Geriatric Psychopharmacology: A Guide to Clinically Relevant Drug Interactions

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FDA FAER Database
Serious Adverse Event Reports (2006-2010)

Number of Reports

- 0
- 100000
- 200000
- 300000
- 400000
- 500000

2006 2007 2008 2009 2010

- 2006
- 2007
- 2008
- 2009
- 2010
In Disguise? Common Presentations of Drug Interactions

- **Serious Adverse Effects (SAEs):** sudden death, seizures, cardiac arrhythmias, serotonin syndrome, malignant hypertension, delirium
- **Poor tolerability** (drug “sensitivity”)
- **Lack of efficacy** (treatment resistance)
- **Symptoms that mimic other diseases**
- **Apparent worsening of the disease(s) being treated**
- **Withdrawal symptoms or “drug seeking behavior”**
Drug Interaction

• Presence of a co-prescribed drug (the Perpetrator) alters the nature, magnitude, or duration of effect of a given dose of another drug (the Victim)
Case Example: TS

- 65 year-old married man presenting for cognitive evaluation at his wife’s urging
- Past medical history
  - CAD, s/p cardiac arrest with anoxia (2001), CHF, heart transplant 2004
  - DM, OA, gout
- Drinks one glass of wine daily
- History of depression
- Family history: negative for dementia
- Retired, volunteers and does occasional handyman work
Case Example

• **Cognitive rehabilitation 2001-2002**
  – Improved, but some residual deficits in attention, executive functioning. Independent in ADLs.
  – Resumed driving in 2003
  – Stable until ~ 6 months prior to current evaluation

• **Recent changes**
  – Gradual worsening of memory
  – Brief confusional episodes while driving in familiar places
  – Forgets to take medications
  – Increasingly irritable and angry towards wife
  – Increased sleeplessness and c/o muscle pain and stiffness
  – Intentional weight loss (30lb over 6 months – BMI = 27.5)
Case Example

- **Physical & Neurologic Exam**
  - **Results**
    - Vital signs: WNL
    - Walks with slight limp, R knee OA, c/o pain
    - Reflexes diffusely decreased
  - **Mood**
    - Restricted affect, endorsed depressed mood, anhedonia, anxiety and “jumpiness”, irritability. No suicidal ideation
  - **Mental Status**
    - Oriented to person, time, and mostly to place (misstated floor of building)
    - Irritable, but cooperative
    - MMSE = 28/30; recall = 2/3; 1 error on “w-o-r-l-d”
    - 3MS=90/100
    - 2006: MMSE =29/30; 3MS:96/100
Medications

- Cyclosporine 175mg bid
- Diltiazem 300mg qd
- Metoprolol XL 50mg qd
- Lisinopril 5mg qd
- Furosemide 80mg qd
- KCL 40meq qd
- Glipizide 10mg qd
- Atorvastatin 20mg qd
- ASA 325mg qd
- Ibuprofen 200mg tid
- Lantus 70U qpm
- Famotidine 20mg qd
- FeS04 325mg bid
- Colace 100mg qd
- Trazodone 100mg qhs
- Zolpidem 10mg qhs prn sleep
- Venlafaxine XR 300mg qd
- Bupropion SR 200mg bid
- MTV qd
- St. Johns Wort tid
Differential Diagnosis: TS

- Mild Cognitive Impairment
- Infectious process
- Recurrent major depression
- Drug-induced cause
Drug Interaction Overview
Pharmacodynamic Interactions

- Related to the drug effects on the body
  - Hyponatremia associated with SSRIs
- Elderly experience increased pharmacodynamic effects at lower serum concentrations than younger peers
- Additive, synergistic, or antagonistic effects from co-administration of two or more drugs
  - Examples: anticholinergic toxicity, serotonin syndrome, seizures (tramadol + selective serotonin reuptake inhibitor (SSRI))

Serotonin Syndrome

• Excess stimulation of 5-HT receptors in CNS and periphery
  – Combination of 2 or more serotonergic drugs
  – SSRI overdose
  – With one serotonergic drug at therapeutic dose
  – Can occur weeks after discontinuation of fluoxetine

• Classic triad presentation:
  – Altered mental status
  – Autonomic hyperactivity/instability
  – Neuromuscular excitation

• Variation in severity of symptoms
  – Life-threatening to low grade (e.g. diarrhea and tremor)
  – Mild chronic form?

Post-Discontinuation Fluoxetine Levels in a 67 Year Old Female

Average total plasma levels achieved on 20 mg/day
Pharmacokinetic Interactions

- Related to the body’s effects on the drug
  - Alterations in the absorption, distribution, metabolism, or elimination of a drug
    - May be caused by one drug acting upon another
  - Alterations in drug metabolism and elimination
    - CYP450 interactions
      - Alterations in elimination
      - Protein binding interactions
      - CYP450 interactions
Hepatic Cytochrome Isoenzymes

• Superfamily of heme-containing enzymes essential to human survival
  – Metabolize endogenous products (e.g. steroids)
  – Metabolize drugs, foods, and toxins
• Cytochrome P450 (CYP) microsomal enzymes
  – CYP 450 Isoforms
  • CYP1A2
  • CYP3A
  • CYP2C9
  • CYP2C19
  • CYP2D6
CYP Genetic polymorphisms: Ethnobiological Considerations

- Norm is the “extensive metabolizer” (EM)
- Gene inactivation = “poor metabolizer” (PM)
- CYP2D6 linked more commonly to slow/poor metabolizers
  - 1% - Asians
    - Variant of gene (Intermediate PM) - 20% of Asians -- low level of functional CYP - “not quite poor metabolizer”
    - 2-5% - African Americans
    - 6-10% Caucasians
- Ultrarapid Metabolizers
  - 29% of East Africa population
- CYP2C9 and 19 also have genetic poor metabolizer variants that are clinically important
Potential Treatment Outcomes with CYP2D6 Polymorphisms

- Ultrarapid metabolisers:
  - Delayed therapeutic response or treatment resistance

- Poor metabolizers
  - Risk of drug toxicity even at standard doses - poor adherence, ADRs
  - May have treatment resistance to prodrugs that require activation

- Potent inhibitors can transform EM→PM; URM→EM or PM
Mortality Risk Associated with Antidepressant Use During Tamoxifen Treatment

Kelly CM, et al. BMJ. 2010 Feb 8;340
CYP 450 Substrates (AKA “Victims”)

• Predominant metabolism by a single isozyme
  – Few examples of clinically used drugs
    • Desipramine/CYP2D6

• Metabolism by multiple isozymes
  – Most drugs metabolized by more than one isozyme
    • Imipramine: CYP2D6, CYP1A2, CYP3A4, CYP2C19
  – **If co-administered with CYP450 inhibitor, some isozymes may “pick up slack” for inhibited isozyme**
Fluoxetine, Sertraline, & Desipramine
CYP 2D6 Interaction

CYP 450 Inhibitors (AKA Perpetrators)

• Drugs can inhibit a specific CYP even though they are not metabolized by that isozyme
  – Quinidine - most potent CYP2D6 inhibitor but metabolized primarily by CYP3A4
  – Bupropion is metabolized by CYP2B6 but is a potent inhibitor of CYP2D6

• Drugs which are metabolized by a specific CYP may also be an inducer at that CYP
  – Same drug can be an inhibitor and a substrate
    • Carbamazepine is metabolized by and inhibits CYP3A4
<table>
<thead>
<tr>
<th>CYP3A4</th>
<th>Substrates*</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>Lovastatin</td>
<td>Atorvastatin</td>
<td>Quetiapine</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Risperidone</td>
<td>Desipramine</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Clozapine</td>
<td>Olanzapine</td>
<td>Cyclobenzaprine</td>
</tr>
</tbody>
</table>

*Primary metabolic pathway
Antidepressant Treatment Within Complex Drug Regimens

Group A
Citalopram
Escitalopram
Mirtazapine
Venlafaxine
Desvenlafaxine

Group B
Bupropion
Duloxetine
Sertraline

Group C
Fluoxetine
Fluvoxamine
Nefazodone
Paroxetine

Clinically Significant Drug Interactions

Lowest Risk
Highest Risk
Medications: Initiation Date

- ASA (1995)
- MTV (1995)
- Famotidine (2001)
- Colace (2001)
- Lisinopril (2002)
- Furosemide (2002)
- Bupropion SR (2002)
- Cyclosporine (2004)
- Diltiazem (2004)
- Lantus (2006)
- FeS04 (2007)
- Venlafaxine XR (5/2008)
- Trazodone (6/2008)
- Atorvastatin (change from fluvastatin 7/2008)
- Ibuprofen 200mg tid (8/2008)
- St. Johns Wort tid (8/2008)
Medications: Initiation Date & Risk Profile

- ASA (1995)
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Imaging and Labs

- **Workup**
  - **Brain MRI:** No acute changes, mild to moderate cortical atrophy; mild increased T2 signal in periventricular white matter, unchanged from 2006
  - **Labs:** LFTs, B12, thyroid WNL,  lytes WNL
    - Glucose 185 (non-fasting); HgbA1C=8.0
    - Bun 59mg/dl; Cr 2.0 mg/dl Est Cl\textsubscript{Cr}=40ml/min
    - HGB/HCT 12.5g/dl/36.8%; albumin 3.2mg/dl
  - **Cyclosporine:** (trough-July 2006) 259ng/ml (range 100-200)
  - **EKG:** No significant change from 2008
Drug Interaction and Adverse Event Cascade

↑ Cyclosporine Level → Cognitive Changes → ↑ Depressive Symptoms → Add Venlafaxine

Change Statin (Atorvastatin) → Muscle Aches/Pain → Start Ibuprofen

Serotonin Syndrome?

↑ Sleep Disturbance → Add Trazodone

↑ ↑ Cognitive and Mood Symptoms → Start St. Johns Wort
Cyclosporine (CSA): Perpetrator 1

- Precipitating event: weight loss
- CSA has a narrow therapeutic window
- Dosed on weight: range 4-10mg/kg/day for heart transplant patients
- Neuropsychiatric adverse effects: cognitive impairment, depression, neurotoxicity, posterior reversible encephalopathy syndrome (PRES)
- Drug interactions: potent inhibitor of statin and many other drugs’ metabolism, CSA breakdown increased by CYP3A4 inducers
Bupropion: Perpetrator 2

• Several metabolites of bupropion are potent inhibitors of CYP450 2D6
  – Bupropion 300mg qd converted > 50% of CYP450 2D6 EM to PM in less than 3 weeks\(^1\)

St. John’s Wort: Perpetrator 3

- MANY drug-herb interactions
- Induces CYP3A4 and increases expression of P-glycoprotein
  - Hyperforin potency determines the magnitude of potential drug interactions
- Serotonin syndrome with SSRIs
  - Inhibits 5-HT reuptake

Multiple Victims

- CSA + atorvastatin → muscle pain & increased risk of rhabdomyolysis
- Zolpidem + trazodone → increased daytime somnolence
- CSA + ibuprofen → increased risk of nephrotoxicity
- Venlafaxine + Trazodone + St. Johns Wort → serotonin syndrome
- St. Johns Wort + CSA → increased risk of transplant rejection
Improving Outcomes of Drug Therapy
Proactively Identify High Risk Patients

- Advanced age
- > 6 active medical dx
- Prior ADR
- Low body weight
- Decreased renal function

- Narrow therapeutic index drugs
- Anticonvulsants, antipsychotics, hypnotics, narcotics, benzodiazepines, anticholinergics
- Polypharmacy

No One Can Remember All Drug Interactions

- Document all medications, including OTCs and herbals

- Working knowledge of CYP pathways of frequently prescribed drugs

- Use an *updated* CYP chart or drug reference
  - Clinical Pharmacology (www.gsm.com)
  - www.epocrates.com
  - www.drug-interactions.com (P450-mediated drug interactions)
Remember Drug Interaction Patterns

• Focus on the last med change
• Watch for new symptoms that occur in a time frame consistent with DDI “patterns”
• Early effects more likely when
  – Add drug to inhibitor at steady state
  – Add potent inhibitor to narrow therapeutic index drug at steady state
  – Remove a potent inhibitor with short $t_{1/2}$
AVOID Drug Interactions

**Allergies:** Are there any medicines we shouldn’t give you for any reason?

**Vitamins and Herbal:** Do you take any herbal medicines?

**OTC:** Do you take any over-the-counter medicine?

**Interactions:** Check for interactions

**Dependence:** Are there any medicines that you feel we should not stop? If so, why?
Summary

• Clinically significant drug interactions are associated with adverse outcomes in older adults

• Age related physiologic changes and multiple medications increase the risk of drug interactions and complicate recognition

• Multidisciplinary care teams can decrease the incidence of clinically significant drug interactions