Psychiatric Drug Interactions in Primary Care: When bad apples spoil the bushel!

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Objectives

- Identify mechanisms for drug-drug interactions encountered in patients being treated for psychiatric conditions in the context of primary care
- Examine patient cases highlighting the importance of psychiatric drug-drug interactions
- Determine clinical relevance and practice choosing alternative therapies based on patient characteristics when interactions are identified
- Compare and contrast resources for identification and interpretation of drug-drug interactions

Statistics in Psychiatry

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Annual Occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of visits to physician offices with mental disorders as the primary diagnosis</td>
<td>59.8 million</td>
</tr>
<tr>
<td>Number of hospital emergency department (ED) visits for mental disorders</td>
<td>5.7 million</td>
</tr>
<tr>
<td>Prescriptions written during physician office visits</td>
<td>3.7 billion</td>
</tr>
</tbody>
</table>

Drug Interaction Risk

Factors increasing the likelihood of interactions:
- Increased number of medications
- Increased number of medical conditions
- Age
- Genetics
- Duration of concomitant use

Rationale for Polypharmacy

1. To treat a concomitant disorder
2. To treat an acute phase of illness
3. To treat an adverse event
4. To boost or augment desired effect
5. To speed the onset of desired effect

Potential Misadventures

- Errors: Prescribing, Transcribing, Dispensing, Administration
- Interactions: Drug-Drug, Drug-Supplement, Drug-Disease State, Drug-Food
- Reactions: Medication Side Effect, Drug Allergies

Patient Worries in Primary Care

- Cost of Prescriptions upon discharge
- Being given the wrong drug
- Receiving too much medicine
- Receiving too little medicine
- Receiving an incorrect dose
- Receiving an incorrect medication
- Receiving a medicine that causes complications
- Cost of treatment
- Getting an infection in the office/hospital
- Being given drugs that interact
- Suffering pain
- Side effects from a medicine
- Being given the wrong drug
- Having enough information
- Complications of treatment

% of Patients

N = 1008

Pharmacodynamic Interactions

- Medications may exhibit similar pharmacological effects
  - Blood thinner + antiplatelet
    - Increased bleeding risk
  - Combination may potentiate specific therapeutic or adverse effects

Pharmacokinetic Interactions

- Use of activated charcoal following a tricyclic antidepressant overdose
- Depakote and phenytoin compete for protein binding sites
- Carbamazepine reduces effectiveness of oral contraceptives
- Penicillin + probenecid = Reduced rate of elimination for Penicillin
Goals for Case Selection

- Identify frequently encountered issues
- Avoid zebras
- Apply key concepts to global practice
- Improve patient care

The case of Ms. White...

- Ms. White is a 32 year old single, Caucasian female who is brought by her seven roommates
- CC: “My roommates think I’m too sleepy.”

Ms. White: Mental Status

- Appearance: Dress casual, grooming poor
- Attitude: Cooperative but unable to give logical information
- Psychomotor activity: Lethargic, tremulous
- Speech: Slow, slurred, dysarthria
- Orientation: + Person, + place, - time, - situation
- Mood & Affect: Irritable
- Thought process: Illogical, nonsensical
- Thought content: Delusions
- Attention: Short-span, distractible
Ms. White: Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lisinopril/HCTZ</td>
<td>20/25 mg PO</td>
<td>q am</td>
</tr>
<tr>
<td>Lithium</td>
<td>300 mg tab</td>
<td>300 mg PO q am, 600 mg PO q hs</td>
</tr>
<tr>
<td>Ortho-Tri-Cyclen</td>
<td>1 tab PO</td>
<td>q am</td>
</tr>
<tr>
<td>Naproxen</td>
<td>250 mg PO</td>
<td>q 6 h PRN pain &amp; inflammation</td>
</tr>
</tbody>
</table>

- Pertinent laboratory results
  - Serum lithium concentration = 2.21 mEq/L
  - Na = 131
  - SrCr = 1.4

Lithium

- Lithium is a salt and is undergoes nearly 100% renal elimination

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Lithium Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE Inhibitors &amp; ARBs</td>
<td>Increased</td>
</tr>
<tr>
<td>Thiazide Diuretics</td>
<td>Increased</td>
</tr>
<tr>
<td>Non-Steroidal Anti-inflammatory Drugs (NSAIDs)</td>
<td>Increased</td>
</tr>
<tr>
<td>Methylxanthines</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Lithium + NSAID

- NSAIDs increase lithium concentrations by decreasing renal clearance
- NSAIDs inhibit prostaglandin synthesis at the afferent arterioles of the nephron causing constriction
- Aspirin has a different mechanism with minimal impact on lithium concentration
Diuretic Sites of Action

Lithium + Diuretics

<table>
<thead>
<tr>
<th>Diuretic Class</th>
<th>Effect on Lithium (Serum Concentration)</th>
<th>Clinical Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazide</td>
<td>↑</td>
<td>+++</td>
</tr>
<tr>
<td>Loop</td>
<td>↓ or ↑</td>
<td>+</td>
</tr>
<tr>
<td>Osmotic</td>
<td>↓</td>
<td>++</td>
</tr>
<tr>
<td>K⁺ sparing</td>
<td>↑</td>
<td>+</td>
</tr>
</tbody>
</table>


Lithium + ACE Inhibitors

- ACE inhibitors can cause a clinically relevant increase in lithium concentrations
- Multiple mechanisms responsible
- Monitor serum lithium concentrations closely following induction of ACE inhibitor or change in dose

Lithium Toxicity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Level</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>1.5 – 2.0  mmol/L</td>
<td>Lethargy, drowsiness, coarse hand tremor, muscle weakness, nausea, vomiting, diarrhea</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.0 – 2.5  mmol/L</td>
<td>Confusion, nystagmus, ataxia, myoclonic twitches, ECG changes</td>
</tr>
<tr>
<td>Severe</td>
<td>&gt; 2.5 mmol/L</td>
<td>Impaired consciousness, increased deep tendon reflexes, seizures, syncope, renal insufficiency, coma, death</td>
</tr>
</tbody>
</table>

The case of Eve...

- Eve is a 64 year old married, female brought to the ED by her husband
- CC: "It started with a stupid fight over an apple. All this pain is making me irritable, and the medication doesn’t help!"

Eve: Mental Status

- Appearance: Dress casual, grooming fair
- Attitude: Cooperative
- Psychomotor activity: Retarded, slight B/L hand tremor
- Speech: Normal prosody but slowed rate
- Orientation: + Person, + place, + time, + situation
- Mood & Affect: Irritable, dysphoric, & anxious with congruent affect
- Thought process: Goal directed
  - Thought content: Hopeless, helpless
  - Attention: Short-span
### Eve: Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>80 mg</td>
<td>Q am</td>
</tr>
<tr>
<td>Hydrocodone/APAP</td>
<td>7.5/500 mg</td>
<td>TID</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>0.25 – 0.5 mg</td>
<td>BID</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg</td>
<td>Q am</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>10 mg</td>
<td>Q hs PRN</td>
</tr>
</tbody>
</table>

- History of early refills for pain medication
- Husband suspects she takes more hydrocodone/APAP than she is prescribed

### Cytochrome P450 Nomenclature

**Example for CYP2D6**

- CYP = cytochrome P450
- 2 = genetic family
- D = genetic sub-family
- 6 = specific gene

### Relative Importance of P450s

- **CYP2C19**
- **CYP2D6**
- **CYP2C19**
- **CYP2C19**

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Genetic Variability

- Patients expressing a polymorphism for a specific enzyme will metabolize drugs at different rates
- Approximately 7% of Caucasians are poor metabolizers of CYP2D6

Predicting Enzymatic Interactions

- Induction of liver enzymes by one drug may ↑ the rate of metabolism and thus ↓ the plasma concentration and therapeutic effect of another
- Inhibition of liver enzymes by one drug may ↓ the rate of metabolism and thus ↑ the plasma concentration and risk of toxicity of another

CYP2D6

- Substrate for...
  - Codeine
  - Many β-blockers
  - Many tricyclic antidepressants
- Inhibited by...
  - Fluoxetine
  - Paroxetine
  - Quinidine

### Opiate Metabolism

<table>
<thead>
<tr>
<th>Prodrug: A inactive drug that must be metabolized to active forms within the body</th>
</tr>
</thead>
<tbody>
<tr>
<td>codeine $\xrightarrow{\text{CYP2D6}}$ morphine</td>
</tr>
<tr>
<td>hydrocodone $\xrightarrow{\text{CYP2D6}}$ hydromorphone</td>
</tr>
<tr>
<td>oxycodone $\xrightarrow{\text{CYP2D6}}$ oxymorphone</td>
</tr>
</tbody>
</table>

CYP3A4

- Fluoxetine is a CYP3A4 inhibitor
- Alprazolam is metabolized by CYP3A4
- Concomitant use of fluoxetine and alprazolam can increase concentrations of alprazolam by up to 50%

The case of Mr. Appleseed

- Johnny Appleseed is a 52 year old Caucasian male brought to the ED by the Wichita Police Department
- CC: “As soon as my total body cleanse is done I will return to my true mission... planting trees.”
Mr. Appleseed: Mental Status

- Appearance: Dress casual, grooming poor
- Attitude: Attempts to be cooperative
- Psychomotor activity: Retarded, slowed gait
- Speech: Slow, slurred, word finding difficulties
- Orientation: + Person, + place, - time, - situation
- Mood & Affect: Irritable, sedated
- Thought process: Concrete, perseverative
- Thought content: Paranoia, somatic concerns
- Attention: Short-span, distractible, preoccupied

Mr. Appleseed: Medications

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>20 mg</td>
<td>Q hs</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20 mg</td>
<td>Q hs</td>
</tr>
<tr>
<td>Aspirin</td>
<td>81 mg</td>
<td>Q hs</td>
</tr>
<tr>
<td>Benztropine</td>
<td>2 mg</td>
<td>Q 4 h PRN stiffness</td>
</tr>
</tbody>
</table>

- Smoked 2 packs/day x 30 years
- Stopped smoking 4 days ago due to new beliefs about “body cleansing”

When the Smoke Cleared

- Aromatic hydrocarbons in cigarette smoke induce CYP1A2
- Olanzapine is a substrate for CYP1A2 (major) and CYP2D6 (minor)
- Plasma levels of olanzapine are lower in smokers than non-smokers
- Smoking cessation in patients on drugs that are CYP1A2 substrates can result in increased plasma levels
Interventions & Limitations

- System interventions
  - Electronic prescription entry and bar coding
  - Computerized medication records
  - Drug interaction software
- Limitations
  - Fragmented healthcare delivery and tracking of prescription filling

Online Drug Interaction Resources

<table>
<thead>
<tr>
<th>Cytochrome P450 Chart</th>
<th>Indiana University – School of Medicine</th>
<th><a href="https://drug-interactions.medicine.iu.edu/">https://drug-interactions.medicine.iu.edu/</a></th>
</tr>
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<tbody>
<tr>
<td>Herbal Interactions</td>
<td><a href="http://personalhealthzone.com/herbsafety">http://personalhealthzone.com/herbsafety</a></td>
<td></td>
</tr>
<tr>
<td>HIV Drug Interactions</td>
<td><a href="http://www.hiv-druginteractions.org">www.hiv-druginteractions.org</a></td>
<td></td>
</tr>
</tbody>
</table>

Words of Wisdom

The rotten apple spoils his companion.

- Benjamin Franklin