Drug Interactions

Update on Mechanisms and Clinical Relevance

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Drug Interactions

• Greater acceptance of polypharmacy in psychiatry and more vigorous treatment of psychiatric problems among medically ill and elderly
• Widespread use of dietary health supplements and other OTCs along with prescription drugs
• Advances in pharmacokinetics and knowledge concerning molecular targets of drug action
• Increased focus on preventable drug errors in populations
• Increased application of informatics (state-of-the-art computational and statistical methods) to large population databases to predict drug-drug interactions
• Development of information technologies (e.g., Clinical Decision Support Software) to reduce adverse drug interactions in clinical settings
What are Drug-Drug Interactions?
Alterations in Drug Plasma Levels, Tissue Concentrations, and/or Drug Effects

• Associated with the use of two or more agents (prescribed, over-the-counter, and/or recreational)

• In close temporal proximity (recent as well as concurrent use)
Potential Consequences of Drug Interactions

• **Serious adverse events:**
  - Delirium, cardiac arrhythmias, GI/CNS bleeding, falls, seizures, serotonin syndrome, hypertensive crises
  - Serious adverse events related to drug-drug interactions account for up to 2-5% of all hospital admissions for patients > 55 years old

• **Unexpectedly high or low serum drug levels:**

• **Side effects:**
  - Side effects if levels or effects are enhanced;
    - poor tolerability may jeopardize adherence
  - Withdrawal/discontinuation effects if levels fall as a result of drug interactions
  - Side effects (e.g., headaches, nausea, dizziness) may lead to misdiagnosis or unnecessary medical work-ups

• **Reduced efficacy:**
  - Non-response to usual doses
  - Loss of previous response/relapse
Case 1

27 yo with migraine, on propranolol, admitted with psychotic depression and treated with duloxetine (Cymbalta), bupropion (Wellbutrin) and risperidone (Risperdal).

Now c/o lightheadedness. Worse still, migraines are uncharacteristically refractory to acetaminophen with codeine.

He suspects foul play.
Case 2

49 yo with schizoaffective disorder receives levomilnacipran (Fetzima) from the covering MD. She returns with confusion, diarrhea, fever and brisk reflexes.

Current meds are: aripiprazole (Abilify), lamotrigene (Lamictal), lithium and hydrochlorothiazide.

Multiple treatment trials over the past year include ziprasidone (Geodon), desvenlafaxine (Pristiq), mirtazapine (Remeron), selegiline (Emsam)
32 yo with OCD, bipolar disorder, asthma, and GERD presents with grand mal sz days after switching from clomipramine (Anafranil) to fluvoxamine (Luvox).

Other meds: clozapine, lithium, theophylline, omeprazole, and prednisone taper.
Case 4

Agitated and incoherent 67 yo with schizophrenia brought in by police. Meds: olanzapine (Zyprexa), mirtazapine (Remeron), and diphenhydramine (Benadryl).

Doxepin (Sinequan) recently added for atopic dermatitis.
Case 5

52 year old with panic disorder, refractory depression, and chronic insomnia, presents with dizziness, drowsiness, nausea and slurred speech.

Meds: alprazolam (Xanax), eszopiclone (Lunesta), suvorexant (Belsomra), quetiapine (Seroquel) and vilazodone (Viibryd). She was recently started on clarithromycin (Biaxin) for sinusitis. She’s trying to stay well-hydrated.
Case 6

37 yo with MDD, GAD, atypical facial pain. Meds: escitalopram *(Lexapro)*, clonazepam, and an OCP.

Recently switched from gabapentin (Neurontin) to carbamazepine *(Tegretol)*. Modafinil *(Provigil)* added to offset sedation. Offered *St. John’s Wort* by a friend.

Cancels appt this a.m. citing nausea and malaise.
Drug Interaction Errors

- **Type 1**
  - Failure to anticipate
  - Failure to recognize

- **Type 2**
  - Phobic avoidance
  - Therapeutic paralysis
What Next ?

- General precepts
- Classification and mechanisms
- Drug interactions that are worth knowing
- Case vignettes revisited
Interactions are ubiquitous but...

- Serious adverse interactions are uncommon
- Absolute contra-indications are rare
In addition to drug interactions, multiple factors influence inter-individual variability in response to drugs including…

- Treatment adherence
- Age
- Gender
- Nutritional status
- Smoking/ETOH
- Disease states
- Genetic polymorphisms
Consider the True Weight of Evidence

- Inference is often used to fill in gaps in data.
- As of 2006, there were over 520 quadrillion possible combinations of up to five drugs on a patient’s drug regimen yet only 700 drug interactions studies in the literature...
- More studies exist in 2015 but also there are more drugs and possible drug combinations.
- Virtually all published studies are concerned with the “simplest” case (Drug B’s impact on Drug A’s levels or effects) rather than with the more complex, multiple polypharmacy used in real-world clinical settings.

Preskorn and Flockhart, Primary Psychiatry 13:35-64, 2006
Drug interaction warnings are often based on extrapolation from in vitro or animal studies or based on drug interactions in humans involving related but different drugs

- In vitro studies
- Non-human animal studies
- Controlled human pharmacokinetic studies
- Case reports
- Post-marketing surveillance
  - FDA Adverse Event Reporting System (AERS)
  - Health care system databases
- Epidemiological studies
Consider the Clinical Context

Higher level of concern about potential drug interactions should exist whenever:

- Using drugs with a *narrow therapeutic window* (e.g., cyclosporine), *low therapeutic index* (e.g., digoxin), potential for *catastrophic side-effects* (e.g., MAOIs)
- Evaluating patients who present with perplexing clinical presentations, outcomes, or levels
- Treating “brittle” patient populations for whom even small variations in drug effects/levels may pose hazards
- Undertaking (worthy) efforts to simplify (“deconstruct”) a complex regimen
Focus on the most important (i.e., common and/or potentially catastrophic) interactions

Resources are available for the more esoteric interactions:
Website examples:
•  [http://medicine.iupui.edu/flockhart](http://medicine.iupui.edu/flockhart) (updated information on P450 Cytochrome substrates, inhibitors and inducers)
•  [http://www.drugs.com](http://www.drugs.com) (enter under health professionals; user friendly, can enter multiple medications and gives brief blurb and list of other medications that interact with those entered)
•  [http://naturaldatabase.therapeuticresearch.com](http://naturaldatabase.therapeuticresearch.com) (useful info on herbal and non-herbal dietary health supplements including drug interaction checker function)
•  [http://www.hiv-druginteractions.org](http://www.hiv-druginteractions.org) (HIV drug interactions)

Software packages for electronic devices:
•  Published literature (cf. bibliography)
•  Publications (e.g. PDR, Medical Letter)

Clinical Decision Support Systems built into Computerized Physician Order Entry (CPOE) systems and Electronic Health Records (EHR) are increasingly standard in clinical settings
Interactions can be leveraged for benefit

- **Management of overdose**
  - e.g. naloxone (opiates); flumazenil (benzodiazepines); acidifying urine (amphetamines, cocaine)

- **Treatment of side-effects**
  - e.g. anticholinergic rx for EPS; 5HT-3 blockade of nausea on SSRI or SNRIs

- **Augmentation of response**
  - e.g. mirtazapine+venlafaxine

- **Boosting of drug levels/prolongation of drug action**
  - e.g. cyclosporine by ketoconazole or grapefruit juice; olanzapine by fluvoxamine
Classification of Drug Interactions

- Pharmacodynamic
- Pharmacokinetic
- Mixed
- Idiosyncratic
Pharmacodynamic Interactions

Alterations in pharmacological effects produced:

- **directly** by interactions at a common biological site (receptor) (e.g. clonidine and yohimbine at $\alpha_2$-adrenergic receptor; pramipexol [Mirapex] and risperidone at D2 receptor), or;

- **indirectly** through separate but interrelated biological sites (e.g., haloperidol + benztropine)
Selected Pharmacodynamic Drug Interactions

➢ Respiratory Depression: benzodiazepines, barbiturates, alcohol, opiate analgesics

➢ Anticholinergic Toxicity: low potency antipsychotics, clozapine, olanzapine, TCAs, benzotropine, diphenhydramine, paroxetine

➢ Hypotension: TCAs, MAOIs, trazodone, nefazodone, mirtazapine, low potency antipsychotics, and atypical antipsychotics

➢ Metabolic Syndrome: Olanzapine, risperidone, clozapine, quetiapine

➢ Q-Tc prolongation/arrhythmia risk*: TCAs, low potency antipsychotics (e.g., thioridazine), other antipsychotics at high doses (e.g. pimozide, ziprasadone, risperidone, haloperidol, droperidol), citalopram/escitalopram (high dose), methadone

*Added arrhythmia risk exists with hypokalemia, hypomagnesemia, heart or liver disease
Pharmacokinetic Drug Interactions

Alterations in plasma levels and/or tissue concentrations produced by interactions that influence at least one of the following four processes ("ADME"):  

- Absorption  
- Distribution  
- Metabolism  
- Excretion
Mixed Drug Interactions

Interactions believed to involve both a pharmacokinetic and pharmacodynamic component:

Examples:

**Serotonin toxicity on paroxetine and dextromethorphan:** paroxetine inhibits metabolism of dextromethorphan leading to increased levels of dextromethorphan (pharmacokinetics) plus both drugs exert serotonergic effects (pharmacodynamics).

**Increased bleeding risk on fluoxetine and warfarin:** Fluoxetine inhibits metabolism of S-warfarin by P450 2C9 thereby prolonging INR (pharmacokinetics); plus SSRIs may reduce platelet aggregation, thereby increasing bleeding diathesis along with warfarin (pharmacodynamics).
Idiosyncratic Drug Interactions

Sporadic interactions that occur in a small number of individuals and are not yet predicted from known pharmacodynamic or pharmacokinetic properties of the drugs.

Example: sporadic neurotoxicity on lithium and antipsychotics
Pharmacokinetic Interactions

More about the four key pharmacokinetic mechanisms ("ADME")...
Absorption

Interactions involving drug absorption are generally less important than interactions affecting drug clearance (metabolism, excretion).

Absorption interactions may alter time to reach maximum drug concentration ($T_{\text{max}}$) and/or may alter the maximum drug concentration achieved ($C_{\text{max}}$).
Absorption

Decreased Absorption:
- Examples
- Charcoal, antacids, kapolin-pectin, cholestyramine, fatty acid substitutes, orlistat may bind to drug and form unabsorbable complexes.

Increased Absorption:
- Examples
- Drugs that *speed gastric emptying* (e.g. metoclopramide, cisapride [Propulsid]) or *inhibit intestinal motility* (e.g. TCAs, morphine, marijuana) may promote greater contact with absorptive mucosal surface of upper portion of small intestine.
- *Drugs that Inhibit gut enzymes* (including MAO and P450 3A4 enzymes) may increase amount of relevant substrate (e.g. tyramine) reaching portal circulation.
Variable Drug Interactions with Food

Examples:

- Increased absorption of **ziprasidone or lurasidone** with food
- Decreased bioavailability of **thyroxine** with food (particularly with calcium and iron containing foods and supplements, coffee, soy and fiber)
Distribution

- Regional blood flow
- Lipophilicity
- Adipose/ lean body mass
- Protein binding
- Drug transport proteins (e.g. P-glycoprotein [Pgp])
**Protein Binding**

*Competition* for protein-binding sites by two or more drugs resulting in *displacement* of previously bound (inactive) drug which in unbound form is now active.

*Equilibration occurs* as unbound form is also now available for redistribution to tissues and elimination.
## Minimally Protein Bound Psychotropics*

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>&lt; 3%</td>
</tr>
<tr>
<td>Gabapentin [Neurotonin]</td>
<td>&lt; 3%</td>
</tr>
<tr>
<td>Pregabalin [Lyrica]</td>
<td>&lt; 3%</td>
</tr>
<tr>
<td>Levomilnacipran [Fetzima]</td>
<td>&lt; 15%</td>
</tr>
<tr>
<td>Acamprosate [Campral]</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Topiramate [Topamax]</td>
<td>&lt; 20%</td>
</tr>
<tr>
<td>Levomilnacipran [Fetzima]</td>
<td>&lt; 25%</td>
</tr>
<tr>
<td>Venlafaxine, desvenlafaxine</td>
<td>&lt; 30%</td>
</tr>
<tr>
<td>Zonisamide [Zonegran]</td>
<td>&lt; 40%</td>
</tr>
<tr>
<td>Memantine [Namenda]</td>
<td>&lt; 40%</td>
</tr>
<tr>
<td>Lamotrigene [Lamictal]</td>
<td>&lt; 60%</td>
</tr>
</tbody>
</table>

*Unlikely to be involved in protein binding interactions
## Moderately Protein Bound*  

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine [Lamictal]</td>
<td>&lt; 60%</td>
</tr>
<tr>
<td>Guanafacine [Intuniv]</td>
<td>&lt; 70%</td>
</tr>
<tr>
<td>Molindone [Moban]</td>
<td>&lt; 70%</td>
</tr>
<tr>
<td>Carbamazepine [Tegretol]</td>
<td>&lt; 80%</td>
</tr>
<tr>
<td>Fluvoxamine [Luvox]</td>
<td>&lt; 80%</td>
</tr>
<tr>
<td>Citalopram [Celexa]</td>
<td>&lt; 80%</td>
</tr>
<tr>
<td>Paliperidone [Invega]</td>
<td>&lt; 85%</td>
</tr>
<tr>
<td>Bupropion [Wellbutrin]</td>
<td>&lt; 85%</td>
</tr>
<tr>
<td>Quetiapine [Seroquel]</td>
<td>&lt; 85%</td>
</tr>
<tr>
<td>Ramelteon [Rozerem]</td>
<td>&lt; 85%</td>
</tr>
</tbody>
</table>

*Unlikely to be involved in protein binding interactions
Drug Transport Proteins

• Appear to play critical roles in regulating permeability of intestinal epithelia, lymphocytes, blood-brain barrier

• *P-glycoprotein* best characterized (coded for by ‘multiple drug resistance gene-1’)

• Efforts continue to elucidate role in drug interactions (as well as drug resistance and tolerance)
Metabolism (2 Phases)

Phase I Reactions

- Oxidation, reduction, hydrolysis
- Often *rate-limiting*
- Produce potentially *active metabolites* subject to Phase II metabolism
Metabolism (2 Phases)

Phase II Reactions

- Conjugation, acetylation
- Produce typically *inactive metabolites* which are highly polar, water soluble, ready for renal excretion
- Some agents undergo Phase II metabolism only (e.g. valproate, lorazepam, oxazepam, temazepam)
Metabolism of a Substrate* may be Inhibited or Induced**

Inhibition

- *Rapid* impact; substrate **levels rise** quickly
- Mechanisms: **competitive inhibition** (displacement of substrate); **covalent binding** (conformational change of enzyme); **enzyme destruction** (e.g., phytochemicals of grapefruit juice may destroy P450 3A4, in addition to other mechanisms of inhibition)

Induction

- *Gradual* impact; substrate **levels decline** slowly
- Mechanism: **up-regulation of transcription**; enhanced synthesis of metabolic enzyme

*Substrate = a drug metabolized by a given enzyme.
**Inhibitor or inducer = a drug that alters the metabolic activity of that enzyme.*
**Clinically Relevant Inducers**

<table>
<thead>
<tr>
<th>Carbamazepine</th>
<th>Rifampin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td><em>Chronic</em> alcohol</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Chronic smoking</td>
</tr>
<tr>
<td>Primidone</td>
<td>Charbroiled meats</td>
</tr>
<tr>
<td>Prednisone</td>
<td>Cruciferous vegetables</td>
</tr>
<tr>
<td>Ritonavir (chronic)</td>
<td>St. John’s Wort</td>
</tr>
</tbody>
</table>
“Red Flags”: Think Inhibition When You See...

**Clinically Relevant Inhibitors**

<table>
<thead>
<tr>
<th>Antifungals (azoles)</th>
<th>SSRIs</th>
<th><em>Acute</em> alcohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolide antibiotics</td>
<td>Phenothiazines</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Valproic acid</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Antiretrovirals</td>
<td>Nefazodone</td>
<td>Ca++ ch. blockers</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Duloxetine</td>
<td>Grapefruit juice</td>
</tr>
<tr>
<td>Antimalarials</td>
<td>Bupropion</td>
<td>Propafenone</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>β-blockers</td>
<td>Amiordarone</td>
</tr>
</tbody>
</table>
Cytochrome P450 Isoenzymes

- Heterogeneous group of over 30 heme-containing oxidative enzymes (in humans), located predominantly in the endoplasmic reticulum of hepatocytes (also brain, gut)
- Over 500 P450 isoenzymes across all species
- Responsible for *Phase I* metabolism of a wide variety of **endogenous and xenobiotic substrates** (fatty acids, prostaglandins, steroids, carcinogens/pro-carcinogens, toxins).
- Involved in metabolism of > 80% of all available drugs
Cytochrome P450 Isoenzymes

Of the enzymes elucidated, those most relevant to drug metabolism and interactions are:

- 1A2
- 2C subfamily
- 2D6
- 3A subfamily
CYP 450 Polymorphisms

Genetically based differences in enzyme structure (isoforms) resulting in altered activity.

Known polymorphisms among CYP 450 isoenzymes include:

• 2C19 (gene on chromosome 10)
• 2D6 (gene on chromosome 22)

Steadily evolving knowledge on hundreds of alleles for common P450 isoenzymes (cf. www.imm.ki/CYPalleles/)
CYP 450 Polymorphisms

Bimodal distribution of isoforms results in:

- “Extensive metabolizers” EMs (normal activity)
- “Poor metabolizers” PMs

Small numbers of “ultra-rapid metabolizers” UMs (more than usual complement of active enzyme)

Small number of individuals with partially functional enzyme, intermediate between extensive and poor.
Extensive vs. Poor Metabolizers

**Extensive (Normal)**
- Susceptible to normal degrees of induction or inhibition with inducers and inhibitors
- Convert to poor metabolizers functionally in the presence of an inhibitor of the enzyme
- Convert to ultra-rapid metabolizers functionally in the presence of an inducer of the enzyme

**Poor**
- Relatively insensitive to induction and inhibition
- Higher baseline concentrations of parent drug and lower levels of metabolite
- Exaggerated effects of drugs at low doses (e.g., with TCAs)
- Or diminished effects if the parent drug is a pro-drug that must be converted to an active form (e.g., with codeine, tramadol or tamoxifen) via that enzyme
CYP 450 and Ethnicity

- Poor P450 2D6 metabolizers: 5-10% Caucasians vs. 1-3% African Americans and Asian Americans
- Poor P450 2C19 metabolizers: 15-20% Asian Americans and African Americans vs. 1-5% Caucasians
Considerable diversity of metabolic enzymes beyond the CYP 450 enzymes
Non-CYP 450 Metabolic Enzyme Systems involved in Drug Metabolism

- **Flavin-containing monooxygenases (FMOs):**
  - At least 5 isoenzyme families in humans

- **Uridine diphosphate-glucuronosyl-transferases (UGTs):**
  - UGT 1 and UGT 2 subfamilies most important for drug metabolism in humans

- **Methyltransferases:**
  - Numerous families involved in methylation reactions e.g., catechol O-methyltransferase (COMT)

- **Sulfotransferases:**
  - Responsible for sulfation of many endogenous substances and drugs
Drugs are often metabolized through more than a single enzyme or enzyme family...

Examples:

• Tertiary TCAs (e.g. amitriptyline) via P450 1A2, 2C, 2D6, and 3A

• Olanzapine via CYP450 1A2, UGTs and FMOs
Inhibitors of one pathway may induce another and/or have mixed effects...

• Modafinil and armodafinil inhibit P450 2C subfamily but induce P450 3A subfamily and 1A2

• Ritonavir [Norvir] inhibits P450 2D6 and 3A4 with acute administration, but induces glucuronosyltransferase (and may induce P450s with chronic use)
Drug Excretion

Practical significance for drug-drug interactions is mainly for drugs which are not hepatically metabolized (e.g. lithium, gabapentin, pregabalin), or in the presence of disease states (e.g. renal, hepatic insufficiency) or with management of overdose (where changing urine pH may alter renal excretion of acidic or basic agents).

Related terms: drug elimination = all processes that result in clearance of drug from body including liver metabolism, renal excretion, and excretion into bile and sweat.
Nominations for the...

Top Dozen Drug Interactions involving Psychotropic Medications
Hypertensive Crises:

- With sympathomimetics
  - Includes OTCs (pseudoephedrine, phenylephrine, oxymetazoline [Afrin])
  - Involves inhibition of MAO-A primarily (hence selegilene [Emsam] at ≤ 6 mg/24h patch less risk, affecting MAO-B mainly; at higher doses is non-specific for MAO-A and MAO-B)
Serotonin Syndrome:

• With meperidine [Demerol] – ABSOLUTE contraindication !!!

• Other narcotics with serotonergic properties (e.g. tramadol [Ultram]) have rarely caused problems.

• Codeine, morphine are generally safer, though may be potentiated by MAOIs; use with caution
#1 MAOI Interactions

**Serotonin Syndrome**

- *With other highly serotonergic agents:*
  
  Other MAOIs, SSRIs, SNRIs, and atypical antidepressants (nefazodone, mirtazapine), L-tryptophan, dextromethorphan, sumatriptin (Imitrex), sibutramine (Meridia), buspirone, carbamazepine, lithium, dihydroergotamine, St. John’s Wort
#1 MAOI Interactions

- **Serotonin Syndrome/Serotonin Toxicity:**
  
  Often rapidly developing within hours; often no unique lab findings (unlike Neuroleptic Malignant Syndrome)

- **SSRIs+MAOIs are absolutely contraindicated**
  
  - Must wait 5 wks after fluoxetine before MAOI, 4-5 elimination half-lives after other SSRIs and serotonergic agents;
  
  - Must wait 2 wks after MAOI before SSRI or other serotonergic agents to allow MAO to regenerate
### Serotonin Syndrome: Hunter Criteria

**Hunter Serotonin Toxicity Criteria: Decision Rules**

<table>
<thead>
<tr>
<th>In the presence of a serotonergic agent:</th>
</tr>
</thead>
<tbody>
<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>

Dunkley E et al. QJM 2003;96:635-642

Any of the following sets (A-E):

(A) Spontaneous clonus

(B) Inducible clonus plus agitation or diaphoresis

(C) Ocular clonus plus agitation or diaphoresis

(D) Tremor plus hyperreflexia

(E) Hypertonicity plus fever plus ocular clonus or inducible clonus
#2 Lithium Interactions

**Increased Lithium Levels with:**

- Thiazide diuretics
- ACE inhibitors (captopril, enalapril)
- Antiogensin II receptor antagonists (valsartan, losartan)
- Prescription strength NSAIDs (except ASA, sulindac), COX-2 inhibitors
- Metronidazole, tetracycline, spectinomycin
#2 Lithium Interactions

Decreased Lithium Levels with:

- Aminophylline, theophylline
- Urinary alkalization (acetazolamide, sodium bicarbonate)
- Sodium chloride
- Osmotic diuretics (mannitol)
Potential consequences...

- Increased levels of TCAs, β-blockers (lipophilic – including propranolol and metoprolol but NOT atenolol or nadolol), antiarrhythmics, phenothiazines (e.g., thioridazine), atypical antipsychotics (e.g., aripiprazole, iloperidone)

- Inhibited conversion of pro-drugs including tamoxifen, codeine and tramadol to active forms
# SSRIs, SSNRIs and P450 2D6 Inhibition

<table>
<thead>
<tr>
<th>SSRI/SNRI</th>
<th>1A2</th>
<th>2C</th>
<th>2D6</th>
<th>3A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>-</td>
<td>++</td>
<td>++++(+++++)</td>
<td>+</td>
</tr>
<tr>
<td>Sertraline</td>
<td>-</td>
<td>+ (+)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>-</td>
<td>-</td>
<td>++++</td>
<td>-</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>++++</td>
<td>++</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Citalopram</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Vilazodone</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Venlafaxine</td>
<td>-</td>
<td>-</td>
<td>(+)</td>
<td>-</td>
</tr>
<tr>
<td>Desvenlafaxine</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Duloxetine</td>
<td>-</td>
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<td>+++</td>
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<tr>
<td>Levomilnacipran</td>
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<tr>
<td>Vortioxetine</td>
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</tr>
</tbody>
</table>

+ = inhibition  
() = metabolite effect
## Other Antidepressants and P450 Inhibition

<table>
<thead>
<tr>
<th>Drug</th>
<th>1A2</th>
<th>2C</th>
<th>2D6</th>
<th>3A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>-</td>
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<tr>
<td>Nefazodone</td>
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<td>Mirtazapine</td>
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<td>Reboxetine</td>
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<tr>
<td>St. John’s Wort</td>
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</tr>
</tbody>
</table>

--- = suspected induction
CYP450 2D6

Substrates
Amphetamine, aripiprazole, atomoxetine, beta-blockers (lipophilic; including propranolol, metoprolol, carvedilol and nebivolol), brexpiprazole, codeine, debrisoquine, dextromethorphan, diltiazem, donepezil, dextromethorphan, duloxetine, encainide, flecainide, galantamine, haloperidol, hydroxycodone, iloperidone, lidocaine, metaclopramide, mexilitene, mCPP, nifedepine, oxycodon, phenothiazines (e.g., thioridazine, perphenazine), propafenone, risperidone, SSRIs, tamoxifen, TCAs, tramadol, trazodone, venlafaxine, vortioxetine

Inhibitors
Amiodarone, antimalarials, bupropion, cimeditine, duloxetine, fluoxetine, hydroxyzine, mibefradil, methadone, metoclopramide, moclobemide, nelfinavir, paroxetine, phenothiazines, quinidine, ritonavir, sertraline, terbinafine, TCAs, yohimbine

Inducers
Dexamethasone, Rifampin
Potential consequences...

- Increased levels of numerous substrates
  - e.g., carbamazepine, cyclosporine, fentanyl, methadone, oxycodone, calcium channel blockers, statins, OCPs, quetiapine, lurasidone, iloperidone, alprazolam, zolpidem, zaleplon, eszopiclone, suvorexant, ramelteon, buspirone, vilazodone, pimozide
  - Increased pimozide may cause arrhythmias;
  - Increased carbamazepine may cause delirium, seizures
  - Increased methdone, oxycodone, fentanyl may cause respiratory depression
  - Increased statins may increase risk of myopathy (rhabdomyolysis)
CYP450 3A Subfamily

**Substrates**
Alfentanil, alprazolam, amiodarone, amprenavir, aripiprazole, brexipiprazole, bromocriptine, buspirone, calcium channel blockers, caffeine, carbamazepine, cisapride, cocaine, clozapine, cyclosporine, diazepam, disopyramide, efavirenz, estradiol, eszopiclone, fentanyl, guanfacine, iloperidone, indinavir, HMG-CoA reductase inhibitors (lovastatin, simvastatin), levomilnacipran, lidocaine, loratadine, lurasidone, methadone, midazolam, nimodipine, pimozide, prednisone, progesterone, propafenone, quetiapine, quinidine, ramelteon, ritonavir, sildenafil, suvorexant, tacrolimus, testosterone, tertiary TCAs, trazodone, triazolam, vardenafil, vilazodone, vinblastine, warfarin, zolpidem, zaleplon, ziprasidone

**Inhibitors**
Antifungals, calcium channel blockers, cimetidine, efavirenz (also inducer), indinavir, fluvoxamine, fluoxetine (norfluoxetine), fosamprenavir, grapefruit juice, macrolide antibiotics, mibefradil, nefazodone, nelfinavir, norfloxacin, ritonavir

**Inducers**
Armodafinil, carbamazepine, efavirenz (also inhibitor), glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, ritonavir (chronic), St. John’s Wort, troglitazone
#5 St. John’s Wort: Potential Reduction of Efficacy/Levels of ...

- Indinavir
- Cyclosporine
- OCPs
- Others (theophylline, digoxin, coumarin anticoagulants, amitriptyline)

May reflect **P450 3A induction and/or a P-glycoprotein effect**
#6 Carbamazepine [Tegretol] Induction of Metabolism

- Reduces levels of many CNS acting agents (including itself; “auto-induction”) and many non-psychotropics (e.g., OCPs, cyclosporine, calcium channel blockers) via P450 3A induction and other mechanisms
- Conversely, discontinuation may result in drug toxicity as levels of other drugs rise due to lifting of inducing influence
- Oxcarbazeptine and topiramate can also induce metabolism of other agents, generally to lesser extent
Potential consequences...

- Toxicity on clozapine, asenapine, duloxetine, theophylline, thioridazine and other 1A2 substrates

- Increased clozapine, theophylline may cause seizures

- Increased thioridazine may cause arrhythmias
CYP450 1A2

**Substrates**
Acetaminophen, aminophylline, asenapine, estradiol, caffeine, clozapine, cyclobenzaprine, fluvoxamine, haloperidol, mirtazapine, odansetron, olanzapine, phenacetin, procarciniogens, riluzole, ropinirole, tacrine, tertiary tricyclic antidepressants, theophylline, R-warfarin, zileuton, zolmitriptan

**Inhibitors**
Amiodarone, fluoroquinolones, fluvoxamine, cimetidine, grapefruit juice, methoxsalen, ticlopidine

**Inducers**
Armodafinil, charbroiled meats, cigarette smoking, cruciferous vegetables, insulin, omeprazole, modafinil, ritonavir, tobacco
Potential for...

- Additive/synergistic anti-histamine, anti-muscarinic, anti-$\alpha_1$-adrenergic and quinidine-like effects
#9 Oral Contraceptives

- Many psychotropics induce metabolism of OCPs (estrogen component) including carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and high dose topiramate, St. John’s Wort and modafinil and armodafinil
  - Second form of contraception required and/or dose increase if used for other purposes when these agents are added to an OCP regimen

- Reciprocally OCPs may induce metabolism of lamotrigine and valproate, thereby reducing levels of these anticonvulsants by as much as 50%
  - Anticipated dose increase for lamotrigine; possibly for valproate (therapeutic drug monitoring is needed after OCP added)
#10 Valproate Inhibition of Metabolism

Increased levels of:

• Lamotrigene (with increased risk of Stevens-Johnson, Toxic Epidermal Necrolysis, and other serious rashes)
• Carbamazepine 10,11-epoxide metabolite (with CNS activity/risk of toxicity)
• Tricyclic antidepressants (amitriptyline, nortriptyline, clomipramine)
• Anti-neoplastic drugs (cisplatin, etoposide)
# 11 P450 2C Inhibition

Potential for...

- Increased anticoagulant (S-warfarin) and diazepam effects
CYP450 2C Subfamily

**Substrates**
Barbiturates, bortezomib, celecoxib, diazepam, fluvastatin, glipizide, glyburide, irbesartan, losartan, mephenytoin, NSAIDs, nelfinavir, phenytoin, primidone, propranolol, proguanil, proton pump inhibitors, rosiglitazone, rosuvastatin, tamoxifen, tertiary TCAs, THC, tolbutamide, S-warfarin, R-warfarin

**Inhibitors**
Amiodarone, Armodafinil, chloramphenicol, efavirenz, felbamate, fluoxetine, fluvoxamine, isoniazide, ketoconazole, lansoprazole, modafinil, omeprazole, oxcarbazepine, pantoprazole, ritonavir, sertraline, sulfamethoxazole, ticlopidine, topiramate, zafirlukast

**Inducers**
Carbamazepine, norethindrone, phenytoin, prednisone, rifampin
• Best documented with risk of upper GI bleeding on SSRIs+high dose NSAIDs as well as SSRIs+Warfarin

• Risk of SSRIs + aspirin less well elucidated.

• Proton pump inhibitors and H2 blockers may be somewhat protective

• Other bleeding risks (e.g., CNS) suspected in some populations
Homestretch -- Back to the Cases to Wrap Up !
A Case of P450 2D6 Inhibition

27 yo with migraine, on propranolol, admitted with psychotic depression and treated with duloxetine (Cymbalta), bupropion (Wellbutrin) and risperidone (Risperdal)...

• Lightheadedness; propranolol metabolism impeded via 2D6 inhibition by duloxetine and bupropion -- levels rise
• Migraines refractory to acetaminophen with codeine; pro-drug codeine no longer biotransformed into active form by 2D6
A Case of MAOI-SNRI Interaction

49 year old with schizoaffective disorder receives levomilnacipran (Fetzima) from the covering MD. Presents with confusion, diarrhea, fever and brisk reflexes. Current meds are: aripiprazole (Abilify), lamotrigene (Lamictal), lithium and hydrochlorothiazide. Multiple other treatment trials over the past year....

• Serotonin syndrome as MAOI selegiline (Emsam) discontinued only 8 (not 14) days before levomilnacipran (Fetzima)
A Case of P450 1A2 Inhibition

32 yo with OCD, bipolar disorder, asthma, and GERD presents with grand mal sz days after switching from clomipramine (Anafranil) to fluvoxamine (Luvox). Other meds: clozapine, lithium, theophylline, omeprazole, and prednisone taper...

• Clozapine and theophylline toxicity  Clozapine and theophylline levels rise steeply in setting of P450 1A2 inhibition by fluvoxamine -- seizure threshold rapidly lowered
A Case of Anticholinergic Toxicity

Agitated and incoherent 67 yo with schizophrenia brought in by police. Meds: olanzapine (Zyprexa), mirtazapine (Remeron), and diphenhydramine; doxepin (Sinequan) recently added for atopic dermatitis...

- Anticholinergic delirium doxepin added to already high burden of anticholinergic drug effects in an older, susceptible patient already on other medications with anti-muscarinic effects including diphenhydramine and olanzapine
A Case of P450 3A Inhibition

52 year old with panic disorder, resistant depression, and chronic insomnia presents with dizziness, drowsiness, nausea, and slurred speech. Meds: alprazolam (Xanax), eszopiclone (Lunesta), suvorexant (Belsomra), quetiapine (Seroquel), and the vilazodone (Viibryd). She was recently started on clarithromycin (Biaxin) for sinusitis.

She’s trying to stay well-hydrated *(with grapefruit juice !)*...

- Rapidly rising levels of four P450 3A substrates with CNS and GI side-effects in setting of 3A inhibition by macrolide antibiotic and grapefruit juice
A Case of Induction of OCP Metabolism

37 yo with MDD, GAD, atypical facial pain. Meds: escitalopram (Lexapro), clonazepam, and an OCP switched from gabapentin (Neurontin) to carbamazepine (Tegretol) for pain. Modafinil (Provigil) added to offset sedation. Offered St. John’s Wort by a friend. Cancels appt w/malaise...

• Unanticipated pregnancy in setting of reduced OCP levels/efficacy on carbamazepine, modafinil and St. John’s Wort