Special Thanks

Thanks to:
- Dr. Terry Chisholm
- Dr. Margaret Hahn
- Slides taken from their prior presentations were used in preparing the majority of this presentation
Objectives

- Review changes in drug metabolism with aging
- Review changes in drug effects with aging
- Review adverse drug effects in the elderly
- Review inappropriate prescribing practices in the elderly
- Review a responsible general approach to prescribing in the elderly
- Be aware of drug interactions in the elderly
- Review side effect profiles of psychotropic medications including:
  - Antipsychotics
  - Antidepressants
  - Lithium
  - Benzodiazepines
Pharmacokinetics

DEFINITION – “Factors determining availability of a drug to its bioactive sites”
Pharmacokinetics

“All stages of the journey of a drug through the human body may be affected by aging”

- Processes that are affected by aging include:
  - Absorption
  - Distribution (body composition, protein binding)
  - Metabolism (hepatic)
  - Elimination (renal)
Pharmacokinetics: Absorption

- Age related changes affecting absorption:
  - Decreased gastric acid secretion
  - Decreased surface of intestinal epithelium
    - Decreased absorptive surface area
  - Decreased carrier-mediated transport mechanisms
  - Decreased intestinal motility
    - Increased transit time
  - Decreased mesenteric blood flow
  - Reduced tissue blood perfusion
    - Dermal, subcutaneous, and muscular tissue
Pharmacokinetics: Absorption

- **Effects:**
  - In spite of the changes, intestinal absorption of most drugs is NOT significantly affected
  - Decreased rate of absorption of carrier-mediated drugs
    - Calcium, iron, vitamins
  - Decreased transdermal, subcutaneous, and intramuscular absorption

- **Clinical implications:**
  - Onset of action delayed with certain drugs
  - Clinical effect reduced
Pharmacokinetics: Distribution

- Age related changes affecting distribution:
  - Decreased muscle mass
  - Increased total body fat
    - 18 to 36% in men
    - 33 to 45% in women
  - Decreased total body water
    - Falls by 10-15% until age 80
  - Blood-brain barrier (BBB)
    - Decreased integrity with age
  - Decreased albumin, increased $\alpha_1$ acid glycoprotein
Pharmacokinetics: Distribution

- Effects:
  - Increased volume of distribution of lipophilic drugs
    - Greater half-life
    - Longer interval to reach steady-state levels
    - Longer to evaluate drug effect
    - E.g. diazepam, verapamil
  - Decreased volume of distribution of hydrophilic meds
    - Shorter half-life
    - Higher plasma concentrations with “normal” doses
    - E.g. lithium, aspirin
Pharmacokinetics: Distribution

- **Effects (cont):**
  - **Blood-brain barrier**
    - Protein bound, charged, hydrophilic drugs or active metabolites cross easier
    - Increased sensitivity to psychotropic meds
  - **Decreased albumin levels**
    - Unbound drug fraction is pharmacologically active
    - Decreased binding could increase plasma concentrations of free drugs → **TOXICITY**
    - Competition for protein binding by co-administered drugs → **INCREASE IN PLASMA CONCENTRATION**
Pharmacokinetics: Distribution

- Clinical implications:
  - Greatest effects in malnourished pts or those with comorbid medical conditions
  - Need to watch for adverse effects when new medications are added
Pharmacokinetics: Metabolism

- **Hepatic biotransformation**:
  - Intestinal absorption → portal vein → systemic circulation
  - **Phase I, or oxidative reactions**
    - Catalyzed by CYP450 enzyme system
    - Subfamilies CYP1A2, 2D6, 3A3/4 account for metabolism of most psychotropic medications, often to active metabolites through demethylation
    - Yields progressively more water soluble compounds for excretion via the gut and kidneys
    - **Metabolic activity can decrease up to 20-40% with age**
  - **Phase II, or conjugation reactions**
    - Produces polar, hydrophilic compounds devoid of pharmacologic activity
    - **Usually unchanged with age**
Pharmacokinetics: Metabolism

- Age related changes in hepatic clearance:
  - Decreased liver volume
    - 25-35% decrease
  - Decreased hepatic blood flow
    - Up to 40% decrease
  - Decreased oxidative metabolism
  - Decreased N-demethylation
  - Little effect on conjugation
Pharmacokinetics: Metabolism

**Effects:**
- Increased plasma levels
- Variable ratios of parent drug to demethylated drug (active)

**Clinical implications:**
- Reduce dosages
  - Especially upon initiation to avoid excessive plasma levels
- Caution when adding new medications
  - Drug interactions may occur if a new medication inhibits the CYP450 enzymes
- CHF may further decrease hepatic metabolism by compromising blood flow to liver
Pharmacokinetics: Elimination

- **Age related changes:**
  - Decreased renal blood flow
    - 1% decrease/year after age 40
  - Decreased GFR (glomerular filtration rate)
    - Declines by 25-50% between ages 20 and 90

- **Pharmacokinetic effects:**
  - Longer half-life
  - Greater steady-state plasma concentration
Pharmacokinetics: Elimination

Clinical implications:

- Renal function should be evaluated prior to initiation of treatment
  - Plasma creatinine overestimates GFR due to reduction in muscle mass
  - Can use Cockcroft-Gault formula to estimate creatinine clearance (CrCl)
    - CrCl is a good estimate of renal function
- Elevated/potentially toxic steady-state levels of lithium and other drugs excreted by the kidneys may occur
  - Often need to adjust doses as compared to younger counterparts
DEFINITION – “Factors influencing sensitivity to the drug at its receptor”

Factors include:
- Number of receptors in target organ
- Ability of cells to respond to receptor occupation
- Preservation of homeostatic mechanisms
  - Preserve the original functional equilibrium
Pharmacodynamics: Sensitivity

- Age dependant change in tissue sensitivity to drug action:
  - E.g. Increased sensitivity to muscarinic antagonism
    - Results from decreased number of cholinergic neurons
    - Peripheral effects: Constipation, glaucoma, urinary retention, blurred vision, tachycardia
    - Central effects: Mild depression, mild impairment of recent memory, confusion, delirium
Pharmacodynamics: Sensitivity

- E.g. Increased sensitivity to dopaminergic blockade
  - Results from decreased number of dopaminergic neurons
  - Results in increased incidence of motor effects
    - Antipsychotic-induced extra-pyramidal side effects (EPSE)
    - SSRI-induced EPSE
Pharmacodynamics: Sensitivity

- E.g. Increased susceptibility to syndrome of inappropriate anti-diuretic hormone (SIADH)
  - 12% will experience some degree of hyponatremia (low sodium) with SSRI or SNRI use
  - Median time to onset is 13 days
  - Lethargy, weakness, muscle cramps, disorientation, delirium
Pharmacodynamics: Sensitivity

- E.g. Increased risk of GI bleeding
  - Direct effect of SSRI on platelets
  - Recent comprehensive literature review (Yuan et al. 2006):
    - Supports the link between SSRIs and upper GI bleeds (UGIB) at a population level
    - The risk of UGIB increases with concomitant use of SSRIs and NSAIDs and/or aspirin, and advanced age
  - Preventive measures
    - Monitor bleeding parameters in high risk individuals (especially if on anticoagulants)
    - Switch from NSAID to selective COX-2 inhibitor
    - Addition of PPI may be helpful
    - Consider using non-SSRI in pts with bleeding risk
Pharmacodynamics: Sensitivity

- E.g. Increased sensitivity to $\alpha_1$-adrenergic blockade
  - Results from:
    - Reduced central noradrenergic (NA) tone
    - Decreased response to inotropi effects of adrenergic stimulation
  - Results in orthostatic hypotension
    - 5-33% have drug-induced orthostatic reactions
    - Increase in falls and hip fractures
      - 20% one year mortality post-hip fracture
Homeostatic Mechanisms

- With increased age:
  - Impaired orthostatic circulatory responses
  - Impaired thermoregulation
  - Impaired thirst response
  - Impaired glucose tolerance
  - Impaired vascular stability
  - Impaired cognitive reserve
AS DRUG SENSITIVITY INCREASES AND HOMEOSTATIC MECHANISMS DECLINE, WE CAN CONCLUDE THE ELDERLY ARE MORE SUSCEPTIBLE TO SIDE EFFECTS!
## Delicate Balance of Prescribing

<table>
<thead>
<tr>
<th>BENEFITS</th>
<th>MORBIDITY &amp; MORTALITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly patients benefit from drugs</td>
<td>Risk of adverse reaction rises exponentially with # meds</td>
</tr>
<tr>
<td>Puts focus on “appropriate” drugs</td>
<td>Many inappropriate drugs are use</td>
</tr>
</tbody>
</table>
# Compliance

<table>
<thead>
<tr>
<th># MEDS</th>
<th>COMPLIANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>73%</td>
</tr>
<tr>
<td>&gt;5</td>
<td>37%</td>
</tr>
</tbody>
</table>

*most common reason: fear of side effects*
Adverse Drug Reactions

- 8-21% of elderly in the community
- 56-74% nursing home residents
- Often missed:
  - Falls - benzodiazepines, psychotropics
  - Constipation - anticholinergics
  - Dementia - benzodiazepines
Adverse Drug Reactions

- Morbidity and mortality:
  - Hospitalization - 8% of admissions
    - 16% of admissions from nursing homes
    - Leads to increased length of stay
  - Between 4th - 6th leading cause of death in the US
  - Cost to society is more than for diabetes
Prescribing Cascade

- A prescribing cascade occurs when a 2nd medication is used to treat side effects of the 1st medication
  - E.g. Metoclopramide (Reglan) → EPSE
  - Levodopa (Sinemet) then used to treat EPSE
  - E.g. NSAID → HTN
  - HTN then treated with antihypertensive
Inappropriate Medication Use

- Examples of inappropriate med use:
  - Polypharmacy
    - Correlates with adverse drug reactions, noncompliance
  - Use of contraindicated meds
    - Beers Criteria
  - Excessive dosing
  - High risk of interactions
  - Safer choice available
Inappropriate med use is common in the following situations:

- Anxiety (often presenting symptom of depression)
  - 78% get anxiolytic
  - 32% get antidepressant
- Drug side effects misdiagnosed as new disease
- Multiple specialists
  - May be prescribing similar drugs
  - GP’s reluctant to discontinue meds started by specialist
General Approach to Pharmacotherapy

- Identify target symptoms
- Initiate appropriate treatment
- Try non-pharmacologic methods first
- Consider patient: medical conditions, diet, environment, drug interactions
- Start low, go slow
- Initiate at half the normal adult dose
General Approach to Pharmacotherapy

- Simplify the regimen
- Evaluate for response frequently
- Make dose changes only after steady-state achieved
- Increase dose until benefit or toxicity
- Reevaluate and taper as necessary
- Avoid undertreatment
Avoid Certain Medications

Benzodiazepines
- Cognitive impairment, falls, hip fractures, MVAs, addiction
- short-acting benzodiazepines safer (controversial)
- Used by 30% of elderly Nova Scotia women

NSAIDS
- GI bleeds, HTN, CHF, renal failure
- Acetaminophen should be first line for osteoarthritis (OA)
Avoid Certain Medications

Meperidine (Demerol)
- Higher incidence of central nervous system (CNS) effects than other opioids
- Interaction with monoamine oxidase inhibitors (MAOIs)

Amitriptyline (Elavil)
- Strongly anticholinergic
- Postural hyptotenison and falls
- Other tricyclic antidepressants (TCAs) can be use to treat neuropathic pain
Avoid Certain Medications

- Fluoxetine (Prozac)
  - long half-life
- Benztropine (Cogentin)
  - anticholinergic
- Metoclopramide (Maxeran)
  - EPSE
- Dimenhydrinate (Gravol), diphenhydramine (Benadryl), hydroxyzine (Atarax)
  - anticholinergic
Use Appropriate Doses

<table>
<thead>
<tr>
<th>Medication</th>
<th>Too high</th>
<th>Why</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCTZ</td>
<td>&gt;25 mg</td>
<td>↓Na,↓K,↑glucose</td>
</tr>
<tr>
<td>Iron</td>
<td>&gt;325 mg</td>
<td>Abdominal pain, constipation</td>
</tr>
<tr>
<td>Digoxin</td>
<td>&gt;0.125 mg</td>
<td>Delirium, nausea, arrhythmia</td>
</tr>
<tr>
<td>Haldol</td>
<td>&gt;2 mg</td>
<td>EPSE</td>
</tr>
<tr>
<td>Lithium</td>
<td>Level &gt;0.4-0.8</td>
<td>Toxicity</td>
</tr>
</tbody>
</table>
Antipsychotics: EPSE

**Parkinsonism:** shuffling gait (sticky feet), rigidity, tremor, drool, *common in seniors*

**Dystonia:** abnormal postures produced by sustained, contorting, twisting muscle spasms most often involving the head and neck, *uncommon in seniors*

**Akathisia:** subjective sense of restlessness, e.g., shifting from foot to foot, inability to sit still (often misinterpreted as agitation)

Tardive Dyskinesia

- Abnormal writhing involuntary movements
  - Orofacial: tongue, mouth, face
    - Most common site
    - Impaired eating and swallowing, dental problems, speech problems
  - Limbtruncal:
    - Gait disturbances may lead to falls, injuries
- Stigma
- May last years after stopping medication
- 5.6X more prevalent in elderly
Incidence of Tardive Dyskinesia in Older and Younger Patients

<table>
<thead>
<tr>
<th>Cumulative Years of Treatment</th>
<th>% Patients with TD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td>52%</td>
</tr>
<tr>
<td>4</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>19%</td>
</tr>
<tr>
<td>6</td>
<td>26%</td>
</tr>
</tbody>
</table>

Mean Age: 65.5
n = 266

Mean Age: 29
n = 850

Jeste et al. Arch Gen Psychiatry 1995;52:756-765
TD – Atypical Antipsychotics

- Lower incidence of TD than with typical antipsychotics
  - Best established with clozapine
  - Risperidone - compared to haldol after 9 months of treatment
    - Risperidone - 5% TD
    - Haldol - 30% TD
- ? Due to serotonin antagonism
TD – Risk Factors

- Length of drug exposure
  - > 90 days
  - Cumulative amount of antipsychotic (especially high-potency typicals)
- *Increased age
- EtOH abuse/dependence
- Subtle movement disorder at baseline, early EPSE
- Dementia

Jeste, 2001
TD – Prevention

- Avoid typicals, especially in high risk patients
- Use lowest effective doses
- Examine patients at baseline and at regular intervals thereafter
- Reduce and discontinue ASAP after TD detection
  - TD will likely worsen after discontinue of an antipsychotic
- Switch to an atypical (cross over)
Antipsychotic Side Effects

- **Conventional**
  - EPSE (falls) / TD
  - sedation*
  - postural hypotension*
  - anticholinergic*
  - ↓ cognition
  - ↑Prl, osteoporosis
  - cardiac (QTc)

- **Novel**
  - minimal EPSE
  - minimal or no TD
  - ? improve cognition
  - weight gain
  - sedation

*low potency

**Elderly are more vulnerable to SEs**
Anticholinergic Side Effects

- Confusion
  - Incontinence meds or increased anticholinergic load associated with worse cognition
- Tachycardia
- Dry mouth
- Constipation
- Urinary hesitancy / retention
- Blurred vision
- Exacerbation of narrow-angle glaucoma
Common Medical Drugs with Anticholinergic Effects

- Furosemide
- Digoxin
- Theophylline
- Warfarin
- Prednisone
- Triamterene and hydrochlorothiazide
- Nifedipine
- Isosorbide
- Codeine
- Cimetidine
- Captopril
- Ranitidine
- Ditropan

Psychotropic Medications With Anticholinergic Properties

- Thioridazine
- Mesoridazine
- Chlorpromazine
- Perphenazine
- Loxapine
- Cogentin
- Trifluoperazine
- Thiothixene
- Clozapine
- Olanzapine
- Tricyclic antidepressants
SSRIs – Selected Effects

- Hyponatremia
- CP450 interactions
  - Fluoxetine inhibits 3A3/4 (alprazolam), 2D6
  - Fluvoxamine inhibits 3A3/4, 1A2 (warfarin)
  - Citalopram has no reported interactions
- Bleeding (GI, bruising, epistaxis)
  - Low absolute risk but be cautious if there are other risk factors (eg warfarin use)
  - Consider stopping if bleeding occurs
TCAs - Selected Effects

- Sedation
- Orthostatic hypotension
  - Drop of systolic pressure greater than 10mm associated with dizziness
  - Risk of falls/fractures
- Anticholinergic
  - Amitriptyline and imipramine are the worst
  - Desipramine has the least effect
# Lithium – Drug Interactions

<table>
<thead>
<tr>
<th>DRUG</th>
<th>[Li]</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide (HCT)*</td>
<td>↑</td>
<td>-thiazides act in distal tubule</td>
</tr>
<tr>
<td>Loop (lasix)</td>
<td>↑↑</td>
<td>-loop - may not be significant</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>↑</td>
<td>-unknown mechanism</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-1-2 months after started</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>↑</td>
<td>-especially indomethacin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-unpredictable effect</td>
</tr>
</tbody>
</table>

*Pharmacokinetic interaction - interferes with clearance*
## Lithium – SEs and Toxicity

<table>
<thead>
<tr>
<th>System</th>
<th>Side effects</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuro</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Renal</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>CV</td>
<td>+</td>
<td>*</td>
</tr>
<tr>
<td>Endocrine</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Other</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

* Only if severe toxicity
Lithium Toxicity

**Acute**
- overdose
- other cause

- early vomiting
- profuse diarrhea

**Chronic**
- dehydration
- drug interaction
- infection

- progress more slowly
  +/− GI
  gradual progression
  of neuro s/s
Lithium Toxicity

Death due to complications of prolonged coma, resp failure
# Lithium Levels

<table>
<thead>
<tr>
<th>Group</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>QEII Lab</td>
<td>0.6-1.2</td>
</tr>
<tr>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td>Mania</td>
<td>0.8-1.1</td>
</tr>
<tr>
<td>Maintenance</td>
<td>0.8-1.1</td>
</tr>
<tr>
<td>Elderly</td>
<td>0.5-0.8</td>
</tr>
</tbody>
</table>

*Level depends on side effects*
Lithium Toxicity

- Lithium toxicity can lead to irreversible effects
  - Most patients completely resolve
  - Effects can last for months
    - Permanent if > 6 months
  - Cerebellar most common
  - Cognition
    - ↓STM, ↓comprehension, dementia
  - Choreoathetosis
  - EPSE
    - History of antipsychotic use
Lithium Toxicity –
Irreversible Cerebellar Effects

COMMON
- Dysarthria (common, most likely to improve)
- Truncal ataxia
- Gait ataxia
- Incoordination of limb movements

UNCOMMON
- Tremor in head, hands (intention tremor)
- Nystagmus
Benzodiazepines – Risks of Use

- BMJ Nov 05 (Glass et al)
  - They help with sleep, but compared to placebo:
    - 4.8X more adverse cognitive effects
    - 2.6X adverse psychomotor events (falls, dizziness, loss of balance)
    - 3.8X daytime fatigue

- Arch Int Med 2004;164:1567
  - Risk of hip # highest in first two weeks of use
    - 54% increase risk
    - Short half-life probably not safer
Benzodiazepines

- Do not use long-term (> 6 months)
- Recommended in seniors:
  - lorazepam, oxazepam, temazepam, clonazepam
    - Do not rely on liver metabolism
- Taper slowly
  - Over weeks to months
- If abrupt discontinuation:
  - Withdrawal
    - Tremor, tachycardia, delirium, seizures
  - Rebound anxiety
Stopping Benzodiazepines

- Consolidate to one benzodiazepine
  - Consider equivalent dose of clonazepam
- Can take months/years (outpatient)
- Patient involvement in drafting schedule
- Maintain same number of doses for as long as possible
- Can cut by larger amounts in the beginning
  - Up to one half of the dose depending on duration of benzo use
- Cut by smaller amounts later in taper
- Be prepared to hold taper during stress
References