Optimization of polypharmacy

Paul Jansen,
geriatrician clinical pharmacologist

Patiëntenzorg
Onderwijs
Onderzoek

Question

Wich medicines are frequent prescribed to patients over 70 years?

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


27-04-02
NRC H
'Veel 65-plussers onnodig in ziekenhuis'
Door medicijnen 200 opnames per dag

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 aggregration inhibitors
- Vitamin K antagonist
- NSAID's
- Psychopharmaca
- Antidiabetics
- Diuretics
- Glucocorticosteroïds
- 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)

Reduction of polypharmacy is often not succesful

A better way is:

indicated polypharmacy

- pharmacokinetics
- pharmacodynamics
- interactions

Pharmacokinetics:

What is the body doing with the drug

absorption distribution

receptor

metabolisme excretion

absorption

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

absorption

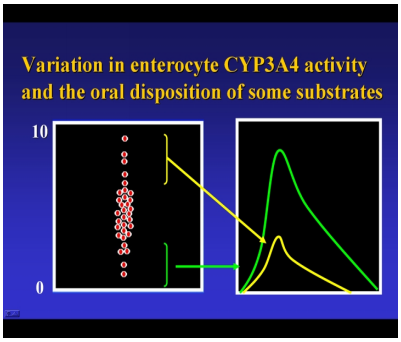
- Is an interaction with food to be expected?

Interaction with food

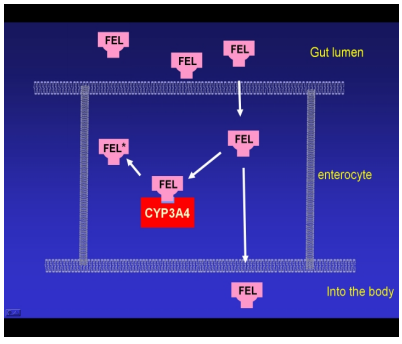
- Bisphosphonates
- levothyroxine
- ferro derivatives
- levodopa

Cytochroom P-450 enzyms

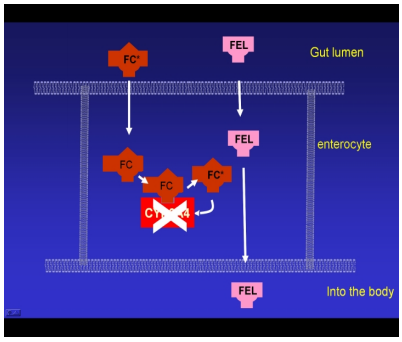
- In liver and gut



P. Watkins, North Carolina



P. Watkins, North Carolina



P. Watkins, North Carolina

Grapefruit and medicines

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

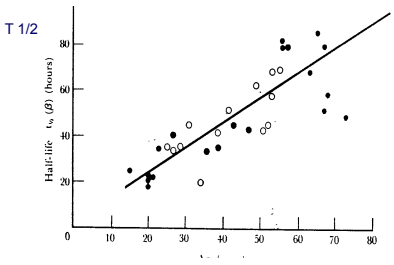
distribution

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

Consequences

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

Diazepam elimination t1/2



metabolisme

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

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

excretion

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

Pharmacodynamics:

what is the drug doing with the body

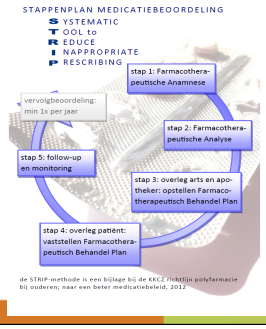
Change in pharmacodynamic properties

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

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

Systematic Tool to Reduce Inappropriate Prescribing (STRIP)



Step 1: drug history

Step 2: analysis

Step 3: treatment plan

Step 4: shared decision

Step 5: follow-up and monitoring

Casus: 84 year old woman uses 16 different medicines

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

Her problems (GP journal)

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

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
- Lomudal 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

Cluster diseases and medicines

- asthma, COPD
- hypertension
- diabetes mellitus type 2
- angina pectoris
- oesophageal reflux
- incontinence
- osteoartritis
- 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

Cluster diseases and medicines

- asthma, COPD
- hypertension
- diabetes mellitus type 2
- angina pectoris
- oesophageal reflux
- incontinence
- osteoartritis
- 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

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/contra-indicated?
- 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 hypoparathyroïdy: 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

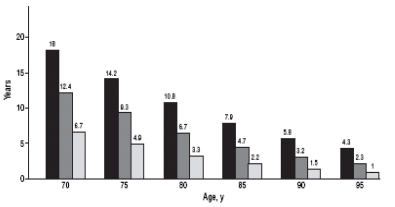
- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- incontinence
- osteoartrotis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances
- ?
- Atrovent, Lomudal
- furosemide, triamterene
- gliclazide
- Tildiem, Isordil
- ranitidine
- estriol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

Guidelines are not made for elderly patients with polypharmacy and multimorbidity

To treat or not to treat depends of:

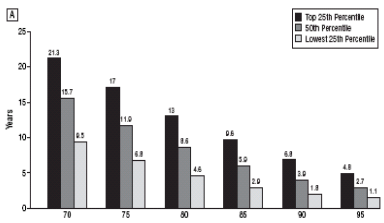
- Evidence in the elderly
- Benefit/harm ratio
- Time until benefit
- Biological age
- The preference of the patient

Levensverwachting bij mannen



Man van 80 jaar: tussen 3 en 11 jaar

Levensverwachting bij vrouwen

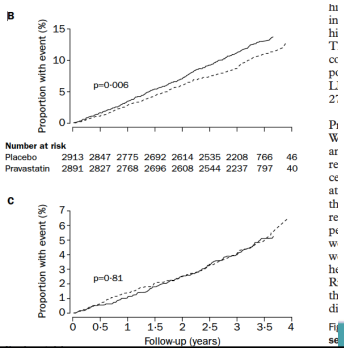


Vrouw van 80 jaar: tussen 4,6 en 13 jaar

Do you prescribe a statine to her?

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

Prosper study
cardial infarction and stroke



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

Six questions to optimize polypharmacy

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

How can you determine causality?

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 afteer dose reductioen
- Objective proof
- doubtful, possible, probable, definite

Adverse effects

- Ask your patient

Case: wich adverse effects?

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoartritis
- 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
- Osteoartritis
- 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
- Osteoartritis
- 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?

Case: a 84-year old woman with 14 drugs

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoartritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances

- Atrovent, Lomudal
- triamterene, ACE-inhibitor
- gliclazide
- Tildiem
- PPI
- Mebutan, paracetamol
- Calcium/vitamin D

- Ascal
- nitrazepam, oxazepam

Case: a 84-year old woman with 14 drugs

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoartritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances

- Atrovent Lomudal
- triamterene, ACE-inhibitor
- gliclazide
- Tildiem
- PPI
- Mebutan, paracetamol
- Calcium/vitamin D
- Ascal
- nitrazepam, oxazepam

she want to use the sleeping pill

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoartritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances

- Atrovent
- ACE-inhibitor
- gliclazide
- Tildiem
- PPI
- paracetamol
- Calcium/vitamin D
- Ascal
- temazepam

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?

Interactions

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

Interactions of medicines

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

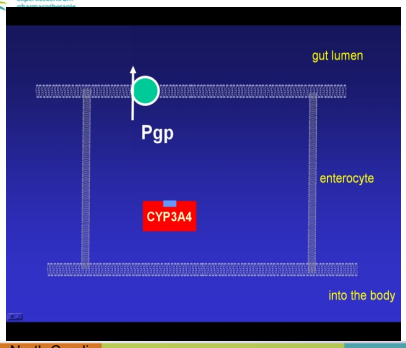
Interactions and the liver

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

St. John's wort

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

P-gp = ABC = MDR



P. Watkins, North Carolina

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

Interactions and the kidney

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

Interactions to remember

D-LAND

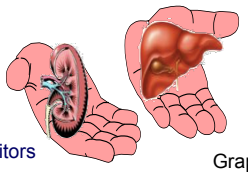
Digoxin

Lithium

ACE-inhibitors

NSAID's

Diuretics



MacGans

Macrolide

Anti-convulsives

Calciumantagonists

Grapefruits

ANtimycotics (-azolen

SSRI's

Case: a woman with 10 drugs: interactions

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

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?
6. Should the dose and dosefrequency be changed? Is there a generic alternative?

Dose, dosefrequency and generic

- Asthma, COPD
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoartritis
- 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

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[illegible]DP)
- look at interactions (POM)
- look at the dose and dosefrequency (POM)

New website: www.ephor.eu