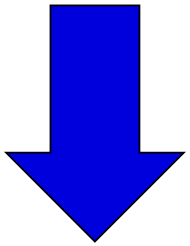
or **milk (Ca^{2+})** → **Unabsorpable complex**

↓

Decrease absorption of ciprofloxacin by 85% due to chelation carbo medicinalis (coal), diosmectin – readsorption of other drugs

4. Drug-induced mucosal damage

Antineoplastic agents cyclophosphamide, vincristine, procarbazin



Inhibit absorption of several drugs such as digoxin

5. Altered motility

Increased motility (diarrhea)

• Prokinetic drugs - metoclopramide, domperidone, itopride

Reduced absorption

Decreased motility (ileus, constipation)

• Opioids, diphenoxylate, loperamide

Increase in AUC of drugs, toxicity

Pharmacokinetic interactions - Distribution

The major plasma proteins to which most drugs bind are

albumin - typically binds acidic, anionic drugs

a1-acid glycoprotein - typically favors basic drugs

Competitive protein binding by another drug will result in increase **concentration of free drug**, and that will yield more drug response

Maximum Fraction Bound in Plasma ($ß_{max}$)	Fraction of Total Drug Bound in the Body	Maximum Possible Increase in Pharmacodynamic Effect Due to Complete Binding Displacement
50%	10%	10%
90%	49.6%	~ two-fold
99%	91.5%	~ 12-fold

Displaced protein binding

- Depends on the **affinity** of the drug to plasma protein. The most likely bound drugs are capable to displace others. It is clinically important if displaced drug is highly **PP binding , with LONG T ½, small Vd, narrow therapeutic range**.

- **Aspirin, Phenylbutazone, Clofibrate** displace:

Oral Anti-coagulants (Dicumarol, Warfarin)	→	Bleeding
Oral Hypoglycemics (Tolbutamide)	→	Hypoglycemia
Bilirubin in Neonate.	→	Jaundice & Kernicterus

Table

Examples of medications that are >90% protein-bound (not inclusive)

Category	Medication(s)
Antibiotics	Ceftriaxone, doxycycline, ertapenem
Antidepressants	Duloxetine, fluoxetine, nortriptyline, sertraline
Antipsychotics	Chlorpromazine, clozapine, haloperidol
Anxiolytics	Chlordiazepoxide, diazepam, lorazepam
Cardiac	Amiodarone, bumetanide, furosemide, nicardipine, verapamil, warfarin
Chemotherapy	Paclitaxel, tamoxifen
Diabetes	Glipizide
Pain	Bupivacaine, buprenorphine, ibuprofen
Seizure	Phenytoin, valproic acid

Source: Reference 1

Distribution

- **glycoprotein P** - most important - works in tandem with CYP3A4 (mutual substrates, **inductors and inhibitors**)

reduced activity of P-gp
(present in a quarter of the population)

Increased absorption of drugs

- OATP (organic anion transport protein) significant system ensuring the transfer of org. anions - risk of **inhibition or competition or induction**

Distribution

Useful mnemonics:

P glycoprotein

Increase **Qu**antitative **A**bsorption **Ver**y **E**ffectively

- **I**traconazole
- **Qu**inidine
- **A**miodarone
- **Ver**apamil – most potent Pg inhibitor
- **E**rythromycin

Distribution of drugs in relation to P-glycoprotein

Medications that act as substrates, inhibitors or inducers of P-gp		
Substrate	**Inhibitors**	**Inducers**
Cyclosporine	Amiloride	Aspirin
Dipyridamole	Amiodarone	Cyclosporine
Digoxin	Atorvastatin	Paclitaxel
Diltiazem	Carvedilol	Reserpine
Losartan	Cyclosporine	
Quinidine	Digoxin	
Tacrolimus	Diltiazem	
	Dipyridamole	
	Doxazosin	
	Felodipine	
	Lidocaine	
	Lovastatin	
	Nifedipine	
	Propafenone	
	Propranolol	
	Quinidine	
	Simvastatin	
	Spiroanlactone	
	Verapmil	

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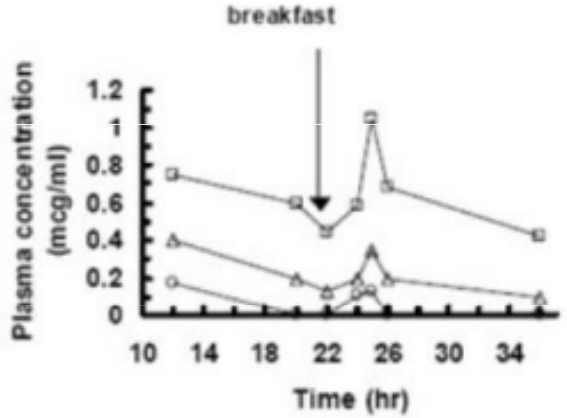
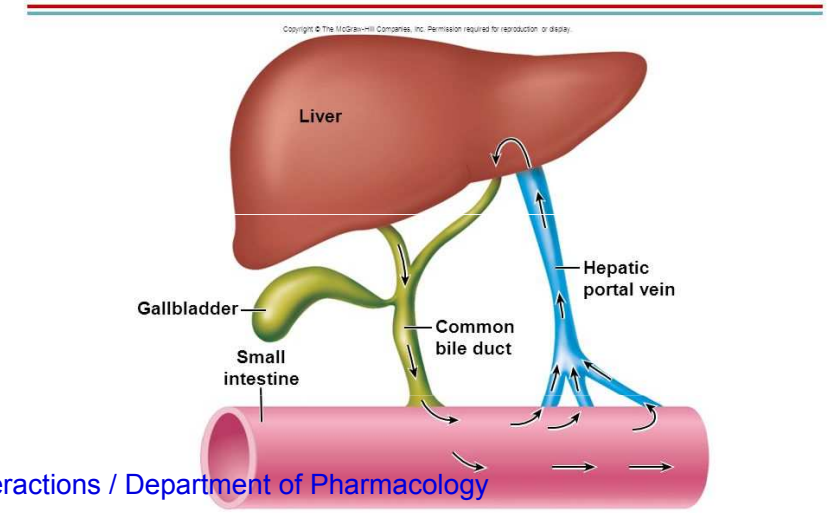
Influence of enterohepatic recirculation



Effect of Interruption of Enterohepatic Cycling on Drug Elimination	
Condition	*Half-life*
Digitoxin	6 days
Digitoxin + cholestyramine	4.5 days
Dapsone	20.5 hr
Dapsone + charcoal	10.8 hr



EXAMPLES OF XENOBIOTICS EXCRETED INTO BILE AND SUBJECT TO ENTEROHEPATIC RECIRCULATION

Compound	*Species in bile*
Cefoperazone	unknown
Estradiol	conjugates
Valproic acid	glucuronide
Chloramphenicol	glucuronide
Digitoxin	conjugates
Spironolactone	metabolites
Imipramine	parent and desmethyl

Pharmacokinetic interactions - Metabolism

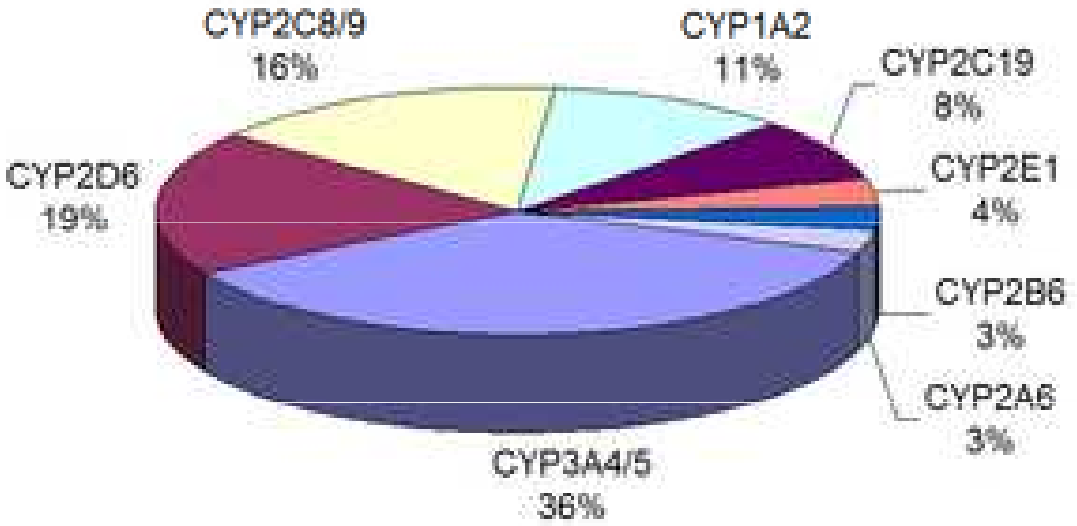
- The effect of one drug on the metabolism of the other is well documented. The liver is the major site of drug metabolism but other organs can also do e.g., WBC, skin, lung, and GIT.

- **CYP450 family** is the major metabolizing enzyme in phase I (oxidation process). Therefore, the effect of drugs on the rate of metabolism of others can involve the following examples

CYP P450

- a key enzyme in the metabolism of xenobiotics mainly responsible for Phase I biotransformation processes occurring in the liver, lungs, kidneys, brain, skin, small intestine and other organs

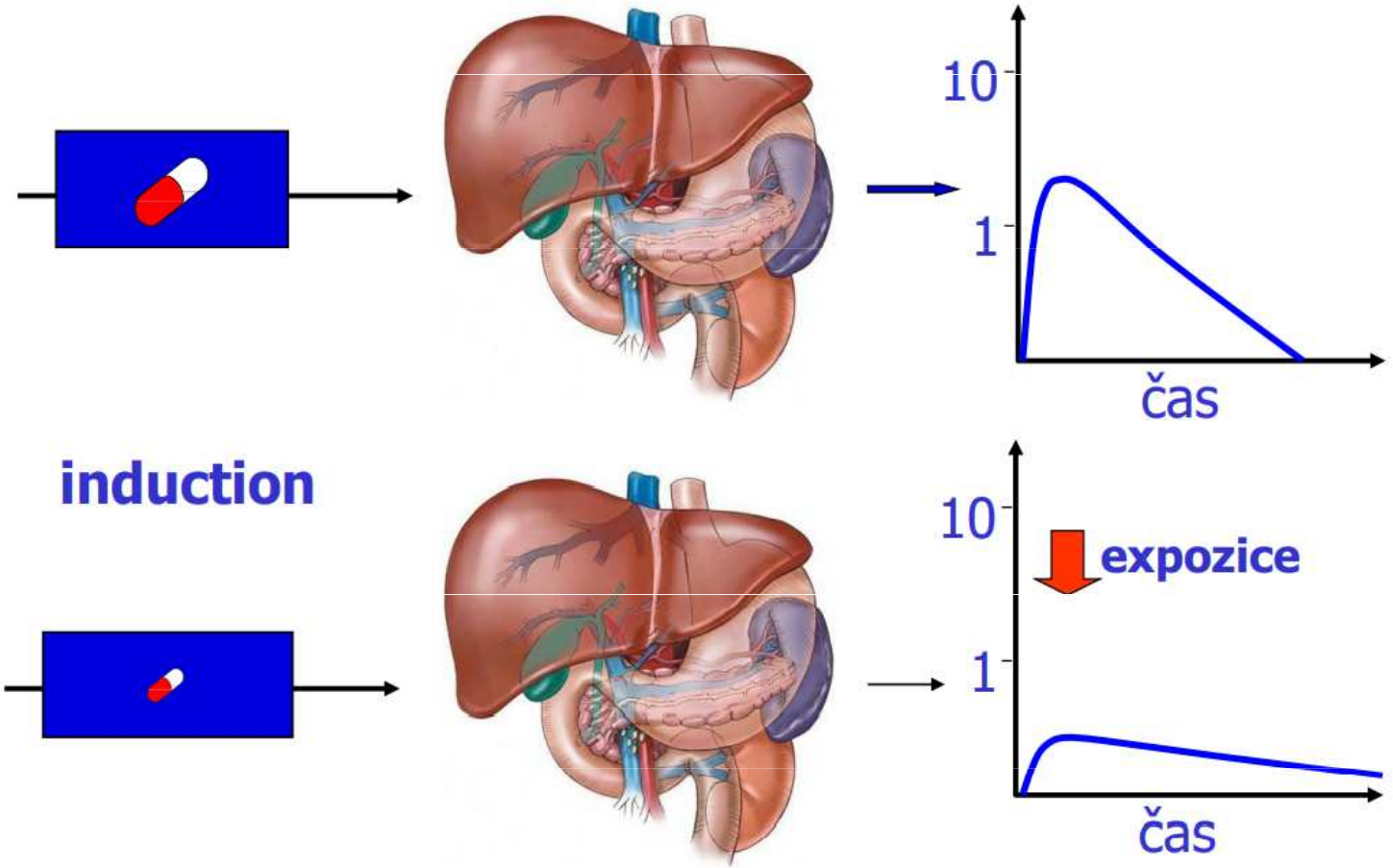
- Substrates P450
  - drug metabolizing using this enzyme
- Inducers of cytochrome P450
  - increased degradation of the drug from the organism
  - subtherapeutic plasma levels of the drug
  - reduce the effect of drugs
- Inhibitors of cytochrome P450
  - accumulation of the drug in the body
  - increased plasma levels
  - Increased toxicity



Polymorphism of enzymes

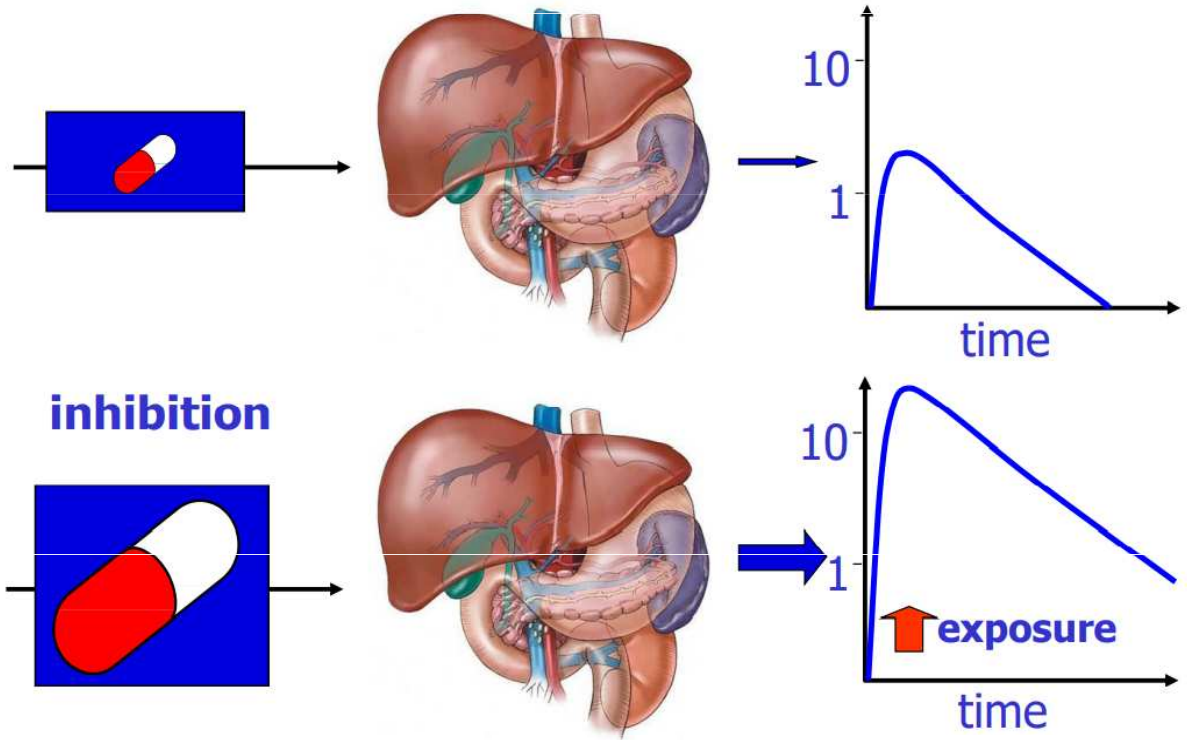
- **slow** metabolizer - all defective alleles
- **medium** metabolizer - an intact allele
- **rapid** metabolizer - all intact allele (wild type)
- **ultrarapid** metabolizer - multiplication of a gene or a higher enzyme activity

Drug interactions - induction



- It may take seconds up to weeks in case of enzyme induction (weeks for protein synthesis), while enzyme inhibition occurs rapidly.

Basic mechanisms - inhibition



Mnemonics

Barb's: PheNOBarbitol
Funny: Phenytoin
Mom: Modafinil

Refuses: Rifampin
Greasy: Griseofulvin
Carb: Carbamazepine
Shakes: St. John's wort
Liver P450 INDUCERS

P450 Inhibitors

SICKFACES.COM Group

Sodium valproate
Isoniazid
Cimetidine
Ketoconazole
Fluconazole
Alcohol..binge drinking
Chloramphenicol
Erythromycin
Sulfonamides
Ciprofloxacin
Omeprazole
Metronidazole
Grapefruit juice

P450 Inducers

CRAP GPS induce me to madness!!

Carbemazepines
Rifampicin
Alcohol (chronic)
Phenytoin

Griseofulvin
Phenobarbitone
Sulphonylureas

CYP450 inducers

BullShit CRAP GPS induces my rage!

Barbituates
St. John's wort
Carbamazepine
Rifampin
Alcohol (chronic)
Phenytoin
Griseofulvin
Phenobarbital
Sulfonylureas

CYP450 inhibitors

VICK'S FACE All Over GQ stops ladies in their tracks.
Valproate
Isoniazid
Cimetidine
Ketoconazole
Sulfonamides
Fluconazole
Alcohol (acute)
Chloramphenicol
Erythromycin (macrolides)
Amiodarone
Omeprazole
Grapefruit juice
Quinidine

High interindividual variability

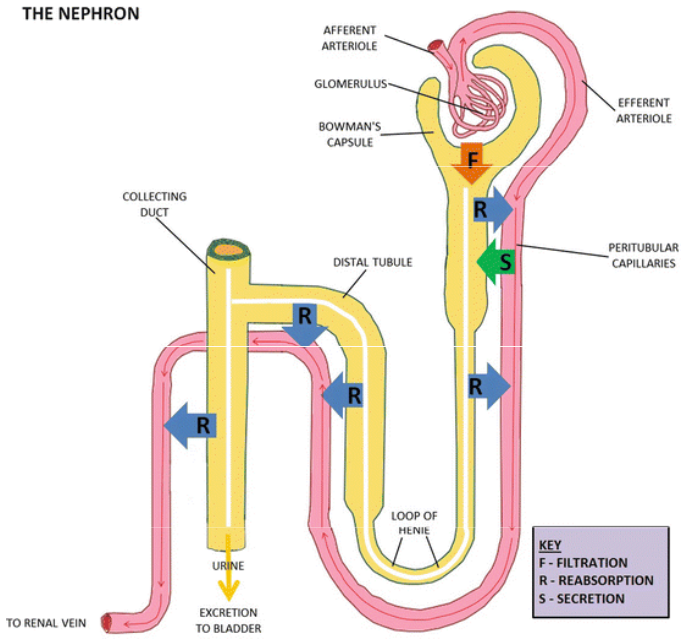
Enzyme	Becomes active at	Substrates	Inhibitors	Inducers
CYP 1A2	1–3 months	Caffeine Paracetamol	Ciprofloxacin	Tobacco Insulin Omeprazole
CYP 2D6	Hours, days	Amphetamines Codeine Flecainide Lignocaine Metoclopramide	Cocaine Methadone Ranitidine	Phenobarbitone Phenytoin
CYP 2C9	First weeks	Ibuprofen Phenytoin	Fluconazole Sulfamethoxazole	Rifampicin
CYP 2C19	First weeks	Omeprazole Phenytoin Indomethacin	Omeprazole Indomethacin	Carbamazepine Prednisone
CYP 3A4	First weeks	Steroids Clarithromycin Midazolam	Fluconazole Grapefruit Juice	Phenobarbitone Phenytoin
CYP 2E1	Hours	Ethanol Paracetamol	disulfiram	Ethanol Isoniazid

Elimination

- **glomerular filtration** has only a limited effect on protein-bound substances
- **active tubular secretion** - active transport of strong acids and bases in the proximal tubule
- **passive tubular resorption** - is possible only for non-ionized forms
- **competition** - reduction of the capacity for excretion of drugs eliminated exclusively by the kidneys
- **urine pH** - alcalinisation / acidification

Hepatic clearance - Enterohepatic recirculation

Elimination by **lungs, breast milk, sweat**…



Elimination

Example:

co-administering **methotrexate** and

nonsteroidal anti-inflammatory drugs (NSAIDs), probenecid (Probalan, generics), penicillins, proton pump inhibitors, vitamin C, sulfa, and some other antibiotics

Toxicity (nausea, vomiting, diarrhea, mucositis, stomatitis, esophagitis, elevated hepatic enzymes, renal failure, rash, myelosuppression (leukopenia, pancytopenia, thrombocytopenia), acute lung injury, tachycardia, hypotension, and neurologic dysfunction (depression, headache, seizures, motor dysfunction, stroke-like symptoms, encephalopathy, coma)

Why?

Renal excretion is the major route of elimination for methotrexate (~80%); the drug being actively secreted in the renal tubule by the general organic acid transport system. The renal clearance of methotrexate is decreased by the co- administration of (organic) acids.

Solution?

With high dose methotrexate, routine administration of fluid and/or bicarbonate is recommended to prevent intratubular precipitation of the drug.

The renal clearance of methotrexate is correlated with endogenous creatinine clearance which may provide a guideline to dosage adjustments according to renal function and age.

Summary of PK DDIs

Pharmacokinetic property	Example changes with age	Drug effects	Example pharmacodynamic complication
Absorption	Decreased gastric blood flow	Decreased bioavailability	Chronic salicylate toxicity (aspirin requires acidic gastric pH; decreased absorption may lead to delayed drug accumulation with daily dosing)
	Decreased gastric acid secretion, increased gastric pH		
	Prolonged gastric emptying (e.g. due to anticholinergic drugs)		
Distribution	Decreased muscle mass	Volume of distribution (Vd) of fat-soluble drugs increases; Vd of water-soluble drugs decreases; increased free (non-protein bound) drug levels	Benzodiazepine accumulation in tissues with chronic use (fat-soluble); increased bleeding with warfarin use (highly protein bound)
	Increased body fat		
	Decreased protein binding		
Metabolism	Decreased hepatic mass	Decreased clearance of drugs that undergo considerable first-pass metabolism (leading to increased bioavailability)	Beta blocker toxicity (e.g. metoprolol, propranolol)
	Decreased hepatic blood flow		
	Reduced cytochrome P450 enzyme activity		
Excretion	Decreased renal blood flow	Reduced drug clearance	Digoxin toxicity (narrow therapeutic index, primarily renally excreted)
	Decreased glomerular filtration rate (GFR)		
	Decreased tubular secretion		

[emDOCs.net – Emergency Medicine EducationCommon ED Medication Errors: Polypharmacy - emDOCs.net - Emergency Medicine Education]

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Pharmacodynamics drug interactions

= alteration of the drug action without change in its serum concentration by pharmacokinetic factors.

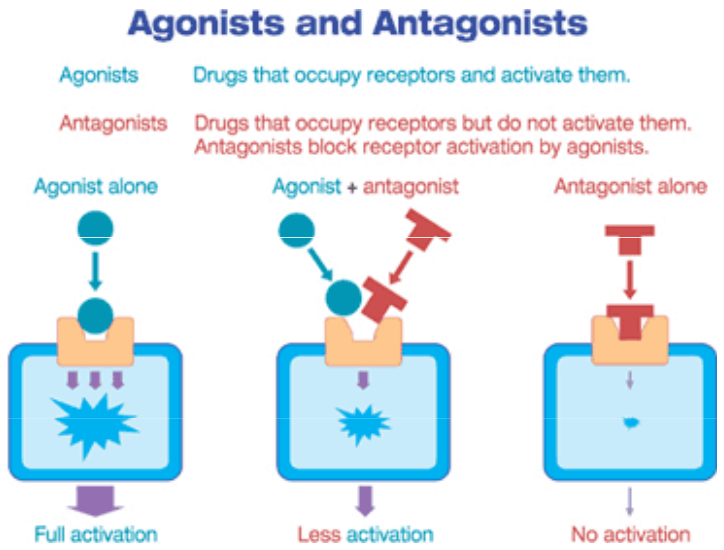
Additive effect : 1 + 1 = 2
Synergistic effect : 1 + 1 > 2
Potentiation effect : 1 + 0 = 2
Antagonism : 1 – 1 = 0

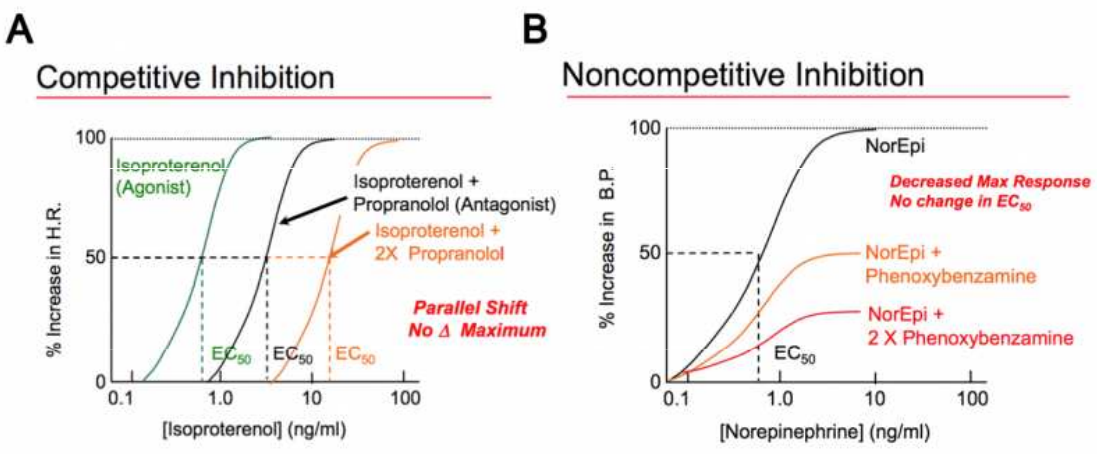
Receptor antagonism

Opioids x naloxone

BDZ x flumazenil

Tubocurarium x neostygmine





Opposing or antagonistic interactions

Drug affected	Interacting drugs	Results of interaction
Anticoagulants	Vitamin K	Anticoagulant effects opposed
Carbenoxolone	Spironolactone	Ulcer-healing effects opposed
Hypoglycaemic agents	Glucocorticoids	Hypoglycaemic effects opposed
Hypnotic drugs	Caffeine	Hypnosis opposed
Levodopa	Antipsychotics (those with Parkinsonian side effects)	Antiparkinsonian effects opposed

Pharmacodynamics drug interactions

Drugs	Result of interaction
Anticholinergics + anticholinergics (anti-parkinsonian agents, butyrophenones, phenothiazines, tricyclic antidepressants, etc.)	Increased anticholinergic effects; heat stroke in hot and humid conditions; adynamic ileus; toxic psychoses
Antihypertensives + drugs causing hypotension (anti-anginals, vasodilators, phenothiazines)	Increased antihypertensive effects; orthostasis
CNS depressants + CNS depressants (alcohol, anti-emetics, antihistamines, hypnosedatives, etc.)	Impaired psychomotor skills, reduced alertness, drowsiness, stupor, respiratory depression, coma, death
QT prolonging drugs + other QT prolonging drugs (Amiodarone + Disopyramide)	Additive prolongation of QT interval, increased risk of torsade de pointes
Methotrexate + co-trimoxazole	Bone marrow megaloblastosis due to folic acid antagonism
Nephrotoxic drugs + nephrotoxic drugs (genta-micin or tobramycin with cefalotin (cephalothin)	Increased nephrotoxicity
Neuromuscular blockers + drugs with neuromuscular blocking effects (e.g. aminoglycoside antibacterials)	Increased neuromuscular blockade; delayed recovery, prolonged apnoea
Potassium supplements + potassium-sparing diuretics (triamterene)	Marked hyperkalaemia

QT interval prolongation

TKI

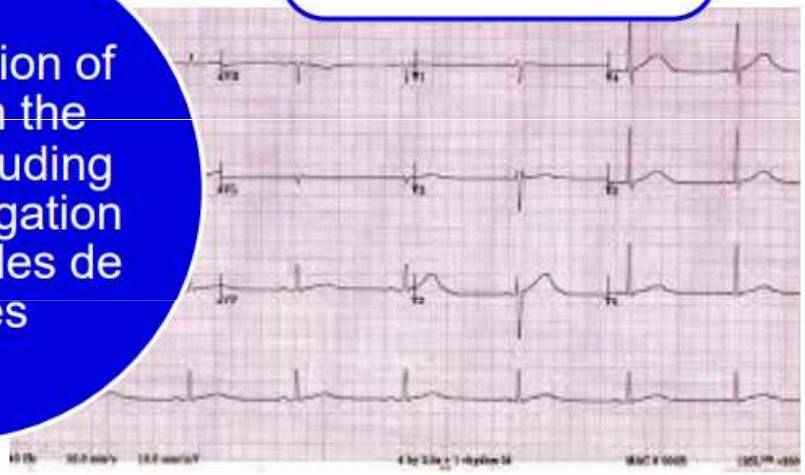
Sorafenib
Sunitinib
Pazopanib
Dasatinib
Nilotinib

+

CYP 3A4
Inhibitors
claritromycin
ciprofloxacin

amiodaron
sotalol
ondansetron
propafenon
chlorpromazine
haloperidol
cisapride
domperidon
pimozide

Deterioration of ADRs on the heart, including QT prolongation and torsades de pointes



Important Drug Interactions in the Elderly

	Example	Mechanism of action	Outcome
Drug–drug, PK	Gatifloxacin+calcium and antacid	Decrease in absorption of gatifloxacin	Treatment failure[26]
	Ciprofloxacin+olanzapine	Ciprofloxacin inhibits CYP1A2 leading to an increase in Cp of olanzapine	Rigidity, falls
Drug–drug, PD	Ciprofloxacin+glibenclamide	Synergy (hypoglycaemic effect)	Profound hypoglycaemia[27]
	Anticholinergic drug+donepezil	Antagonism	Decreased effect of donepezil
Drug–nutritional status	Low albumin+phenytoin	Increase in free phenytoin concentration	Confusion, somnolence, ataxia[28]
Drug–herbal product	Gingko+aspirin	Decrease in platelet function and adhesion	Increased risk of bleeding[29]
Drug–alcohol	Alcohol+chronic use of bromazepam	Synergy	Increased risk of falls
Drug–disease or drug–patient	Metoclopramide for gastric dysmotility in a patient with Parkinson's disease	Increase in dopamine receptor blockade	Worsening Parkinson's disease[30]

Cp=plasma concentration. CYP=cytochrome P450. PD=pharmacodynamic. PK=pharmacokinetic.

Table: **Examples of different types of drug interactions in elderly patients**

Louise Mallet, Anne Spinewine, Allen Huang, The challenge of managing drug interactions in elderly people, The Lancet, Volume 370, Issue 9582, 2007

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Clinically significant drug interactions

Penicillins

Do not administer concomitantly with other **penicillins**

Digoxin - is metabolized by the intestinal microflora - TDM

Oral contraceptives - inform about the use of other contraceptive methods

Metronidazole

Alcohol - disulfiram reaction

Warfarin - risk of bleeding, INR control, dose adjustment

Lithium - toxicity, do not administer simultaneously

Clinically significant drug interactions

Clarithromycine

Theophylline - risk of TDM toxicity, dose adjustment

Carbamazepine - choice of another ATB

Digoxin - TDM, dose adjustment

Cyclosporine - TDM, dose adjustment

Statins - choice of another ATB or replacement with lovastatin, pravastatin

Oral contraceptives - informing about the use of other contraceptives

Warfarin - risk of bleeding

Midazolam - increased sedation

Clinically significant drug interactions

Fluoroquinolones

Antacids, minerals - ↓ absorption of ATB, do not administer together

Caffeine - ↑ toxicity of caffeine

Clindamycine

Azole antifungals

Neuromuscular blockers

prolongation of their effect, toxicity

Clinically significant drug interactions

Acetylsalicylic acid and NSAIDs

Warfarin - increased risk of bleeding

ACE inhibitors, beta-blockers, sartans - reduction of antihypertensive effect

Furosemide - reduction of diuretic effect

Paracetamol

Alcohol

Phenytoin, carbamazepine,

isoniazid - increased risk of hepatotoxicity

Clinically significant drug - food interactions

- St. John´s wort X immunosuppresants (tacrolimus, sirolimus, cyclosporine)
- Tyramine X MAOI
- Grapefruit juice X statins

Drugs – food interactions

Common Food-Drug Interactions

	Food	Drug	What happens?
	Kale, broccoli (vitamin K)	**blood thinners** such as warfarin	Foods that are rich in vitamin K can reduce the effectiveness of blood thinners.
	Grapefruit	**statins** such as atorvastatin, lovastatin, simvastatin	Grapefruit can increase statin levels in your body, thereby increasing statin-related side effects.
	Bananas (potassium)	**ACE inhibitors** such as captopril, enalapril and lisinopril	ACE inhibitors increase potassium in your body. Too much potassium can cause an irregular heartbeat and heart palpitations.
	Walnuts, soybean flour (high fiber)	**thyroid medications** such as levothyroxine	High-fiber foods can prevent the body from absorbing thyroid medications.
	Dairy products (calcium)	**quinolone antibiotics** such as ciprofloxacin and levofloxacin	Calcium reduces the level of these antibiotics in your blood. Avoid eating dairy and calcium-fortified products alone.
	Salami, aged cheese (tyramine)	**oxazolidinone antibiotics** (such as linezolid) and **MAOI-type antidepressants** (such as phenelzine)	Eating a tyramine-rich diet while taking certain meds can cause a sudden, dangerous increase in blood pressure.

www.nclnet.org
www.fda.gov/drugs

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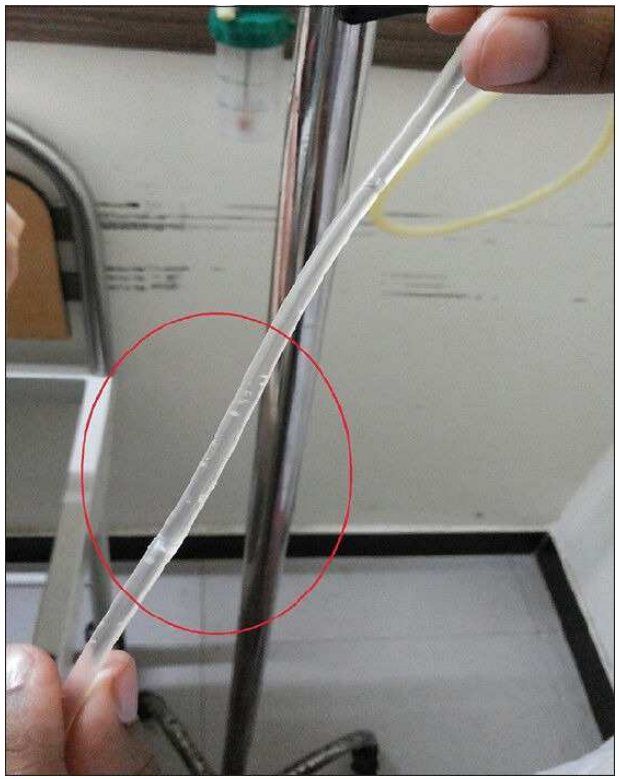
Drugs – food interactions

Drug-Food interactions

- A drug-food interaction happens when the food you eat affects the ingredients in a medicine you are taking so the medicine cannot work the way it should.

1.	Bisphosphonates+ Any drug	Reduced effectiveness of drug`
2.	Benzodiazepines + grapefruit	Inhabit enzymes involved in drug metabolism
3.	Digoxin + Oatmeal	Decreased adsorption of drug
4.	Aspirin + Milk	Upset stomach
5.	Acetaminophen + Alcohol	Liver damage
6.	MAO Inhibitors + food(tyramine)	Severe headache
7.	Tetracycline's + calcium food	Reduced absorption of drug
8.	Warfarin + Vitamin K	Reduced effect of drug
9.	Celecoxib + Milk	Upset stomach
10.	Naproxen + fatty food	Upset stomach
11.	Oxycodon + Alcohol	Coma , asthma
12.	Caffeine + food	Rapid heart beat

Pharmaceutical drug interactions



Incompatibility

- Administration of aminoglycosides and beta-lactams meeting in one of the lumens - inactivation of the free -NH2 in the free aminoglycosides and -COOH in beta-lactams

do not mix in one fluid, split the route of administration, do not give in at the same time

- Amiodarone diluted in 5% glucose solution meets Norepinephrine reconstituted in saline solution - precipitation of amiodarone

dilute NE in 5% glucose solution

- Octreotide meets in one lumen with parenteral nutrition, octreotide is inactivated

separate pathways for parenteral nutrition and octreotide

IV Drug Compatibility Chart

	Acyclovir	Adrenaline	Amiodarone	Amphotericin B	Azithromycin	Calcium Gluconate	Cefepime	Cefuroxime	Dopamine	Fentanyl	Fluconazole	Furosemide	Heparin	Imipenem-Cilastatin	Insulin	Lidocaine	Linezolid	Magnesium Sulfate	Mannitol	Meropenem	Methyl Prednisolone	Metoclopramide	Midazolam	Morphine	Noradrenaline	Ondansetron	Pantoprazole	Phenytoin	Piperacillin - Tazobactum	Potassium Chloride	Sodium Bicarbonate	Vancomycin	Vasopressin	Vecuronium
Acyclovir				C			I	C	I		C		C	C			C	C		I	C	C		I		I			I	C	C	C		
Adrenaline			C			C			C	C		C	C										C	C	C		C			C			C	C
Amiodarone		C		C		C		C	C	C	C	I	I	I	C	C		I			C		C	C	C				I	C	I	C	C	C
Amphotericin B	C		C			I	I		I	C	I	C	I	I		I	I	I	C	I	C	I	I	I		I		I	I	I	I	I		I
Azithromycin								I		I		I		I										I		C			I	I				
Calcium Gluconate		C	C	I			C				I		C				C			I			C						C	C				
Cefepime	I			I		C			I		C	C		C	C			I	I		C	I	I	I		I		I	C		C	I		
Cefuroxime	C		C		I						I						C						I	C		C							I		C
Dopamine	I	C	C	I			I			C	C	I	C		I	C	C				C		C	C	C	C	C		C	C			C	C
Fentanyl		C	C	C	I				C			C	C				C					C	C	C	C		I		C					C
Fluconazole	C		C	I		I	C	I	C			I	C	I			C			C		C	C	C		C		C	C		C	C	C	C
Furosemide		C	I	C	I		C		I	C	I		C				C			C		I	I	I	C	I	C		C	C			I	I
Heparin	C	C	I	I		C			C	C	C	C			C	C	C	C		C	C	C	C	C	C	C		I	C	C	C	I	C	C
Imipenem-Cilastatin	C		I	I	I		C				I				C		C						I			C					I		C	
Insulin			C				C		I				C	C			C			C			C	C	I		C			C	C	C	C	
Lidocaine			C	I					C				C				C							C						C			C	
Linezolid	C			I		C		C	C	C	C	C	C	C		C		C	C	C	C	C	C	C		C		I	C	C	C	C	C	C
Magnesium Sulfate	C		I	I			I						C		C		C							C		C			C	C		C		
Mannitol				C			I										C									C	I		C					
Meropenem	I			I		I					C	C	C		C		C					C		C	C	I				C		C	C	
Methyl Prednisolone	C		C	C			C		C				I				C					C	C	C		I			C	I	C			
Metoclopramide	C			I			I			C	C	I	C				C			C			C			C			C					
Midazolam		C	C	I		C	I	I	C	C	C	I	C	I	C		C			C	C			C	C		I			C	I	C		C
Morphine	I	C	C	I	I		I	C	C	C	C	I	C		C	C	C	C		C	C	C	C		C	C	I	C	C	C	C			C
Noradrenaline		C	C						C	C		C	C		I					C			C	C		I			C			C	C
Ondansetron	I			I	I		I	C	C		C	I	C	C			C	C	C	I	I	C		C					C	C	I	C		
Pantoprazole		C							C			C			C				I				I	C	I					C			C	
Phenytoin				I			I			I	C		I				I							I						I			I	
Piperacillin - Tazobactum	I		I	I	I	C	C		C		C	C	C				C	C	C		C	C		C		C				C	C	I	C	
Potassium Chloride	C	C	C	I	I	C			C	C		C	C		C	C	C	C		C	I		C	C	C	C	C	I	C		C			
Sodium Bicarbonate	C		I	I			C						C	I	C		C				C		I	C		I			C	C		C	C	
Vancomycin	C		C	I			I	I			C		I		C		C	C		C			C	C		C			I		C			C
Vasopressin		C	C						C		C	I	C	C	C	C	C			C					C		C	I	C		C			
Vecuronium		C	C	I				C	C	C	C	I	C				C						C	C	C							C		

C Compatible Drugs

I Incompatible Drugs

No Information Available

Note :

This table can be used for Y-site compatibility at the usual manufacturer's concentration. This table gives information for two drug combinations only. If any drug combination is found to be incompatible then, administer through different IV access site or clarify with the clinical pharmacist.

Things to remember

- ✓ Interactions are easily forgotten when prescribing
- ✓ Interactions are difficult to remember
- ✓ PD interactions can often be predicted across drug classes
- ✓ PK often cannot be predicted – experiments needed
- ✓ Many interactions probably remain undescribed
- ✓ The chances of interaction are 60 times higher in a patient taking 5 drugs than in a patient taking 2

References:

- SmPCs − Stockley's Drug Interactions −
- Micromedex − https://pubmed.ncbi.nlm.nih.gov/ −
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Thanks for your attention