UMC Utrecht

Ephor expertisecentre pharmacotherapy in old persons

Specific needs for research in geriatrics
ESCP 4 May 2011 Utrecht, NL

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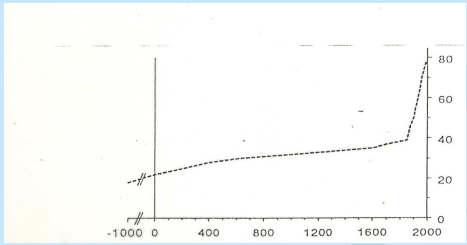
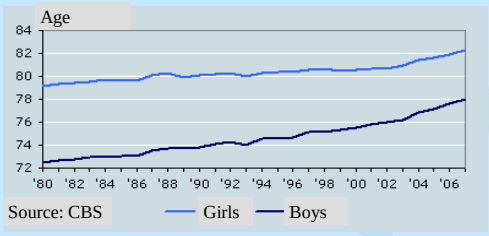
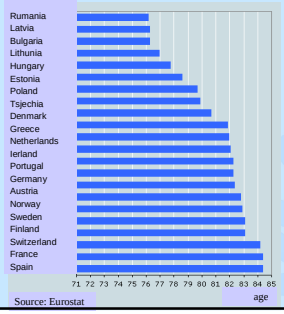
Rise in mean life expectancy



Life expectancy in the Netherlands



Life expectancy in Europe



Reasons for the rise in life expectancy

- Hygiene
- Food
- Exercise
- Health care

Mean drug use in 2010

- At the geriatric department:
  mean 10 medicines
  (spread 2-24)
- mean number of OTC's: 2 (0-6)

- What do we know about these medicines in the elderly? What is needed to know?

Needs for research of medicines in geriatrics

1. Appropriateness of existing medicines
2. Improvement of adherence
3. Prevention of adverse events
4. Improvement of undertreatment
5. Clinical relevant interactions
6. Appropriateness of dose (PK/PD)
7. Best ways of pharmacommunication
8. Appropriateness of new medicines
9. Effective education in gerontoparmacology

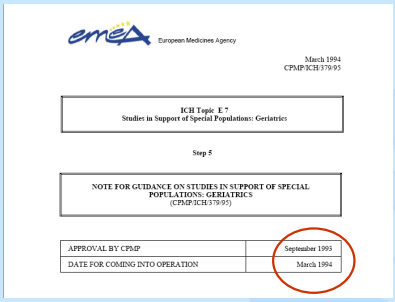
1. Appropriateness of existing medicines

Number (percentages) of original research papers (n=1012) in all issues of *BMJ*, *Gut*, *Lancet*, and *Thorax* between 1 June 1996 and 1 June 1997, by category of study

Study	*BMJ*	*Lancet*	*Thorax*	*Gut*	Total
Specific to elderly people*	11 (9)	6 (4)	0	1 (1)	18 (4)
Excluding elderly people justifiably	10 (8)	14 (10)	7 (8)	6 (4)	37 (8)
Excluding elderly people unjustifiably	**44 (35)**	**37 (27)**	**39 (45)**	**50 (35)**	**170 (35)**
No age limit set	60 (48)	79 (58)	41 (47)	85 (60)	265 (54)
Total	125	136	87	142	490
	202	135	85	100	522

BMJ 1997;315:1059

ICH E7: America, Europe and Japan



European Medicines Agency

March 1994
CPMP/ICH/379/95

ICH Topic E 7
Studies in Support of Special Populations: Geriatrics

Step 5

NOTE FOR GUIDANCE ON STUDIES IN SUPPORT OF SPECIAL POPULATIONS: GERIATRICS
(CPMP/ICH/379/95)

APPROVAL BY CPMP	September 1993
DATE FOR COMING INTO OPERATION	March 1994

2011: Interim results of availability study of E7 itemclusters in 33 licensed products

	total (n=33)		
	SmPC	EPAR	p
definition of the population	26%	84%	<0.01
clinical experience	43%	64%	<0.01
pharmacokinetic studies	78%	89%	<0.01
drug-drug interaction studies	77%	96%	<0.01
overall	59%	84%	<0.01

Appropriateness of existing medicines

JOURNAL OF GENERAL INTERNAL MEDICINE
DOI: 10.1007/s11606-010-1629-x Online First

2011

REVIEWS

Examining the Evidence: A Systematic Review of the Inclusion and Analysis of Older Adults in Randomized Controlled Trials

Donna M. Zulman, Jeremy B. Sussman, Xiuli Chen, Christine T. Cigolle, Caroline S. Blaum and Rodney A. Hayward

- Review of 109 trials
- 20,2% exclusion on base of high age
- 45,6% exclusion of individuals with impact for the elderly
- 38,5% performed an age specific subgroup
- 16,7% were of benefit for old persons

What is needed to do about this?

What have we done in the Netherlands?

EPHOR expertisecentre pharmacotherapy in old persons

ZonMw

Information about appropriateness of existing medicines: Ephor projects

1. Providing prescribers with available information
2. Providing tools for optimization of polypharmacy
3. Providing a validated method to measure kidney function in frail elderly

www.ephor.eu

Providing prescribers with information

- Checklist (23 items) for comparison of applicability of medicines within one group (1)
- Special indications in elderly patients, for example antipsychotics in delirium (often off-label)

1. **Huisman et al. Criteria for drug selection in frail elderly. Drugs and Aging, accepted for publication**

Antipsychotics: advice for medicines per indication

Medicine	Advice Delirium		Advice BPSD		Remark
Aripiprazol	White		White		Evidence for efficacy, few experience in daily practice
Clozapine	Green	Orange	Green	Orange	Only in case of patients with m. Parkinson or Lewy Body Dementia: green. Orange in other patients.
Haloperidol	Green		Green		Evidence for efficacy, much experience in daily practice
Olanzapine	Green		Green		Evidence for efficacy, much experience in daily practice
Quetiapine	White		White		Few evidence for efficacy
Risperidon	Green		Green		Evidence for efficacy, much experience in daily practice
Zuclopentixol	White		White		Few evidence for efficacy

NSAIDs: advice for relevant medicines

Medicine	Advice	Remark
Celecoxib	Green	Cardiovascular risk increases with higher dosages and in high-risk patients
Diclofenac	White	
Etoricoxib	Green	Cardiovascular risk increases with higher dosages and in high-risk patients
Ibuprofen	White	
Indometacine	Orange	dizziness occurs frequent
Meloxicam	White	
Naproxen	Orange	Long elimination half-life
Piroxicam	Orange	High risk on gastro-intestinal adverse effects
Sulindac	White	
Nabumeton	Orange	Nausea occurs frequent

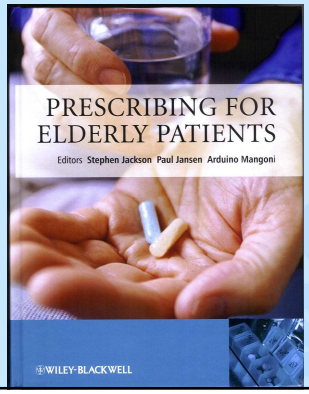
Practical information

Clear treatment options

PK and Key drug interactions

side effects

Dose advises



ISBN:
9780470024287

Providing tools for optimization of polypharmacy

- Several tools are available like the Beers list, the START en STOPP criteria, MAI etc.
- We developed the Polypharmacy Optimization Method (POM) (1): 6 steps
  1. What does a patient really uses (SHIM)
  2. Does the patient suffer adverse efects (SHIM)
  3. Is the patient undertreated (checklist)
  4. Is the patient overtreated (checklist)
  5. Are clinically relevant interactions present (pharmacist data)
  6. Is the dose and dosefrequency appropriate (pharmacist data)

1. Drenth-van Maanen et al. Drugs and Aging 2009; 26: 687-701.

2. What does the patient really takes. What about 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%)
- Ask your patient, but how?

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 (mild to moderate) discomfort because of the discrepancy

3. Prevention of adverse events

Hospital admissions related to adverse events

International studies:

200 admissions daily


27-04-02

NRC H

'Veel 65-plussers onnodig in ziekenhuis'

Door medicijnen 200 opnames per dag

HARM study:

In the Netherlands 100 daily

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

The bad guys:

- Trombocytes aggregration inhibitors
- Coumarinederivatives
- NSAID's
- Psychopharmaca
- Antidiabetics
- Diuretics
- Glucocorticosteroïds
- Antibiotics

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

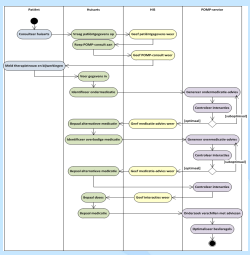
Risk factors for hospital admissions related to medicines

- 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)

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

Results of POM

- Improvement of 39% of correct decisions
- decrease of 27% of potentially harmful decisions
- Next step: digital POM
- Co-operation of doctors and pharmacists



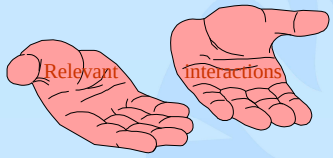
4. Undertreatment geriatric department

- No laxative while using opioids: 62%
- No betablocker after myocardial infarction: 60%
- No ACE-inhibitor for heart failure: 47%
- No coumarine for atrialfibrillation: 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 :130-133.

5. Clinical important Interactions

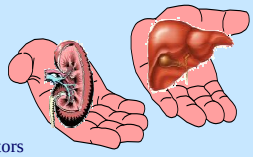
- There are many interactions
- However relevant interactions are countable on two hands



Interactions of medicines

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

Interactions to remember



digoxin
lithium
RAS-inhibitors
diuretics
NSAID's

Anti-convulsives
calciumantagonists
Macrolide
antimycotics (-azolen)
antidepressives (SSRI's)
clopidogrel and PPI's ?

With a little help of the pharmacists

6. Appropriateness of dose: kidney function

- MDRD is widely used.
- Not validated in old frail patients.
- Utrecht patient oriented database (UPOD):
  MDRD 30-50 ml/min: 43% no dose adjustment
  MDRD <30 ml/min: 55% no dose adjustment

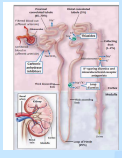
6. Appropriateness of dose

Kidney function in frail elderly: inulineclearance in 24 geriatric patients

	Based on serum creatinin			Based on cystatin C		Based on both	
	CG	MDRD ext	MDRD short	Burkhardt	Larsson	Levey	2-h urine clearance
Pearson Correlation	0.04	0.20	0.34	-0.12	-0.05	0.17	0.04
P-value	0.84	0.36	0.10	0.59	0.61	0.41	0.85
Mean difference (%)	7	-2	-5	-105	-5	2	-18
Range (%)	-120 - +105	-109 - +93	-102 - +93	-364 - +43	-147 - +98	-100 - +95	-145 - +111

What is needed

- Correct method to determine kidney function in frail elderly
- Clinical rules to support prescribers (co-operation between pharmacists, clinical chemists, ICT and prescribers)



7. Pharmacommunication

- Medication stopped because of adverse effects are communicated poorly (1)
- 22% is documented by GPs
- 0% of pharmacist are informed
- 27% represcription of the drug within 6 month

1. Linden van der et al. Archives of Internal Medicine 2006;166:1666-1667.

More Ephor projects

- Electronic medication discharge letters are hand over to the patient and sent to GPs and pharmacists
- Individual Electronic Pharmacovigilance (IEP) is set up in EPD (Catherina Hospital Eindhoven)

What is needed

- ICT support to make electronic communication possible between the different systems
- Implementation studies

8. Appropriateness of new medicines

European

Predict

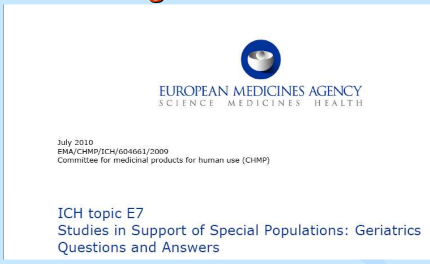
Charter

http://www.predicteu.org

Predict charter

1. Older people have the right to access evidence based treatments
2. Promoting the inclusion of older people in clinical trials and preventing discrimination
3. Clinical trials should be made as practicle as possible for older people
4. Clinical trials should be safe as possible
5. Outcome measures should be relevant
6. The values of older people participating in clinical trials should be respected

8. Appropriateness of new medicines again: ICH E7


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

July 2010
EMA/CHMP/ICH/604661/2009
Committee for medicinal products for human use (CHMP)

ICH topic E7
Studies in Support of Special Populations: Geriatrics
Questions and Answers

EMA: www.ema.europa.eu


EUROPEAN MEDICINES AGENCY

EMA geriatric medicines strategy

Medicines used by geriatric patients are appropriately researched

Improvement of the availability of information

Whats coming up: EMA geriatric expert group

- Francesca Cerreta, EMA
- Catherine Gaudy, EMA
- Manuel Haas, EMA
- J. Ankri, France
- G. Adalst, Iceland
- A. Cherub, Italy
- N. Marchionni, Italy
- S. Morgan, UK
- T. Pepersak, Belgium
- M. Petrovic, Belgium
- J. Serra, Spain
- H. Wildiers, Belgium
- P. Jansen, The Netherlands

Another Ephor Project

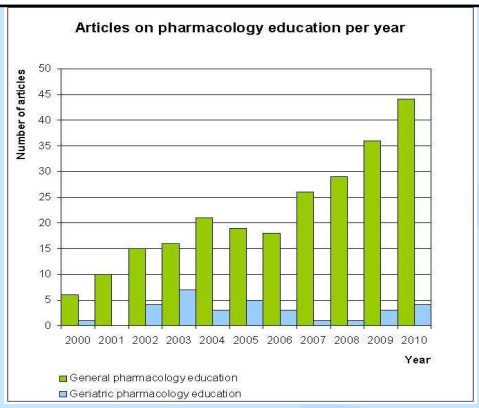
- Checklist for Information on Medicines appropriateness in Elderly (CHIME) is in development
- Based on items of ICH E7 and Dutch Checklist
- Delphi method (international multidisciplinary panel)

What is needed

- Discussion what should be done in the pre-authorization phase
- What should be done in the postauthorization phase
- Method to study the balans between safety (PSUR) and efficacy in older persons

9. Education

- too few education of pharmacology and pharmacotherapy
- education of gerontopharmacology is almost lacking in literature
- systematic review showed:
  - 7 articles for medicine students
  - 5 articles for pharmacy students
  - 1 article for postgraduate physicians
  - 2 articles for postgraduate pharmacists
  - 2 articles for nurses



www.ephor.nl(eu)

Take home message

- There is much to improve in gerontopharmacology
- experts in the field are organizing themselves
- Doctors and pharmacists: do it together
- More and more elderly are waiting for us