

**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

Indicator	Annual Occurrence
Number of visits to physician offices with mental disorders as the primary diagnosis	59.8 million
Number of hospital emergency department (ED) visits for mental disorders	5.7 million
Prescriptions written during physician office visits	3.7 billion



Centers for Disease Control and Prevention: Fact facts, mental health. Source: National Ambulatory Medicine Care Survey 2015

Drug Interaction Risk

15% 40% 80%

15 percent for two medications 40 percent for five medications 80 percent for seven medications

Factors increasing the likelihood of interactions:

- Increased number of medications
- Increased number of medical conditions
- Age
- Genetics
- Duration of concomitant use

<https://www.drugwatch.com/health/drug-interactions/>

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

Preskorn SH, Lacey R. Polypharmacy: When is it rational? J Psychiatr Pract 2007;13(2):97-105.

Potential Misadventures

Errors	<ul style="list-style-type: none"> • Prescribing • Transcribing • Dispensing • Administration
Interactions	<ul style="list-style-type: none"> • Drug-Drug • Drug-Supplement • Drug-Disease State • Drug-Food
Reactions	<ul style="list-style-type: none"> • Medication Side Effect • Drug Allergies

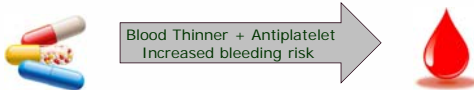
Bertolacci C, Spolding B, Cahaly E, et al. Mechanisms underpinning the polypharmacy effects of medications in psychiatry. International Journal of Neuropsychopharmacology. 2018;21(6):82-91.

Patient Worries in Primary Care

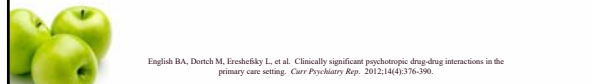


Pharmacodynamic Interactions

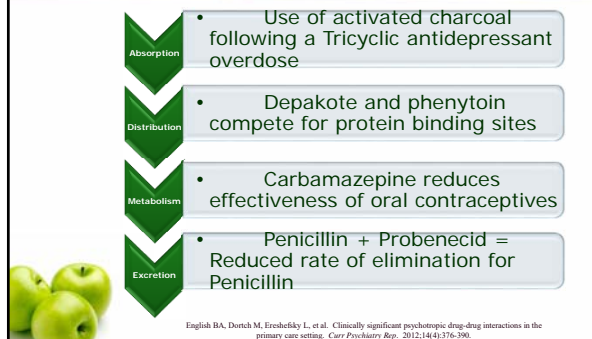
- Medications may exhibit similar pharmacological effects



- Combination may potentiate specific therapeutic or adverse effects



Pharmacokinetic Interactions



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

Medication	Dose	Frequency
Lisinopril/HCTZ	20/25 mg	PO q am
Lithium	300 mg tab	300 mg PO q am, 600 mg PO q hs
Ortho-Tri-Cyclen	1 tab	PO q am
Naproxen	250 mg	PO q 6 h PRN pain & inflammation

- 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

Medication Class	Lithium Concentration
ACE Inhibitors & ARBs	Increased
Thiazide Diuretics	Increased
Non-Steroidal Anti-inflammatory Drugs (NSAIDs)	Increased
Methylxanthines	Decreased



Finley P. Drug Interactions with Lithium: An Update. *Clinical Pharmacokinetics*. 2016;55(8):925-941.

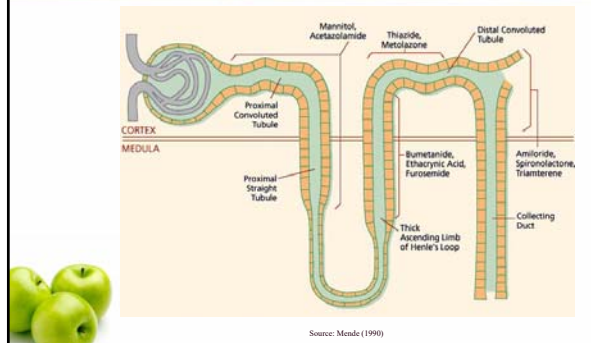
Lithium + NSAID

- 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



Herb E, Pinto A, Moore P. Adverse drug interactions involving common prescription and over-the-counter analgesic agents. *Clinical Therapeutics*. 2007;29(11):2477-2497.

Diuretic Sites of Action



Lithium + Diuretics

Diuretic Class	Effect on Lithium (Serum Concentration)	Clinical Relevance
Thiazide	↑	+++
Loop	↓ or ↑	+
Osmotic	↓	++
K ⁺ sparing	↑	+



Finley P. Drug Interactions with Lithium: An Update. *Clinical Pharmacokinetics*. 2016;55(8):925-941.

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



Finley P. Drug Interactions with Lithium: An Update. *Clinical Pharmacokinetics*. 2016;55(8):925-941.

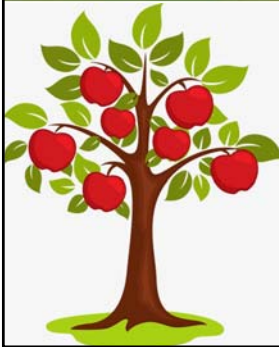
Lithium Toxicity

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



Grandjean E, Aubry J. Lithium: updated human knowledge using an evidence-based approach part II: clinical pharmacology and therapeutic monitoring. *CNS Drugs*. 2009;23(4):331-349.

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

Medication	Dose	Frequency
Fluoxetine	80 mg	Q am
Hydrocodone/APAP	7.5/500 mg	TID
Alprazolam	0.25 – 0.5 mg	BID
Omeprazole	20 mg	Q am
Zolpidem	10 mg	Q hs PRN

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



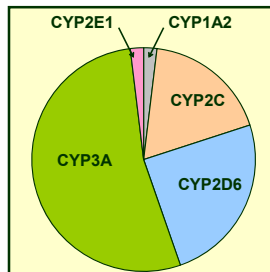
Cytochrome P450 Nomenclature

Example for CYP2D6

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



Relative Importance of P450s



Huang S, Strong J, Zhang. Update on CYP enzymes, transporters and the guidance process. *J Clin Pharmacol*. 2008;48:662-670.



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



Larrott G. The effects of the genetic absence and inhibition of CYP2D6 on the metabolism of codeine and its derivatives, hydrocodone and oxycodone. *Anesth Prog* 1999;45:154-156.

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



Chadwick B, Waller DG, Edwards JG. Potentially hazardous drug interactions with psychotropics. *Advances in Psychiatric Treatment* 2005;11:440-449.

CYP2D6


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



Opiate Metabolism

codeine	→ CYP2D6	morphine
hydrocodone	→ CYP2D6	hydromorphone
oxycodone	→ CYP2D6	oxymorphone


Prodrug: A inactive drug that must be metabolized to active forms within the body



Larocott G. The effects of the genetic absence and inhibition of CYP2D6 on the metabolism of codeine and its derivatives, hydrocodone and oxycodone. *Anesth Analg* 1999;45:154-156.



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

Medication	Dose	Frequency
Olanzapine	20 mg	Q hs
Simvastatin	20 mg	Q hs
Aspirin	81 mg	Q hs
Benzotropine	2 mg	Q 4 h PRN stiffness



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



Zevin S, Benowitz NL. Drug interactions with tobacco smoking. Clin Pharmacokinet 1999;36(6):425-438.

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



Zevin S, Benowitz NL. Drug interactions with tobacco smoking. Clin Pharmacokinet 1999;36(6):425-438.

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

Cytochrome P450 Chart	Indiana University – School of Medicine https://drug-interactions.medicine.iu.edu/
Herbal Interactions	http://personalhealthzone.com/herbsafety
HIV Drug Interactions	www.hiv-druginteractions.org



Last Accessed September 2018

Words of Wisdom

The rotten apple spoils his companion.

-Benjamin Franklin



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