Polypharmacy and drug interactions
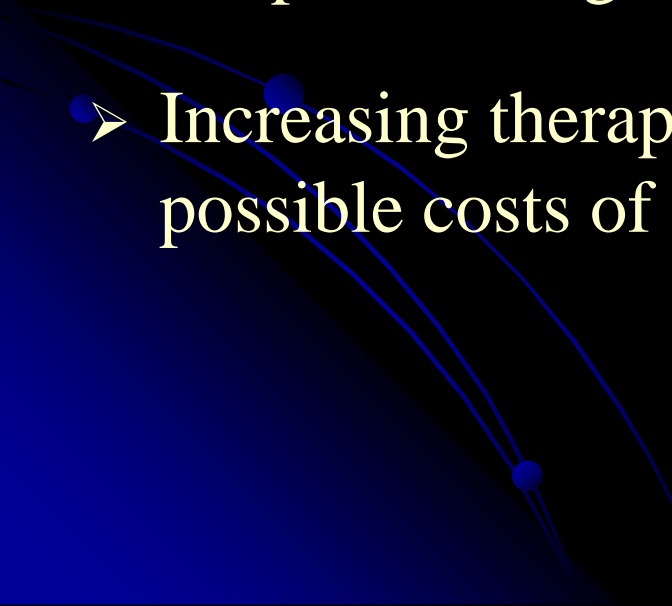
Polypharmacy

Polypharmacy indicates – using of unnecesary drug, treatment longer then optimal period, using over then optimal dose

= overuse of drug(s)

Consequences of polypharmacy:

➤ Increasing frequency of adverse drug reaction (ADR)

➤ Increasing frequency of drug interactions.

➤ Increasing possibility of iatrogenic harm.

➤ Decreasing patient–compliance as result of complicated terapeutical regimen.

➤ Increasing therapeutical costs (farmacotherapy costs and possible costs of terapeutical harm, e.g. hospitalisation).

Reasons for polypharmacy

1. doctor

a) Low respect of recent therapeutical guidelines.

b) Influence of pharmaceutical lobby (promotion, bribes/corruption)

c) Respect to patients´will, induced prescription

d) Absence of effective therapy, doctor using psychological effect of „placebo"

2. Patient

a) Polymorbidity - only acceptable way to polypharmacy

b) Wrong compliance to therapy

– only 11 % of patients precisely respect therapeutical regimen

– 56 % patients have adequate compliance (they use more than 80 % doses of their drug)

– the rest (33 %) presents factual non-compliance (patient use less than 80 % doses of drug) (prof. Smečka, 2000)

c) Increasing numbers of somatising patients (hypochondriacs)

ad 2. Patient

Polypharmacy is problem at first in elderly patients.

Main source? = frequently polymorbidity

In the Czech rep. 17 % people older than 65; they use more than 50 % prescribed drugs.

Demographic progress escalated to deficiency of healt insurance systems all over the world!

3. Effects of pharmaceutical business

a) Directly to patients – promotion (TV, press, net…)

b) To medicians (pharmacists) – congresses, bribes?

c) Lobbing to government institutions (e.g. drug payment)

4. National health system, health insurance

a) Number of medicinal providers; increase of medicians is the reason to increase the prescription.

b) A lot of specialists and low cooperation is the reason to increase numbers of using drugs with often contradictory effects.

c) Patient-friendly funding lead to overuse of health (pharmaceutical) care.

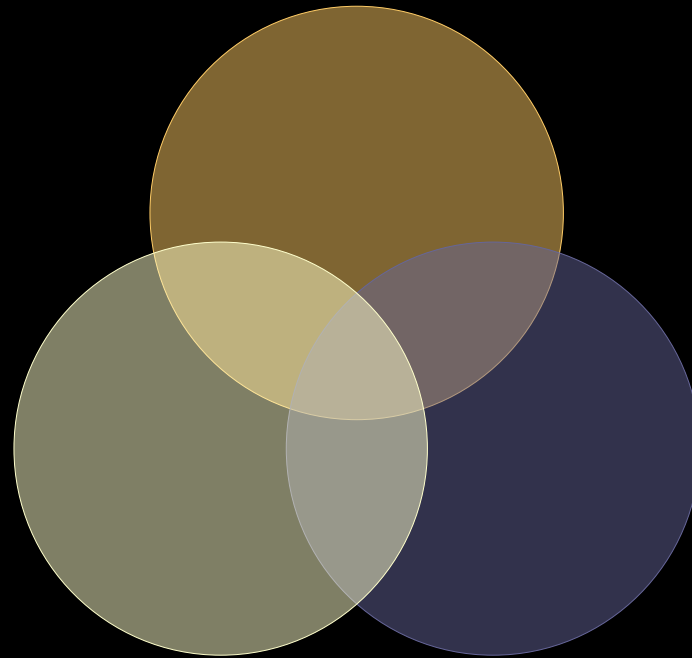## 5. Deficient communication between providers and patient

Non-effective communication chain

      Doctor → Nurse → Pharmacist → Patient

Many partners without central management of information stream.

Communication is Intersection

patient

medic

pharmacist

Inadequate communication with elderly

Seniors perceived as „gray wave"

↓

Gerontofobia

↓

Reducing the frequency and quality of communication

↓

Lower quality of care

Disorders of perception

90 % seniors - decrease in visual perception

30 % worsens hearing (mostly presbyacusis = hearing loss)

± lower intellectual abilities (decrease speed of decision)

Seniors and health literacy?

Health literacy - ability to understanding fundamental health information as a basis to adequate decision.

e.g. information leaflet ?!

→ need to communicate clearly with everyone

→ confirm understanding with everyone

Choice of appropriate terminology and content!

Excellent health literacy only by 12% of the population - health professionals, enlightenment chronics, grumblers ☺

↓

Need for public verbalization health problems

„You have to explain like to own grandmother"

Let us express the layman:

interaction
contraindication
generics
take on an empty stomach
enteric-coated tablet
myorelaxans

Another problematic terms?

Understanding dispensation low

Only 52% of patients correctly interpreted the recommendations „enjoy every 8 hours"!

The Pharmacy Intervention for Limited Literacy Study 2007

What recommendation would be more appropriate?

- Forward important information, but not to overfill patient – depends on index of drug information (information needed to safety use of drug)

- Alert for drugs that the patient does not use regularly (e.g. antibiotics, expectorants, pain medication)

- "Teach-back" for products declared as known

- Adapt informations to understanding of the patient (e.g. not analgesic, but the pain reliever ...)

- Explain the patient how his drug works, if it has any meaning (e.g. diuretics → increase urine production = more frequent urination ...)

Complementary problems of polypharmacy

1) Non–compliance

The therm non–compliance means intentional or unintentional sabotage of recomended therapy.

Source of decreased therapy efficiency, with a lot of negative consequences (clinical, psychological, economical…)

Impacts of non-compliance:

➢ **clinical** (uneffective therapy, increase of ADR, intoxication)

➢ **psychological** (stress in relationship patient – medic, mistrust, wrong communication)

➢ **economical** (increase therapy costs, decrease effectivity of medical service)

Types of therapeutic non–compliance:

1st. – Patient dont´ get drug.

In social systems in EU is this secondary problem, Problem? Strictly economic-oriented states (USA, China etc.) Possible 20 % patients without drugs. Economic crisis and future in EU???

2nd. – Misunderstanding treatment rules? Sabotage rules? The core is in communication of patients´problem → need to upgrade patients´motivation.

Formation pharmaceutical care to health couching

2) Drug error

Drug error definition: undesirable mistake of healthcare chain: doctor – nurse (paramedic) – pharmacist.

Many potential conflict points: prescription, preparation, dispensation of drugs (patient education), service/administration, etc.

To greatest risk are exposed patients with polypharmacy – exponential risk increase, which depends on number contemporary using drugs.

Risk management – way to reduce problematic points of therapy

identification risk → prevention risk

Progress of medicine and pharmaceutical scieces

With progress of sciences we can use more and more new drugs (problem to investigate)

vs

Clinical studies and new guidelines for safety and effective therapy management (answer to practice).
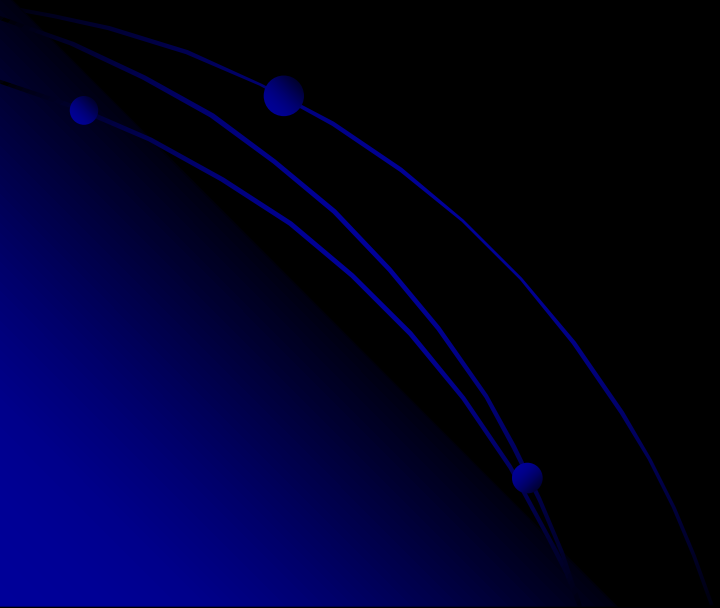
Risk of drug interactions

Study of emergency cases (Goldberg, USA)

➢ target group – patients with two and more together using drugs

➢ target parameter – potencional risk of drug interactions

➢ results: 47 % of patients were endangered with risk of drug interaction. Incidence of drug interactions increased from 13 % for two drugs till 82 % for seven and more drugs.

<u>Attention</u>

By more then 50 % patients were drug interactions main reason to emergency visit!

General practice (Hanlon, 2002)

target - epidemiological study focused to general practice and incidence drug interactions by elderly patients (more 65 years)

findings – total incidence 13 % of potential drug-drug or drug-disease interactions!

– moreover, 11 % of patients used their drugs longer than optimal period or used inadequate doses! (they are underdosed or overdosed).

Drug interactions increase risk of hospitalization (Doucet, USA)

result: at least 6 % of all hospitalizations in US were straight caused by drug interaction
(billions USD expenditures)

Moreover, twice frequent are harms and manifest disorders due to drug interactions.
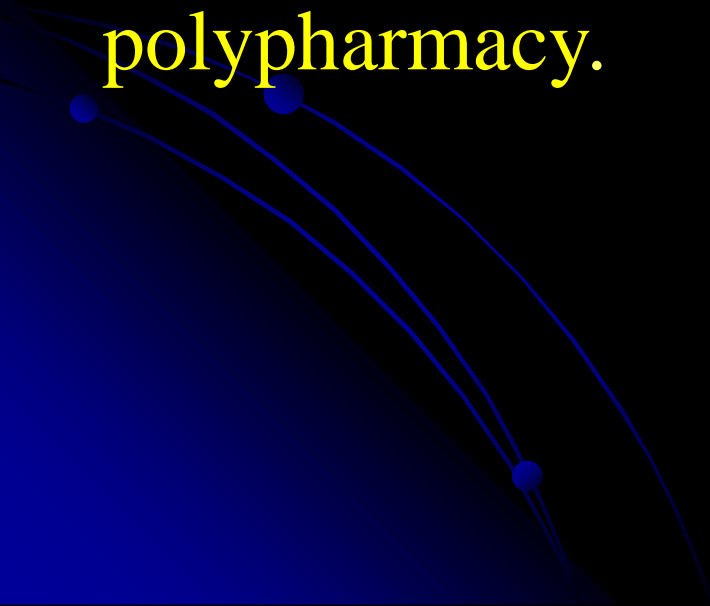
Bedell et al. (2000) – more together participate medics caused significant increase of drug interactions.
reasons – duplicate therapeutic interventions
– medication with opposite effects

Prescribing medic often hasn´t accurate information about participation other medics on therapy

76 %! of personal health documentation at registers of cardiologists and internists contains incorrect pharmacotherapeutic informations.

Significant common points of this mistakes were higher patients age and associated polypharmacy.

Procentual incidence of drug interactions

Number drugs	5	6	7	8 +	Sum
Number patients	39	41	23	21	124
Patients with interact.	27	29	18	18	92
Incidence (%)	69,2	70,7	78,3	85,7	74,2
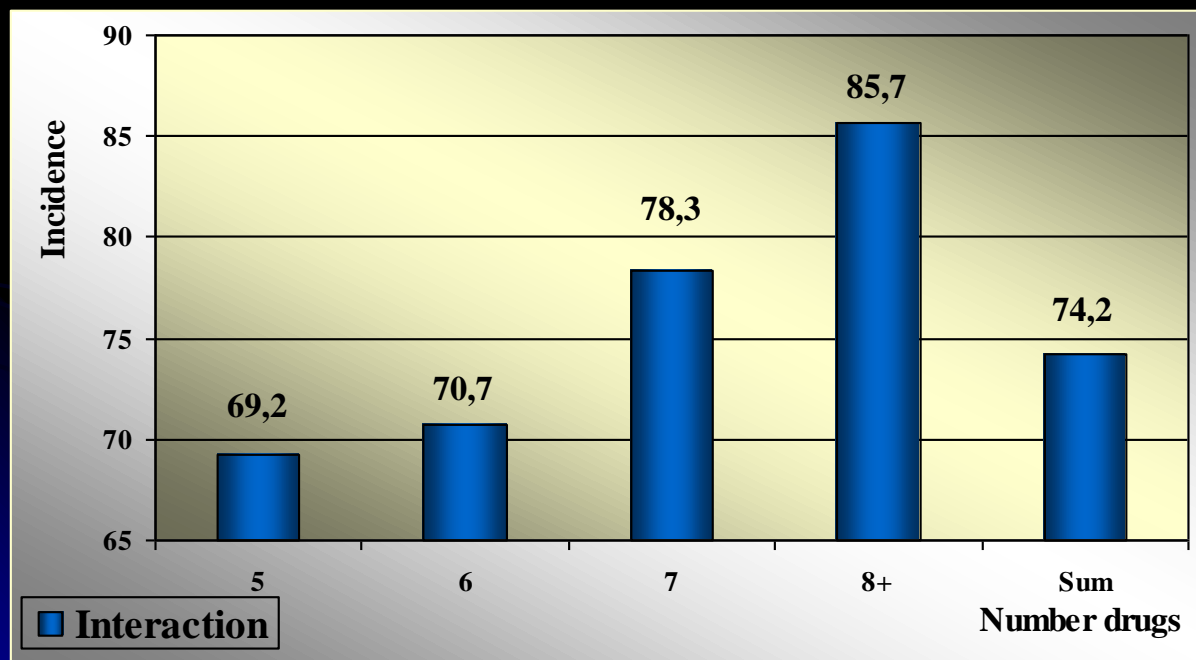
ÚAF FaF Brno, 2005

Study ÚAF FaF Brno, 2007

172 patients used 5 and more drugs

Distribution drug interactions according to ATC groups

Legend:
- A – GIT, metabolism
- B – blood system
- C – cardiovascular system
- H – systemic hormones
- J – systemic antiinfectives
- M – musculosceletal system
- N – CNS
- R – respiratory system
- V – varia

Values shown: 12,91%, 55,14%, 9,65%, 13,91%, 4,64%, 0,13%, 2,63%, 0,50%, 0,50%
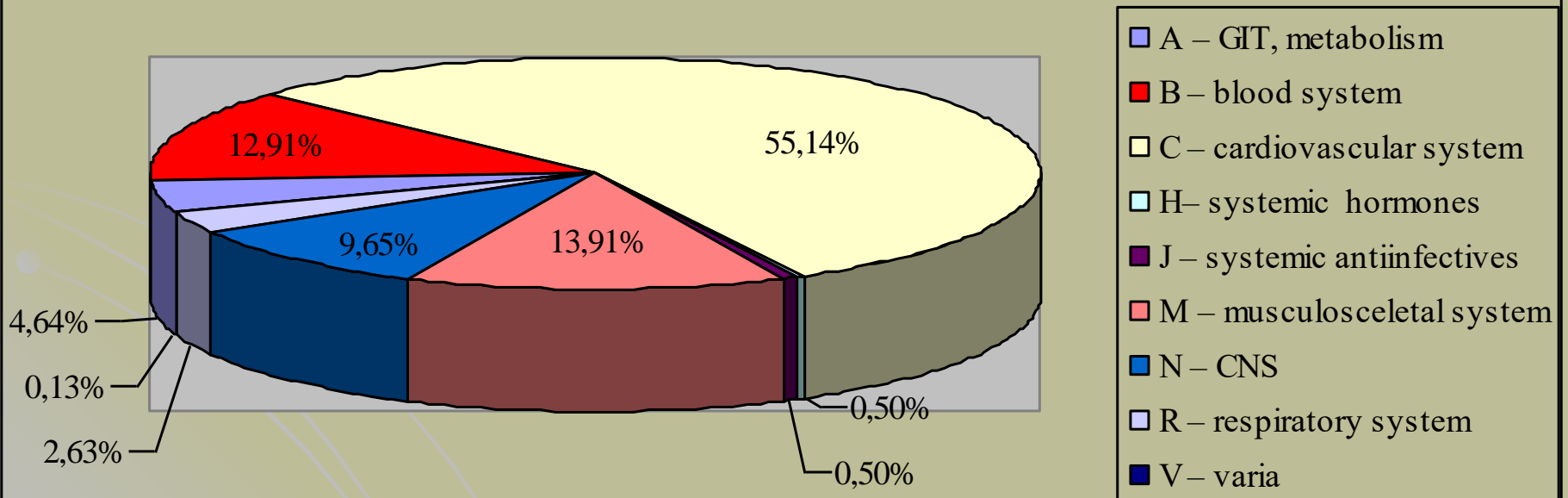
Mechanisms of drug interactions

For simple and rapid (effective) identification
of drug interactions is useful to remember some
basic principles

let's summarize them

Modulated absorption

– drug absorption can be altered by using other pharmacological or physical substance at the same time

– model example can be tetracycline with Ca, Mg,.. ions or antacids.

Other often used substances with absorption principle - charcoal (activated coal), psyllium

<u>Changing GIT motility by one of using drugs</u>

– quite often unidentified mechanism of drug interactions

– gastrointestinal motility deceleration leads to slower absorption other drugs and delayed start of their effects (e.g. opiates, loperamid)

– gastrointestinal motility acceleration leads to faster absorption or elimination (e.g. prokinetics and some laxatives)

Changing of gastric acidity

– by changing of gastric acidity is modulated disociation drugs (weak acids or bases)

– impact on disolution enterosolvent peroral drug forms → cause premature disolving drug form
→ gastrotoxicity
→ deactivation of drug (e.g. digestive enzymes)

– important because of frequently use gastric acid inhibitors (e.g. omeprazole, ranitidine…)

Changing distribution parameters

– most often situation is modificate relation drug to binding plasmatic albumine. Mechanism is competition for binding capacity this protein fraction of blood plasma.

– result is increase free fraction drug, which is responsible for main pharmacological effect

– clinical importance has this interaction by drugs with strong binding to albumine, and on other hand with close therapeutic profile.

well-known example = warfarin + NSAID – minor change free fraction of warfarin can caused increase INR (Quick test) and this way risk of fatal hemorrhage (bleeding).

– by drugs without close therapeutic profile (safety drugs) is complication faster clearance. This situation cause, that drug is faster eliminated and to adequate therapy we have to use higher doses.

Fraction binding to albumine creates depot, which can supply therapeutic needs for longer time.

If depot function is impaired, biological halftime is reduced all at once with effectivity of pharmacotherapy.

Changing of metabolism drugs

Most clinical significant group of drug interactions.

Crucial is in this metabolic way family of cytochrome P450 (CYP450).

In human genome were found at least 59 cytochromes P450.

The most important are CYP3A4 a CYP2D6.

Cytochromes P450 are responsible for majority of drug metabolism (its´ estimated at least 55 %).

Highest levels have P450s in liver, but they are represented all over body - GIT (small intestine), lung, kidneys, brain…

More than 50 % drugs are metabolized by way the CYP3A4!

This cytochrome is also most frequevent form, in human liver represent 30 % contained cytochromes.

Importance CYP3A4 represents by elderly patients, because his activity decreases with every decade by 8 %.

A lot of drugs have potencial to induce CYP3A4 activity (e.g. dexametasone, barbiturates, BZD). Result is faster metabolism drug, which is substrate of this cytochrome.

On other hand, we can often observe competition different drugs for binding place of enzyme – result is slowdown of metabolism both.

We can investigate two extremes:

- failure therapy – low concentration of drug

- toxic harm – high concentration of drug

Main inhibitors CYP3A4:

➢ macrolide ATB – erytromycine, claritromycine, roxitromycine (azitromycine using other metabolic way; no interaction)

➢ azol antimycotics – mostly clotrimazole, ketoconazole

➢ bergamotine and his derivates (grapefruit) – deactivates only small intestine fraction CYP3A4 (cause higher intake of drug). Liver fraction without impact.

Other examples at table 1.

Main inductors CYP3A4:

- rifampicin (ATB, antituberculotic)
- fenytoin (antiepileptic)
- karbamazepin (antiepileptic)
- fenobarbital (antiepileptic, hypnotic)
- hyperforin (Hypericum perforatum, antidepressant)

Most often significant interactions CYP3A4

substráty nebo látky interagující s CYP3A4		typické inhibitory CYP3A4
Alfentanil	Loratadin	Amiodaron
Alpidem	Losartan	Bromokryptin
Alprazolam	Lovastatin	Cimetidin
Ambroxol	Meloxicam	Clotrimazol
Amiodaron	Metadon	Cyklosporin
Amitriptylin	Mibefradil	Danazol
Astemizol	Midazolam	Diltiazem
Atorvastatin	Mifepriston	Ergotamin
Budesonid	N-hydroxyarginin	Erytromycin
Bupivakain	Nefazodon	Etinylestradiol
Buprenorfin	Nevaripin	Flukonazol
Buspiron	Nifedipin	Fluoxetin
Cisaprid	Nikardipin	Fluvoxamin
Citalopram	Nimodipin	Gestoden
Cyklobenzaprin	Nisoldipin	Grapefruitový džus
Cyklofosfamid	Nitrendipin	Chinidin
Cyklosporin A, G	Omeprazol	Indinavir
Dapson	Paklitaxel	Itrakonazol
Dehydroepiandrosteron	Pantoprazol	Ketokonazol
Delaviridin	Paracetamol	Klaritromycin
Dexametazon	Pimozid	Midazolam
Dextrometorfan	Progesteron	Mikonazol
Diazepam	Propafenon	Nefazodon
Digitoxin	Rapamycin	Nifedipin
Diltiazem	Retinová kyselina (tretinoin)	Nikardipin
Docetaxel	Rifabutin	Omeprazol
Erytromycin	Ritonavir	Progesteron
17β-estradiol	Ropivakain	Ritonavir
Etinylestradiol	Salmeterol	Saquinavir
Etylmorfin	Saquinavir	Testosteron
Etoposid	Sertralin	Troleandomycin
Extrakt třezalky	Sildenafil	Verapamil
Felodipin	Simvastatin	
Fentanyl	Sufentanil	
Finasterid	Sulfametoxazol	typické induktory CYP3A4
Flutamid	Tacrolimus	Dexametason
Gallopamil	Tamoxifen	Fenobarbital
Gestoden	Teniposid	Fenytoin
Granisetron	Terbinafin	Karbamazepin
Haloperidol	Terfenadin	Rifabutin
Chinidin	Tergurid	Rifampicin
Ifosfamid	Testosteron	Troglitazon
Imipramin	Tetrahydrokanabinol	Třezalka tečkovaná (hypericum perforatum)
Indinavir	Teofyllin	
Irinotecan	Tolterodin	
Ivermectin (veterinarium)	Triazolam	
Karbamazepin	Trimetadon	
Klaritromycin	Troglitazon	
Klomipramin	Troleandomycin	
Klozapin	Verapamil	
Kodein	Vinblastin	
Kolchicin	(R-)Warfarin	
Kortisol	Zatosetron	
Lansoprazol	Zolpidem	
Lidokain	Zopiklon	
Lisurid		

Second significant cytochrome is CYP2D6, which funkcion we estimate 25 % metabolised drugs.

Conditions are complicated by the way of genetic polymorphism, which can significantly change metabolic operations. This fact worsens study of potential drug-drug interaction risk.

In present time we can calculate (based on studies), that european population (with Caucasus progenitors) contains 7 % slow metabolisers (this lead to increase of plasmatic drug concentration).

On other hand, east Asian population contains about 50 % slow metabolisers!

Little satisfaction – based on recent studies isn´t CYP2D6 inducible.

Typical substrates are some antidepressants and β-blockers, in which we can observe the most of interactions.

Most important substrates and inhibitors of CYP2D6 are contained in table 2.

Most often significant interactions CYP2D6

Substrates CYP2D6

Ajmalin	Kodein	
Amitriptylin	Melperon	
Bufuralol	Metipranol	
Bupranolol	Metoxyamfetamin	
Cinarizin	Metoprolol	
Citalopram	Mexiletin	
Debrizochin	Mianserin	
Deprenyl	Nortriptylin	
Dezipramin	Ondansetron	
Dextrometorfan	Paroxetin	
Dexfenfluramin	Perhexilin	
Enkainid	Perfenazin	
Flekainid	Propafenon	
Fluoxetin	Propranolol	
Fluvoxamin	Risperidon	
Flunarizin	Spartein	
Flufenazin	Tioridazin	
Galantamin	Timolol	
Haloperidol	Tramadol	
Hydrokodon	Trifluperidol	
Chlorpromazin	Tropisetron	
Imipramin	Tomoxetin	
Kaptopril	Venlafaxin	
Klomipramin		

Typical inhibitors CYP2D6

Amiodaron
Buproprion
Celecoxib
Cimetidin
Difenhydramin
Doxorubicin
Fluoxetin
Chinidin
Chlorpromazin
Klemastin
Klomipramin
Kokain
Levomepromazin
Metoklopramid
Metadon
Mibefradil
Moklobemid
Paroxetin
Perfenazin
Ranitidin
Ritonavir
Sertralin
Terbinafin

Changing of drug elimination by kidney

Two drugs can compete to secretory mechanism. Result of this situation is slowdown of elimination, increase drug(s) concentration and this way increase risk of toxic harm.

Change of pH of urine can cause slowdown elimination too. Alkalisation of urine decreases elimination of drugs on the base of weak bases and conversely.

Problem of this interaction is the most significant by elderly patients. The reason is, that this patients have lower glomerular filtration and often lower drinking regimen.

Optimal drinking regimen?

Farmacodynamic interactions

Caused by aditive/synergic, or on other hand antagonistic effects of drugs

Frequently we don't understand this relations exactly → increase risk ADR, side effects

X

These effects are often used, because combination of two or more drugs can be more effective or safety than higher dose of one drug (therapy of hypertension, diabetes NID, painful conditions…)

Issues of natural products in therapy

Todays trend in self care medicine is comeback to the nature products.

Often patients underestimated potential risk – „nature is holy, perfect, safety…" Botulinum toxine? Viperatoxine? St. John's Wort?

Other potential risks are:

-wrong replacement of mother plant by unprofessional preparation

- contamination – aflatoxines, other plants, drugs…

Specific problem of „natural" products in chinese medicine – „upgrade" with use external chemical substances.

e.g.: acetaminophene (paracetamolum)

indomethacin

hydrochlorothiazide

prednisolone

caffeine (Huang 1997).

Moreover, these substances are not declared on the final product.

It was found that 24 %! from 2609 specimens traditional herb mixtures from Taiwan hospitals contained chemical compounds.

Non-steroidal antiinflamatory drugs (e.g. diclofenac) and benzodiazepines (e.g. diazepam) were identified in many chinese patented herb mixtures outside Asia (Gertner 2005).

warfarine – garlic (Allium sativum) → increase INR (International Normalization Ratio – Quick test = protrombine time). Garlic decrease agregation of trombocytes and can caused bleeding.

ASA – Ginkgo biloba → increase bleeding; ginkgolides are strong inhibitors of PAF (Platelet Activatig Factor)

lithium – psyllium (Plantago ovata) → decrease of blood serum concentration of lithium; psyllium effects like absorbent stuff

digoxine – St. Johns´wort → decrease AUC and maximal concentration of digoxine; induction CYP 3A4

digoxin - hawthorn (effective in reducing angina attacks by lowering blood pressure and cholesterol levels). Should never be taken together → mix can lower heart rate too much (possible heart failure)

antihypertensives, caffeine - ginseng → increase the risk of overstimulation, hypertension and gastrointestinal upset. Ginseng, when taken with the blood-thinning drug (warfarin) can caused bleeding!

Top ten drug interactions most dangerous to seniors in long-term care

Numerous studies have shown, that senior citizens are the most prone to danger from drug interactions.

American Society of Consultant Pharmacists identified ten drug interactions most commonly associated with dangerous reactions by residents in long-term care.

warfarin – NSAIDs → NSAIDs increase gastric irritation and erosion of the protective lining of the stomach, assisting in the formation of a GI bleed. Additionally, NSAIDs decrease the cohesive properties of platelets necessary in clot formation. Prothrombin time and INR should be monitored every week with co-administration of warfarin with NSAID.

<u>warfarin – sulfa drugs</u> (e.g. sulfamethoxazole) → increased effects of warfarin, with potential for bleeding.

Currently, the mechanism for interaction with sulfa drugs is unknown; however, clinicians hypothesize that warfarin's activity is prolonged due to a decreased production of vitamin K by intestinal flora affected by systemic antibiotic administration.

<u>warfarin – macrolides</u> (clarithromycin) → Increased effects of warfarin, with potential for bleeding.

Macrolide inhibits the metabolism and subsequent clearance of warfarin from the body. The activity of warfarin may also be prolonged due to alterations in the intestinal flora and its production of vitamin K for clotting factor production.

Possible solution is using of azithromycin (other metabolism)
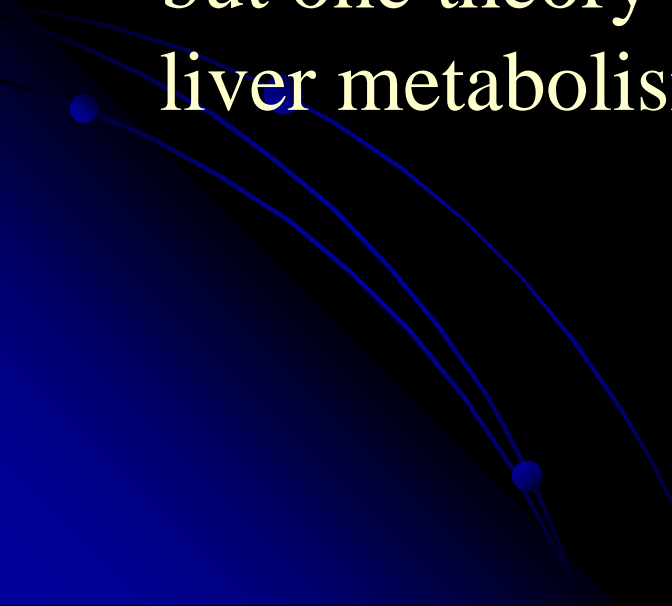
<u>warfarin – quinolones</u> (ciprofloxacine) → Increased effects of warfarin, with potential for bleeding.

The exact mechanism for warfarin-quinolone drug interaction is unknown. Reduction of intestinal flora responsible for vitamin K production by antibiotics is probable as well as decreased metabolism and clearance of warfarin.

warfarin – phenytoin (antiepileptic) → increased effects of warfarin and/or phenytoin.

Mechanism of interaction is currently unknown, but one theory suggests a genetic basis involving liver metabolism of warfarin and phenytoin.

ACE-inhibitors – potassium supplements → elevated serum potassium.

Inhibition of ACE results in decreased aldosterone production and potentially decreased potassium excretion (risk of cardiovascular failure)

ACE-inhibitors – spironolactone (diuretic) → both elevated serum potassium levels, additive effect.

digoxin – amiodarone (antidysrhythmic) → increase digoxin toxicity.

Multiple theories exist, but actual mechanism is unknown. Amiodarone may decrease the clearance of digoxin, resulting in prolonged digoxin activity. There may also be an additive effect on the sinus node of the heart.

digoxin – verapamil (antihypertensive) → increase digoxin toxicity.

Synergistic effect of slowing impulse conduction and muscle contractility, leading to bradycardia and possible heart block.

theophylline – quinolones → increase theophylline toxicity.

Inhibition of hepatic metabolism of theophylline by the quinolones.

Criteria drug suitability by elderly patients

1991 – team of Dr. Beers (US specialist) realized first list of not recomended drugs for elderly (more then 65). This drugs are not only dangerous; possible is little theraeutical benefit or potential drug interactions.

This list most important revisions were realized 2003, 2007. Last 2012

http://www.americangeriatrics.org/files/documents/beers/2012BeersCriteria_JAGS.pdf

Main problematic drugs:

- Non–COX-selective NSAIDs (especially piroxicam a indomethacin)
- Long acting benzodiazepines
- Sedative antihistaminics
- Sedative antipsychotics
- Anticholinergic acting antidepressants
- Barbiturates
- High dose of digoxin (not antiarhytmic use)
- pentoxiphylline

Etc.

Similar to Beers criteria exists in Canada list of McLeods´criteria (1997)

Problematic of inappropriately drug using was studied by multicentric european AdHOC study (Aged in HOme Care)

8 european countries (representative groups of home-care elderly from Czech rep., Denmark, Finland, Iceland, Italy, Netherland, Norway and GB).

Average prevalence using of inappropriate drugs was the same in Europe and US (about 20 %)

! international european differences was deep !

Most inappropriate drugs - Czech rep. – 41 % users !!!
(last years improvement; todays about 20 %)

Least - Denmark – 5,8 % users

Fialová D, Topinková E, Gambassi G. et al.: Potentially inappropriate medication use among elderly home care patients in Europe. JAMA, 2005, 293(11):1348-58.

Thank you for your attention