Pharmacology and Aging: Safe and Effective Drug Use in Older Adults

Richard W. Besdine, MD, FACP
Professor of Medicine
Greer Professor of Geriatric Medicine
Director, Division of Geriatrics
Director, Center for Gerontology and Health Care Research
Learning Objectives

1. Equip you to be able to demonstrate understanding of
   - Categories of medication-related problems in older adults
   - Reasons why elders are especially vulnerable to medication problems

2. And most important, equip you to use strategies to reduce the risk that you will cause medication-related problems for your older patients
Role of Drugs in Care of Elders

Medications are probably the single most important health care technology in preventing illness, disability, and death in the geriatric population


In older people, stopping a drug is generally better than starting one

Anderson F. Dunham Lecture. Harvard Medical School. 1974

A pair of docs disagreeing, or truly a Paradox?
Resolving the Paradox

- Older persons have more disease, and thus benefit most from effective medications.
- But taking more drugs generates more opportunities for adverse effects.
- Many medication-related problems are predictable and thus preventable.
- Avoiding medication problems is neither easy nor simple – we welcome complexity.
- Goals of medication use: healthy aging (less morbidity, enhanced function), fewer hospitalizations, reduced health care costs.
Taxonomy of Drug-Related Problems

- Needed drug not given
- Too little or too much of a drug is given
- Improper drug selection - “best” drug not used
- Drug no longer needed is continued
- Failure to take drug as ordered (non-adherence)
- Adverse drug reactions – toxic, idiosyncratic
- Drug-drug, drug-disease, drug-food interactions
- Drug use only for symptoms (unless palliative)

Body Composition Changes with Age

- Reduced total body water (15-20%), $\downarrow V_d$ for water-soluble drugs
- Reduced lean body mass (15-20%; more in frail, especially if sarcopenia)
- Increased % body weight as fat, $\Rightarrow V_d$ for fat-soluble drugs
- Serum albumin declines (within nl. range); less drug bound, larger free fraction, greater effects – and hypoalbuminemia is very common
Pharmacokinetics – How the Body Handles a Drug

- Absorption - Little net change with normal aging
  - Diminished gastric acid secretion – calcium, ASA less absorbed; L-dopa more absorbed
  - Delayed gastric emptying; ➫ motility, blood flow
Pharmacokinetics - Distribution

Distribution ($V_d$) – a theoretical space, whose major determinant is body composition

- $V_d \rightarrow$ for fat-soluble drugs – aging $\rightarrow$ fat compartment; $\rightarrow$ blood level, more accumulation, delayed clearance (diazepam (and most psychoactive drugs, verapamid, thiopental, trazodone))

- $V_d \rightarrow$ for water-soluble drugs – aging causes $\rightarrow$ water compartment, resulting in $\rightarrow$ blood level and faster clearance (lithium, dig, ethanol)

- Drugs bind variably to albumin, major protein carrier; albumin declines with age, but remains in normal range – beware in frail ($\downarrow\downarrow$); more free drug, more toxicity
Pharmacokinetics – Renal Clearance

Increased % of sclerotic glomeruli, focal GS; A-V shunts bypass sclerosed glomeruli; number ↓30-50% by 80 - ↑ GFR for surviving glomeruli

- Overall decline in function
- Renal blood flow ↓10%/decade
- ↓Response to salt or water load
- ↓Renal tubular secretion
- Glomerular filtration rate ↓1 ml/min/yr>40

Creatinine clearance ↓ in parallel with GFR; imperative to calculate $C_{\text{CR}}$ in elders
Age-related glomerulo-sclerosis (right) – replacement of normal cellularity (left) with matrix, and adherence to Bowman’s capsule
Serum Creatinine, BUN Overestimate Renal Function ($C_{Cr}$)

- ↓ lean body mass → lower creatinine production, which requires less glomerular filtering capacity (GFR) to maintain normal serum value
- ↓ lean body mass → ↓ protein intake, and thus less urea nitrogen (from protein metabolism), so less renal function required for normal BUN

Result: In older persons, serum creatinine and BUN stay in normal range, masking change in creatinine clearance ($C_{Cr}$)
CALCULATING $C_{Cr}$

- **Measure directly:**
  - Time-consuming, usually inaccurate
  - Requires 24-h urine collection
  - 8-h collection may be accurate, not widely accepted

- **Estimate by the Cockcroft and Gault equation:**
  \[(\text{Ideal weight in kg}) \times (140 - \text{age}) \times (0.85 \text{ if female}) = (72) \times (\text{serum creatinine in mg/dL})\]

- **Estimate by MDRD (modification of diet in RD)**
Pharmacokinetics – Hepatic Function

- Clearance ↓ - decline in blood flow with age
- Metabolism
  - Phase I – cytochrome microsomal enzyme-mediated deoxidation, hydroxylation and phosphorylation all decline (e.g., H2 blockers, long-acting benzodiazepines, theophylline)
  - Phase II - conjugation (glucuronidation, sulfation), acetylation show little change (lorazepam)
  - Smoking stimulates mono-oxygenase enzymes, ↑ clearance of theophylline - ↓ therapeutic efficacy

Plasma and tissue levels usually increased, and demand dose reduction, esp. for phase I agents
Renal and Hepatic Clearance Change with Age

Age-related change in half-life for different drug clearance mechanisms (geometric means ± SE)
Clearance Goes Down, Half-Life Goes Up

Age-related change in clearance and half-life for all drugs (geometric means ± SE)
Pharmacodynamics in Elders

Drug effect on the body (end organ sensitivity)

Receptor number, binding, or altered signaling changes receptor-initiated cellular response:

- Greater effect – most psychoactive agents (e.g., narcotics – more pain relief at lower doses; benzos - ↑sedation, confusion, postural instability); bleeding from warfarin; parkinsonism of neuroleptics; hyperkalemia of spironolactone (well understood – hyporenin, hypoaldosteronism of aging)
Pharmacodynamics in Elders

- Increased receptor response seen for warfarin, benzodiazepines, opiates; CNS, bladder, bowel more sensitive to anticholinergics

- Less effect - β-blockers - well understood; down-regulation of β-receptors with aging results in less bradycardia; less tachycardia with β-agonist. But still see peripheral vasoconstriction and bronchoconstriction
Older Persons Use Lots of Drugs

- 30% of prescriptions, 40% OTC; 20% of discretionary funds
- 18 prescriptions/yr; average of 3 Meds/day over age 70 - if taking any at all, average is 6
- Demographics – now 13% (39 mil), 6 million >85; in 2030, nearly 80 M >65 and 15 M >85
- Older persons have many diseases, for which drugs are the most cost-effective treatment
- Many complaints, sometimes generating medications aimed only at symptoms
Adverse Drug Reactions (ADR)

- Cause 15% of all hospitalizations, and half of ADR admissions are > 65
- Risk of ADR doubles over age 60
- ADR pts >60 have prolonged hospitalizations
- ADR \( \propto \) age, but age is proxy for drug and disease burden
- ADR rate is dose-related within the therapeutic range
Risks for Adverse Drug Reactions

- Multiple medications (poly-pharmacy, poly-medicines)
- Multiple co-morbid diseases, symptoms
- Body composition changes with aging
- Non-adherence to complex drug regimens
- Pharmacokinetic and pharmacodynamic changes with age
Figure 7. Age-specific rates of adverse drug reactions before and after adjusting for drug consumption. Modified from Begaud et al. (2002).
Data from Odense (Denmark) Pharmaco-epidemiological Database (OPED) for all prescriptions in one County (Funen, n=466 567). The number of individuals with concurrent use of ≥5 drugs
Polymedicine (AKA Polypharmacy)

How does it happen?

- Multiple prescribers
- Doctor shopping
- Old prescriptions
- Swapping prescriptions
- New drugs for side effects of old drugs
- OTC, especially NSAIDs, but also antidiarrheals, antihistamines, laxatives
Polymedicine (AKA Polypharmacy)\textsuperscript{2}

Warning signs

- Drugs without clear indications
- Drugs whose only indication is a symptom (except palliative care)
- Duplicate drugs
- Conflicting drugs
- Dangerous drugs – e.g., NSAIDs, warfarin, anticonvulsants, anti-arrhythmics
National estimate of Total Long-term Care Facility Prescription Drug Spending (in $ M) by Top 10 Therapeutic Categories, 2001

- Gastrointenstials, $694M
- Psychotherapeutics, $1,428M
- Autonomic, $348M
- Cardiovascular, $347M
- Central Nervous System, $282M
- Cardiac, $267M
- Antiinfectives, $237M
- Antiarthritics, $194M
- Blood Modifiers, $161M
- Hormones, $160M
Adherence Problems (AKA Compliance)

- Chronic disease
- Low SES, education
- Non-English-speaking, cultural differences
- Multiple drugs, complex regimens
- Drugs with frequent side effects
- Dementia
- Sensory deficits - vision and hearing
- Difficult containers, large pills
- Poverty – expensive meds; omit or stretch
- Inadequate communication with physician
Adherence Problems (AKA Compliance)

- Rates for non-adherence are 25-50% 
- Identify and address problems of previous slide 
- But: sophisticated, informed, protective non-compliance
  - Beware giving all drugs in all doses in institutional setting 
  - New toxicity $2^\circ$ new compliance
Principles

- Inventory all drugs regularly – look for OTCs, expired, duplicate, obsolete, DDIs, risks for non-adherence, cost
- Use “best” in class - side effects, therapeutic window, therapeutic index; consider dose and dose interval by age and presence of diseases, especially renal and cardiac disease
- Identify indication
- Set and monitor therapeutic goals - determine measurable end points, assess often
Principles

- Before adding new drugs, review current ones - consider new symptoms as side effects
- Educate the patient - regimen, drug purpose, side effects, therapeutic effects
- Ask the patient about drugs at every visit - adherence, side and therapeutic effects for each
- Address non-adherence
- Stopping one generally better than starting one
- Do not withhold drugs because of age
- DON’T BE GREEDY