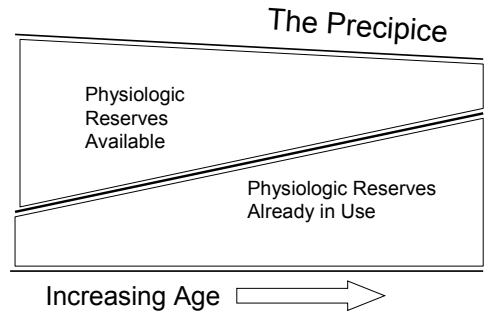


Optimizing Drug Therapy in the Elderly

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DRUGS ARE POISONS WITH THERAPEUTIC SIDE EFFECTS!!!



Demographics

- 1900 - 1 in 25 Americans older than 65
1984 - 1 in 8
2050 - 1 in 4.6
- Life expectancy:

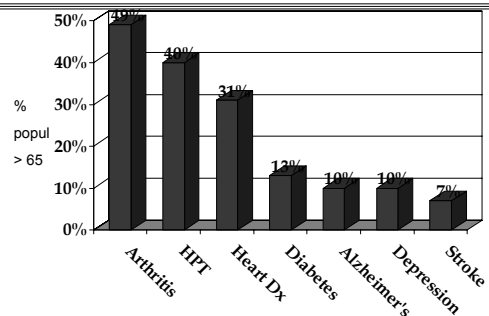
	Men	Women
1950	65.6	71.1
1990	72.7	79.5
- Chronic illness



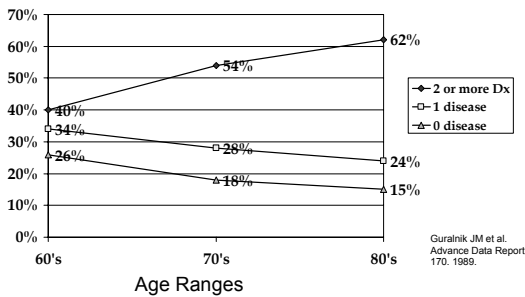
What is "elderly" anyway?

- Germany established 65 as the age to receive benefits from their "social security" system.
- U.S. adopts this same age for its social security.
- Chronologic age versus Physiologic age
- Better delineation of aging population
65-75 "younger-old" 76-85 "older-old"
86+ "oldest-old"

Disease Prevalence in the Elderly



Comorbidity Increases with Age



Impact of Drug-Related Problems

- 30% of hospital admission in elderly can be linked to ADE's
 - » Horton JT, et al. J Am Geriatr Soc 1997;45:945-948
- ADE's linked to preventable problems in the elderly such as depression, constipation, falls immobility, confusion & hip fractures
 - » Bootman JL, et al. Arch Intern Med; 157:2089-2096
- 35% of ambulatory older adults experience ADE and 29% required health care services
 - » Cooper JW, Sough Med J 1999; 92:586-490
- 67% of nursing facility residents have ADE's, 1 of 7 require hospitalization.
 - » Cooper JW J Am Geriatr Soc: 1999;195-197

Leading Causes of Death 65 years and older

- Heart disease
- Cancer
- Stroke
- Chronic obstructive pulmonary disease
- Pneumonia and influenza
- Diabetes

Polypharmacy Risk

Number of Medication	Risk
2 - 5	4%
5 - 8	50%
> 8	100%

Sloan RW, Practical geriatric therapeutic. Oradel, NJ: Medical Economics Books, 1986:39-50.

Medication Use

- Persons > 65 y/o consume 25-40% of all prescription items
- 40-50% of all OTC medications
- 1/3 of annual healthcare cost (\$300 billion)
- Issues relating to "polypharmacy"
 - » Cost
 - » Adverse Drug Reactions
 - » Drug Interactions
 - » Hospital Admissions

Polypharmacy, Adverse Drug-Related Events, and Adverse Drug Interactions in Elderly Patients Presenting to an ED

Hohl CM, et al, Annals of Emergency Medicine 2001;38(6):666-671

- 300 randomly selected charts of patients 65 years and older
- 90.8% of patients were taking 1 or more regular OTC or prescribed medications
 - » mean regular medication = 4.2 drugs/patient
- Adverse drug related events accounted for 10.6% of all ED admissions
 - » 1 med 0%; 2-5 meds 11.5%; > 6 meds 16.9%
- 31% of patients had a Possible drug related event present in their drug regimen

Polypharmacy, Adverse Drug-Related Events, and Adverse Drug Interactions in Elderly Patients Presenting to an ED
Hohl CM, et al. Annals of Emergency Medicine 2001;38(6):666-671

- Most Frequently Implicated Drug Groups
 - » NSAID
 - » Diuretics
 - » Hypoglycemics
 - » Beta-Blockers
 - » Calcium-channel blockers
 - » Chemotherapeutic

Physiologic Changes with Aging

- Body Composition
- Cardiovascular System
- Central Nervous System
- Digestive System
- Renal System
- Hepatic System
- Endocrine System
- Skeletal System

To Err Is Human: Building a Safer Health System

Kohn L, et al. Institute of Medicine (IOM) 1999 Report

- Medications related problems causes 106,000 deaths annually
- Resulting Cost: \$8 billion annually

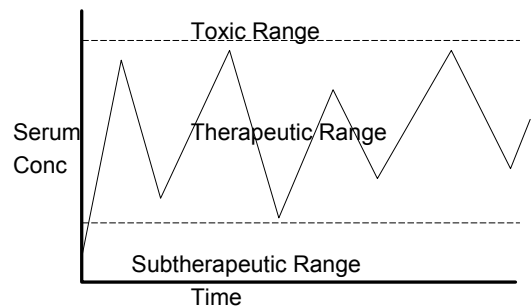
Physiologic Determinants of Drug Distribution

- **Absorption** Elevated gastric pH
Decreased GI blood flow
Decreased active transport
- **Distribution** Decreased total body water
Increased body fat
Decreased serum albumin
- **Metabolism** Decreased liver blood flow
Possibly decreased enzyme activity
- **Excretion** Decreased renal blood flow
Decreased glomerular filtration rate

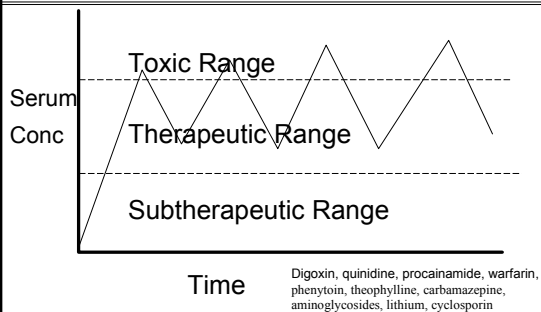
Other Costs Associated With Medication Related Problems

- Ambulatory Care: \$77 billion annually
 - » Bootman JL, et al. Arch Intern Med; 157:2089-2096
- Hospitals: \$20 billion annually
 - » Bates DW, et al. JAMA 1997; 277: 307-311
- Nursing Home Facilities: \$4 billion annually
 - » Johnson JA et al. Arch Intern Med 1995; 155: 1949-1956

Wide Therapeutic Window



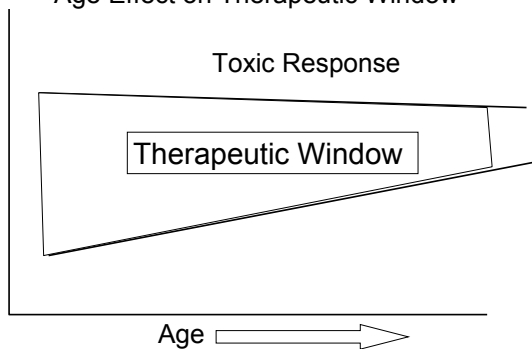
Narrow Therapeutic Window



Altered Distribution

- Protein Binding
 - » Drugs highly bound to serum albumin (>90%) can be affected by other highly protein bound drugs, competing for the same binding sites
 - » Only free drug (unbound drug) is active
 - If only 5% of the total serum drug level is free (and active) any changes can have a significant effect on circulating free drug
- Changes in serum circulating albumin and protein concentrations.

Age Effect on Therapeutic Window



Phenytoin (Dilantin, 10-20 mcg/ml)

Measured Phenytoin (mcg/ml)	Patient's Serum Albumin (gm/dl)			
	3.5	3	2.5	2
5	6	7	8	10
10	13	14	17	20
15	19	21	25	30

Winter-Tozer Equation $\text{Conc (adjusted)} = \frac{\text{Conc (observed)}}{(0.2 \times \text{albumin}) + 0.1}$

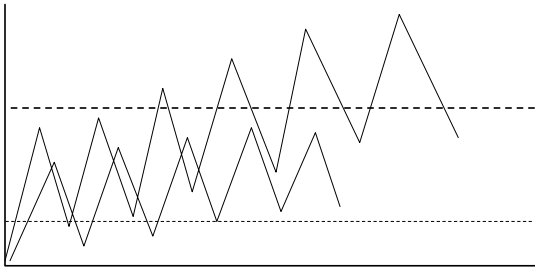
Distribution

- Water : Lean Body Mass : Fat Distribution
 - » Infants: Higher per cent water
 - water soluble drugs- larger dose per weight
 - Antibiotics
 - » Elderly: Higher per cent fat
 - lipid soluble drugs- smaller dose per weight
 - Benzodiazepines (Diazepam, Chlordiazepoxide vs. Lorazepam, Oxazepam)
- Serum Albumin
 - » Decreased in elderly person
 - Combinations of highly protein bound drugs
 - Warfarin , Phenytoin, Sulfonamide Antibiotics

Age Related Decrease in Renal Function

- Loss of glomeruli
 - » Demonstrated 46% decline in inulin clearance from age 20 to 90
- Decreased renal blood flow
- Decrease in tubular function
- Decreased concentrating ability

Graphic Representation of Decreased Renal Elimination



Anticholinergic Side Effects

- Peripheral Effects
 - » Dry Mouth
 - » Mydriasis
 - » Constipation
 - » Tachycardia
 - » Urinary retention
 - » Thermoregulatory Impairment
- Central Effects
 - » Sedation
 - » Confusion
 - » Delirium
 - » Dizziness

Cockcroft-Gault Equation Estimation of Creatinine Clearance

Men

Estimated Creatinine Clearance (ml/min)=

$$\frac{(140 - \text{age}) \times \text{Body Wt in Kg}}{72 \times \text{Serum Creatinine}}$$

Women

0.85 x above value

Commonly Used Medications with Anticholinergic Side Effects

- Antidepressants
 - » Amitriptyline (Elavil)
 - » Imipramine (Tofranil)
- Antihistamines
 - » Diphenhydramine
 - » Chlorpheniramine
- Antivertigo
 - » Scopolamine (TransDerm Scop)
 - » Meclizine (Antivert)
- Antidiarrheals
 - » Diphenoxylate (Lomotil)
- Antiarrhythmics
 - » Disopyramide (Norpace)
- Antiemetics
 - » Prochlorperazine
 - » Promethazine (Phenergan)
 - » Hydroxyzine (Atarax)
- Urinary Antispasmodics
 - » Oxybutynin (Ditropan)
- Antipsychotics
 - » Chlorpromazine (Thorazine)
 - » Haloperidol (Haldol)
 - » Fluphenazine (Prolixin)
- Muscle Relaxants
 - » Cyclobenzaprine (Flexeril)
 - » Orphenadrine (Norflex)

Digoxin (Lanoxin)

- Renally cleared; long half-life - 42 hours
- CNS effects common
 - » blurred vision, altered cognition, depression
- GI effects: anorexia, nausea
- Periodic serum level monitoring
 - » blood levels versus therapeutic effect
- treat patient NOT THE NUMBERS
- CHF versus atrial fib rate control

Nonsteroidal Antiinflammatory Agents

- Effect on the GI System
 - » Inhibition of protective prostaglandins leading to gastritis, symptomatic/ asymptomatic bleeding
- Effect on the Renal System
 - » Inhibition of renal prostaglandins required when renal blood flow is decreased resulting in reversible acute renal failure, sodium retention, hypertension, increases in BUN/Cr
 - » Meta analysis of 54 published studies (N=1324)
 - Greatest effect Naproxen, Indomethacin

Considerations for NSAID Use in the Elderly

- GI side effect generally well known
- Decreased renal function, sodium and water retention ARE OFTEN UNDER-RECOGNIZED
- Adverse effects are often dose related
 - » adjust starting dose down and advance slowly
- COX-2 Inhibitors may be safer.
 - » ~~Rofecoxib (Vioxx)~~, celecoxib (Celebrex), ~~Valdecoxib (Bextra)~~
- Routine acetaminophen a possible alternative.

Side Effects

Sedation	Ataxia
Delirium	Amnesia
Dizziness	Hangover effects
Confusion	Slurred speech
Dysphoria	Paradoxical excitement
Diplopia	Blurred vision
Hypotension	Bradycardia
Dependence rate	

Benzodiazepines

- Side effects often associated with differences in fat:water solubility and production of active metabolites

Diazepam		Lorazepam
Chlordiazepoxide	>	Oxazepam
Flurazepam		Temazepam

Histamine-2 Receptor Antagonists

- Low renal clearance associated with CNS side effects:
 - » Dizziness Somnolence Confusion
 - » Agitation Arrhythmias
- Cimetidine>Ranitidine>Nizatidine>Famotidine
- All side effects are dose related and resolve with discontinuation or dose adjustment.
- Proton Pump Inhibitors - very expensive for general use
 - » omeprazole (Prilosec), lansoprazole (Prevacid), rabeprazole (AcipHex), pantoprazole (Protonix)

Anxiolytic and Hypnotic Use in the Elderly Considerations

- Avoid long half-life benzodiazepines with active metabolites
 - » Diazepam (Valium), Chlordiazepoxide (Librium), Chlorazepate (Tranxene)
 - » Flurazepam (Dalmane), Temazepam (Restoril)
 - » Diphenhydramine (Benadryl) for sedation generally a BAD IDEA
- Use shorter, "clean" half-life agents at adjusted doses with caution (ADR's, "drug hang-over")
 - » lorazepam (Ativan), Oxazepam (Serax)
 - » zolpidem (Ambien), estazolam (ProSom)
 - » triazolam (Halcion)... Safe????
 - » eszopiclone (Lunesta), data on new sedative in the elderly equate to more safe medication (?)

Treatment of Depression

- Tricyclics
 - » Anticholinergic side effects
 - » orthostatic hypotension
- Bad: amitriptyline (Elavil), doxepine (Sinequan)
- Better: nortriptyline (Pamelor)
- SSRI's; fluoxetine (Prozac), sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Calexia)
 - » Safer and fewer side effects, BUT don't get a false sense of security.
 - » GI distress, anorexia, weight loss, CNS stimulation
- DRUG INDUCED CAUSES OF DEPRESSION AND TRUE CLINICAL DIAGNOSIS

Beers MH, et al. "Explicit Criteria for Determining Inappropriate Medication Use in Nursing Home Residents". Arch Intern Med.

1991;151:1825-1832,

- Two round survey of 13 experts in the field of geriatric medicine
- Agreed on 30 factors defining "inappropriate use"
- Criteria on the use and dose of:
 - » Sedative-hypnotics Antidepressants
 - » Antipsychotics Antihypertensive
 - » NSAID's Oral hypoglycemics Analgesics
 - » Platelet Inhibitors H-2 blockers Antibiotics

Beers MH, et al. "Inappropriate Medication Prescribing in Skilled-Nursing Facilities".

Ann of Intern Med 1992;117:684-689.

- Applied criteria of "inappropriate use" to a total of 1106 nursing home residents
- 40% of residents received at least one of the medications meeting criteria
- 10% received 2 or more
- 7% of all prescriptions were "inappropriate" by their criteria.

Criteria for Inappropriate Use

Beers. Arch Intern Med 1991;151:129

- | | |
|--|--|
| <ul style="list-style-type: none"> ● Sedative-hypnotics <ul style="list-style-type: none"> » chlordiazepoxide, diazepam, flurazepam » Meprobamate » Any use > 4 weeks ● Antidepressants <ul style="list-style-type: none"> » Avoid Amitriptyline » Avoid combinations ● Antipsychotics <ul style="list-style-type: none"> » Haloperidol > 3mg/day » Thioridazine >30mg/day | <ul style="list-style-type: none"> ● Antihypertensives <ul style="list-style-type: none"> » HCTZ > 50mg/day » Avoid Methylodpa, Propranolol, Reserpine ● Oral Hypoglycemics <ul style="list-style-type: none"> » Avoid Chlorpropamide ● Analgesics <ul style="list-style-type: none"> » Avoid Propoxyphene » Avoid Pentazocine ● Dementia treatments <ul style="list-style-type: none"> » Avoid cyclandelate » Avoid Isoxsuprine |
|--|--|

Beers MH, et al. "Inappropriate Medication Prescribing in Skilled-Nursing Facilities".

Ann of Intern Med 1992;117:684-689.

- 51% of "inappropriate" use was with agents expert agreed should generally be "avoided".
- 34% involved drugs with limitation on duration of use
- 15% involved doses exceeding recommended dose limits

Criteria for Inappropriate Use

Beers. Arch Intern Med 1991;151:129

- | | |
|---|--|
| <ul style="list-style-type: none"> ● Histamine Blockers <ul style="list-style-type: none"> » Cimetidine >900mg/day » Ranitidine >300mg/day ● Antibiotics <ul style="list-style-type: none"> » Use >4 wks with exceptions ● Decongestants <ul style="list-style-type: none"> » Afrin, Neo-Synephrine, Sudafed use > 2 weeks ● Iron <ul style="list-style-type: none"> » Doses > 325mg/day ● Platelet Inhibitors <ul style="list-style-type: none"> » Avoid Dipyridamole | <ul style="list-style-type: none"> ● Muscle relaxants <ul style="list-style-type: none"> » Avoid Cyclobenzaprine, Carisoprodol, Methocarbamol ● GI antispasmodics <ul style="list-style-type: none"> » Avoid long term Donnatal, Levisin, Pro-Banthine. ● Antiemetics <ul style="list-style-type: none"> » Avoid Tigan ● NSAID <ul style="list-style-type: none"> » Avoid Indomethacin » Phenylbutazone |
|---|--|

Inappropriate Drug Prescribing for the Community-Dwelling Elderly

- Using the 1987 National Medical Expenditure Survey (n=35,000 patients)
- Incidence of prescribing 20 potentially inappropriate drugs as defined by Beers
- 32% of patients >65 received at least one of the 20 contraindicated medications (6.4 million pts)
- 20.4% received two or more
- dipyridamole, diazepam, indomethacin, chlordiazepoxide, propranolol, methylodpa, reserpine

Willcox SM et al. JAMA 1994; 272 (4):292-296

Explicit Criteria for Determining Potentially Inappropriate Medication Use by the Elderly: An Update
Beers MA Arch Intern Med 1997; 157:1531-1536

- Four goals established
 - » Reevaluate the criteria to include new products and incorporate new information available in the scientific literature
 - » Generalize the criteria to a population of persons older than 65 y/o regardless of the level of frailty or place of residence
 - » Assessing a relative rating of severity
 - » Identify additional alerts specific diagnosis

Other Proponents of Explicit Prescribing Criteria

- Institutes of Medicine
- Center for Medicare Service (CMS)
- Agency for Healthcare Research and Quality (AHRQ)
- HEDIS Measure for 2006
- American Association of Healthcare Plans (AAHP)
 - » Managed care organizations
 - » Pharmacy Benefits Managers
- State Medicaid Programs
- Computer software vendors
 - » "Rules engines" for computer order entry
- Plaintiff's Legal Council

Updating the Beers Criteria for Potentially Inappropriate Medications Use in Older Adults
Fick DM, et al. Arch Intern Med 2003; 163:2716-2724

- Reevaluate the 1997 criteria include new products and incorporate new information available from scientific literature
- To assign or reevaluate a relative rating or severity for each medication
- Identify new conditions or considerations not addressed in 1997

HCFA Medication Use Guidelines

- Medications to avoid (except under specific circumstances); Option for use of other med.
 - » Doxepine (Sinequan)
 - » Pentazocine (Talwin)
 - » Disopyradamide (Norpace)
 - » Methyldopa (Aldomet)
 - » Chlorpropamide (Diabinese)
 - » Barbiturates for sedative/hypnotic
 - » Meperidine (especially orally)

Application of Beer's Criteria

- Criteria is not without controversy
 - » To simplistic, cannot take into account special needs of individual patient
 - » Limiting the freedom of physician to prescribe
- Criteria based prescribing recommendations need to be continually updated to be effective and usable

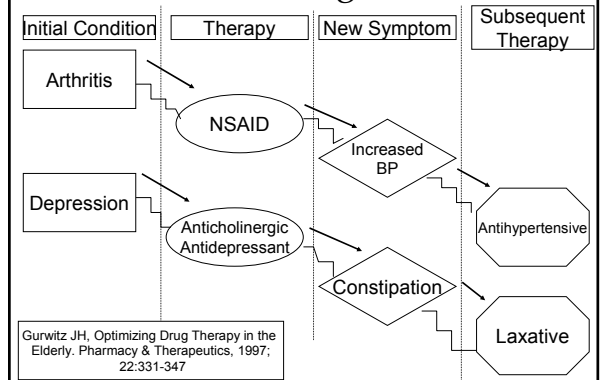
HCFA Medication Use Guidelines

- Medications to avoid (except under specific circumstances); Option for use of other med.
 - » Phenylbutazone (Butazolidin)
 - » Trimethobenzamide (Tigan)
 - » Dipyridamole (Persantine)
 - » Reserpine
 - » Ergot mesyloids (Hydergine) for dementia

HCFA Medication Use Guidelines

- Medications for use with limitation
 - » Amitriptyline (Elavil) - neurogenic pain
 - » Digoxin - Dose 0.125mg for CHF; 0.25 Atr Fib
 - » Ticlopidine (Ticlid) - only in documented ASA allergy
 - » NSAID in GI disease
 - » Antiplatelet agents in anticoagulated states
 - » Diphenhydramine for sleep - < 7 doses/ quarter
 - » Muscle relaxants (baclofen, cyclobenzaprine) < 7 doses/quarter
 - » Dose limitation on all antipsychotic agents
 - » Various medications for insomnia- < 7 consecutive days

The Prescribing Cascade



Assessing Care of Vulnerable Elders (ACOVE)

- Evaluate the PROCESS for caring for the elderly
- Establishment of valid evidence-based measures of quality for frequently encounter health issues.
- Still the measure may not fill the needs of all elderly patients.

Practical Issues in Drug Use in the Elderly

- Drug Regimen Review
 - » DC therapy for condition that no longer exist
 - » Reduction in dosage
 - Dosing based on renal function
 - Start Low and Go Slow
 - » Treatment of two conditions with single agent
 - Hypertension; Heart Disease; BPH; Renal Disease
 - » Assess OTC, vitamins, herbal supplements
 - » Review Rx containers for accuracy and clarity of directions.

Assessing Care of Vulnerable Elders (ACOVE)

Annals of Internal Medicine October 16, 2001;135 (8,part 2)

- | | |
|--------------------------------|----------------------------|
| ● End-of-life care | ● Dementia |
| ● Falls and mobility disorders | ● Depression |
| ● Hospital care | ● Diabetes mellitus |
| ● Hearing impairment | ● Heart failure |
| ● Malnutrition | ● Hypertension |
| ● Osteoarthritis | ● Ischemic heart disease |
| ● Pain Management | ● Pharmacologic management |
| ● Pressure ulcers | ● Pneumonia and influenza |
| ● Urinary Retention | ● Screening and prevention |
| | ● Stroke and atrial fib |
| | ● Vision Impairment |

Practical Issues in Drug Use in the Elderly (con't)

- Recognizing Adverse Drug Events
 - » Misinterpretation of ADR as a medical condition
 - » Avoiding the "Prescribing Cascade"
- Use of Safest Possible Drug
 - » Long vs. short half-life drugs
- Identify the Lowest Feasible Dose
 - » Potential for side effects and cost
 - » Knowledge base of patient about medications
 - "Tell me what you take this medication for"
 - » CLEAN OUT THE MEDICINE CABINET

Practical Issues in Drug Use in the Elderly

● Problems of Nonadherence

- » Compliance under the best of conditions is approximately 50%
- » Premature discontinuation
- » Excessive consumption
- » Visual impairment, functional disability and cognitive dysfunction
 - Written and/or verbal medical illiteracy
- » Misunderstanding of written/verbal instructions
- » Use of weekly pill-box reminders