



Factors for ADRs in frail elderly

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EAMA, Sion, 30 January 2008

Incidence of Drug Related Problems (DRP) in elderly

DRPs leading to hospitalisation:

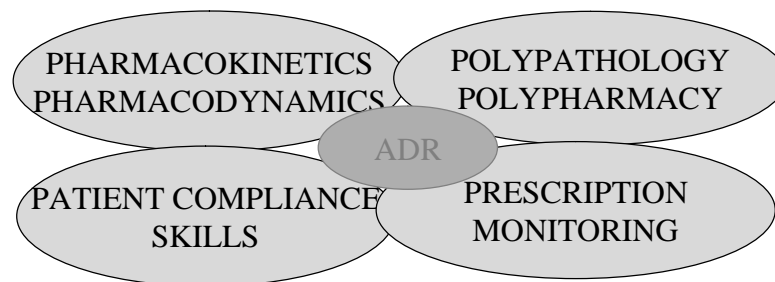
Author	Reference	Type DRPs	Incidence
Beijer	Pharm World Sci 2002;24:46-54	ADR	17%
Mannesse	Age and Ageing 2000;29:35-39	ADR	12%
Nelson	Pharmacotherapy 1996;16:701-07	ADR + DTF	16%
Cunningham	Age and Ageing 1997;26:375-382	ADR + DTF	5%
Chan	Intern Med J 2001;31:199-205	ADR + DTF	30%
Courtman	Can J Hosp Pharm 1995;48:161-66	ADR + DTF	31%

ADR: adverse drug reaction

DTF: drug therapy failures



Factors for Adverse Drug Reactions (ADRs) in frail elderly

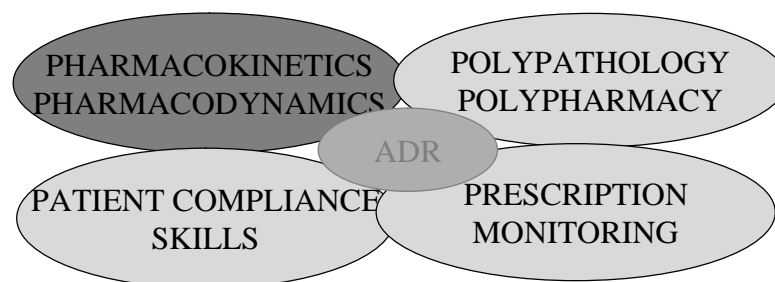


Most important factor for ADRs is the number of prescribed drugs.

J Am Geriatr Soc 1996;44:194-7



Factors for Adverse Drug Reactions (ADRs) in frail elderly



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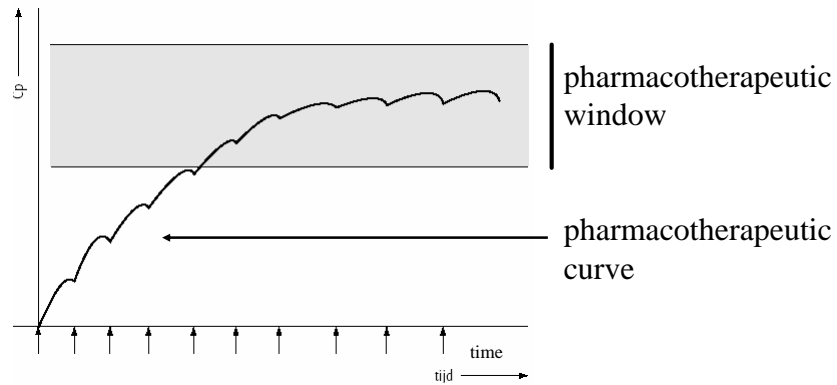
J Am Geriatr Soc 1996;44:194-7

Pharmacokinetics

the effect of the body on the drug

Pharmacodynamics

the effect of the drug on the body



de Vries Th et al. WHO guide to good prescribing.

Pharmacokinetics

- Defined as : The handling of a drug within the body
 - Including:
 - Absorption
 - Distribution
 - Metabolism
 - Elimination

McLean AJ. Pharmacol Rev 2004;56:163-84



Drug absorption changes in the elderly

gastrointestinal system (rarely clinically significant)

- acid production unchanged or decreased
i.e. bioavailability of penicillin ?
- multiple prescriptions increase the probability of drug-drug interaction which may alter absorption
i.e. antacids containing Al and Mg with tetracyclines, Fe, prednisolon ...
- splanchnic blood flow decreases (with little effect on drug absorption)

Hilmer SN. Fund Clin Pharm 2007; 21:217-30



Age-related changes which affect pharmacokinetics (distribution)

- **decreased lean body mass**
 - fat/water ratio? ? hydrophilic drugs? Vd?
 - ? lipophilic drugs ? Vd?
- **decreased levels of serum albumin**
 - affects unbound fraction (F_u) ?
more important for drugs with high protein binding

EXAMPLES

2% ? 98% bound ? 96% F_u ? : 2 ? 4% (100%)
20%?60% bound ? 40% F_u ? : 40 ? 60% (50%)

In reality damping of the increase due to ?distribution and elimination
- **no change in α -acid glycoprotein levels**

Cusack BJ. Am J Ger Pharmacother 2004; 2:274-302



Age-related changes which affect pharmacokinetics (metabolism)

decreased liver function

- affects drug metabolism/biotransformation
- ? liver flow: mainly important for drugs with high extraction ratio (ER)
extraction = liver flow x ER
- CYP 450 metabolism more affected than conjugation
www.drug-interactions.com
substrates – inhibitors – inducers
- disease states
 - heart failure: ? liver flow
 - liver failure: ? liver flow, protein binding ...

Cusack BJ. Am J Ger Pharmacother 2004; 2:274-302



Age-related changes which affect pharmacokinetics (elimination)

- **renal** elimination:
 - glomerular filtration
 - tubular secretion
- other minor pathways of elimination:
 - feces
 - breath
 - sweat
 - saliva

Cusack BJ. Am J Ger Pharmacother 2004; 2:274-302



Drug elimination changes in the elderly

decrease in renal functions

- decreased blood flow to the kidneys
- decreased glomerular filtration rate (GFR)
- decreased tubular secretion (mostly combined with ?GFR)

Assesment of renal function

- Creatinine clearance (Clcr)
- serum creatinine is NOT an accurate reflection of Clcr in the elderly

Dose correction

- decrease dose according to ?Clcr and % renal excretion of drug

Noble R. Metabolism 2003; 52:27-30

Renal function in elderly

COCKCROFT-GAULT formula

$$\frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} = \dots \text{ ml/min} \times 0,85 (\text{V})$$

Example:

Female

88 yrs

43 kg

Creatinine 1,1

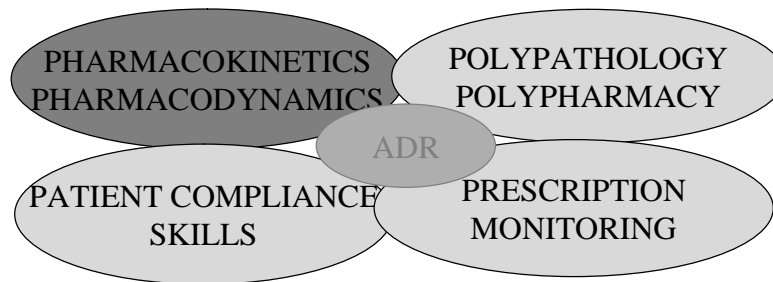
→ Clcr: 24 ml/min

Normal serum creatinine: 1,2 mg/dl

100 - 120 ml/min: normal
60 - 30 ml/min: moderate RF
< 30 ml/min: severe RF
< 10 ml/min: terminal RF



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Most important factor for ADRs is the number of prescribed drugs.

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Physiological changes in elderly patients affecting pharmacodynamics

target organ changes

- increased target organ sensitivity
- decreased desirable effects of pharmacotherapy
- increased adverse effects

homeostasis changes

- decreased capacity to respond to physiological challenges and the adverse side effects of drug therapy (eg. orthostatic hypotension)

Vuyk J. Best Pract Res Clin Anaesthesiol. 2003;17:207-18
Barat I. Br J Clin Pharm 2001;51:615-22



Pharmacodynamic changes in elderly

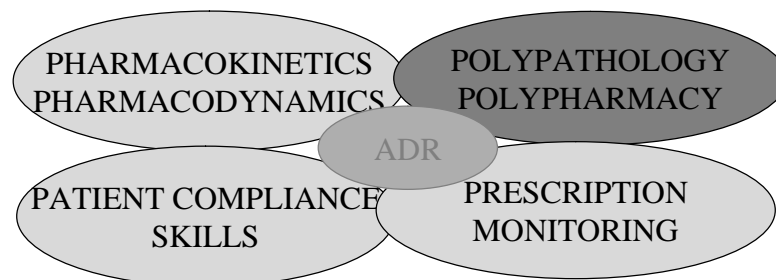
- decreased organ function
- increased risk for adverse drug reactions (ADRs)

EXAMPLES

- | | |
|-----------------------------------|---------------------|
| • anticholinergic drugs (bladder) | urine retention |
| • CNS drugs (benzo, opioids) | sedation, confusion |
| • beta-blockers, digoxin | depression |
| • ACE-inhibitors, neuroleptics | hypotension |
| • NSAIDs | renal failure |
| • ACE-inhibitors, spironolacton | hyperkalemia |
| • beta-blockers, sympathomimetics | sensitivity |



Factors for Adverse Drug Reactions (ADRs) in frail elderly



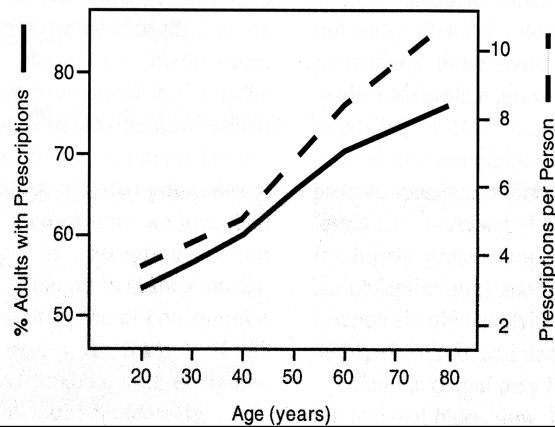
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Co-Morbidity \longrightarrow Polypharmacy

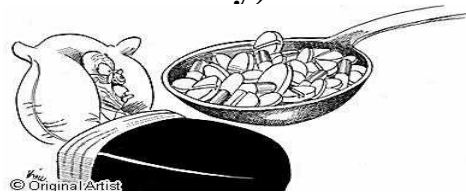


The percentage of population with prescriptions, and the number of medications per individual, increase with age.



Ostrom JR. Med Care 1985; 23: 157-164

Chronic medication in nursing homes in Belgium (PHEBE study)



- 1.1% of the residents had no medication
- 22.7% of the residents had 1-4 chronic medications
- 53.1% of the residents had 5-9 chronic medications
- 20.8% of the residents had 10-14 chronic medications
- 2.1% of the residents had more than 14 chronic medications

Polypathology - polypharmacy

- Pathologies:
 - heart failure
 - hypertension
 - osteoarthritis
 - depression, memory loss
 - digestive problems, constipation
 - diabetes
 - eye and ear dysfunctions
 - ...
- Polypharmacy:
 - diuretics
 - antihypertensives
 - analgesics & NSAIDs
 - neuroleptics / antidepressants / anti-epileptics
 - prokinetics and laxatives
 - antidiabetics
 - ...

• Features of Polypharmacy

Medication not indicated
Duplicate medications
Concurrent interacting medications
Contraindicated medications
Inappropriate dosage
Drug treatment of adverse drug reaction
Improvement following discontinuance

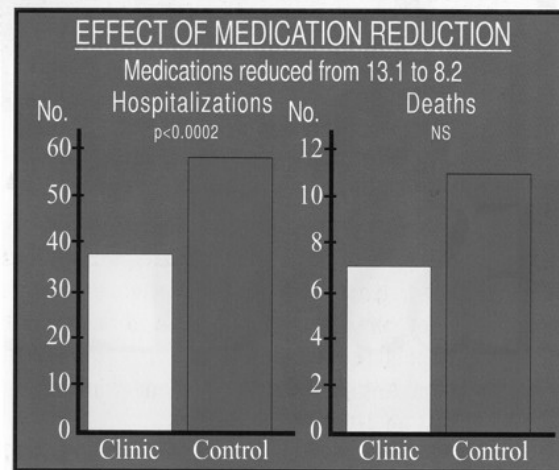
ElDesoky ES. Am J Ther 2007; 14: 488-98



Considerations for pharmacotherapy in the elderly



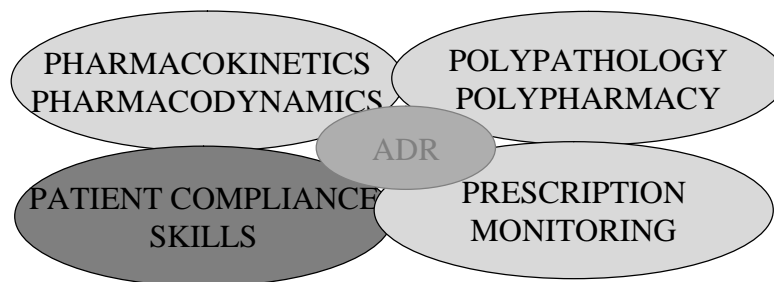
- Is drug therapy required?
- Choice of appropriate drug and preparation
- Dosage regimen to accommodate changes in physiology
- Detailed monitoring and periodic re-evaluation of drug therapy
- Clear and simple instructions



Rollason V. *Drugs & Aging* 2003; 20: 817-832

Figure 1. Effects of medication reduction on hospitalization and death rates.

Factors for Adverse Drug Reactions (ADRs) in frail elderly



Most important factor for ADRs is the number of prescribed drugs.

J Am Geriatr Soc 1996;44:194-7

Factors affecting patient compliance

1. side effects
2. dosing frequency (once daily is the best)
3. number of tablets/day
4. motivation and mental status (female gender, personal believes, age, cognitive function, low educational status, environment ...)
5. duration of therapy
6. physician-patient relation

Social aspects - skills

- Impact on patient compliance

> 3 drugs	OR 2,5
> 1 physician	OR 2,5
lives alone	OR 2,0
possibly demented	OR 9,0

Barat et al. Br J Clin Pharmacol 2001;51:615-22

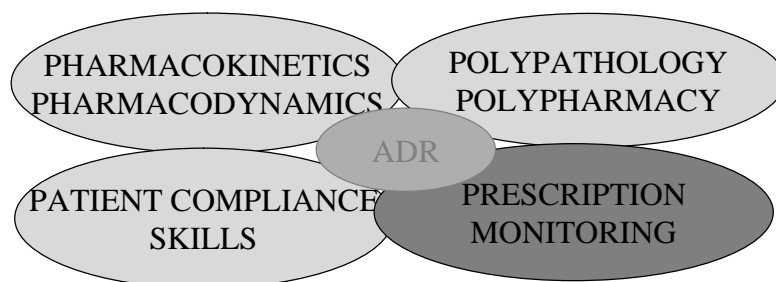
- Skills to take the medication

self-supporting	73%
with help	15%
unable	12%

Factors affecting effectiveness

- **patient compliance (drug adherence)**
- **functional status (patient's skills)** i.e.
breaking tablets
opening of bottles
swallow tablets
synchronized inhalation
- **financial issues**
low socio-economic status

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J Am Geriatr Soc 1996;44:194-7



Closer monitoring needed

The elderly are 2-3 times more at risk for adverse drug reactions due to:

Pirmohamed M. BMJ 2004; 329:15-19.

- altered pharmacokinetics
- altered pharmacodynamics
- cumulative insults to the body (*eg.*, disease, diet, drug abuse)

Barat I. Br J Clin Pharm 2001;51:615-22

- noncompliance
- polypharmacy
- lack of available data



Close monitoring needed for drugs with narrow therapeutic window

monitored by plasma levels (TDM)

digoxine phenytoin
theophylline lithium

therapeutic drug monitoring may fail in elderly

i.e. the case of digoxin

due to altered pharmacodynamics, digoxine levels within the therapeutic range may be TOXIC



Close monitoring needed for QT prolonging drugs

(www.torsades.org)

may lead to fatal arrhythmias (torsades de pointes)

Predisposing conditions

- Arrhythmogenic conditions:
 - low K, Mg, CA
 - Arrhythmogenic drugs
- QT prolongation
 - Congenital, heart disease, drugs (high concentrations)

Effect of herbs: St John's wort

1. Enzym induction of

CYP 3A4, 2C9, 1A2 and PgP by St John's wort

? reduced effect of many drugs like:

- Digoxine, theofylline, cyclosporin,
- Anticoagulants: Warfarine, Fenprocoumon
- HIV protease inhibitors
- Sex hormones including OAC

2. ? risk of serotonin syndrome with:

SSRI's, Trazodone, Venlafaxine ...

agitation, hypertension, hyperthermia, convulsions, arrhythmias

Br J Clin Pharmacol 2002; 54:349-356

Effect of food

Increased bioavailability

Resorption - (by high fat meal)

e.g. nitrofurantoin, Mebendazol (Vermox®)

Enzym inhibition

CYP 3A4 (and P-gP) by Grapefruit (juice) →

↑ Effect of Ca channel blockers, anti AIDS,
benzodiazepines, cisapride ...

interaction with alcohol

Interactie met paracetamol

-Microsomal ethanol-oxidizing system (MEOS)
metabolizes alcohol and some other drugs like
paracetamol

-Chronic alcohol use → MEOS induced

→breakdown paracetamol ↑→ toxic metabolites ↑

In alcohol addicts therapeutic doses of paracetamol
may be toxic!

increased risk of ADRs in elderly

Special attention needed

- drugs with narrow therapeutic window
- drugs prolonging QT interval
- extended release formulations (swallow)
- drugs with anticholinergic effects (sedation, bladder)
- drugs inducing orthostatic hypotension (a-blockers)
- avoid grapefruit juice
- avoid St John's wort
- chronic alcohol abuse and paracetamol
- Fluoxetine (Prozac®) 5 weeks washout (SS)
- Laxatives and digoxin

BEERS list

- Drugs with risk > benefit in elderly patients
- developed by expert group in US in 1991, updated in 1997 en 2003
- 2 parts:
 1. forbidden drugs (never to be given) to elderly patients
 2. conditionally forbidden drugs (not to be given in defined conditions)

Arch Intern Med 1997;157:1531-1536

Examples of forbidden drugs in elderly:

Generic name	Generic name
Propoxyphene	Triazolam > 0,25 mg daily
Indometacine	Diazepam
Phenylbutazone	Digoxine > 0,125 mg daily
Pentazocine	Dipyridamole
Oxybutynin	Methyldopa
Flurazepam	Chlorpropamide
Amitriptyline	Belladonna alkaloids
Perphenazine-amitriptyline	Chlorpheniramine
Doxepine	Diphenhydramine
Meprobamate	Hydroxyzine
Lorazepam > 3 mg daily	Cyproheptadine
Oxazepam > 60 mg daily	Promethazine
Alprazolam > 2 mg daily	Dexchlorpheniramine
Temazepam > 15 mg daily	Ergot mesyloids
Zolpidem > 5 mg daily	Iron suppelements > 325 mg daily
	Ticlopidine

conditionally forbidden drugs in elderly:

Pathology	treatment
heart failure	sodium containing drugs (sodium carbonate: effervescent tablets)
gastric ulcer	NSAIDs, aspirin
Arrhythmia	Tricyclic antidepressants
Depression	methyldopa
Obesity	Olanzapine



Utility and clinical significance

- positive correlation between potentially inappropriate drug prescribing, as defined by the **Beers** criteria, and adverse drug reactions
- Geriatric evaluation and management reduces serious adverse drug reactions by 35%
- Reduces suboptimal prescribing, in frail elderly patients.

Schmader K.E. *Am J Med* 2004; 116: 394-401
Chang C.M. *Pharmacotherapy* 2005; 25: 831-8



Clinical Significance

- Inappropriate medication use increased the likelihood of experiencing at least one adverse health outcome (hospitalizations, emergency department visits, or deaths) more than twofold.

Perri M. *Ann Pharmacother* 2005; 39: 405-11



Good news

Significant decline in the use of potentially inappropriate drugs by elderly patients, particularly those drugs linked to the most severe outcomes. (25% - 21%)

Bad news

- Approximately 7 million elderly patients still received potentially inappropriate drugs in 1999
- Underscoring the continued need for effective interventions to improve prescribing for this vulnerable population.

Stuart B. *Am J Geriatr Pharmacother* 2003; 1: 61-74



Rules of prescribing in older adults

- Start low, go slow
- Try to limit number of medications and avoid prescribing “a pill for every ill”
- Try not to start two drugs at the same time
- Make sure it is the right dose
- Avoid “inappropriate medications”- Beers criteria
- Watch out for potential drug-drug, drug-disease interactions
- Make sure patient and caregiver understand what the medication is for, how and when to take it, possible side effects
- Avoid expensive new medications that have not been shown to be superior to less expensive generic alternatives

Currow DC. *Arch Int Med* 2006;166:2404.



Rules of prescribing monitoring

- Ask patient about all medications (including OTC, herbal prep)
- Ask patient how each medication is being taken
- Look for medications with duplicate therapeutic or pharmacologic profiles
- Eliminate unnecessary medications
- Simplify the medication regimen – fewest possible number of medications and doses per day
- Always review any changes in writing with the patient and caregiver
- If possible, use technology to monitor parameters of efficacy and eliminate duplicate therapy, and also to detect potential drug–drug interactions and drug disease interactions

Currow DC. Arch Int Med 2006;166:2404.



Summary

- changes in the physiology of the elderly alter responses to drug therapy
- pharmacokinetic changes affect the effective concentration of drug in the body
- pharmacodynamic changes alter the body's response to the drug therapy
- adverse drug reactions are more common in the elderly and can be avoided with better primary care