Managing Drug-Drug Interactions (DDIs) in Psychopharmacology

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Declarations

- Dr. Teter has **no relevant financial relationships** with any commercial interests.

Learning Objectives

At the end of this program, participants should be able to:

1. Provide the definition and potential clinical presentation of drug-drug interactions (DDIs).
2. Categorize DDIs based on mechanism (e.g., pharmacodynamic, pharmacokinetic).
3. Choose from a variety of DDI resources that are available for purchase or free online.
Case Study

- MW is a 52 year old male with a long-standing history of major depressive disorder, hypertension, and asthma. MW was recently admitted to the hospital with difficulty breathing and extreme fatigue. He is receiving multiple medications that were recently adjusted as an outpatient.

- As a clinician, do you know of any publicly available, trusted, drug-interaction tools that will help you search for possible drug interactions as the cause of MW's symptoms?

DDI Definition

- DDI: the presence of a co-prescribed drug alters the nature, magnitude, or duration of the effect of a given dose of another drug
  - Nature: effect is qualitatively different
  - Magnitude: more or less same effect
  - Duration: shorter or longer same effect

Adapted from: Preskorn & Flockhart (2006)

DDI Clinical Presentation

Many possibilities:
- Adverse events (e.g., serotonin syndrome)
- Poor tolerability (e.g., patient “sensitive” to drug effect)
- Lack of efficacy (e.g., patient “resistant” to drug effect)
- Symptoms mimic new disease
- Apparent worsening of disease being treated
- Withdrawal symptoms

Adapted from: Preskorn & Flockhart (2006)
Identifying DDIs in Psychopharmacology

- Psychotropic medications act on the brain
  - Identification of DDIs associated with psychiatric medications may be difficult
  - May be interpreted as worsening of patient’s condition
- Presenting symptoms of psychotropic DDIs may include changes in any of the following:
  - Changes in mentation
  - Reality testing
  - Emotional control
  - Interpersonal relationships
  - Memory function

DDI Variables (likelihood and severity)

- **Patient-related**
  - Age (2 distinct reasons)
  - Patients ‘accumulate’ medications (#)
  - Altered PK/PD
  - ‘Metabolizer’ status
  - Irrespective of age
- **Medication-related**
  - Polypharmacy
  - Psychiatric medications ‘signal’ for polypharmacy
  - Number of alternate CYP pathways
  - Therapeutic index (LD50/ED50)
  - Narrow (e.g., lithium)
  - Wide (e.g., venlafaxine)

Categories of DDIs

- **Pharmacodynamic (PD)**
  - Medications act on the same receptors
  - Antagonistic or synergistic effects on target organ(s)
  - Easier to predict based upon pharmacology
- **Pharmacokinetic (PK)**
  - Medication alters the absorption, distribution, metabolism, or elimination (ADME) of another medication
  - Increase or decrease in medication blood levels
Pharmacokinetics (ADME)

- Absorption DDIs
  - Not common in psychiatry

- Distribution DDIs
  - Not common in psychiatry
  - Aspirin: ↑ free valproate

- Metabolism
  - Most drug interactions occur via this mechanism!
  - See following slides (induction vs. inhibition)
  - Phase I vs. Phase II metabolism

- Elimination
  - Example: NSAIDs ↑ lithium levels

Metabolism

INDUCTION VS. INHIBITION

Cytochrome P450 (Phase I)
Glucuronidation (Phase II)

Time course

- Inhibition (varies)
  - Competitive inhibition
  - Onset and offset: depend on half-life of inhibitor

- Induction (days)
  - Onset: inducer accumulates (depends on half-life) and enzyme is produced
  - Offset: depends on both half-life of inducer and degradation of enzyme
Metabolism

- **Cytochrome P450**
  - Key enzyme system for metabolizing medications
  - Individual enzymes:
    - CYP1A2
    - CYP2C9
    - CYP2C19
    - CYP2D6
    - CYP3A4

- Genetic variability (polymorphisms)
  - CYP2D6

http://www.pharmgkb.org/index.jsp
Clinically Relevant PK DDIs

- **Induction**
  - CYP1A2
    - Cigarette smoking: ↓ clozapine, olanzapine
  - CYP3A4
    - St. John’s Wort: ↓ ethinyl estradiol
    - Carbamazepine: ↓ carbamazepine (auto-induction)

- **Inhibition**
  - Glucuronidation
    - Valproic acid: ↑ lamotrigine, ↓ risk of serious rash
    - Example of potentially fatal DDI
  - CYP1A2
    - Fluvoxamine: ↑ clozapine levels, ↓ toxicity
    - Also used as ‘augmentation strategy’
  - CYP2D6
    - Fluoxetine: ↑ risperidone active moiety, ↑ EPS
    - Example of DDI leading to non-adherence
  - CYP3A4
    - HIV medications: ↑ buprenorphine, ↓ side effects
    - Example of medications commonly used in same patient population

Clinically Relevant PD DDIs

- **Serotonin syndrome**
  - SSRIs
  - MAOIs
  - SNRIs
  - Linezolid
  - “Triptans” (migraine)
  - Sibutramine

- **Hypertensive crisis**
  - MAOIs + long list of other medications and food/drink
DDI Resources

- Software packages (examples)
  - Lexi-Comp Online, Lexi-Comp, Inc.
    - Available at: http://online.lexi.com
  - MICROMEDEX Healthcare Series
    - Available at: https://www.thomsonhc.com
  - Facts & Comparisons
    - Available at: http://www.factsandcomparisons.com/

- Websites (examples)
  - http://medicine.iupui.edu/flockhart/

Patient Case

CC: Patient is a 60 year old white male with bipolar disorder who presents to the adult inpatient psychiatric unit with a three week history of depressive symptoms.

HPI: The patient endorsed increasing sadness and extreme fatigue over the past few weeks. Particularly bothersome is his inability to “think clearly” and his difficulty playing cards, which is one of his favorite hobbies. The patient feels these symptoms developed after his olanzapine dose was increased, which was around the same time the symptoms started to appear.

PSYCHIATRIC HISTORY: Patient has long-standing history of BPAD with at least three inpatient hospitalizations, the last occurring in 2002. Patient has history of responding to atypical antipsychotics for his bipolar disorder and is known to be very adherent to his prescribed regimen. He has been relatively stable besides a recent increase in his olanzapine dose following a hypomanic episode.

PMH: Seasonal allergies

SH: (+) tobacco, patient reports that he recently quit smoking
(-) ETOH/drugs

FAMILY HISTORY: None
Patient Case

MPTA:
- Olanzapine 40 mg OD (since 2002, dose recently increased 2009)
- Amitriptyline 50 mg CHS (since 1994)
- Flovent 1 PUFF BID (since 2004)
- Diphenhydramine 50 mg OD (recently started by patient)
- Nicotine patch (recently started by patient)

PE:
- BP: 140/87  HR: 78  RR: 18  T: 98.4°F
- PERRL (although pupils mildly dilated), EOMI, heart normal rate and rhythm, cranial nerves II-XII intact.

Appearance: well-dressed, well-groomed male with flat affect and cooperative.

MMSE: score = 18

LABS: WNL

Is there a potential DDI taking place in this patient?

At least two possibilities:

1. ANTICHOLINERGIC LOAD
2. Lack of tobacco CYP1A2 induction

Is there a free, publicly available website that you could use to examine this medication regimen in more detail?

ANSWER: http://medicine.iupui.edu/clinpharm/DDIs/
Strategies to ↓ DDIs

- Personal formulary
  - Generic and brand names
  - Pharmacokinetics
  - Half-life
  - Pharmacodynamics
  - MOA
  - Adverse effects
  - Potential DDIs

Adapted from: Preskorn & Flockhart (2006)
Strategies to ↓ DDIs

- AVOID algorithm
  - Allergies
  - Vitamins & Herbs
  - OTC
  - Interactions search (software, websites)
  - Dependence

Adapted from: Preskorn & Flockhart (2006)

U.S. Food and Drug Administration

What is MedWatch?

FSA has the responsibility for assuring the safety and efficacy of all regulated/unregulated medical products.

MedWatch: The FDA Safety Information and Adverse Event Reporting Program serves both healthcare professionals and the medical products industry. It provides important and timely clinical information about safety issues involving medical products, including prescription and over-the-counter drugs, biologicals, medical and radiological devices, and some nutritional products (i.e., dietary foods, dietary supplements, and infant formulas).

Medical product safety alerts, recalls, withdrawals, and important labeling changes that may affect the health of all Americans are quickly disseminated to the medical community and the general public via its website and the MedWatch E-mail. Select Safety Information to see reports, safety bulletins, and labeling changes posted to the website since 1999. MedWatch allows healthcare professionals and consumers to report serious problems that they suspect are associated with the drugs and medical devices they prescribe, dispense, or use. Reporting can be done online, by phone, or by submitting the MedWatch 350h form by mail or fax. Select How to Report for more details.

DDI vs. X-Taper

- General rule: Start low and go slow
- Half-life rule: 3-5 \( t_{1/2} \) to reach steady state
  - One half-life to reach 50%
  - Two half-lives to reach 75%
  - Three half-lives to reach 87.5%
  - Four half-lives to reach 93.75%
  - Five half-lives to reach >95.00%
Conclusions

- Keep resources handy and use them!
  - PDA software and online resources can be very helpful
- Logic over memorization
- Therapeutic monitoring
- Be familiar with…
  - Your commonly prescribed medications
  - Narrow therapeutic index medications
- Patients can help!
  - Filling their RXs at one pharmacy
  - Current and complete list of medications, OTC, herbals, etc.