#### AGING PHYSIOLOGY, PHARMACOKINETICS & PHARMACODYNAMICS

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#### **HRSA Statement**

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### **Objectives**

- 1. Describe the physiologic, pharmacokinetic, and pharmacodynamic factors which affect drug use in the elderly
- 2. Describe risk factors and identify drugs commonly associated with adverse drug events in the elderly
- 3. Recognize potentially inappropriate drug use and recommend alternative therapy where appropriate
- 4. Discuss principles of optimal prescribing for older patients

# **Challenges of Geriatric Pharmacotherapy**

- Impact of aging physiology on drug therapy
  - Pharmacokinetics
  - Pharmacodynamics
- Polypharmacy
- Inappropriate prescribing (Beers, and others)
- Adverse drug events
- Medication adherence



# **Effects of Aging on Absorption**

#### Passive diffusion: unchanged

- No change in overall F of most drugs
- Decreased GI motility & blood flow counterbalanced by increased drug transit time & increased time for absorption

#### Active transport:

- Decreased F for some drugs: ions, vitamins (e.g. B12), minerals (e.g. Fe2+, Ca2+)
- Ca2+ in the setting of increased GI pH

#### First pass extraction:

- Decreased hepatic blood flow
- Increased F for high extraction drugs: e.g. TCAs, methylphenidate, propranolol, NTG
- Slowed or reduced activation of produgs: e.g. enalapril

#### Effects of Aging of Volume of Distribution (Vd)

Aging Effect	Vd Effect	Examples
↓ Total body water	<ul> <li>↓ Vd for hydrophilic drugs</li> <li>↑ plasma concentration</li> </ul>	Ethanol, lithium, digoxin, propranolol, HCTZ, theophylline, cimetidine, aminoglycosides, procainamide, quinidine
↑ Fat stores	<ul><li>↑ Vd for lipophilic drugs</li><li>↑ terminal half-life</li></ul>	Benzodiazepines, trazodone, amiodarone, haloperidol
↔ or ↓ Albumin	↑ % of unbound or free drug (active drug)	Phenytoin, warfarin, NSAIDs, diazepam, valproic acid, furosemide, propranolol, quinidine, salicylate

#### **Effects of Aging on Hepatic Metabolism**

Pathway	Effect	Examples
<u>Phase I</u> : oxidation, reduction, hydroxylation, demethylation	↓ Hepatic mass and blood flow	Diazepam, alprazolam, chlordiazepoxide TCAs, citalopram, paroxetine Risperidone, haloperidol Propranolol, metoprolol, CCBs
(active metabolites)	↓ Clearance and ↑ t1/2 for some drugs	Diclofenac, ibuprofen Theophylline Quinidine Carbamazepine, phenytoin Omeprazole Erythromycin
<u>Phase II</u> : conjugation, glucuronidation, acetylation, sulfation (inactive metabolites)	No change	Lorazepam, temazepam, oxazepam Warfarin Ethanol Prazosin Isoniazid

Note: Medications undergoing only phase II metabolism preferred in elderly

### **Renal Excretion**

- Renal function progressively declines with age, independent of disease
  - $\downarrow$  Renal mass and blood flow
  - ↓ Number of functional nephrons
  - ↓ Tubular reabsorption
  - Renal tubular flow is mostly preserved due to increase in filtered fraction (increased filtration pressure d/t efferent arteriolar vasoconstriction)
- By age 85y, ave. CrCl declines to 50% of what it was at age 25y
- Decreased clearance of renally eliminated drugs and active metabolites
  - Drugs: e.g: Aminoglycosides, vancomycin, quinolones, atenolol, quinidine, digoxin, furosemide, spironolactone, HCTZ, gabapentin, H2-blockers, allopurinol, lithium, NSAIDs, ACE inhibitors
  - Metabolites: n-acetyl procainamide, 0-desmethylvenlafaxine, M3G, M6G

# **Estimating GFR in the Elderly**

- CrCl is used to estimate GFR
- SCr alone <u>not</u> accurate in the elderly
  - $\downarrow$  lean body mass  $\rightarrow$  lower creatinine production
  - $\downarrow$  glomerular filtration rate
  - SCr stays in normal range, masking changes in CrCl
- Cockroft-Gault equation:

(ABW in kg) x (140-age) ------72 x (Scr in mg/dL)

x (0.85 for females)

Use adjusted body weight (AjBW) if BMI  $\geq$ 40 kg/m<sup>2</sup> BMI = ABW in kg/[ht in meters]<sup>2</sup> OR 703 x (WT (lbs)/[HT (in)]<sup>2</sup>)

#### **Example: CrCl vs Age in a 5'5" 55kg Female**

Age (yr)	SCr (mg/dL)	CrCl (mL/min)
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

#### **Pharmcodynamics**

- Evidence of altered drug response or sensitivity of older adults to some drug classes
- Mechanisms:
  - Changes in receptor numbers/density
  - Changes in receptor affinity
  - Changes in signal transduction mechanisms
  - Impaired cellular response in affected organs
  - Age-related changes in homeostatic mechanisms

## **Pharmacodynamics and Aging**

- Increased sensitivity
  - Digoxin
  - Warfarin
  - Alpha-blockers
  - Diuretics
  - Vasodilators
  - Anticholinergics
  - Alcohol
  - Opioids
  - Benzodiazepines
  - Antipsychotics

#### Decreased sensitivity

- Beta-blockers
- Beta-agonists
- CCB (cardiac conduction)

# **Adverse Drug Events (ADEs)**

- Rate of ADEs in older adults: 2.5-50.6%
- Responsible for 5-28% of acute geriatric hospital admissions
- 106,000 deaths and \$85 billion spent for medication related problems in 2000
- >95% of ADEs are predictable
- ~50% of ADEs are preventable
- Most errors occur at the ordering and monitoring stages



#### **Most Common Medications Associated with ADEs**

- Opioid analgesics
- NSAIDs
  - GI bleed
  - Fluid retention (HTN, CHF, peripheral edema)
  - Renal impairment
- Anticholinergics
- Benzodiazepines
- <u>Also</u>: cardiovascular agents, CNS agents, and musculoskeletal agents

Adverse Drug Reaction Risk Factors in Older Outpatients. Am J Ger Pharmacotherapy 2003;1(2):82-89.



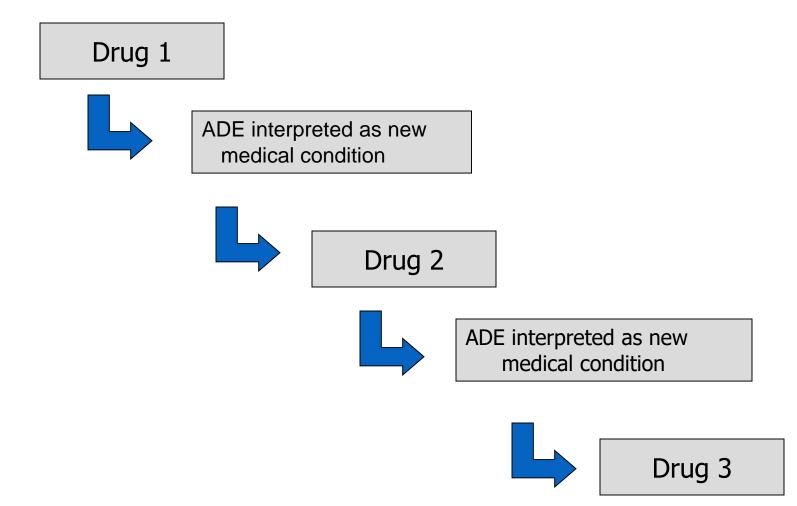
### **Patient Risk Factors for ADEs**

- Polypharmacy
- Inappropriate prescribing
- Medication underuse
- Medication non-adherence
- Other factors:
  - Multiple co-morbid conditions
  - Prior adverse drug event
  - Low body weight or body mass index
  - Age > 85 years
  - Estimated CrCl <50 mL/min</li>

# Polypharmacy

- Definition: administration of more medications than are clinically indicated
- Rate is 55-59% of older outpatients
- SNF: 27.1% take 9 or more medication regularly
- Average 2-9 prescription medications daily in community dwelling elderly
- Use of dietary supplements adds to burden
  - 46-59% use vitamin/mineral supplement
  - 11-14% use herbal supplements

#### **Prescribing Cascade**



Rochon PA, Gurwitz JH. Optimizing drug treatment in elderly people: the prescribing cascase. BMJ 1997;315:1097.

# **Avoiding Polypharmacy**

- Avoid prescribing before diagnosing
- Not every complaint requires a pill
- Consider non-pharmacologic therapy
- Be reluctant to start drugs that will be hard to stop
- Beware of the "prescribing cascade"

## **Inappropriate Prescribing**

- <u>Definition</u>: prescribing drugs that should be avoided because risk outweighs benefit
  - 20% of home care patients
  - 25% of long term care residents
- Explicit criteria:
  - Beers
  - Start/Stopp
  - FORTA-US
  - HEDIS
  - PRISCUS

Drug	Concern	Alternatives
Anticholinergics: First-generation antihistamines	Highly anticholinergic Decreased CL with advanced age	Intranasal saline, intranasal steroids
e.g. diphenhydramine, hydroxyzine, meclizine	Tolerance to hypnotic effects	2 <sup>nd</sup> generation agents: fexofenadine, loratadine
	Exception: DPH in acute allergic reactions	For itching: moisturizers
Gastrointestinal agents: PPIs	Risk of <i>C. difficile</i> infection, bone loss and fractures	Antacids PRN
	Avoid scheduled use for >8 weeks unless high-risk patient (chronic NSAID or steroid use, erosive esophagitis, Barrett's esophagus, ZE, or demonstrated need for maintenance treatment)	H2 blockers

Drug	Concern	Alternatives
<u>CNS agents</u> <b>Antidepressants</b> : e.g. amitriptyline, doxepin, nortriptyline, paroxetine	Highly anticholinergic Cause orthostatic hypotension	For depression: SSRIs (except paroxetine), SNRIs, bupropion For neuropathic pain: SNRIs, gabapentin, pregabalin, topical capsaicin, lidocaine patch
CNS agents: Antipsychotics	Increased risk of CVA and greater rate of cognitive decline and mortality in persons with dementia.	Behavioral interventions
Antiemetics e.g. promethazine, prochlorperazine	Avoid for behavioral problems associated with dementia or delirium unless non-pharmacologic options have failed or are not feasible AND the older adult presents substantial risk of harm to self or others.	For N/V: Ondansetron
	Exceptions: schizophrenia, BPAD, or ST use as entiemetic during chemotherapy	

Drug	Concern	Alternatives
<u>CNS agents</u> : <b>Benzodiazepines</b> : alprazolam lorazepam diazepam clonazepam	Increased sensitivity and decreased metabolism in older adults Increase risk of cognitive impairment, delirium, falls, fractures, and MVAs Exception: May be appropriate for seizure disorders, REM sleep disorders, benzodiazepine withdrawal, ethanol withdrawal, severe GAD, periprocedural anesthesia	For anxiety: SSRIs, SNRIs, buspirone
<u>CNS agents</u> : <b>BZRA hypnotics</b> : eszopiclone zolpidem zalpelon	Adverse effects similar to BZD: delirium, falls, fractures Increased ER visits, hospitalizations, MVAs Minimal improvement in sleep latency and duration	Sleep hygiene (preferred) Melatonin Low-dose trazodone Low-dose mirtazapine

Drug	Concern	Alternatives
<u>CV agents</u> : <b>Alpha<sub>1</sub> blockers</b> : e.g. doxazosin, prazosin	Avoid use for HTN due to high risk of OH Not recommended for routine treatment of hypertension Alternative agents have superior risk/benefit profile	ACE-I, ARB CCB Thiazide
<u>CV agents</u> : Digoxin	A-fib: Avoid as first-line agent due to safer and more effective alternatives	For A-fib: BB or LA non-DHP CCB For CHF: BB, ACE-I/ARB,
	CHF: Evidence for benefit and harms is conflicting; most evidence in HFrEF; other first-line agents have strong evidence to support reduced hospitalizations and mortality	spironolactone
	Avoid doses >0.125mg/d; decreased CL may increase risk of toxicity	

Drug	Concern	Alternative
<u>CV agents</u> : <b>Alpha agonists, central</b> : e.g. clonidine	Not recommended for routine treatment of hypertension High risk of CNS adverse effects May cause bradycardia and OH	Thiazides** ACE-I, ARB* LA CCB** *preferred for DM, CKD, CHF **preferred in African Americans
<u>CV agents</u> : Antiarrhythmics: amiodarone	Greater toxicity than other antiarrhythmics Exception: A-fib + HF or LVEF when rhythm control is preferred over rate control	Rhythm control: dofetilide, flecainide, propafenone

Drug	Concern	Alternatives
Endocrine agents: Androgens	Potential for cardiac problems Contraindicated in men with prostate cancer	
	Avoid unless indicated for confirmed hypogonadism with clinical symptoms	
Endocrine agents: Estrogens (systemic)	Evidence of carcinogenic potential Lack of cardioprotective effect and cognitive protection in older women	For dyspareunia and vulvovaginitis: vaginal estrogen
	Avoid systemic use	For vasomotor symptoms: SSRI, SNRI, gabapentin
	Exception: Intravaginal estrogen safe and effective for vaginal atrophy	
Endocrine agents: sulfonylureas, LA:	Higher risk of severe prolonged hypoglycemia in older adults	SA sulfonylureas (e.g. glipizide, gliclazide)
e.g. glyburide, glimepiride		Metformin

Drug	Concern	Alternatives
Pain medications: <b>Non-COX II selective NSAIDs (PO):</b> e.g. naproxen, ibuprofen, meloxicam, diclofenac, aspirin >325mg	Increased risk of GI bleeding and PUD in high risk groups (>75y; concomitant corticosteroids, anticoagulants, antiplatelet agents)	Scheduled APAP Tramadol Opioids Topical lidocaine
	Use of PPI or misoprostol reduces, but does not eliminate risk	Topical capsaicin Counter irritants Non-pharmacologic: TENS
	Upper GI ulcers, gross bleeding, or perforation occurs in ~1% of patients treated for 3-6 months and ~2-4% of patient treated for 1 year; trend continues with longer duration	
	Increased risk of elevated BP and AKI	
	Avoid chronic use unless other alternatives not effective and patient can take gastroprotective agent (PPI or misoprostol)	

Drug	Concern	Alternatives
Pain medications: Skeletal muscle relaxants: methocarbamol carisoprodol chlorzoxazone metaxalone cyclobenzaprine	Poorly tolerated by elderly due to anticholinergic effects, sedation, and risk of fracture Questionable effectiveness at doses tolerated in older adults	For mild or moderate pain: APAP, salsalate, propionic acid derivatives (e.g. ibuprofen, naproxen)

# Deprescribing

- <u>Definition</u>: systematic process of dose reduction or medication discontinuation
  - Medication risk > benefit
  - Expected benefit no longer consistent with patient care goals
  - Medication ineffective or no longer necessary
- Conceptual benefit, but outcomes not well studied

#### Considerations:

- Quality of evidence
- Potential for harm
- Patient values & preferences
- Costs of deprescribing

#### **Barriers to Deprescribing**

- Unknown indication
- Little guidance on when or how to stop medications
- Concern about adverse outcome due to stopping medication
  - Recurring symptoms or disease exacerbation
  - Adverse drug withdrawal effects (ADWE)
- Deviation from clinical guidelines

## **Clinical Factors for Deprescribing**

- Documentation of factors that warrant continued use
- How can patients be engaged in the process?
- How should tapering be approached?
- What should be monitored and how often?
- How to manage recurring symptoms?

Guidelines by: <a href="http://www.deprescribing.org">www.deprescribing.org</a>

- PPIs
- Benzodiazepines and BDRAs
- Antipsychotics
- Antihyperglycemics
- AChEIs and memantine

#### **Medication Non-Adherence**

- <u>Definition</u>: extent to which a person's medication taking behavior corresponds with agreed recommendations from a health care provider
  - Failure to fill prescription
  - Stopping a medication before completed
  - Taking more or less of a medication than prescribed
- Prevalence in elderly is 40-80% (mean 50%)

#### **Medication Non-Adherence**

- Factors in non-adherence
  - Financial, cognitive, or functional status
  - Beliefs and understanding about disease and medications
  - Polypharmacy, adverse effects
  - Caregiver support
- Non-adherence associated with increased ADEs and healthcare costs
  - Factor in ~10% of hospital admissions
  - Cause of 21% of preventable ADEs

#### **Assessing Non-Adherence**

- Socioeconomic factors: cost, cultural beliefs
- Provider-patient relationship
- Condition-related factors
- Therapy-related factors: e.g. complexity
- Patient related factors: functional/cognitive impairment

#### **Prescribing to Enhance Adherence**

- Use the least expensive alternative
- Simplify the regimen
- Give clear written instructions
- Utilize pill organizers, drug calendars
- Provide tools:
  - large print, magnifying glass, easy open bottles, and tablet splitters or crushers, special packaging, dose measuring devices, spacers for inhalers
- Educate patient on medication, purpose, benefits, and potential risks/ADEs

#### **Rational Medication Use in the Elderly**

- Consider risk vs. benefit for specific patient
- Consider non-pharmacologic therapy
- Start with a low dose and titrate slowly
- Avoid starting two agents at one time
- Avoid therapeutic duplication
- Reach max tolerated dose of single agent before adding 2nd
- Use one drug to treat two conditions

#### **Rational Medication Use in the Elderly**

- Consider drug-drug and drug-disease interactions
- Adjust doses for renal and hepatic impairment
- Avoid the "prescribing cascade"
- Plan for assessment
- Learn the common drug classes that are likely to cause problems in the elderly (Beers List)
  - anticholinergic agents
  - benzodiazepines
  - NSAIDs

#### **Rational Medication Use in the Elderly**

- Take ownership of patient's medication list
- Be able to justify each medication on the list
- Be reluctant to start medications that will be hard to stop
- Review medications regularly and keep accurate records
- Manage the patient, not the numbers
- Consider drug-holidays or d/c trial
- Stop drugs patient isn't taking or refuses to take
- Enthusiastically stop drugs of dubious benefit



#### **KEY POINTS**

- PK and PD changes generally result decreased clearance and increased sensitivity to medications in older adults
- Knowledge of aging physiology and PK/PD changes is critical in optimizing drug therapy in population
- ADEs and drug-related problems are a common cause of increased morbidity and functional impairment in older adults
- Tools (e.g. Beer's Criteria) exist to help identify inappropriate prescribing in older adults
- Optimizing drug therapy can play a major role in reducing drug-related problems and increasing quality of life

#### **Recommended References**

- Geriatrics at Your Fingertips (AGS)
- Geriatric Dosage Handbook (Lexi-Comp)
- 2019 American Geriatrics Society Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2019; 67(4):674-694.

#### Questions

