Psychotropic Prescribing in the Elderly: Avoiding the pitfalls

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Prescription Drugs

- Elderly account for 1/3 of prescription drug use, while only 13% of the population
- One survey: Average of 5.7 prescription medicines per patient
- Average nursing home patient on 7 different medicines
Costs of Drugs

- Medicare A/B does not pay for prescription drugs
- Average prescription drug cost for an older person is $500/year, but highly variable
- Nonprescription drugs and herbals can be quite expensive
- Many Medicare Part D plans have severely limited drug coverage
- Drugs cost more in US than any other country
- New drugs cost more
Non-prescription Drugs

- Surveys indicate that elders take an average of 2-4 nonprescription drugs daily.
- Laxatives are used in about 1/3-1/2 of elders - many who are not constipated.
- Non-steroidal anti-inflammatory medicines, sedating antihistamines, sedatives, and H2 blockers are all available without a prescription, and all may cause major side effects.
Decrease in total body water (due to decrease in muscle mass) and increase in total body fat affects volume of distribution.

Water soluble drugs: lithium, aminoglycosides, alcohol, digoxin
  - Serum levels may go up due to decreased volume of distribution

Fat soluble: diazepam, thiopental, trazadone
  - Half life increased with increase in body fat
Pharmacokinetics

- Absorption: Not highly impacted by aging, unless hx of gastric surgeries/bypass.
- Variable changes in first pass metabolism due to variable decline in hepatic blood flow (elders may have less first pass effect than younger people, but extremely difficult to predict).
Pharmacokinetics and the Liver

- Acetylation and conjugation do not change appreciably with age
- Oxidative metabolism through cytochrome P450 system does decrease with aging, resulting in a decreased clearance of drugs
- Hepatic blood flow extremely variable
# Drugs with Cytochrome P450 Effects (partial)

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Inhibitors</th>
<th>Inducers</th>
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<tbody>
<tr>
<td>Allopurinol</td>
<td>Metronidazole</td>
<td>Barbiturates</td>
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<tr>
<td>Amiodorone</td>
<td>Quinolones</td>
<td>Carbamazepine</td>
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<td>Azole antifungals</td>
<td>Alprazolam</td>
<td>Phenytoin</td>
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<tr>
<td>Cimetidine</td>
<td>INH</td>
<td>Rifampin</td>
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<tr>
<td>SSRIs</td>
<td>Grapefruit juice</td>
<td>Tobacco</td>
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Pharmacokinetics: Excretion and Elimination

- GFR generally declines with aging, but is extremely variable
  - 30% have little change
  - 30% have moderate decrease
  - 30% have severe decrease
- Serum creatinine is an unreliable marker
- If accuracy needed, do Cr Cl
Pharmacodynamics: What the Drug does to the Body

- **Some effects are increased**
  - Alcohol causes increase in drowsiness and lateral sway in older people than younger people at same serum levels
  - Fentanyl, diazepam, morphine, theophylline

- **Some effects are decreased**
  - Diminished HR response to beta-blockers
About 15% of hospitalizations in the elderly are related to adverse drug reactions

The more medications a person is on, the higher the risk of drug-drug interactions or adverse drug reactions

The more medications a person is on, the higher the risk of non-adherence
Drug-Drug Interactions

- Common cause of ADEs in elderly
- Almost countless – good role for pharmacist and computer or on-line programs
- Some common examples
  - Statins and erythromycin and other antibiotics
  - TCAs and clonidine or type 1 Anti-arrhythmics
  - Warfarin and multiple drugs
  - ACE inhibitors increase hypoglycemic effect of sulfonylureas
Drug-disease Interactions

- Patient with PD have increased risk of drug-induced confusion
- NSAIDs (and COX-2’s) can exacerbate CHF
- Urinary retention in BPH patients on decongestants or anticholinergics
- Constipation worsened by calcium, anticholinergics, calcium channel blockers
- Neuroleptics and quinolones lower seizure thresholds
The “Prescribing Cascade”

- Common cause of polypharmacy in elderly
- Some common examples
  - NSAIDs -> HTN -> antihypertensive therapy
  - Metoclopramide -> Parkinsonism -> Sinemet
  - Calcium channel blockers -> edema -> furosemide
  - NSAIDs -> H2 blocker -> delirium -> Haldol
  - HCTZ -> gout -> NSAIDs -> 2nd antihypertensive
  - Sudafed or Benedryl -> urinary retention -> alpha blocker
  - Antipsychotic -> akathisia -> more meds
**NSAIDs**

- Acetaminophen as effective as NSAIDs in mild OA
- NSAIDs side effects
  - GI hemorrhage (less with COX-2)
  - Decline in GFR (COX-2 as well)
- Decreased effectiveness of diuretics, anti-hypertensive agents
- Indication should justify the increased toxicity of NSAIDs
Drugs and Cognitive Impairment

- Common cause of potentially reversible cognitive impairment
- Demented patients are particularly prone to delirium from drugs
- Anticholinergic drugs are common offenders (TCAs, Benadryl and other antihistamines, many others)
- Other offenders cimetidine, steroids, NSAIDs

Medical Letter 2000  Drug Safety 1999  Drugs and Aging 1999
Drugs and Falls

- Biggest risk drugs are long acting benzodiazepines and other sedative-hypnotics
- Both SSRIs and TCAs associated with increased risk of falling
- Beta blockers NOT associated with increased risk of falling in published literature
- Mild increase in fall risk from diuretics, type 1A anti-arrhythmics, and digoxin

Leipzig, JAGS
Drug-Food Interactions

● Interactions between drugs and food
  – warfarin and Vitamin K containing foods (remember green tea, as well)
  – Phenytoin & vitamin D metabolism
  – Methotrexate and folate metabolism

● Drug impact on appetite
  – Digoxin may cause anorexia
  – Acetylcholinesterase inhibitors (ie Aricept) decrease appetite
  – ACE inhibitors may alter taste
Drugs And Dosages to Avoid in Most Instances

- Meperidine (Demerol)
- Diphenhydramine (Benedryl)
- The most anticholinergic tricyclics: amitryptiline, doxepin, imipramine
- Long acting benzodiazepines such as diazepam
- Long acting NSAIDs such as piroxicam
- High dose thiazides (>25mg)
- Iron: 325 mg once daily is enough
Drug Problems in the Nursing Home

- In nursing homes, $1.33 spent on ADEs for every $1.00 spent on medications
- Estimated that RPh review saves more than $3.6 billion/year and that does not begin to touch problem!!
- Average nursing home patient takes > 6 drugs daily and 20% take more than 10.
- Reporting rate of ADE in nursing home is notoriously low!!
- Neuropsychiatry events such as confusion, over sedation, delirium, falls, and hemorrhage most common reported ADE’s in NH.
Anticipate Side Effect’s

- **Narcotics**
  - Begin lactulose or sorbitol and a stimulant laxative
  - Colace is NOT sufficient in most instances

- **Steroids**
  - Think about osteoporosis prevention
  - Remember steroid induced diabetes
  - Psychotic symptoms

- **Levothyroxine**
  - Calcium interferes with absorption of levothyroxine
Severe ADE’s In a Nursing Home

- Cardiovascular 36%
  - Digoxin 11%
  - Furosemide 7%
- Analgesics 13%
  - Ibuprofen 11%
- CNS 19%
  - Phenytoin 9%
- ASA 7%

Gerety JAGS 1993
Risk Factors For ADE’s

- 6 or more concurrent chronic conditions
- 12 or more doses of drugs / day
- 9 or more medications
- Prior adverse drug reaction
- Low body weight or body mass index
- Age 85 or older
- Estimated CrCl < 50 mL / min
Drug Discrepancies

- Difference between medical record and medication bottles in 76% of cases
  - 51% of time medication not recorded
  - 29% medication recorded that patient not taking
  - 20% dosage discrepancy

- Risk Factors: Age, number of medications
  - Bedell et al Arch Intern Med 160, 2000
<table>
<thead>
<tr>
<th></th>
<th>Discrepancy Present</th>
<th>Discrepancy Absent</th>
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<tr>
<td>Cardiologist</td>
<td>82%</td>
<td>18%</td>
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<tr>
<td>Internist</td>
<td>65%</td>
<td>35%</td>
<td>&lt;.001</td>
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<tr>
<td>&gt;1 MD</td>
<td>80%</td>
<td>56%</td>
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<tr>
<td># meds</td>
<td>7.0</td>
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High Risk Situations

- Patient seeing multiple providers
- Patient on multiple drugs
- Language barriers
- Patient lives alone and/or has cognitive impairment
- Discharge from hospital or any change in venue
Hospitalization: A High Risk Time

- At hospitalization:
- 40% of admission medications stopped
- 45% of discharge medications were started
- Serious prescribing problems in 22%
- Other prescribing problems in 66%
  - Beers JAGS 1989, Lipton Medical Care 1992
Nonadherence

- Lack of understanding of how to take
  - High risk times: Hospital discharge, new meds added, complex regimens
- Unable to take
- Conscious nonadherence
  - Side effects
  - Lack of understanding of benefits of drug
  - Financial
Complementary Therapies

Very commonly used in the elderly

Some common herbs and alternative therapies:

- “Anti-aging” DHEA, growth hormone
- Dementia Gingko biloba
- BPH Saw palmetto
- OA Chondroitin sulfate, glucosamine
- Depression St. John’s Wort, SAMe
Adulterants in Products

- California Department of Health Services, Food and Drug Branch
  - screened 250 Asian herbal products
  - collected from herbal stores in California
  - assayed products using gas chromatography, mass spectrometry, and atomic-absorption techniques
  - Ko, NEJM 1998; 339; 847

- 32% contained unlabeled medications, 14% mercury, 14% arsenic, 10% lead
Herbals and Supplements: Regulation

- Demonstration of safety is NOT required prior to marketing
- Manufacturing standards are not required
- Can have *health* claims, but not claims about treating, preventing, or curing
- For glucosamine/chondroitin, on third of combinations did not contain listed ingredient
- [www.consumerlabs.com](http://www.consumerlabs.com) has some drug information
Herbals and Supplements: Potential interactions with Rx Drugs

- SAMe may increase homocysteine levels
- St. John’s wort and Oral contraceptives
- Ginkgo may increase anticoagulant effects of ASA, warfarin, NSAIAAs, ticlopidine, and may interact with MAOIs
- Bottom line: Try to know what your patient is taking, and ask in a non-judgmental way
Antipsychotics in dementia

- **WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® CONSTA® (risperidone) is not approved for the treatment of patients with dementia-related psychosis.
From: Impact of FDA Black Box Advisory on Antipsychotic Medication Use


**Figure Legend:**

Joinpoint Regression Program analysis for atypical antipsychotics use among elderly patients with dementia. The data points represent patients 65 years and older with dementia (smoothed 6-month averages); the solid line, fitted joinpoint time series.
Figure Legend:
Covariate-Adjusted Survival Function by Days of Exposure in a Study of Mortality Risk Among Individual Antipsychotics
Many psychotropic drugs can delay cardiac repolarization and thereby prolong the rate-corrected QT interval (QTc).

A prolonged QTc often arouses concern in clinical practice, as it can be followed, in rare cases, by the life-threatening polymorphic ventricular tachyarrhythmia called torsade de pointes (TdP).
QT Prolongation Risk Factors

- Age over 65 years;
- Female sex (longer QTc interval than men and twice the risk of drug-induced TdP);
- Myocardial hypertrophy (e.g., in arterial hypertension);
- Congenital QT syndrome;
- Bradycardia (leads *per se* to QTc prolongation; sinus bradycardia; 2nd- and 3rd-degree atrioventricular block);
- Electrolyte disturbances (hypokalemia, hypomagnesemia);
- High plasma concentrations of the offending drug because of overdose, intoxication or inhibition of drug metabolism by concomitantly administered drugs and/or reduced drug clearance due to renal or hepatic insufficiency, or because of rapid infusion of the drug.
QT Prolongation by Drug

- **Highest Risk**
  - thioridazine, methadone, haloperidol (IV only)

- **Moderate Risk**
  - quetiapine, risperidone, ziprasidone, desipramine, nortryptiline, doxepin, imipramine, amitryptiline, lithium

- **Lower Risk**
  - citalopram, fluoxetine, olanzapine

- **No risk**
  - perphenazine, aripiprazole, bupropion, sertraline, paroxetine
Haloperidol markedly elevates the risk of TdP, mainly when high doses (>35 mg/d) are given intravenously; in one study, the observed probability of TdP under these circumstances was 11%.

Multiple psychoactive drugs that prolong the QTc only mildly or not at all when used individually can prolong it to a pathological extent and cause TdP when given in combination.

Most published cases of TdP associated with psychotropic drugs involved additional risk factors such as heart disease, age over 65 years, female sex, and/or hypokalemia.

When psychotropic drugs that elevate the risk of TdP are prescribed, regular monitoring of the ECG and the serum electrolytes is recommended, particularly for patients at high risk. The serum potassium concentration should lie in the high normal range.
Metabolic Syndrome – AHA Definition

- Elevated waist circumference:
  - Men — greater than 40 inches (102 cm)
  - Women — greater than 35 inches (88 cm)
- Elevated triglycerides: Equal to or greater than 150 mg/dL (1.7 mmol/L)
- Reduced HDL ("good") cholesterol:
  - Men — Less than 40 mg/dL (1.03 mmol/L)
  - Women — Less than 50 mg/dL (1.29 mmol/L)
- Elevated blood pressure: Equal to or greater than 130/85 mm Hg or use of medication for hypertension
- Elevated fasting glucose: Equal to or greater than 100 mg/dL (5.6 mmol/L) or use of medication for
Metabolic Syndrome and Antipsychotics

- **Highest Risk:**
  - olanzapine, clozapine
- **Moderate risk:**
  - risperidone, quetiapine, palperidone
- **Least risk:**
  - aripiprazole, ziprasidone, lurasidone
Other Psychotropics Associated with Significant Weight Gain

- Lithium
- Pregabalin
- Valproic acid
- Mirtazepine
- Amitryptiline
- Diphenhydramine
Newer drugs

- What is unique about this compound?
- What clinical data is available?
- How does it compare with traditional therapy?
- How expensive is it?
- Will third party payers cover this product?
- Does the potential advantage of this new drug justify the risk of using a new drug?
Specific Psychiatric Drug Concerns

- Citalopram (Celexa)
  - Maximum FDA dosage limited to 20mg/day in elderly
  - QT prolongation, esp. in combination w/ other meds

- Zolpidem (Ambien)
  - Maximum FDA dosage limited to 5mg/day (in women)
  - Blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving
Principles for Managing Drugs

- Complete drug history, including herbs and nonprescription drugs
- Avoid medications if benefit is marginal or if non-pharmacologic alternatives exist
- Consider the cost
- Start low, go slow, but get there!
- Keep regimen as simple as possible
- Write instructions out clearly
- Have patient bring in medications at each visit
Principles (continued)

- Consider medication box or “mediset”
- If things don’t make sense, consider a home visit
- Discontinue drugs when possible if benefit unclear or side effects could be due to drug
- Be cautious with newer drugs
- Consider if the benefit of the 7th or 8th drug is sufficient to justify the cost, increase in complexity of regimen, and risk of side effects