Optimizing Drug Therapy in the Elderly

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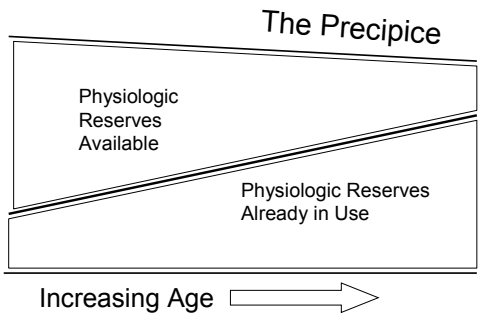
DRUGS ARE POISONS WITH THERAPEUTIC SIDE EFFECTS!!!

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"



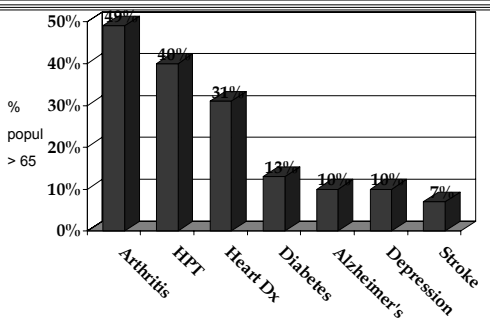
Demographics

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

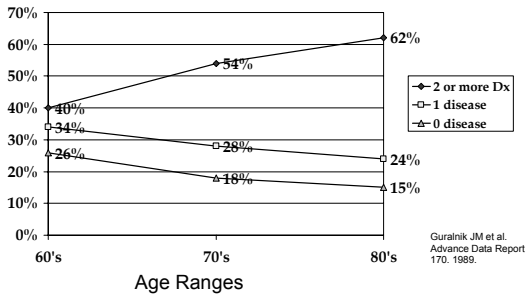
	Men	Women
1950	65.6	71.1
1990	72.7	79.5

- Chronic illness

Disease Prevalence in the Elderly



Comorbidity Increases with Age



Guralnik JM et al. Advance Data Report 170. 1989.

Leading Causes of Death

65 years and older

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

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

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

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.

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 evens 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

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

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

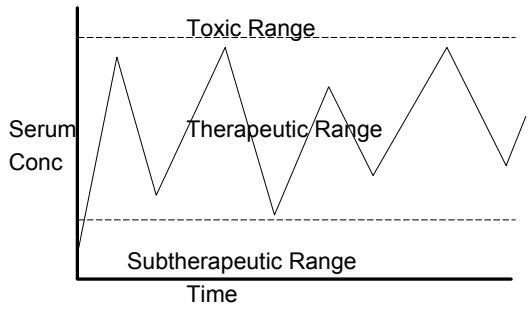
Physiologic Changes with Aging

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

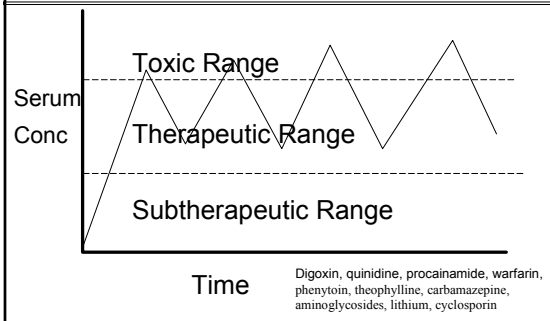
Physiologic Determinants of Drug Distribution

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

Wide Therapeutic Window

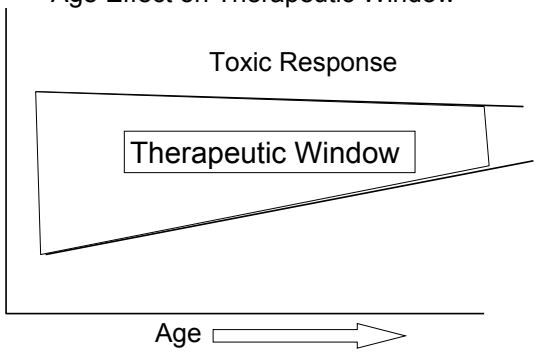


Narrow Therapeutic Window



Digoxin, quinidine, procainamide, warfarin, phenytoin, theophylline, carbamazepine, aminoglycosides, lithium, cyclosporin

Age Effect on Therapeutic Window



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

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.

Phenytoin (Dilantin, 10-20 mcg/ml)

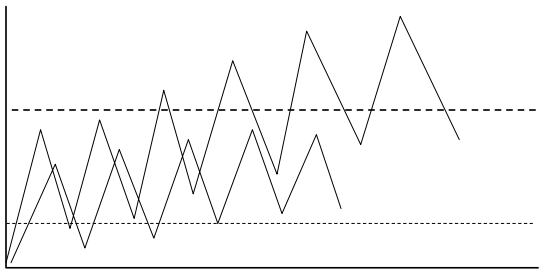
Measured	Patient's Serum Albumin (gm/dl)			
Phenytoin	3.5	3	2.5	2
(mcg/ml)	*Adjusted Total Phenytoin Conc (mcg/ml)*			
5	6	7	8	10
10	13	14	17	20
15	19	21	25	30

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

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



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

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

Anticholinergic Side Effects

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

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)

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), c~~elecoxib (Celebrex), ~~Valdecoxib (Bextra)~~
- Routine acetaminophen a possible alternative.

Benzodiazepines

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

Diazepam		Lorazepam
Chlordiazepoxide	>	Oxazepam
Flurazepam		Temazepam

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 (?)

Side Effects

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

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), pantropazole (Protonix)

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

Criteria for Inappropriate Use

Beers. Arch Intern Med 1991;151:129

- Sedative-hypnotics
  - » chlordiazepoxide, diazepam, flurazepam
  - » Meprobamate
  - » Any use > 4 weeks
- Antidepresants
  - » Avoid Amitriptyline
  - » Avoid combinations
- Antipsychotics
  - » Haloperidol > 3mg/day
  - » Thioridazine >30mg/day
- Antihypertensives
  - » HCTZ > 50mg/day
  - » Avoid Methyldopa, Propranolol, Reserpine
- Oral Hypoglycemics
  - » Avoid Chlorpropamide
- Analgesics
  - » Avoid Propoxyphene
  - » Avoid Pentazocine
- Dementia treatments
  - » Avoid cyclandelate
  - » Avoid Isoxsuprine

Criteria for Inappropriate Use

Beers. Arch Intern Med 1991;151:129

- Histamine Blockers
  - » Cimetidine >900mg/day
  - » Ranitidine >300mg/day
- Antibiotics
  - » Use >4 wks with exceptions
- Decongestants
  - » Afrin, Neo-Synephrine, Sudafed use > 2 weeks
- Iron
  - » Doses > 325mg/day
- Platelet Inhibitors
  - » Avoid Dipyridamole
- Muscle relaxants
  - » Avoid Cyclobenzaprine, Carisoprodol, Methocarbamol
- GI antispasmodics
  - » Avoid long term Donnatal, Levisin, Pro-Banthine.
- Antiemetics
  - » Avoid Tigan
- NSAID
  - » Avoid Indomethacin Phenylbutazone

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.

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

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, methyldopa, 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

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 revaluate a relative rating or severity for each medication
- Identify new conditions or considerations not addressed in 1997

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

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

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 (Diabenese)
  - » Barbiturates for sedative/hypnotic
  - » Meperidine (especially orally)

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

Assessing Care of Vulnerable Elders (ACOVE)

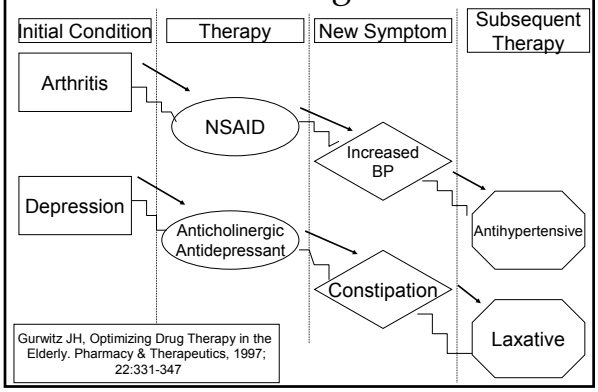
- Evaluate the PROCESS for caring for the elderly
- Establishment of valid evidence-based measures of quality for frequently encounter health issues.
- Still the measure may not fill the needs of all elderly patients.

Assessing Care of Vulnerable Elders (ACOVE)

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

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

The Prescribing Cascade



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.

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