Optimization of polypharmacy

Paul Jansen, geriatrician clinical pharmacologist

**Question**

Which 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**

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)
- Polymorbidty (>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
- Metabolism
- 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
Cytochrome P-450 enzymes

- In liver and gut
Grapefruit and medicines

- Calcium antagonists
- Statines (simvastatine en atorvastatine)
- Midazolam, diazepam
- Carbamazepine
- Ciclosporine

Distribution

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

Consequences

- Concentration of 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

Cytochrome P450 and antipyrine clearance

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>20-29</th>
<th>50-59</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipyrine clearance (ml/min)</td>
<td>46 ± 15</td>
<td>42 ± 19</td>
<td>33 ± 12</td>
</tr>
<tr>
<td>CYP-450 (nmol/g)</td>
<td>7.2 ± 2.6</td>
<td>6.4 ± 2.3</td>
<td>4.8 ± 1.1</td>
</tr>
</tbody>
</table>


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 kidney function (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 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.
Her problems (GP journal)

- asthma, COPD
- aortavalve sclerose/insuf
- hypertension
- diabetes mellitus type 2
- 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 1 dd
- Isordil s.i. zonodig
- Atrvent 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
- isosorbidinitrate
- ipratropium, cromoglicin 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, cromoglicin acid
- triamterene, furosemide
- gliclazide
- diltiazem, isosorbidinitrate
- ranitidine
- estriol vaginal ovule
- paracetamol, lactulose
- 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?

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

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
• alfacalcid 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
• Hypertension
• Diabetes mellitus type 2
• Angina pectoris
• Oesophageal reflux
• incontinence
• ostearthrosis
• Osteoporosis
• Hypercholesterolemia
• Stroke (2000)
• Sleep disturbances
• ?

• Atrovent, Lomudal
• furosemide, triamterene
• gliclazide
• Tildien, Isordil
• ranitidine
• estrol
• 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 on:

- 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


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

- 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
Adverse effects

- Ask your patient

Case: which 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

under treatment geriatric department UMC Utrecht 2006

- No laxative while using opioids: 62%
- No beta-blocker 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%


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
- Osteoarthritis
- 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
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances

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

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
- Ascald
- 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 herbal s
- With other medicines

**Interactions and the liver**

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrate</th>
<th>Inhibitor</th>
<th>Inducer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>clozapine</td>
<td>cimetidine</td>
<td>tobacco</td>
</tr>
<tr>
<td></td>
<td>theophylline</td>
<td>rifampicin</td>
<td></td>
</tr>
<tr>
<td>2C9</td>
<td>tolbutamide</td>
<td>ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>coumarine</td>
<td>fluconazole (p)</td>
<td></td>
</tr>
<tr>
<td>2C19</td>
<td>clopidogrel</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D6</td>
<td>haloperidol</td>
<td>some PPI’s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>metoprolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3A4</td>
<td>carbamazepine</td>
<td>fluoxetine</td>
<td>st. John’s wort</td>
</tr>
<tr>
<td></td>
<td>calcium-antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>pimozide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

St. John’s wort

- Induction of several drugs
- Influence on p-glycoprotein efflux pump (PGP)

P-gp = ABC = MDR
Interactions:

- **St John's wort**
  - amitriptyline: Steady-state concentration decreased by 22%
  - ciclosporine: Steady-state concentration decreased by 52%
  - tacrolimus: Steady-state concentration decreased by 80%
  - digoxine: Steady-state concentration decreased by 25%
  - simvastatin: AUC decreased by 50%
  - coumarin derivatives: 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 (potassium-sparing) 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
- Hypertension
- Diabetes mellitus type 2
- Angina pectoris
- Oesophageal reflux
- Osteoarthritis
- Osteoporosis
- Hypercholesterolemia
- Stroke (2000)
- Sleep disturbances

- Atrovent
- ACE-inhibitor
- gliclazide
- Tildem
- 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?
6. Should the dose and dosefrequency be changed? Is there a generic alternative?

Polypharmacy is often:

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

Dose, dosefrequency and generic

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

- Atrovent 4dd → Iotopium (Spiriva) 1x
- ACE-inhibitor 1x
- Glicazide 1x
- Tildiem XR → diltiazem mga 1x
- PPI 1x
- paracetamol 3-4x
- calcium/vitamin D 1x
- acetylsalicylic 1x 100 mg
- temazepam 10 mg as needed

New website: www.ephor.eu