Pharmacodynamics of Aging
Narrowing of the Therapeutic Index
in the Face of Therapeutic Opportunity

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Areas of expertise:
Clinical pharmacology of aging
Geriatric Medicine
Systems Pharmacology
Educational Objectives

• Understand that older individuals taking more than 5 concurrent medications are at increased risk for side-effects from those medications
• Describe the main changes in cardiovascular hemodynamics with aging and provide two examples of their effect on drug responses
• Describe the changes in pharmacokinetics with aging, including the effects of renal function, and provide an example of a Phase I metabolism change and its effect on drug response
• Understand that increasing the drug burden for drugs with anticholinergic and sedative effects in older individuals leads to worse functional outcomes
Overview

- Older individuals and polypharmacy
- Cardiovascular pharmacodynamics of aging
- Pharmacokinetics of aging
- Multimorbidity and polypharmacy
- Assessment of functional effects of polypharmacy
- Resources
- References
Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACh</td>
<td>Acetylcholine</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse Drug Events</td>
</tr>
<tr>
<td>AV node</td>
<td>Atrioventricular node</td>
</tr>
<tr>
<td>BP</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Ca</td>
<td>Calcium</td>
</tr>
<tr>
<td>Cr</td>
<td>Creatinine</td>
</tr>
<tr>
<td>CL&lt;sub&gt;Cr&lt;/sub&gt;</td>
<td>Creatinine clearance</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>DBI</td>
<td>Drug burden index</td>
</tr>
<tr>
<td>DSST</td>
<td>Digit symbol substitution test</td>
</tr>
<tr>
<td>EKG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>HABC</td>
<td>Health ABC score</td>
</tr>
<tr>
<td>HR</td>
<td>Heart rate</td>
</tr>
<tr>
<td>MCC</td>
<td>Multiple chronic conditions</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric oxide</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>PWV</td>
<td>Pulse wave velocity</td>
</tr>
<tr>
<td>VE</td>
<td>Vascular endothelium</td>
</tr>
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</table>
Older Individuals Have Multiple Concurrent Illnesses

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Frequency per 1000 persons in USA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt;45 yrs</td>
</tr>
<tr>
<td>Arthritis</td>
<td>30</td>
</tr>
<tr>
<td>Hypertension</td>
<td>129</td>
</tr>
<tr>
<td>Hearing Impairment</td>
<td>37</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>31</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>19</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
</tr>
</tbody>
</table>

Nursing Home Residents Take 5-8 Concurrent Drugs on Average to Treat Multiple Illnesses

Ref: Figure 1. Medication prescriptions per resident in the 12 nursing homes.
15 Oct 1992, Annals of Internal Medicine, Vol 117, Number 8, 685
Incidence of Adverse Drug Effects Increases Dramatically Above Five Concurrent Medications

Ref: Adapted from Cluff LE et al: JAMA 188:976,1964
Overview

• Older individuals and polypharmacy
• Cardiovascular pharmacodynamics of aging
• Pharmacokinetics of aging
• Multimorbidity and polypharmacy
  • Following guidelines for treating individual diseases leads to polypharmacy
• Assessment of functional effects of polypharmacy
  • Drugs with anticholinergic and sedative effects have direct effects on function and outcomes
• Resources
• References
Alterations in the Cardiovascular System of the Elderly: Cardiovascular Hemodynamics

- Tendency to contracted intravascular volume
- Increased peripheral vascular resistance
- Tendency to lowered cardiac output
- Decreased baroreceptor sensitivity
- Increased blood pressure variability
- Suppressed plasma renin activity
- Decreased vascular endothelium production of nitric oxide

Most data from Baltimore longitudinal study on aging (https://www.blsa.nih.gov/) – ongoing for about 50 years
The Amount of Isoproterenol Required to Increase Heart Rate Goes up Dramatically With Age

- Isoproterenol (Beta-1 agonist drug, increases heart rate)
- Beta-1 adrenergic function is impaired with increased age

\[ I_{25} = \text{Dose required to increase the heart rate by 25 beats/min} \]

The Amount of Labetolol Required to Decrease Heart Rate Also Shows a Large Increase With Age

- Labetolol (alpha-, beta- adrenergic blocker, decreases heart rate)
- Beta-adrenergic hypoactivity seen in older people
- Suppression of beta-adrenergic activity is impaired with age

Abernethy et al, Am J Cardiol, 1987;60:697-702
Decrease in BP from Labetolol Causes a Reflex Increase in Heart Rate in the Young but not in the Elderly

- After decrease in BP, expect to see reflex increase in heart rate. Seen in young, but not in elderly.

- Beta-adrenergic function with vasodilation (alpha blocker) is impaired in the elderly. Their capacity for a reflex heart rate response is blunted.

Abernethy et al, 1987;60:697-702
Regulation of smooth muscle contraction.

agonists (norepinephrine, angiotensin II, endothelin-1, etc.)

receptor

Go

βγ

RhoGEF

RhoA-GTP (active)

RhoA-GDP (inactive)

IP₃

DG

PKC

Ca²⁺

sarcoplasmic reticulum

Ca²⁺

Ca²⁺/calmodulin

MLC kinase (active)

actin + MLC (contracted)

MLC (relaxed)

myosin phosphatase (active)

myosin phosphatase (inactive)

Rho-kinase

ATP


Advances in Physiology Education

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Arterial Changes Related to Normal Aging are Enhanced with Cardiovascular Disease

- Increased calcium and collagen
- Reduces elasticity and compliance
- Increased pulse pressure (Systolic higher than diastolic)
- Decreased baroreceptor sensitivity
- Hyaline thickening in arterioles, small arteries
- Increased peripheral resistance
Decreased Vascular Compliance in Elderly Changes the Shape of the Aortic Pulse Wave and Increases its Velocity

Young (left): With each heartbeat, a pulse wave travels in the aorta. Waveform shows systole, then diastolic relaxation. Arrow shows incisura (maintained arterial pressure during coronary artery filling).

Older (right): Increased PWV in less compliant vessels. The incisura occurs earlier, during systole. Pressure to fill coronary arteries is lower.

O’Rourke, MF, Arterial Function in Health and Disease, 1982
Higher Exposure is Seen after Verapamil Dose in Older Normotensive Individuals

Verapamil (L-type Ca channel blocker) is used in hypertension

Verapamil Suppression of Atrioventricular (AV) Node Activity is Markedly Greater in Young than in Old Individuals

Study: Suppression of AV node activity is measured by EKG. When AV conduction is delayed, the P-R interval is prolonged.

Verapamil Causes a Greater Decrease in Mean Blood Pressure in Elderly
Greater variability seen among older individuals

Normal baroreflex function (young): with a greater decrease in blood pressure (BP), see an increase in heart rate (HR) to protect BP

Blunted baroreflex function (elderly): impairments in beta-1 adrenergic sensitivity

Heart Rate Responses Change with Age

- Decreased heart rate responses
  - Impairment in capacity to respond to reflex sympathetic outflow
  - Parasympathetic changes with age are possible as well

- Differing sensitivity to calcium channel blockade of the sinus node
Nitric Oxide (NO) From Vascular Endothelial Cells Modulates Vascular Smooth Muscle Cells

- Stimulation of vascular endothelial cells (e.g. by acetylcholine) results in elaboration of NO
- A cascade of reactions leads to vascular smooth muscle relaxation

More Acetylcholine is Required in Older Individuals to Achieve the Same Vasorelaxation

Dark blue bars: infusion of acetyl choline (ACh) in brachial artery and measurement of forearm vascular resistance and blood flow

Intact vascular endothelium (young): ACh induces elaboration of NO, then vasorelaxation

Impaired vascular endothelium (VE, old): ACh has less response. If VE destroyed, then ACh has direct vasoconstricting effect on vascular smooth muscle.

EC\textsubscript{50}: Dose required to achieve 50% max response in vasorelaxation

Coronary Artery Relaxation is also Impaired in Older Individuals

**Study:** Individuals with atypical chest pain without atherosclerosis were administered ACh until maximal coronary vasodilation had occurred.

**Results:** In young individuals, coronary blood flow may increase 5-6 fold with ACh. With age, coronary vasorelaxation is progressively impaired.

Ref: Chauhan et al, JACC, 1996; 28:1796-1804
Overview

- Older individuals and polypharmacy
- Cardiovascular pharmacodynamics of aging
- **Pharmacokinetics of aging**
- Multimorbidity and polypharmacy
- Assessment of functional effects of polypharmacy
- Resources
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Pharmacokinetics

RENAL CLEARANCE

KIDNEY

HEPATIC CLEARANCE

LIVER

METABOLITES

PARENT DRUG
Drugs Metabolized in the Liver Undergo Degradation in Phase I and Synthesis in Phase II
PK changes in aging are mostly seen in Phase I
Some Phase I Drugs Commonly Used in Older Individuals are Biotransformed by Specific Cytochrome P450 Enzymes

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>duloxetine, olanzapine</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>phenytoin, warfarin</td>
</tr>
<tr>
<td>CYP3A</td>
<td>midazolam, cyclosporine, clarithromycin, amlodipine</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>carvedilol, duloxetine</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>diazepam, phenytoin, clopidogrel</td>
</tr>
</tbody>
</table>

From Drug Interaction Table, Indiana University, Clinical Pharmacology Research Institute (http://medicine.iupui.edu/CLINPHARM/ddis/main-table)
Exposure to Triazolam is Markedly Higher in an Older than in a Younger Individual
This large effect is atypical for Phase I drugs

Triazolam (sleeping pill)
Higher exposure is also associated with increased sedation

Midazolam, a Prototype CYP3A Drug, Shows Some Decrease in Clearance in Older Individuals

Typically, across CYP3A drugs, a 20-30% decrease in drug clearance is seen with age

Greenblatt et al, Anesthesiology, 1984;61:27-35
Some Widely Used Drugs Undergo Significant Renal Excretion (not metabolized)

- Amantadine
- Aminoglycoside antibiotics
- Cimetidine
- Digoxin
- Furosemide
- Lithium
- Nitrofurantoin
- Ouabain
- Penicillin antibiotics
- Phenobarbital
- Quinidine
- Sulfonamides
- Tetracycline
Changes in Renal Function are the Most Important PK Change in Older Individuals

Cockroft and Gault equation provides a good measure of drug clearance in the older population:

\[
\text{CL}_{\text{Cr}} = \frac{(140 - \text{age}) \times \text{weight in kg}}{72 \times \text{serum Cr in mg/dL}}
\]

[reduce estimate by 15% for women]

\[\text{Cr} = \text{creatinine, a product of muscle breakdown (serum creatinine is decreased in older individuals because of decreased muscle mass)}\]

\[\text{Cr}_{\text{cl}} = \text{creatinine clearance, a measure of glomerular filtration rate (GFR)}\]
Pharmacokinetic Changes in the Elderly – Absorption, Distribution, and Plasma Protein Binding

<table>
<thead>
<tr>
<th>Process</th>
<th>Change with Age</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Absorption</strong></td>
<td>None</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Distribution</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central compartment volume</td>
<td>None or ▼</td>
<td>Rapid distribution</td>
</tr>
<tr>
<td>Peripheral compartment volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Lipophilic drugs</td>
<td>▲▲</td>
<td>Drugs that distribute into fat have a higher distribution volume than drugs that distribute into water</td>
</tr>
<tr>
<td>- Hydrophilic drugs</td>
<td>▼▼</td>
<td></td>
</tr>
<tr>
<td><strong>Plasma Protein (PP) Binding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding to albumin</td>
<td>▼</td>
<td>Free drug conc increases with age, and α1-acid glycoprotein binding increases in inflammation</td>
</tr>
<tr>
<td>Binding to α1-acid glycoprotein</td>
<td>None or ▲</td>
<td>Changes in PP are only relevant for single-dose administration (not for chronic administration)</td>
</tr>
</tbody>
</table>
### Pharmacokinetic Changes in the Elderly – Elimination

<table>
<thead>
<tr>
<th>Process</th>
<th>Change with Age</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Elimination</td>
<td>▼▼</td>
<td></td>
</tr>
<tr>
<td>Hepatic Elimination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase I reactions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- CYP3A</td>
<td>▼</td>
<td>20-30% decrease in drug clearance with CYP3A enzymes</td>
</tr>
<tr>
<td>- CYP1A2, 2D6, 2C9, 2C19, 2E1</td>
<td>↔ or ▼</td>
<td>Others do not show much change</td>
</tr>
<tr>
<td>Phase II reactions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Glucuronidation</td>
<td>↔</td>
<td>Phase II reactions change little with age</td>
</tr>
<tr>
<td>- Acetylation</td>
<td>↔</td>
<td></td>
</tr>
<tr>
<td>- Sulfation</td>
<td>↔</td>
<td></td>
</tr>
</tbody>
</table>
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Older Individuals, if Treated Appropriately for Each of Their Diseases, Will be Taking Multiple Medications
Assessment of Functional Effects of Polypharmacy: Anticholinergic and Sedative Drugs

• Functional capacity is a more important marker of longevity and correlates better with outcomes than physiologic measures
  - E.g. for congestive heart failure, walking speed is a more important marker than cardiac output
• Anticholinergic and sedative effects are common off-target effects
Little Evidence Available to Evaluate Drug Burden in the Elderly: A model is needed

- Older people carry a high burden of illness
  - Medications are indicated
  - Risk of adverse drug events is increased
- Limited evidence base to guide prescribing

Need evidence-based model to assess functional risk/benefit
Equation Derived for Drug Burden Index (DBI)

\[ DBI = \sum \frac{D_{AC}}{\delta_{AC} + D_{AC}} + \sum \frac{D_S}{\delta + D_S} \]

 DBI  Drug Burden Index  
 AC  Medications with anticholinergic properties  
 S  Medications with sedative properties  
 D  Daily dose  
 δ  Minimum recommended daily dose approved by US FDA; estimate of DR50

The DBI represents the cumulative effects of drugs in the context of the dose response relationship.

Hilmer et al, Arch Int Med 2007;167:781-787
Functional Measures of Physical Function
Health ABC Score (HABC)

- **Objective measures:**
  - Chair stands
  - 6 m walk
  - Narrow 6 m walk
  - Standing balance
- Higher score, better physical function
- Validated (Established Populations for Epidemiologic Studies of the Elderly)
Functional Measures of Sedation
Digit Symbol Substitution Test (DSST)

• Psychomotor performance, attention, concentration
• Higher score, better cognitive function
• Validated (Wechsler Adult Intelligence Scale)
Higher Anticholinergic Burden Decreases Both Function and Sedation Scores

![Graph showing the relationship between anticholinergic burden and HABC score and DSST scores. The graph illustrates a downward trend as anticholinergic burden increases.](image-url)
Higher Sedative Burden Decreases Both Function and Sedation Scores
Relative Impact of Drug Burden Index on Function:
1 pt increase in DBI = ~3 additional co-morbidities

- Multiple regression analysis
- Degree of variance in HABC score captured by a one point increase in drug burden index is:
  - ~ 3 additional physical co-morbidities
  - > cognitive impairment, depression or anxiety
Longitudinal Association Between DBI and Function in Health ABC Study Participants

Found an association of:

- Drug Burden Index at each time point
- Cumulative drug burden exposure with function over 5 years
Conclusions

- In Health ABC participants, Drug Burden Index at Years 1, 3, and 5 and total drug burden exposure (AUCDB) are associated with reduced functional performance at Year 6.
- Drug burden predicted impairments in physical function and cognition years later.
Similar Results Were Found in Other Populations

- Women’s Health and Aging Study (WHAS)
  - Community dwelling frail older women (USA)
- Concord Health in Ageing Men Project (CHAMP)
  - Community dwelling older men (Australia)
- FREEDOM
  - Older people living in low level residential aged care (Australia)
- Department of Veterans Affairs
  - DVA linked data bases (Australia) - pending
Patients with Multiple Chronic Conditions (MCC) (Mostly Older) Should be Included in Clinical Trials

- Guidelines (US, EU, Japan) encourage sponsors to incorporate study populations that are same as the patients likely to receive the drug upon approval
Patients with Multiple Chronic Conditions (MCC) (Mostly Older) Should be Included in Clinical Trials

• Efficacy
  • Is the same therapeutic benefit seen on the background of multiple illnesses and medications used to treat them?
  • Should the trial be powered to independently assess efficacy for the MCC patients?

• Safety
  • Is the safety profile adequately characterized without direct study of the MCC patient population?
  • What are the “off-target” drug effects that may have particular impact in MCC patients?

Are Older Patients Being Included?
Older Patients with MCC?
Goals for Treating the Older Patient:
Administer drugs judiciously to optimize therapeutic effects

- Decrease morbidity & mortality
- Avoid or minimize drug-related problems
- Improve the quality of life
"By the time a man gets well into the seventies, his continued existence is a mere miracle"

AES Triplex
R.L. Stevenson (1850-1894)