Managing and Preventing Drug-Drug and Drug Disease Interactions

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Objectives

- Identify psychiatric medications that have a greater risk for drug-drug interactions
- Improve awareness of diseases and aging on psychiatric medications effectiveness
- Improve understanding of the mechanisms behind drug-drug interactions and ways to avoid them
Drug-Drug Interactions
Pharmacokinetics
Pharmacokinetic Processes

- Absorption
- Distribution
- Elimination
  - Hepatic metabolism
  - Renal clearance
Changes in Absorption

- Onset of action may be delayed
- Comparative steady state concentrations variable
- Impact of food, antacids, and anticholinergic drugs should be considered
  - Sertraline (Zoloft) bioavailability ≥ 40% with food
  - Ziprasidone (Geodon) bioavailability ≥ 100% with food
  - Lurasidone (Latuda) bioavailability ≥ 100% with food
  - Sibutramine (Meridia) bioavailability ≥ 150% with food
Changes in Distribution (e.g., Elderly)

- Decreased muscle mass
- Decreased total body water
- Increased total body fat
  - If fat-soluble med: ↑volume of distribution → ↑ half-life
  - Blood-brain barrier (changes with age)
    - Integrity of blood-brain barrier decreases with age and certain disease states (e.g., Alzheimer's dementia)
Donald

- Donald is a 60-year-old man with a h/o HTN currently controlled on Toprol XL (metoprolol) 100 mg/day (last BP=116/72; HR=64). Recently, he came in for his annual physical complaining of low energy, poor appetite, and general apathy. He was given a prescription for Prozac (fluoxetine) 20 mg QD.

- One week later, Donald returns to the clinic with marked dizziness and lightheadedness upon standing. His blood pressure is 90/60 with a heart rate of 53. An EKG shows second-degree AV block, which was not present in the past.

- What is wrong with Donald?
Cytochromes

- 85-90% of Rx drugs require oxidative metabolism
- Cytochromes are heme-containing enzymes found in the liver, GI tract, kidneys, lungs, and brain
- Responsible for phase I reactions (demethylation and hydroxylation)
- Cytochrome P450 refers to the wavelength of light absorbed by pigment in cytochromes
- CYP450 3A4 is most prevalent; >50% of all Rx drugs are metabolized via 3A4
Considerations in Pharmacokinetic Interactions

- Impact of each medication on enzyme (substrate, inhibitor, inducer)
- Relative potency of each medication on enzyme
- Relative concentration of medication in plasma
- Saturability of enzyme
- Presence of multiple metabolic pathways
- Presence of active metabolites
- Therapeutic index for medication (narrow vs. broad)
- Genetic predisposition of metabolic capacity (e.g., CYP2D6)
- Sensitivity to adverse effects (e.g., elderly)

Percentage of Poor Metabolizers (CYP450 2D6)

By Ethnicity

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Psychiatric Medications That Inhibit Cytochrome P450 Enzymes

- **Summary of inhibitors of cytochrome P450 pathways**
  - **CYP2C19:** fluox, fluvox, modafinil, oxcarbazepine, topiramate
    - substrates: citalopram, TCA, PPI
  - **CYP2D6:** fluox, parox, dulox, buprop > sert, cital, escital
    - substrates: β-blockers, narcotics (codeine, hydrocodone, tramadol), TCA
  - **CYP3A4:** norfluox, fluvox
    - substrates: CCB, estrogen, corticosteroids, statins (atorvastatin, lovastatin, simvastatin not pravastatin), protease inhibitors, alprazolam, triazolam, buspirone, sildenafil, ‘z’ drugs

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Comparison of Duloxetine, Escitalopram, and Sertraline Effects on Cytochrome P450 2D6 Function in Healthy Volunteers

- Single dose PK parameters of metoprolol measured after 17 days of treatment with antidepressant
- Antidepressant doses
  - Duloxetine (60 mg/d)
  - Escitalopram (20 mg/d)
  - Sertraline (100 mg/d)

Opioid Prodrugs

Several opioids are prodrugs that require metabolism by CYP2D6 to a more active opioid species

- Codeine → Morphine
- Hydrocodone → Hydromorphone
- Oxcodone → Oxmorhone
- Tramadol → O-desmethyltramadol

Clinical significance:

- Poor metabolizers (PM) of CYP2D6 or those receiving medications that inhibit CYP2D6 will have low circulating levels of active opioid metabolites and will exhibit minimal analgesic effects
- If previously stabilized on an opioid regimen, the introduction of a 2D6 inhibitor will result in loss of analgesia
Joan

- Joan is a 39-year-old mother of 2 toddlers who was diagnosed with stage IV breast cancer 2 years ago. She has successfully recovered from chemotherapy but was diagnosed with an acute episode of major depression 6 months ago. She had a partial response to sertraline 100 mg daily and achieved remission with the addition of bupropion SR 150 mg daily 2 months ago. She has noted that this augmentation strategy relieved the anorgasmia she had been experiencing.
- Today she calls your office after visiting her oncologist, who insists that she begin tamoxifen to prevent breast cancer recurrence. She wonders if you have any concerns about starting this medication in the context of her depression history.
- What do you tell her?
Antidepressant Interactions: Tamoxifen

- Tamoxifen is an antiestrogen medication commonly used for the prevention and treatment of ER-positive breast cancer; SSRIs/SNRIs are commonly used to treat hot flashes associated with tamoxifen treatment.
- Tamoxifen has much lower affinity for blocking estrogen receptors than its active metabolites (4-OH tamoxifen and endoxifen).
- CYP2D6 required for metabolism to both active metabolites:
  - Extensive metabolizers (EM) of CYP2D6 found to have 6-fold increase in 4 OH tamoxifen and 3-fold increase in endoxifen (vs poor metabolizers).
  - Dramatic decreases in endoxifen concentrations have been demonstrated in women who are EM BUT are also receiving either paroxetine or fluoxetine.
  - Poor metabolizers (PM) of CYP2D6 receiving tamoxifen found to have higher risk for recurrence and lower survival rates.
- Bottom line: CYP2D6 inhibitors will convert EMs to PMs, decreasing concentrations of tamoxifen metabolites and placing women with breast cancer at risk for relapse.

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Antidepressant Interactions: Warfarin

- Warfarin exists as a racemic mixture; S-warfarin is the active moiety and is metabolized via CYP2C9
- Fluoxetine, sertraline, paroxetine, citalopram, and escitalopram do NOT affect the pharmacokinetic disposition of warfarin
- Fluvoxamine inhibits CYP2C9 and \( \uparrow \) warfarin concentration by 65%
- Caution: many reports of \( \uparrow \) INR in warfarin patients after SSRI/SNRI started
  - Idiosyncratic reaction
  - Unknown mechanism
  - Recommendation: monitor INR frequently after initiation of SSRI/SNRI (in patients concurrently receiving warfarin)
Drug Interactions With Grapefruit

- Grapefruit juice (or sections) can inhibit CYP3A4 – CYP3A4 substrates include CCB, statins, BZD, buspirone
- Inhibition is rapid and may persist for up to 3 days
- MOA: inhibition is believed to be due to furanocoumarins
  - Furanocoumarins are also found in pomelos, Seville oranges, and limes
  - Effects of grapefruit juice on P-glycoprotein are not believed to be clinically significant
  - Grapefruit may significantly inhibit organic anion-transporting polypeptide (OATP)
- Doses used in PK grapefruit studies were usually large (e.g., 240 mL of double-strength juice)
Time Course of Recovery of Cytochrome P450 3A Function After Single Dose of Grapefruit Juice

- Methods – Volunteers (n=25) received 6-mg dose of midazolam
- 2 days later, volunteers received same dose 2 hours after 300 mL of single-strength grapefruit juice
- Results (hours after grapefruit administration)
  - Cmax
    - 2 hrs: 54%
    - 26 hrs: 25%
    - 50 hrs: 5%
    - 74 hrs: 0%
  - AUC
    - 2 hrs: 65%
    - 26 hrs: 21%
    - 50 hrs: 21%
    - 74 hrs: 6%
- Half-life of enzyme recovery estimated to be 23 hours

Medications with which Grapefruit Should not be Consumed

- Statins
- Antihistamines-Allegra
- Calcium Channel Blockers-nimodipine, felopdipine, nosolodipine, nicardipine, verapamil
- Psychiatric Medications-buspirone, triazolam, carbamazepine, diazepam, midazolam, sertraline
- Immune suppressants-cyclosporine, tacrilomus
- Pain Medications-methadone
- Impotecence Drugs- sildenafil
- HIV medications-saquinavir
- Antiarrythmics-amiodarone, disopyramide
### Foods and OTC Medications That Modulate CYP Enzymes

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrates</th>
<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Acetaminophen</td>
<td></td>
<td>Brussel Sprouts</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
<td></td>
<td>Char-grilled meats</td>
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<tr>
<td></td>
<td>Naproxen</td>
<td></td>
<td>Inhaled smoke</td>
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<tr>
<td></td>
<td>Theophylline</td>
<td></td>
<td>Broccoli</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Omeprazole</td>
</tr>
<tr>
<td>2C9</td>
<td>NSAIDs</td>
<td>Ketoconazole</td>
<td>Lansoprazole</td>
</tr>
<tr>
<td>2C19</td>
<td>Ketoconazole</td>
<td>Lansoprazole</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lansoprazole</td>
<td>Propranolol</td>
<td>Ketoconazole</td>
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<tr>
<td></td>
<td>Propranolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2D6</td>
<td>Codeine</td>
<td></td>
<td>Ranitidine</td>
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<tr>
<td></td>
<td>Dextromethorphan</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Propranololol</td>
<td></td>
<td>Ranitidine</td>
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<tr>
<td></td>
<td>Ranitidine</td>
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</tbody>
</table>

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<tr>
<th>CYP</th>
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<th>Inhibitors</th>
<th>Inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>2E1</td>
<td>Acetaminophen, Caffeine, Ethanol, Theophylline</td>
<td>Fluconazole, Grapefruit Juice, Itraconazole, Ketoconazole, Star Fruit</td>
<td>Ethanol</td>
</tr>
<tr>
<td>3A4/5/7</td>
<td>Antihistamines, Caffeine, Codeine, Cyclosporine, Dextromethorphan, Fluconazole, Grapefruit juice, Itraconazole, Lidocaine, Propranolol</td>
<td></td>
<td>St. John’s Wort</td>
</tr>
</tbody>
</table>
Potential Drug-Drug Interactions With Antipsychotic Medications

- Antipsychotic
  - Haloperidol
  - Perphenazine
  - Chlorpromazine
  - Clozapine
  - Risperidone
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Aripiprazole
  - Paliperidone
  - Asenapine
  - Iloperidone
  - Lurasidone

Primary Metabolic Pathway

- CYP1A2, 3A4
- CYP2D6
- CYP1A2, 3A4
- CYP1A2 > 3A4 3A4
- CYP2D6 >
- CYP1A2
- CYP3A4
- CYP3A4 (+ aldehyde oxidase)
- CYP2D6, 3A4
- CYP2D6 > 3A4
- CYP1A2 > 2D6
- CYP3A4 > 2D6
- CYP3A4

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# Potential Drug Interactions With Recreational Drugs

<table>
<thead>
<tr>
<th>Drug Metabolic Pathways of Substrates</th>
<th>Metabolic Pathways of Substrates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>CYP2D6 &gt; 3A4, 2C9</td>
</tr>
<tr>
<td>Cocaine</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>MDMA (ecstasy)</td>
<td>CYP2D6 &gt; 1A2, 2B6, 3A4</td>
</tr>
<tr>
<td>GHB</td>
<td>CYP3A4 (?)</td>
</tr>
<tr>
<td>LSD</td>
<td>Unknown</td>
</tr>
<tr>
<td>Marijuana</td>
<td>CYP3A4, CYP2C9</td>
</tr>
<tr>
<td>PCP</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Ketamine</td>
<td>CYP2B6</td>
</tr>
</tbody>
</table>

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Keith

- Keith is a 53-year-old recipient of a liver transplant who has been treated with Sandimmune (cyclosporine) for the past 3 months to prevent organ rejection. Keith has been depressed ever since he found out about his serious liver problems and has recently decided to self-treat his mood disorder with St. John's wort 300 mg PO TID.
- One month later, Keith comes in for his monthly check-up and blood draw. He is found to have subtherapeutic blood levels of cyclosporine and is beginning to show signs consistent with organ rejection.
- Why is Keith rejecting his new liver?
Psychiatric Medications That Induce Cytochrome P450 Enzymes

- Summary of inducers of cytochrome P450 pathways

- **CYP1A2**  
  - modafinil, anticonvulsants (e.g., CBZ, phenytoin, phenobarbital)  
  - substrates TCAs, haloperidol, clozapine, olanzapine, theophylline, ramelteon

- **CYP2C19**  
  - carbamazepine  
  - substrates citalopram, TCA, PPI

- **CYP2D6**  
  - none  
  - substrates beta-blockers, narcotics (codeine, hydrocodone, tramadol), TCAs

- **CYP3A4**  
  - St. John’s wort, modafinil, anticonvulsants (e.g., CBZ, phenytoin, phenobarbital, topiramate)  
  - substrates CCB, estrogens (OC), corticosteroids, statins, protease inhibitors, alprazolam, triazolam, buspirone, sildenafil, z-drugs (e.g., zolpidem)

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Pharmacokinetic Interactions With Anticonvulsants

- Carbamazepine (Tegretol) enzyme inducer (CYP1A2, 3A4)
- Phenytoin (Dilantin) enzyme inducer (CYP1A2, 3A4)
- Phenobarbital (Solfoton) enzyme inducer (CYP1A2, 3A4)
- Topiramate (Topamax) enzyme inducer (CYP3A4)
- Oxcarbazepine (Trileptal) enzyme inducer (CYP3A4)
- Valproic acid (Depakote) enzyme inhibitor (minor)
Drug Interactions With Lithium

- Lithium has a narrow therapeutic index (range = 0.6-1.2 mEq/L)
- Lithium cleared renally by glomerular filtration (no metabolism)
- Examples –
  - Diuretics (thiazides not loops) ~
    - Increase lithium concentrations by 20-30%
    - Lithium not affected by loop diuretics (furosemide)
  - NSAIDs (indomethacin, ibuprofen, naproxen) and COX-2 inhibitors
    - Increase lithium concentrations by 20-400%
    - Only significant if dosed around the clock
    - Lithium NOT affected by sulindac, ASA, APAP
  - ACE inhibitors • Increase lithium levels by 40% • Interaction is worse in the elderly (?)
P-glycoprotein (P-gp)

- Drug transporter present on the membrane of many cells
- Found in intestine, liver, kidney, and brain
- Genetic deficiency may lead to inability to transport drugs out of compartment
- Much similarity to cytochrome P450 3A4
- P-gp inhibitors: quinidine, clarithromycin, propranolol, progesterone, fluphenazine
- P-gp inducers: dexamethasone, diltiazem, erythromycin, phenothiazines, tamoxifen, verapamil, St. John's wort
- P-gp substrates: amitriptyline, nortriptyline, morphine, digoxin, protease inhibitors

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## Medication Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Medication</th>
<th>Effect on Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interactions involving TCAs</strong></td>
<td></td>
</tr>
<tr>
<td>Type 1a antiarrhythmics</td>
<td>Delay in cardiac conduction; heart block</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>Cause orthostatic hypotension</td>
</tr>
<tr>
<td>Sublingual nitrates</td>
<td>Dry mouth inhibits oral absorption</td>
</tr>
<tr>
<td>α-adrenergic blocking agents</td>
<td>Potentiate antihypertensive effect</td>
</tr>
</tbody>
</table>

| **Interactions involving serotonergic antidepressants (SNRI, SSRI, mirtazapine)** | |
| Lipophilic β-blockers | Increase blood levels due to decreased hepatic degradation |
| Digitoxin/digoxin | Transiently increase bioavailability due to displacement from protein binding sites |
| Platelet aggregation inhibitors | Increased risk of bleeding or bruising |

| **Interactions involving lithium** | |
| Diuretics that cause sodium loss | Increase blood lithium levels |
| Calcium Channel Blockers | Enhance lithium toxicity and bradycardia |
| ACE inhibitors | Enhance lithium toxicity |
| Methyldopa | Enhance lithium toxicity |

Drug-Drug Interactions
Pharmacodynamic
Clara

- Clara is an 88-year-old woman with a h/o BAD previously stabilized on Celexa (10 mg QD) and Depakote (250 mg TID). Other meds include Accupril (quinapril) 5 mg BID and ASA 80 mg/day (following MI 10 years ago). After suffering a fall at home, she was seen in the ER and given Ultram (tramadol) 50 mg/day for pain.

- On the second day, she developed nausea and reduced the dose of Ultram to 50 mg BID.

- On the third day, she developed rigidity, diaphoresis, vomiting, anxiety, and confusion. She refused to return to the ER but was advised over the phone by her internist to stop her Ultram. She was also given an Rx for Periactin (cyproheptadine) 4 mg TID.

- Her nausea resolved after 2 doses of Periactin, and her other symptoms resolved over the next 3 days.
Serootonin Syndrome

- Rare, idiosyncratic, sometimes fatal
- Mechanism: 5HT excess
- Symptoms (see Hunter criteria):
  - Mental status changes
  - Chills/sweating
  - Myoclonus
  - Autonomic instability (↑ or ↓ BP & HR)
  - Fever (malignant hyperthermia)
<table>
<thead>
<tr>
<th>Hunter Serotonin Toxicity Criteria: Decision Rules</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In the presence of a serotonergic agent:</strong></td>
</tr>
<tr>
<td>1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES</td>
</tr>
<tr>
<td>2. ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES</td>
</tr>
<tr>
<td>3. ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES</td>
</tr>
<tr>
<td>4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES</td>
</tr>
<tr>
<td>5. ELSE IF (hypertonic = yes) AND (temperature &gt; 38°C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] THEN serotonin toxicity = YES</td>
</tr>
<tr>
<td>6. ELSE serotonin toxicity = NO</td>
</tr>
</tbody>
</table>
Serotonin Syndrome (cont.)

Most Commonly Associated •
  • MAOI (Emsam, Nardil, Parnate)

Commonly Associated
  • SSRIs (all) • SNRI (both) • Clomipramine (Anafranil) •
    Sibutramine (Meridia) • 5HTP

Occasionally Associated
  • Tramadol (Ultram) • Meperidine (Demerol) • Linezolid
    (Zyvox) • Dextromethorphan (high-dose)

Rarely Associated • Sumatriptan (Imitrex) • St. John's wort •
  Trazodone (Desyrel)
Serotonin Syndrome: Clinical Management

- Recommend
  - 5-week washout after fluoxetine before MAOI
  - 2-week washout after another SSRI before MAOI
  - Other 5HT drugs: washout of 4-5 half-lives before MAOI
- If serotonin syndrome is suspected, discontinue all agents increasing or augmenting serotonin
- If severe symptoms or impaired consciousness, consider antidotes
  - Cyproheptadine (Periactin)
  - Methysergide (Sansert)
  - Propranolol (Inderal)
  - Memantine (Namenda)
  - Dantrolene (Dantrium)
SSRIs and QT Prolongation

- FDA warning (Aug 2011) that citalopram should not be prescribed in daily doses > 40mg (> 20mg if over 60yo) due to QTc prolongation
  - 20mg daily associated with QTc of 8.5 msec
  - 60mg daily associated with QTc of 18.5 msec

- FDA also warned that citalopram should be avoided in
  - 1) patients with pre-existing QT prolongation
  - 2) those who are 2C19 poor metabolizers
  - 3) those receiving CYP2C19 inhibitors (eg - cimetidine, omeprazole)

- QTc prolongation appears to be greater risk with citalopram than other SSRIs
  - Note: Retrospective review of overdoses reported that serious prolongation of QTc reported in 7.9% of citalopram cases (n=316) and 6.3% of escitalopram cases (n=63) [Yilmaz. Clin Toxicol 2010]

- Proposed mechanism: citalopram metabolite (DDCT) accumulates and blocks HERG channels. Both S and R enantiomers appear to have this effect.
Comparison of QTc Prolongation

Medications

- Thioridazine
- Ziprasidone
- Citalopram 60 mg
- Citalopram 20 mg
- Nortriptyline
- Desipramine
- Clarithromycin
- Erythromycin
- Cetirizine (OTC)

QTC Prolongation

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Miscellaneous Pharmacodynamic Interactions

- Clozapine (Clozaril) and carbamazepine (Tegretol)
  - Absolute contraindication: increased bone marrow suppression
- TCAs (all) and clonidine (Catapres)
  - Increased blood pressure
- Lithium (various) and verapamil (Calan)
  - Increased neurotoxicity
- SSRIs and NSAIDs (?)
  - Increased risk of GI bleeds

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Drug Disease Interactions
Psychoactive Medications and Medical Comorbidity

- **Diabetes**
  - TCAs, mirtazapine, paroxetine: weight gain
  - Clozapine, olanzapine, quetiapine, risperidone: weight gain
  - Lithium, valproic acid: weight gain
  - Norfluoxetine: inhibit metabolism of sulfonylureas

- **Cardiovascular disease** –
  - Fluoxetine, paroxetine, duloxetine, bupropion: inhibit metabolism of beta-blockers
  - Norfluoxetine: inhibit metabolism of calcium channel blockers, statins
  - TCAs, ziprasidone: increased risk of arrhythmia (?)

- **Hypertension**
  - Venlafaxine, duloxetine, bupropion: increased blood pressure
Psychoactive Medications and Medical Comorbidity (cont.)

- Epilepsy
  - Bupropion: contraindicated due to seizure risk
- Parkinson's disease
  - Risperidone, conventional antipsychotics: may worsen EPS
- Alzheimer's disease
  - Antipsychotics (all): increase CV events and death (?)
  - TCAs, paroxetine: additive anticholinergic effects
  - Clozapine, olanzapine: additive anticholinergic effects
Fritz

Fritz is a 72-year-old German immigrant brought into the clinic today by his daughter for his 3-month follow-up appointment following a mild to moderate left frontal stroke. Although he has relatively minor speech and motor deficits, Fritz's daughter is concerned that her father is much less active during the day and that he complains of a decreased appetite and poor sleep. He has also become more irritable and has shown little progress in physical therapy. Fritz admits that nothing interests him much anymore.
Patient Case: Fritz (cont.)

- SH: lives alone; wife passed away 13 years ago; denies tobacco; stopped ETOH 8 years ago
- FH: mother committed suicide; father died in WWII
- PsychHx: none
- PMH:
  - HTN x 2rs (Rx: verapamil 120mg/day, enalapril 20 mg/day)
  - Insomnia x 2 mos (Rx: triazolam 0.25 mg qHS)
  - Anxiety/irritability x 2 mos (Rx: alprazolam 1 mg TID prn)
  - Seasonal allergies (OTC Rx: Robitussin Max Strength 15 mL prn)
    - Contents: 1.4% ETOH, dextromethorphan 15 mg/5 mL
  - Hyperlipidemia x 8 yrs (Rx: lovastatin 40 mg/day)
- Impression: major depression (acute episode)
- Plan: start fluoxetine 10 mg po daily; RTC in 4 weeks
- Question: How many potential drug interactions can you find?
Fritz: Potential Interactions

- Pharmacokinetic (CYP2D6, 3A4 inhibition)
  - Fluoxetine – verapamil
  - Fluoxetine – lovastatin
  - Fluoxetine – triazolam
  - Fluoxetine – alprazolam
- Pharmacodynamic (5HT syndrome) – Fluoxetine – dextromethorphan
- Other antidepressant options?
Recommended References for Drug Interactions

- **Web sites**
  - [www.medicine.iupui.edu/flockhart/](http://www.medicine.iupui.edu/flockhart/) (comprehensive CYP450 table with references)
  - [www.efactsweb.com](http://www.efactsweb.com) (*Facts and Comparisons*)
  - [www.rxlist.com](http://www.rxlist.com) (consumer-oriented)
  - [www.naturalstandard.com](http://www.naturalstandard.com) (EBM review of herbs and supplements)

- **PDA software**
  - Lexi-Comp Drug Interactions
  - Epocrates Rx
  - Medical Letter's Handbook of Adverse Drug Interactions
  - Drug Therapeutic Screening System (DTSS) from Wolters Kluwer

- **Textbooks**
  - Managing Clinically Important Drug Interactions (*Hansten and Horn 2002*)
  - Drug Interaction Facts (*Tatro 2006*)
  - Psychotropic Drug Handbook (*Perry et al. 2007*)
Summary/Recommendations

- Obtain complete medication history from patient – Including OTC meds, herbs, and supplements
- Identify high-risk patients – Elderly, >2 Rx meds daily, organ damage/compromise
- Access up-to-date computer software or Web sites
- Consult with Drug Information Service or a trusted drug interaction expert
- Encourage your patients to use one pharmacy