



An approach to prescribing in the elderly



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Preamble

- Advances in medical technology, surgical procedures, medical practice and innovative drug development
- An increasing proportion of the population attains elderly status
- Claims a disproportionate share of medical care
- The elderly population has a higher prevalence of chronic and multiple diseases
- Managing several co-morbidities in an elderly patient often mandates the prescription of numerous drugs.

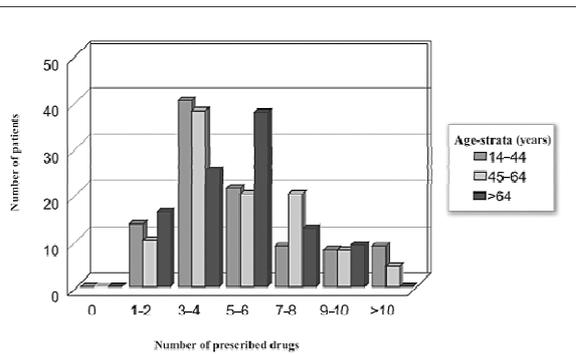


Figure 1. Distribution of the number of prescribed drugs according to age group (years).

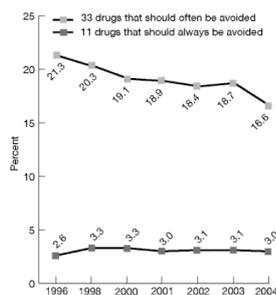
Preamble

- Compared to other age groups, the risk for adverse drug reactions and drug-drug interactions is greatest in the elderly.¹
- As the number of medications used by patients increases, the incidence of side effects increases exponentially (from 6% when two drugs are taken to 100% when eight or more drugs are taken).
- Adverse drug effects rank highest amongst the most preventable health threats among the elderly.²



Preamble

- Drug related side effects are estimated to contribute nearly one fifth of all hospital deaths in elderly patients
- About half of these are associated with doctors prescribing unnecessary or inappropriate drugs, at the wrong dose or formulation.³



Drugs that should **always be avoided** for elderly patients include barbiturates, flurazepam, meprobamate, chlorpropramide, meperidine, pentazocine, trimethobenzamide, belladonna alkaloids, dicyclomine, hyoscyamine, and propantheline.

Drugs that should **often be avoided** for elderly patients include carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, amitriptyline, chlordiazepoxide, diazepam, doxepin, indomethacin, dipyridamole, ticlopidine, metildopa, reserpine, dsopyramide, oxybutynin, chlorpheniramine, cyproheptadine, diphenhydramine, hydroxyzine, promethazine, and propoxyphene

Appropriate prescribing in the elderly

Comprises three broad areas:

1. The patient's clinical needs and wants
2. Scientific evidence including the clinical pharmacology of the drug
3. The general good.⁴

Appropriate prescribing:
Specific factors that require addressing

in the context of sound clinical judgement:

- the indication
- effectiveness
- dose
- correct instructions and practical directions
- drug-drug interactions
- drug-disease interactions
- duplication
- duration and
- cost.⁵



Appropriate prescribing

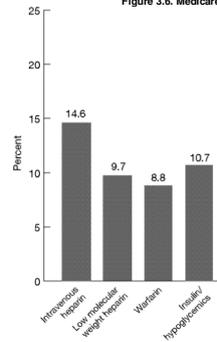
- Selecting optimal pharmacotherapy is a complex and challenging process.
- Inter-individual variability in health, disease and disability increases substantially with aging.
- This heterogeneity means that the health status of elderly people ranges widely
 - fit
 - frail (little physiological reserve, reduced homeostasis, dysregulation in immune and inflammation mechanisms, several co-morbidities and taking many drugs)
- Makes generalisations of prescribing decisions difficult.⁴



Pharmaco- dynamics and kinetics

- Most frequent adverse drug reactions in elderly persons:
 - Bleeding due to oral anticoagulants,
 - Hypoglycaemia from diabetes treatment
 - Gastric complications from non-steroidal anti-inflammatory drugs
- Adverse drug reactions in elderly usually not idiosyncratic
- Rather extensions of the usual effects of the drug

Figure 3.6. Medicare patients with adverse drug events, 2004



Pharmacokinetics and dynamics

Uncovering the aetiology of unwanted drug effects has therefore involved examination of:

- drug pharmacokinetics (the time course of drug absorption, distribution, metabolism and excretion) and
- pharmacodynamics (particularly the clinical aspects of altered physiological adaptive capacity and responses to drug action).¹



Pharmacodynamics

- The aging process is accompanied by diminished compensatory homeostatic responses.
- Changes occur in end-organ responses to drugs, possibly as a result of decreasing receptor numbers, altered receptor binding or changing biochemical modulators.
- Elderly patients are more sensitive to the effects of some drugs e.g. warfarin (perhaps due to decrease in clotting factor synthesis), opioids and benzodiazepines.
- They are less sensitive to the effects of others such as beta blockers.

Pharmacodynamics

- The elderly may be more susceptible to adverse drug reactions:
 - ? diminished vasomotor regulation
 - ? impaired glucose tolerance and
 - ? greater morbidity from infections.
- Adverse drug reactions often present in an atypical manner and are often mistakenly attributed to the effects of aging or disease.⁶



Pharmacokinetics Absorption

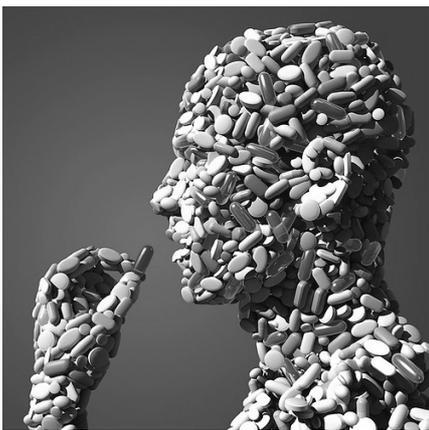
- Most drugs are absorbed via the gastro-intestinal tract after oral administration.
- Factors which ordinarily are expected to reduce drug absorption:
 - decreased motility and blood flow in the digestive tract
 - increased gastric pH
- But the extent of drug absorption is not necessarily affected as there is a longer time interval for this process.
- When adequate plasma concentrations need to be attained rapidly, alternative routes of administration should be considered.⁷

Pharmacokinetics Distribution

- Lean body mass and total body water decrease with age with a proportionate increase in body fat which affects the volume of distribution (Vd) of drugs.
- Drugs that distribute into muscle (digoxin) or into body water (aminoglycosides) will achieve a higher initial plasma concentration
- Increased risk for toxicity
- Water soluble drugs in general (atenolol, propranolol, hydrochlorothiazide, lithium, cimetidine, etc) are distributed less effectively throughout the body and this is compounded by the presence of cardiovascular disease which compromises blood flow to organs.

Pharmacokinetics distribution (fat soluble)

- The increase in adipose tissue increases the Vd of lipophilic drugs (diazepam, haloperidol)
- Fat acts as a depot for these agents.
- Prolonged action of lipid-soluble drugs



Pharmacokinetics distribution: protein binding

- Total serum albumin (the protein binding capacity) decreases by approximately 12% in the elderly.
- Chronic debilitating diseases may further depress albumin levels
- Increased unbound, free drug
- responsible for
 - increased effect
 - escalating the risks of drug-drug interactions when other highly protein drugs (salicylates, phenytoin, warfarin, sulphonamides, theophylline) are co-administered.⁷

Pharmacokinetics Metabolism

- Most studies support an age-related decline in phase I (oxidative) drug metabolism.
- Drugs requiring phase I metabolism (tricyclic antidepressants, antipsychotic drugs, diazepam, calcium channel blockers) need to be dosed cautiously as their bioavailability is increased.
- Phase II (conjugative) metabolism appears to be unaffected by the aging process.

Pharmacokinetics Metabolism

- Some drugs are particularly dependent on hepatic blood flow (in order to undergo first pass metabolism)
- decreased by 12% - 40% in the elderly population.
- The ability of the liver to extract and metabolise a drug may be surpassed
- A small increase in drug will lead to a disproportionately large increase in plasma concentration.⁷

Pharmacokinetics Elimination

- Many drugs are excreted by the kidneys.
- In the elderly, renal blood flow decreases by about 1% per year after the age of 50 years.
- Higher plasma levels and accumulation of drugs are found when the glomerular filtration rate decreases.
- Drugs eliminated by the kidney (digoxin, lithium, aminoglycosides, NSAIDs, fluoxetine) need to be given in reduced doses.⁷



Recommendations and Conclusions

The challenge is:

- to ensure that older people gain maximum benefit from their medication in order to maintain or enhance their quality of life, and
- to avoid unnecessary suffering caused by inappropriate drug therapy.



Recommendations and Conclusion

Appropriate prescribing in the elderly requires

1. Establishing a firm diagnosis
2. Formulating a therapeutic goal
3. Selecting the proper drug for the correct treatment period.⁸

Recommendations and Conclusions

4. Drugs should be initiated at low doses (50%)
5. Long acting agents should be avoided.
6. Some drugs require an adequate trial of therapy (angiotensin-converting enzyme inhibitors and antidepressants) to attain therapeutic benefit

Recommendations and Conclusion

7. Drug regimens should be kept simple and reviewed frequently
 8. Drugs that are no longer required should be discontinued.
 9. Sudden declines in cognitive or physical functioning may be drug-induced;
- Attributing adverse drug effects to a new medical condition may lead to a counterproductive prescribing cascade.

Recommendations and Conclusions

10. It should be recognised that individuals become more dissimilar as they age
- It therefore becomes increasingly important to resist stereotyping the elderly
 - Conscientiously individualise care decisions to unique needs.⁶



References:

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Appendix

- Drugs deemed inappropriate in elderly
- Case study: drug interactions in elderly

Drugs deemed inappropriate for the elderly

Medscape		www.medscape.com	
I Sedatives and hypnotics	VIII Platelet inhibitors	18 Dipyridamole	19 Ticlopidine
1 Flurazepam	19 Ticlopidine	IX Muscle relaxants/antispasmodics	20 Cyclobenzaprine
2 Mesopropamate	20 Cyclobenzaprine	21 Methocarbamol	22 Carisoprodol
3 Diazepam	21 Methocarbamol	23 Oxycodone	24 Chlorzoxazone
4 Chloridiazepoxide and combinations	22 Carisoprodol	25 Metaxalone	
5 All barbiturates (except phenobarbital)	23 Oxycodone	X Antiemetic agents	26 Trimethoprim
II Antidepressants	24 Chlorzoxazone	XI Antiarrhythmics	
6 Amitriptyline and combinations	25 Metaxalone	27 Disopyramide	
7 Doxepin	X Antiemetic agents	XII Gastrointestinal antispasmodics	
III Antihypertensives	26 Trimethoprim	28 Dicyclanide	
8 Methyldopa and combinations	XI Antiarrhythmics	29 Hyoscyamine	
9 Reserpine and combinations	27 Disopyramide	30 Propantheline	
IV NSAIDs	XII Gastrointestinal antispasmodics	31 Belladonna alkaloids	
10 Indomethacin	28 Dicyclanide	XIII Antihistamines	
11 Phenybutazone	29 Hyoscyamine	32 Chlorpheniramine	
V Analgesics	30 Propantheline	33 Cyproheptadine	
12 Propoxyphene	31 Belladonna alkaloids	34 Diphenhydramine	
13 Meperidine	XIII Antihistamines	35 Hydroxyzine	
14 Pentazocine	32 Chlorpheniramine	36 Promethazine	
VI Oral hypoglycemics	33 Cyproheptadine	37 Triprolidine	
15 Chlorpropamide	34 Diphenhydramine	38 Deschlorpheniramine	
VII Dementia treatments	35 Hydroxyzine		
16 Ergot mesylate	36 Promethazine		
17 Cyclospasmol	37 Triprolidine		
	38 Deschlorpheniramine		

Source: Reference 21.
NSAIDs = nonsteroidal anti-inflammatory drugs.
*These subjects of drugs were deemed inappropriate for the elderly regardless of dosing, duration, or disease conditions. This list was used in most of the studies reviewed. The original lists included conditionally inappropriate drugs categorized as inappropriate when given in certain doses, for long durations, or to patients with severe conditions or certain diseases.

J Am Pharm Assoc © 2002 American Pharmaceutical Association

Table - Most common inappropriate and underused medications

Inappropriate
Histamine antagonists
Digitalis glycosides
Loop diuretics
Proton pump inhibitors
Tricyclic antidepressants
Urinary antispasmodics
Nasal anti-inflammatories
Sedating antihistamines
NSAIDs
Underused
Antihypertensives
Anticoagulants
Lipid-lowering agents
Sublingual nitroglycerin
Proton pump inhibitors
Hypoglycemic agents
Calcium
Bronchodilators (anticholinergics)
Bronchodilators (sympathomimetics)

Adapted from Steiner MA et al. J Am Geriatr Soc. 2006.²

Table 1
Potentially Inappropriate
Independent of Diagnosis

Medication	Severity
Anticholinergics, antihistamines	High
Diphenhydramine	High
Traditional NSAIDs, including naproxen (used long-term)	High
Mineral oil	High
Ferrous sulfate >325 mg/day	Low
Cimetidine	Low

NSAID: nonsteroidal anti-inflammatory drug.
Source: Reference 3.

Table 2
Potentially Inappropriate
Based on Disease/Condition

Disease/Condition	Medication	Severity
Heart failure	Those containing sodium (including Fleet enema)	High
Hypertension	Pseudoephedrine, diet pills	High
Gastric or duodenal ulcer	NSAIDs, aspirin (>325 mg)	High
Blood-clotting disorder or on anticoagulant therapy	NSAIDs, aspirin	High
Bladder outflow obstruction	Anticholinergics, 1st-generation antihistamines	High
Insomnia	Decongestants	High
Cognitive impairment	Anticholinergics	High
Chronic constipation	Anticholinergics	Low

NSAID: nonsteroidal anti-inflammatory drug.
Source: Reference 3.

Table 1
Medications Especially Likely to
Cause Problems in the Elderly

Amitriptyline, doxepin
Antihistamines (e.g., chlorpheniramine, cyproheptadine, diphenhydramine, hydroxyzine, promethazine, tripelemamine)
Antipsychotics (e.g., chlorpromazine, haloperidol, thioridazine, thiothixene)
Antispasmodics (e.g., belladonna alkaloids, clidinium, dicyclomine, hyoscyamine, propantheline)
Barbiturates (e.g., phenobarbital, secobarbital)
Benzodiazepines, long-acting (e.g., diazepam, flurazepam)
Carbamazepine
Chlorpropamide
Cimetidine, famotidine, ranitidine, nizatidine
Digoxin
Disopyramide
Indomethacin
Iron supplements (e.g., ferrous sulfate)
Lithium
Meperidine, pentazocine, propoxyphene
Meprobamate
Methyldopa
Muscle relaxants (e.g., carisprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol)
Phenytoin
Procainamide
Quinidine
Reserpine
Theophylline
Trimecibenzamide
Warfarin
Source: Reference 9, 25.

Case study

Mr Anderson, an 81 year old man, presents to Casualty, (accompanied by his 60 year old daughter) with visual hallucinations and confusion.

Whilst awaiting the Psychiatric assessment, you notice that he has epistaxis and so you decide to ask some questions.



Warfarin

- Collateral history from his daughter reveals that Mr A. has been on **Warfarin** for many, many years, “for his fluttering heart”. This is prescribed by one of his GPs and his INR is checked three times a year.

Aspirin

- Three months ago, Mr A decided to start taking an **Aspirin** every day. He had heard a talk on the radio, extolling the virtues of this drug. He buys his aspirin at the supermarket when he does his weekly shopping and has never missed a dose.

Cimetidine

- Mr A visited another GP a month ago complaining of “heartburn”. His doctor said it was a result of “wear-and-tear” and prescribed **Cimetidine**, an H₂-receptor antagonist.
- Mr A started hallucinating three days ago, and has been becoming gradually more confused.
- His heartburn continues to trouble him.

Questions: side effects drug interactions



- Which of these drugs may be causing his nose bleed? (Side effects)
- Are there any potential drug-drug interactions contributing to the bleeding?
 - Pharmaco-dynamic drug interactions?
 - Pharmaco-kinetic drug interactions?

Side effects heartburn

- Which drug /s may be responsible for his “heartburn”?
- Why?



Side effects: Confusion, hallucinations

- Incredibly, a scan excludes an intracerebral bleed. Could confusion and hallucinations be drug induced? If so, which drug is the likely culprit and why?



Benzodiazepines?

- Would you recommend giving this patient a benzodiazepine such as diazepam to “calm him down”?
- What advice would you give to the patient and to his family?

Table 1 – Quality indicators for appropriate medication use in vulnerable elders

Quality indicator	Description
Drug indication	If a new drug is prescribed, it should have a clearly defined indication documented in the record.
Patient education	If a new drug is prescribed, the patient (or a caregiver) should be educated about the purpose of the drug, how to take it, and expected side effects or important adverse reactions.
Medication list	For all patients there should be an up-to-date medication list in the outpatient medical record of every physician and in the hospital medical record.
Response to therapy	Every new drug that is prescribed on an ongoing basis for a chronic medical condition should have a documentation of response to therapy within 6 months.
Drug regimen review	All patients should have a drug regimen review at least annually.
Monitoring warfarin	If warfarin is prescribed, an INR should be determined within 4 days after initiation of therapy and at least every 6 weeks.
Monitoring of diuretic therapy	If a thiazide or loop diuretic is prescribed, electrolytes should be checked within 1 month after initiation of therapy and at least yearly thereafter.
Oral hypoglycemic medications	Chlorpropamide should not be used as a hypoglycemic agent.
Anticholinergic medications	Avoid drugs with strong anticholinergic properties if alternatives are available.
Barbiturates	If a patient does not require control of seizures, barbiturates should not be used.
Opioid analgesic	Meperidine should not be used as an analgesic.
Monitoring new ACE inhibitor	Serum potassium and creatinine levels should be checked within 1 month of the initiation of ACE inhibitor therapy.

INR, international normalized ratio; ACE, angiotensin-converting enzyme.
Adapted from Knight EL, Weems J. Ann Intern Med. 2001;7

