




Optimization of polypharmacy

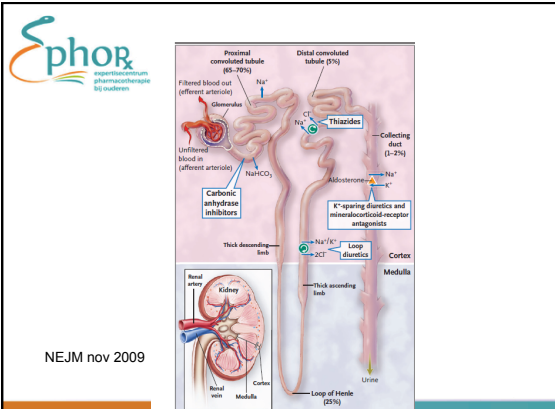
Paul Jansen,
geriatrician clinical pharmacologist

Patientenzorg
Onderwijs
Onderzoek




Question

Wich medicines are frequent prescribed to patients over 70 years?



NEJM nov 2009


Proximal convoluted tubule (65-70%)
Distal convoluted tubule (5%)
Thiazides
Carbonic anhydrase inhibitors
K⁺-sparing diuretics and mineralocorticoid-receptor antagonists
Loop diuretics
Loop of Henle (20%)



Top 10 medicines in 70+


- acetylsalicylic acid
- metoprolol
- simvastatine
- omeprazol
- furosemide
- lactulose
- bumetanide
- enalapril
- amlodipine
- calciumcarbasalate

Source: Drug Information Project, CVZ 2010




In the elderly often multimorbidity and polypharmacy

What is the mean drug use in geriatric patients?




Mean drug use

- At the geriatric department:
mean 10,2 medicines
(spread 2-24)
- number of OTC's: 2,0 (0-6, 83%)
- What about the adherence?



Adherence

- 85% with 1 medicine
- 75% with 2-3 medicines
- 65% with 4 or more medicines
- ..% with 16-20 medicines
- Especially bad adherence with use of antihypertensives en statines (40-70%)



Question

How many patients are daily admitted to a hospital because of an adverse effect?




international




HARM study (2006):
In the Netherlands 100 per day
How many are preventable?

Leendertse et al. Archives Int Med 2008; 63 (22): 2716-2724




Almost half is potentially preventable

Which medicines cause these severe adverse effects?



The good and the bad guys

- Trombocytes aggregation inhibitors
- Vitamin K antagonist
- NSAID's
- Psychopharmaca
- Antidiabetics
- Diuretics
- Glucocorticosteroids
- Antibiotics



Risk factors

- Cognitive disorder (HR 11,9; 3,9-36,3)
- Polymorbidity (>5 HR 8,7; 3,1-24,1)
- Decreased renal function (HR 3,1; 1,9-5,20)
- Not living at their own (HR 3,0; 1,4-6,5)
- Polypharmacy (>5 HR 2,7; 1,8-3,9)
- Non adherence (HR 2,3; 1,4-3,8)

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More Recent study
Ruiters et al.
Drugs Aging. 2012;29:225-32

- aged ≥ 75 years more than 4-fold increased risk of being hospitalized in comparison with 55-64 years (RR 4.15; CI95 4.12-4.18).
- females increased risk of an ADR-related hospitalization in comparison with males. (RR 1.05; CI95 1.03-1.08)
- anticoagulants (RR 2.20; CI95 2.12-2.28) antidiabetic agents (RR 3.53; CI95 3.39-3.66), salicylates (RR 1.70; CI95 1.54-1.86) and antirheumatics (RR 2.19; CI95 2.06-2.33).

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Reduction of polypharmacy is often not succesful
A better way is:

indicated polypharmacy

- pharmacokinetics
- pharmacodynamics
- interactions

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Pharmacokinetics:

What is the body doing with the drug


absorption distribution
receptor
metabolisme excretion

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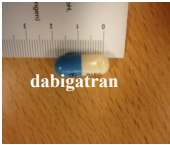
absorption

- How does the medicines look alike? How big, or small?
- How does it taste?
- Is it possible to swallow the drug easily?

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celecoxib 200 mg
amoxicilline disper 375 mg
mirtazapine soltab 30 mg
paracetamol 500 mg
piracetam 400 mg
gabapentine 400 mg
mesalazine 500 mg



dabigatran

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absorption

- Is an interaction with food to be expected?

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Interaction with food

- bisphosphonates
- levothyroxine
- ferro derivatives
- levodopa

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Interaction with fluids

Grapefruit
 Jean Raney
 \$ 1325



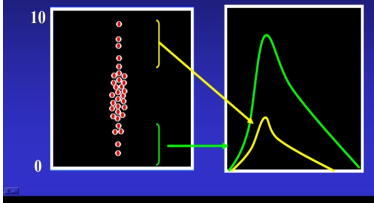
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Cytochrome P-450 enzymes

- In liver and gut

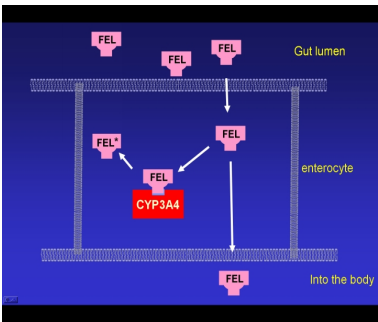
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Variation in enterocyte CYP3A4 activity and the oral disposition of some substrates



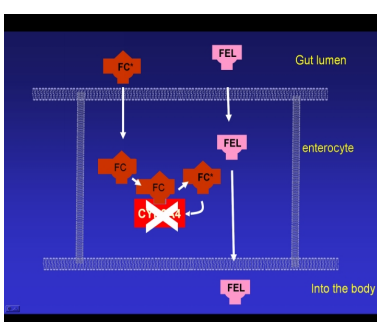
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Grapefruit and medicines

- calciumantagonists
- -statines (simvastatine en atorvastatine)
- midazolam, diazepam
- carbamazepine
- ciclosporine

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distribution

- Total amount of bodywater decreases
- Total amount of fat increases

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Changes in distribution in the elderly

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Consequences

- concentration hydrophilic drugs is higher: decreased loading dose is necessary
- lipophilic drugs remain a longer time in the body (eg benzodiazepines)

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Diazepam elimination t1/2

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metabolisme

- Decreased liver size
- Decreased liver bloodflow
- Decreased CYP-450 enzym activity

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Cytochroom P450 and antipyrineclearance

Age (yr)	20-29	50-59	>70
Antipyrine clearance (ml/min)	46 ± 15	42 ± 19	33 ± 12
CYP-450 (nmol/g)	7.2 ± 2.6	6.4 ± 2.3	4.8 ± 1.1

Sotaniemi et al. Clin Pharm Ther 1997

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excretion

- Decreased kidney bloodflow
- Decreased glomerular filtration
- Decreased tubular excretion

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Pharmacodynamics:

what is the drug doing with the body

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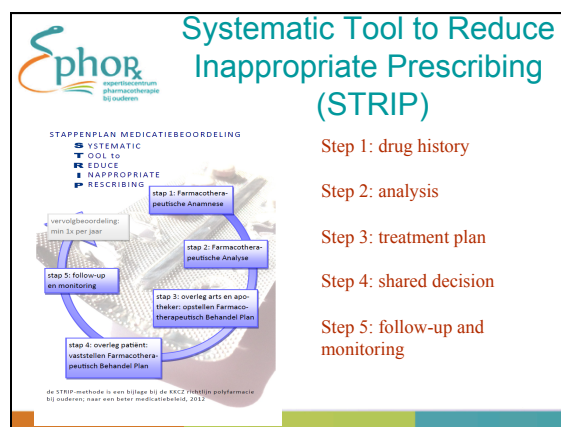
Change in pharmacodynamic properties

- antidepressives
- antipsychotics
- benzodiazepines
- digoxine
- vitamine K-antagonists

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Medication review: STRIP

- **Selection of patients for medication review:**
 - 65 years and older
 - and polypharmacy (5 or more medicines)
 - **And minimally one** risk factor:
 - Decreased kidneyfunction (eGFR<50 ml/min/1,73 m²)
 - Decreased cognition
 - Increased risk for falls
 - Signs of decreased adherence



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Casus: 84 year old woman uses 16 different medicines

She lives independently at home, she gets some help with house-keeping and with showering. She uses a rollator. She stays most of the time at home.

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Her problems (GP journal)

- asthma, COPD
- aortavalve sclerose/ insuf
- hypertension
- diabetes mellitus type2
- angina pectoris
- oesophageal reflux
- incontinence
- osteoarthritis
- osteoporosis
- fam. hypercholesterolemia
- total knee leftside
- stroke (2000)
- poststroke depression
- sleep disturbances

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Her medication

- triamterene 50 mg 1dd
- furosemide 40 mg 1 dd
- Ascal 38 mg 1 dd
- Tildiem XR 200 mg 1dd
- Isordil s.l. zonodig
- Atrovent aerosol 4 dd
- Lomodol forte
- Zocor 10 mg 1 dd
- gliclazide 80 mg 1 dd
- ranitidine 150 mg 1 dd
- nitrazepam 5 mg an 1
- oxazepam as needed 1
- lactulose
- estriol vaginal ovule
- paracetamol 500mg 3-4dd1
- mebutan 1gr 1dd

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Cluster diseases and medicines

- asthma, COPD
- hypertension
- diabetes mellitus type 2
- angina pectoris
- oesophageal reflux
- incontinence
- osteoarthritis
- osteoporosis
- fam. hypercholesterolemia
- stroke (2000)
- sleep disturbances

triamterene, furosemide
acetylsalicylic acid
diltiazem
isosorbidedinitrate
ipratropium,
cromoglicine acid,
simvastatine,
gliclazide,
ranitidine,
nitrazepam, oxazepam,
lactulose,
estriol vaginal ovule,
paracetamol, nabumeton

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Cluster diseases and medicines


- asthma, COPD
- hypertension
- diabetes mellitus type 2
- angina pectoris
- oesophageal reflux
- incontinence
- osteoarthritis
- osteoporosis
- fam. hypercholesterolemia
- stroke (2000)
- sleep disturbances
- ?
- ipratropium, cromoglicine acid
- triamterene, furosemide ?
- gliclazide
- diltiazem, isosorbidedinitrate
- ranitidine
- estriol vaginal ovule
- paracetamol, nabumeton
- ?
- simvastatine
- acetylsalicylic acid
- nitrazepam, oxazepam
- lactulose

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Case: a 84-year old woman uses 16 different medicines


After the coffee break:
What is your strategy to optimize this medication?
Wich steps do you take?




 **STRIP**

- What does she really takes?
- Does she suffer adverse effects?
- Which drug(s) should be added?
- Which drug(s) are not necessary/contraindicated?
- Which clinical relevant interactions are to be expected?
- Should the dose or dosefrequency be changed?

Drenth et al. Drugs and Aging 2009; 26: 687-701; www.ephor.eu


 **Six questions to optimize polypharmacy**

1. What does she really takes?


 **Results in 100 patients of the Structured History taking of Medication (SHIM)**

- In 92% discrepancies
- Mean 3.7 ± 3.3
- Omission was the most common discrepancy
- 21% had discomfort because of the discrepancy

Drenth et al. JAGS 2011;59(10):1976-1977 www.ephor.eu

 **Results**


- Potential clinical relevance:
 - class 1: 28%
 - class 2: 56%
 - class 3: 16%

 **Examples of relevance**


- Acenocoumarol in atrialfibrillation: not known (AIOS), not on list pharmacist
- alfacalcidol hypoparathyroidy: too high dose on list pharmacist
- Bumetanide in heartfailure: not known (AIOS)
- citalopram for depression stopped because of nausea: not known, prescribed by AIOS and on list pharmacist
- Flucloxacilline for hip infecton: not known (AIOS), not on list pharmacist

 **What she didn't took**

• Asthma, COPD	• Atrovent, Lomudal
• Hypertension	• furosemide, triamterene
• Diabetes mellitus type 2	• gliclazide
• Angina pectoris	• Tildiem, Isordil
• Oesophageal reflux	• ranitidine
• incontinence	• estriol
• osteoartritis	• nabumeton, paracetamol
• Osteoporosis	• ?
• Hypercholesterolemia	• Zocor
• Stroke (2000)	• Ascal
• Sleep disturbances	• nitrazepam, oxazepam
• ?	• lactulose




Guidelines are not made for elderly patients with polypharmacy and multimorbidity

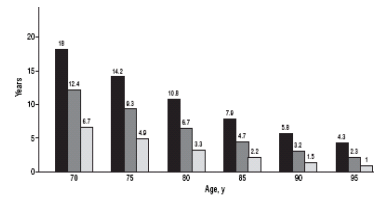


To treat or not to treat depends of:


- Evidence in the elderly
- Benefit/harm ratio
- Time until benefit
- Biological age
- The preference of the patient

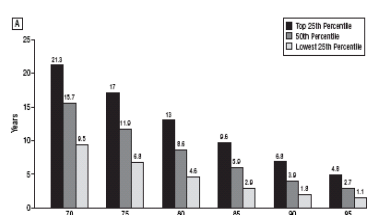
Life expectancy in men




Man of 80 years: between 3 and 11 years



Life expectancy in women

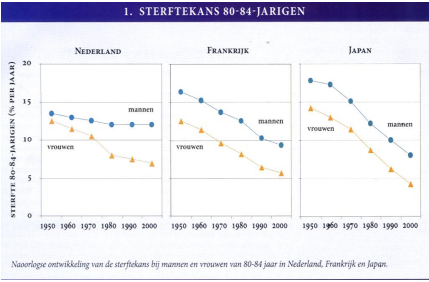


Woman of 80: between 4,5 and 13 years



expectation of death of people aged 80-84 years

1. STERFTEKANS 80-84-JARIGEN



Nieuwogse ontwikkeling van de sterftekans bij mannen en vrouwen van 80-84 jaar in Nederland, Frankrijk en Japan.

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Do you prescribe a statine to her?

What is the evidence,
 the benefit/risk ratio
 and the time until benefit?

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Prosper study
 cardiac infarction and stroke

B

Proportion with event (%)

p=0.006

C

Proportion with event (%)

p=0.81

Follow-up (years)

Group	0	0.5	1	1.5	2	2.5	3	3.5	4
Placebo	2913	2847	2775	2692	2614	2535	2208	768	46
Pravastatin	2891	2827	2768	2696	2658	2544	2237	797	40

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NNT and TUB: pravastatine
 in 70-82 years old patients

- 2 year (cardiovascular events)
- NNT: cardiovascular events
 - placebo: 12,2%
 - pravastatine: 10,1%
 - difference: 2,1% NNT: 48

Prosper-study: Shepherd et al. Lancet 2002;360:1623-30

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Six questions to optimize
 polypharmacy

1. What does she really takes?
2. Does she suffer adverse effects?

How can you determine causality?

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Causality according
 to Naranjo

Clin Pharmacol Ther 1981;30:239-245

- Adverse reaction is known (WHO/Lareb.nl)
- Time relation and rechallenge
- Other reasons
- Serumconcentration too high
- More severe after increase of dose or less severe after dose reduction
- Objective proof
- doubtful, possible, probable, definite


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Adverse effects


- Ask your patient

Therapeutic Advances in Drug Safety


New antiepileptic medication linked to blue discoloration of the skin and eyes

 **Case: wich adverse effects?**


- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- ?
- Atrovent, Lomudal
- triamterene
- gliclazide
- Tildiem
- ranitidine
- nabumeton, paracetamol
- ?
- Ascal
- nitrazepam, oxazepam
- lactulose (flatulency)

 **Six questions to optimize polypharmacy**


1. What does she really takes?
2. Does she suffer adverse effects?
3. Which drugs should be added?

 **Case: what want you to add?**

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- Atrovent, Lomudal
- triamterene
- gliclazide
- Tildiem
- ranitidine
- nabumeton, paracetamol
- ?
- Ascal
- nitrazepam, oxazepam


 **Case: a 84-year old woman with 10 + 4 drugs**

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- Atrovent, Lomudal
- Triamterene, [ACE-inhibitor](#)
- gliclazide
- Tildiem
- [Protonpumpinhibitor](#)
- nabumeton, paracetamol
- [Calcium/vitamin D](#)
- Ascal
- nitrazepam, oxazepam

 **undertreatment geriatric department UMC Utrecht 2006**

- No laxative while using opioids: 62%
- No betablocker after myocardial infarction: 60%
- No ACE-inhibitor for heart failure: 47%
- No coumarine for atrial fibrillation: 42%
- No treatment for osteoporosis: 29%
- No statine for hypercholesterolemia: 23%
- No stomach protection with NSAID's use: 21%

Kuijpers et al. Br J Clin Pharmacol 2008;65:28-35.

 **Six questions to optimize polypharmacy**

1. What does she really takes?
2. Does she suffer adverse effects?
3. Which drugs should be added?
4. What is not necessary/contra-indicated?

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Case: a 84-year old woman with 14 drugs

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- Atrovent, Lomudal
- triamterene, ACE-inhibitor
- gliclazide
- Tildiem
- PPI
- Mebutan, paracetamol
- Calcium/vitamin D
- Ascal
- nitrazepam, oxazepam

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Case: a 84-year old woman with 14 drugs

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- Atrovent Lomudal
- triamterene, ACE-inhibitor
- gliclazide
- Tildiem
- PPI
- Mebutan, paracetamol
- Calcium/vitamin D
- Ascal
- nitrazepam, oxazepam

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she want to use the sleeping pill

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- Atrovent
- ACE-inhibitor
- gliclazide
- Tildiem
- PPI
- paracetamol
- Calcium/vitamin D
- Ascal
- temazepam

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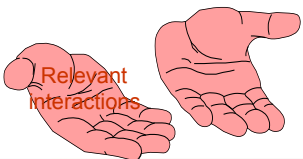
Six questions to optimize polypharmacy

1. What does she really takes?
2. Does she suffer adverse effects?
3. Which drugs should be added?
4. What is not necessary/contra-indicated?
5. Which relevant interactions do you expect?

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Interactions

- There are many interactions
- However relevant interactions are countable on two hands




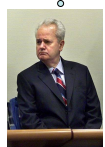
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Interactions of medicines

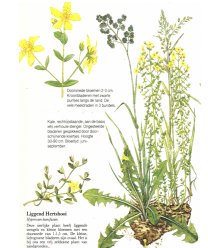
- With food
- With drinks
- With smoking
- With herbals
- With other medicines

Sphor Interactions and the liver

CYP 1A2	Substrate clozapine theophylline	Inhibitor cimetidine fluvoxamine(p) ciprofloxacin fluconazol (p)	inductor tobacco
2C9	tolbutamide	some PPI's	st. John's wort
2C19	coumarine clopidogrel		wort rifampicine
2D6	haloperidol metoprolol	fluoxetine paroxetine bupropion	rifampicine
3A4	carbamazepine calcium-antagonist pimozide	-azolen (p) macroliden verapamil diltiazem grapefruit (p)	carbamazepine fenytoine pioglitazon rifampicine st. John's wort

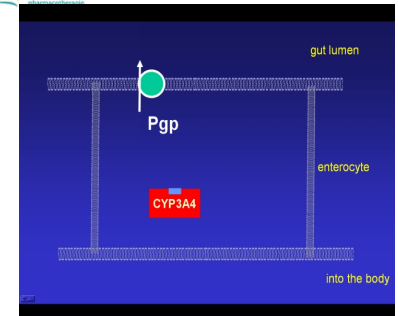



Sphor St. John's wort



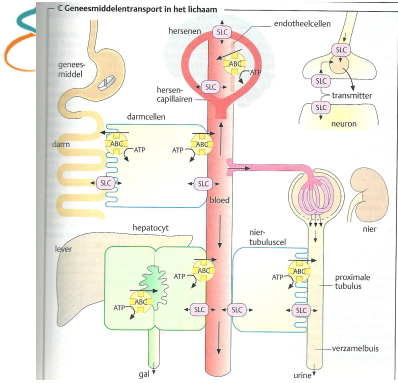
- Induction several drugs
- Influence on p-glycoprotein effluxpump (PGP)

Sphor P-gp = ABC = MDR



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Sphor C-Genesmiddelentransport in het lichaam



PGP (ABC) in:

- Brain
- Small Bowels
- Blood vessels
- Tubuli
- Liver

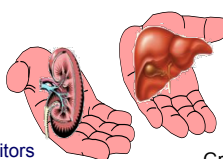
Sphor St Johns wort

amitriptyline	Steady-state concentration decreased with 22%
ciclosporine	Steady-state concentration decreased with 52%
tacrolimus	Steady-state concentration decreased with 80%
digoxine	Steady-state concentration decreased with 25%
simvastatine	AUC decreased with 50%
cumarinederivatives	INR 50% decreased

Sphor Interactions and the kidney

- Digoxin and NSAID's
- Digoxin and diuretics
- Lithium and NSAID's and diuretics
- RAS-inhibitors and NSAID's and (potassiumparing) diuretics
- Diuretics and NSAID's

Sphor Interactions to remember




D-LAND

- Digoxin
- Lithium
- ACE-inhibitors
- NSAID's
- Diuretics

MacGans

- Macrolide
- Anti-convulsives
- Calciumantagonists
- Grapefruits
- ANTimycotics (-azolen)
- SSRI's



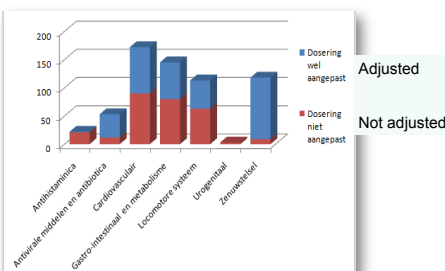
Sphor Case: a woman with 10 drugs: interactions

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- Atrovent
- ACE-inhibitor
- gliclazide
- Tildiem
- PPI
- paracetamol
- Calcium/vitamin D
- Ascal
- temazepam

Sphor Six questions to optimize polypharmacy

1. What does she really takes?
2. Does she suffer adverse effects?
3. Which drugs should be added?
4. What is not necessary/contraindicated?
5. Which relevant interactions do you expect?
6. Should the dose and dosefrequency be changed? Is there a generic alternative?

Sphor Dose reduction in renal insufficiency (10-30 ml/min)



Drug Category	Dosering niet aangepast (Not adjusted)	Dosering wel aangepast (Adjusted)
Antibiotica	~10	~10
Antiviraal middel en antibiotica	~10	~10
Cardiovasculair	~10	~10
Gastro-intestinaal & en metabool	~10	~10
Locomotorie systeem	~10	~10
Urogenitaal	~10	~10
Zenuwstelsel	~10	~10

Sphor Dose, dosefrequency and generic

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- Atrovent 4dd → tiotropium (Spiriva) 1x
- ACE-inhibitor 1x
- Gliclazide 1x
- Tildiem XR → diltiazem mga 1x
- PPI 1x
- paracetamol 3-4x
- calcium/vitamin D 1x
- acetylsalicylic 1x 100 mg
- temazepam 10 mg as needed

Sphor Polypharmacy is often: indicated

- ask the patient what she/he not uses (SHIM)
- ask for adverse effects
- look at undertreatment (POM, START)
- look at (contra)indications (POM, S, CP)
- look at interactions (POM)
- look at the dose and dosefrequency (POM)

