



# Drug Interactions

## *Mechanisms and Clinical Relevance*

*Jonathan E. Alpert, MD, PhD*

*Dorothy and Marty Silverman Department Chair*

*Department of Psychiatry and Behavioral Sciences*

*Professor of Psychiatry, Neuroscience, and Pediatrics*

*Montefiore Medical Center*

*Albert Einstein College of Medicine*

**Psychopharmacology 2022**



# Disclosures

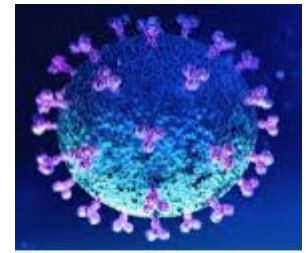
**Speaker's honoraria:** American Society of Clinical Psychopharmacology, American Psychiatric Association, Eli Lilly & Co., LIJ/Zucker-Hillside, Nevada Psychiatric Association, New York University, North Shore Medical Center, Organon Inc., Psicofarma, Primedia, Reed Medical Education, University of Louisville, Xian-Janssen

**Royalties:** Belvoir Publishing, Cambridge University Press, Marcel Dekker, Institut la Conference Hippocrate

**Consultant fees:** Consulting Medical Associates, Luye Pharmaceuticals, PamLab LLC, Pharmavite

**Research support:** Abbott Labs, Alkermes, Aspect Medical Systems, Astra-Zeneca, Axsome Therapeutics, Bristol-Myers Squibb, Cephalon, Eli Lilly & Co., Forest Pharmaceuticals, GlaxoSmithKline, J&J Pharmaceuticals, Lichtwer Pharma, Lorex Pharmaceuticals, NARSAD, NIH, Novartis, Organon, Otsuka, PamLab LLC, PCORI, Pharmavite, Roche Laboratories, Solvay Pharma, Sanofi/Synthelabo, Wyeth-Ayerst Laboratories

# Relevance of Drug Interactions



- Ubiquitous polypharmacy
- Treatment of psychiatric conditions with medical comorbidity
- Use of dietary health supplements/OTCs
- Focus on preventable drug errors
- Advances in pharmacokinetics and pharmacodynamics and in bioinformatics
- Bioinformatics
- Clinical decision support software in EHRs
- Pharmacogenomic testing

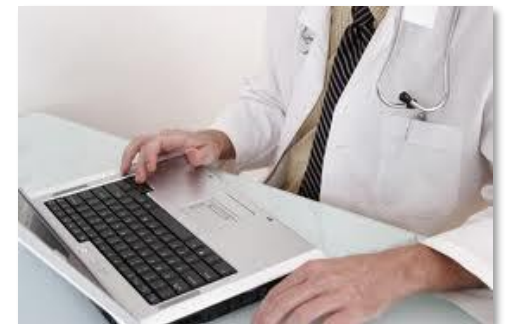
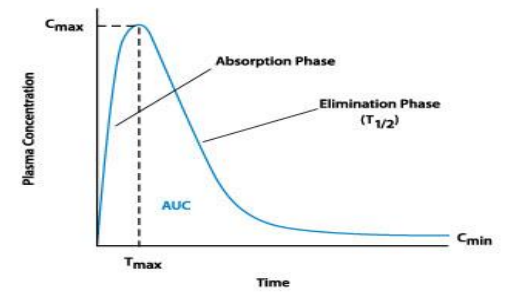
Guthrie et al. *BMC Medicine* (2015) 13:74  
DOI 10.1186/s12916-015-0322-7

**BMC Medicine**

**RESEARCH ARTICLE** Open Access

The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010

Bruce Guthrie<sup>1\*</sup>, Boikanyo Makubate<sup>2</sup>, Virginia Hernandez-Santiago<sup>1</sup> and Tobias Dreischulte<sup>3</sup>



# 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 (SAEs):**

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

- **Increased levels/effects:**

- Side-effects (e.g., headaches, nausea, dizziness) -> misdiagnosis and/or unnecessary medical work-ups
- Poor tolerability -> risks to adherence

- **Reduced levels/effects:**

- Non-response to usual doses -> relapse
- Potential withdrawal or discontinuation emergent effects

# 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 uncharacteristically refractory to **acetaminophen with codeine**.

He suspects foul play.

# Case 2

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

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

Multiple treatment trials over the past year: **ziprasidone (Geodon)**, **mirtazapine (Remeron)**, **selegiline (Emsam)**, **vortioxetine (Trintellix)** and **esketamine (Spravato)**



# Case 3

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.**

# 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)**, **quetiapine (Seroquel)** and **vilazodone (Viibryd)**.

Recreational **cannabis**. Recently started on **clarithromycin (Biaxin)** for sinusitis. Trying to stay well-hydrated with fruit juice.

# 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 friend.

Cancels appt this a.m. due to nausea and malaise.

# Drug Interaction Errors

- **Type 1**

- Failure to anticipate
- Failure to recognize

- **Type 2**

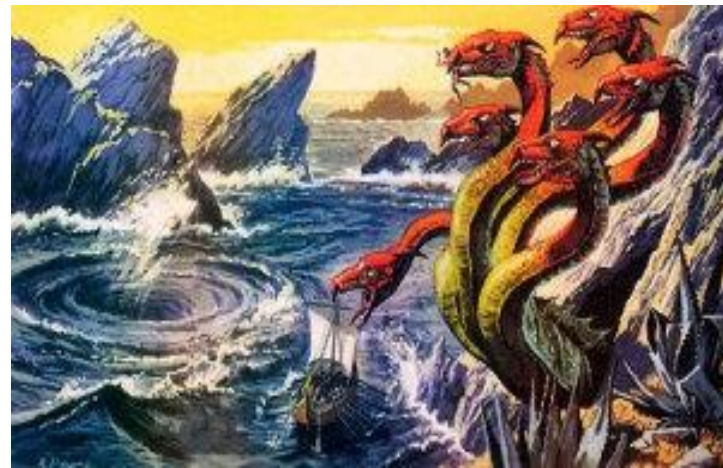
- Phobic avoidance
- Therapeutic paralysis



# Navigating between denial and paralysis

## What next?...

- General precepts
- Classification and mechanisms
- Drug interactions worth knowing
- Case vignettes revisited



Scylla and Charybdis

# Maintain Perspective

Interactions are ubiquitous but...

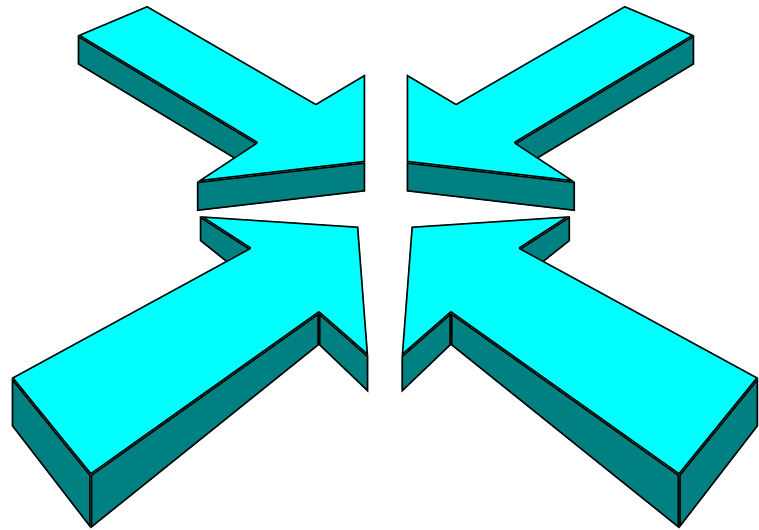
- Serious adverse interactions are uncommon
- Absolute contra-indications are rare



# Maintain Perspective

*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 theoretically possible combinations of up to five drugs** on a patient's drug regimen **yet only 700 drug interactions studies in the literature...**
- Many more studies exist in 2022 but also many 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

# Studies Range Widely in Rigor and Relevance

*Drug interaction warnings 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
- 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 when:

Using drugs with a *narrow therapeutic window* (e.g., cyclosporine), *low therapeutic index* (e.g., digoxin), or 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

Embarking on (worthy) **efforts to simplify (“deconstruct”) a complex regimen**

# Focus on the most important (i.e., common and/or potentially catastrophic) interactions

## Interaction checker resources are widely available:

- **Open Access**
  - Drugs.com
  - Medscape (WebMD)
  - Epocrates (Athenahealth)
- **By Subscription**
  - Lexicomp (Wolters Kluwer) - included in UpToDate
  - Clinical Pharmacology - ClinicalKey (Elsevier)
  - Micromedex (IBM)
- **Clinical Decision Support Systems** increasingly standard in Electronic Health Records (EHRs) and Computerized Physician Order Entry systems (CPOEs), albeit with low thresholds for flagging interactions -> “alert fatigue”

**Caveat emptor:** inter-rater agreement on potential DDIs across available drug interaction databases is **strong ( $\kappa > 0.6$ ) for drug interactions classified as “severe” but only fair ( $\kappa < 0.3$ ) for drug interactions considered “moderate”**. Work in progress on *international standards*. Monteith S, Glenn T *Psychiatry Research* 275:366-372, 2019; *Hum Psychopharmacol Clin Exp* 2021 DOI: 10.1002/hup.2802

**Good practice:** check more than one resource and consider literature search (e.g., PubMed) for original sources when stakes are high and/or when perplexed

# Not always a negative; can be leveraged therapeutically

- 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
- Boosting of drug levels/modification of metabolite ratios/prolongation of drug action
  - E.g. cyclosporine by ketoconazole or grapefruit juice; olanzapine by fluvoxamine

# Classification of Drug Interactions

**Pharmacodynamic**

**Pharmacokinetic**

**Mixed**

**Idiosyncratic**

# Pharmacodynamics and Pharmacokinetics

**Pharmacodynamics**



*The effects of drug  
on the body*

**Pharmacokinetics**



*How the body  
handles drug*

# Pharmacodynamic Interactions

Alterations in **pharmacological effects** produced:

- directly by interactions of two or more drugs at a common **biological site (receptor)** (e.g. clonidine and yohimbine at  $\alpha_2$ -adrenergic receptor; pramipexol and risperidone at D2 receptor; naltrexone and buprenorphine at the  $\mu$  opioid receptor)
- indirectly through separate but interrelated biological sites (e.g., haloperidol + benztropine)



# Pharmacokinetic Drug Interactions

Alterations in plasma levels and/or tissue concentrations produced by interactions that influence at least one of the following four processes relating to how the body handles drug (“**ADME**”):

- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**

# Mixed Drug Interactions

Interactions believed to involve pharmacokinetic and pharmacodynamic components:

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*

CLINICAL  
NEUROPHARMACOLOGY  
Volume 31, Number 3  
May - June 2008

*Case Report*

## Delirium Associated With Lithium-Quetiapine Combination

*Chanock Miodownik, MD, Awad Alkatmany, MD, Katherina Frolova, MD, and Vladimir Lerner, MD, PhD*

### Abstract

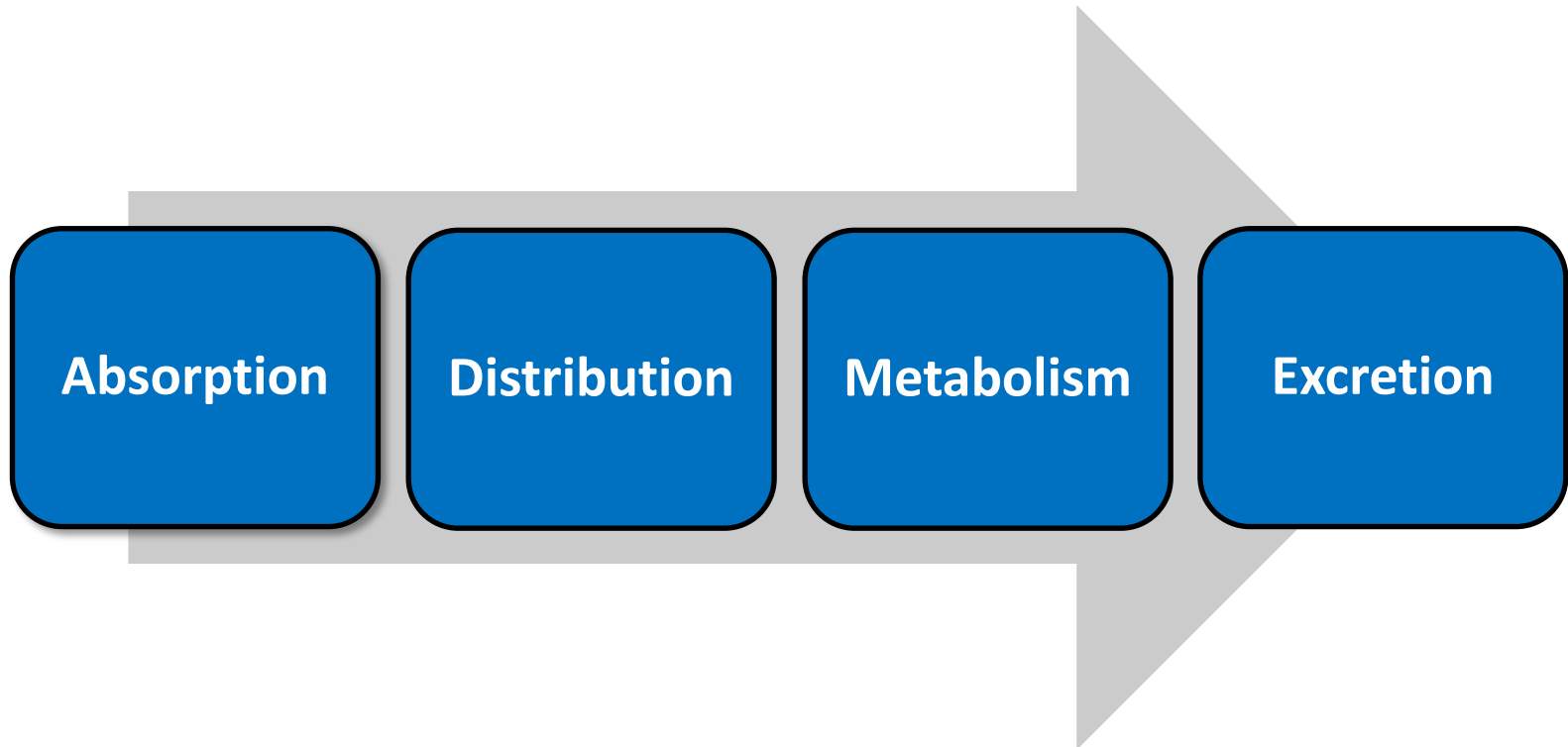
#### Objectives:

Acute lithium intoxication is a frequent complication of this treatment used for manic depressive disorders. Because lithium has a narrow therapeutic index and widespread use, its neuropsychiatric side effects are more prevalent than those of other

although sometimes, it may lead to different adverse events, including delirium and other side effects.<sup>3-19</sup> The safety of adding lithium to other medications is of a major concern, and extensive clinical experience has accumulated on several significant drug

# Pharmacokinetic Interactions

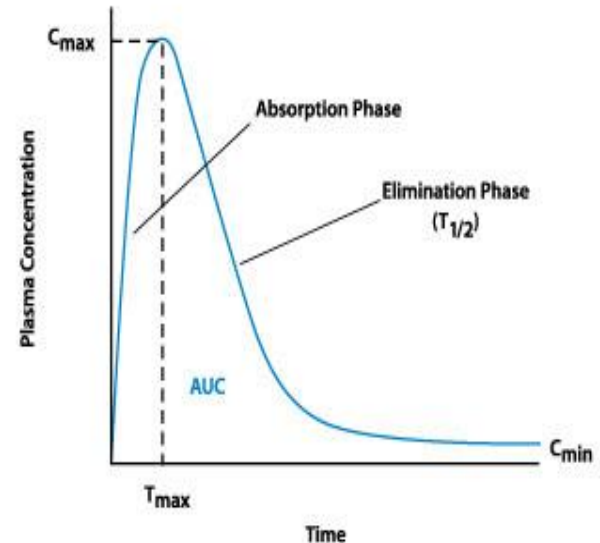
More about the four key pharmacokinetic mechanisms (**ADME**)...



# 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 ( $T_{max}$ ) and/or may alter the maximum drug **concentration** achieved ( $C_{max}$ )



**AUC = area under the curve**

# Absorption

## Decreased Absorption:

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

## Increased Absorption:

- **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.

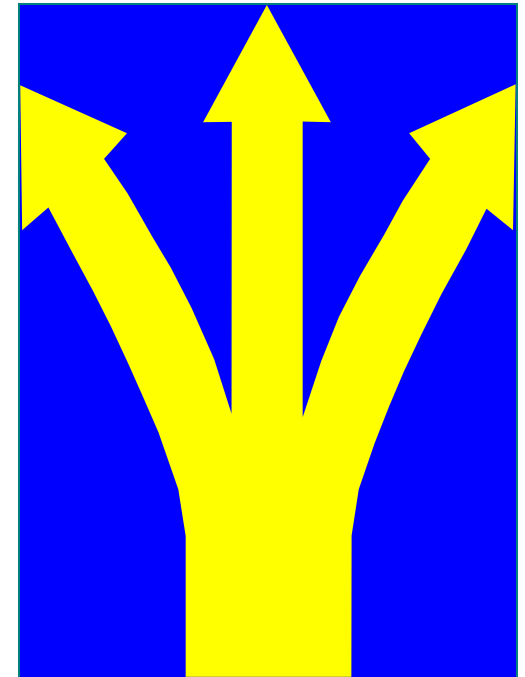
# Variable Drug Interactions with Food

- **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)
- **Decreased absorption of oral nicotine (e.g., gum) in presence of acidic foods/beverages (e.g., coffee, juices, soda)**



# Distribution

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

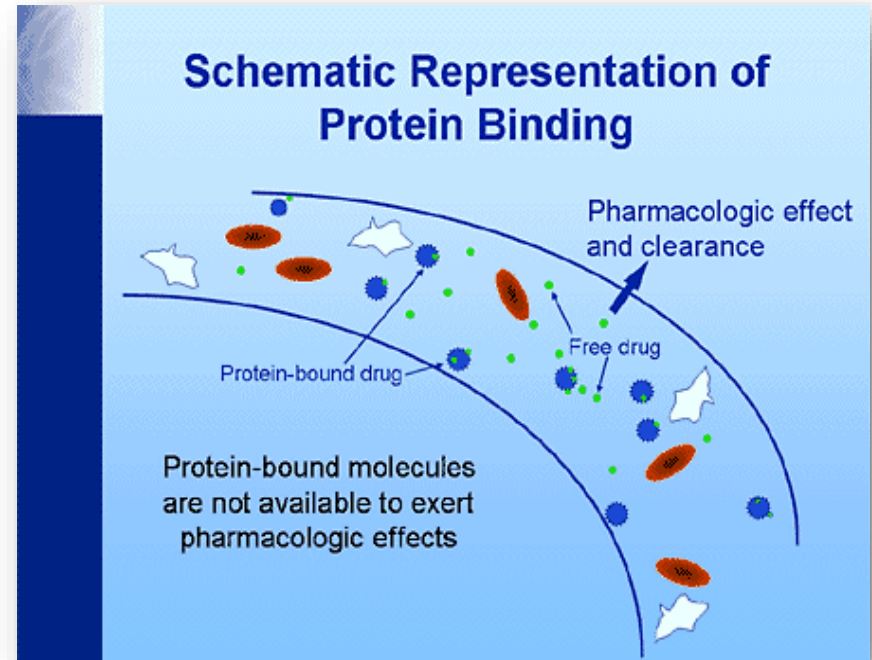




# Protein Binding

**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\*    % Bound

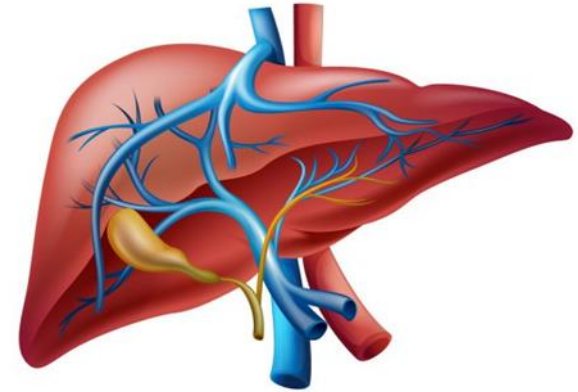
Lithium	< 3%
Gabapentin [Neurotonin]	< 3%
Pregabalin [Lyrica]	< 3%
Levomilnacipran [Fetzima]	< 15%
Acamprosate [Campral]	< 20%
Topiramate [Topamax]	< 20%
Levomilnacipran [Fetzima]	< 25%
Venlafaxine, desvenlafaxine	< 30%
Zonisamide [Zonegran]	< 40%
Memantine [Namenda]	< 40%
Lamotrigine [Lamictal]	< 60%

**\*Hence all very unlikely to be involved in protein binding interactions**

# Metabolism (2 Phases)

## Phase I Reactions

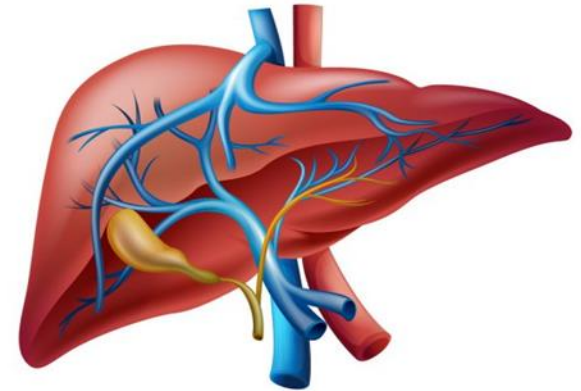
- Oxidation, reduction, hydrolysis
- Often *rate-limiting*
- Produce potentially *active metabolites*  
subject to Phase II metabolism
- Some agents require Phase I to convert pro-drug to active drug (e.g., tamoxifen, codeine, tramadol)



# 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.

A drug can be a substrate for a given enzyme and an inhibitor or inducer of that enzyme or another enzyme



# Think **Induction** When You See ...

Carbamazepine

Rifampin

Phenobarbital

*Chronic* alcohol

Phenytoin

Chronic smoking

Primidone

Charbroiled meats

Prednisone

Cruciferous vegetables

Ritonavir (chronic)

St. John's Wort



# Think **Inhibition** When You See...

Antifungals (azoles)

SSRIs

*Acute* alcohol

Macrolide antibiotics

Phenothiazines

Cimetidine

Fluoroquinolones

Valproic acid

Quinidine

Antiretrovirals

Nefazodone

Ca<sup>++</sup> ch. blockers

Isoniazid

Duloxetine

Grapefruit juice

Antimalarials

Bupropion

Propafenone

Disulfiram

$\beta$ -blockers

Amiodarone

# Cytochrome P450 Isoenzymes

- Heterogeneous group of over 50 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**
- **2C9 and 2C19**
- **2D6**
- **3A4**

# 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/](http://www.imm.ki/CYPalleles/))

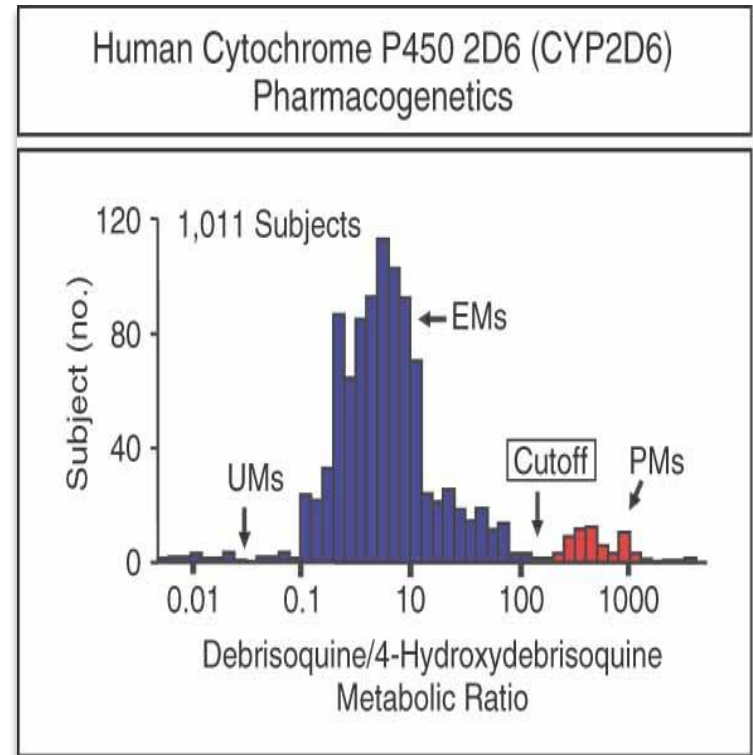
# CYP 450 Polymorphisms

**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 presence of an inhibitor of the enzyme
- Convert to ultra-rapid metabolizers functionally in 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

# Multiple Metabolic Enzyme Systems involved in Drug Metabolism

- Cytochrome P450 isoenzymes
- Flavin-containing monooxygenases (FMOs)
- Uridine diphosphate-glucuronosyltransferases (UGTs)
- Methyltransferases
- Sulfotransferases



# 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 10 Drug Interactions involving Psychotropic Medications



# #1 MAOI Interactions

## *Hypertensive Crisis:*

- *With sympathomimetics*
  - includes OTCs (pseudoephedrine, phenylephrine, oxymetazoline [Afrin])
  - Involves **inhibition of MAO-A** primarily (hence selegiline [Emsam] at  $\leq 6$  mg/24h patch less risk, affecting MAO-B mainly; at higher doses is non-specific for MAO-A and MAO-B)
  - Potential increased risk of BP elevation with esketamine + MAOIs

# #1 MAO Interactions

## *Serotonin Syndrome*

- Life-threatening syndrome associated with concomitant use of highly serotonergic agents.
- Alterations in consciousness, agitation and autonomic instability develop within hours; no unique lab findings

### **Hunter Criteria for Serotonin Toxicity (any of the following):**

- (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

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

# #1 MAOI Interactions

## *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 , VMAT2 inhibitors

# #1 MAOI Interactions

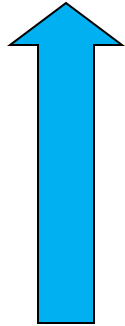
- ***Serotonin Syndrome/Serotonin Toxicity:***

Often rapidly developing within hours; often no unique lab findings (unlike Neuroleptic Malignant Syndrome)

- ***SSRIs+MAOIs are absolutely contraindicated***

- Must wait 4-5 elimination half-lives after SSRIs or other serotonergic agents before ; 4-5 starting MAOIs; 4-5 weeks for fluoxetine (norfluoxetine).
- Must wait 2 wks after MAOI before starting SSRI or other serotonergic agents to allow MAO to regenerate
- Antibiotic **linezolid** has limited MAOI inhibitory properties; should be used with caution/awareness with serotonergic agents

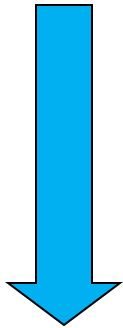
# #2 Lithium Interactions



## Increased Lithium Levels with:

- Thiazide diuretics
- ACE inhibitors (captopril, enalapril)
- Angiotensin 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)



# #3 P450 2D6 Inhibition

## Potential consequences...

- Increased levels of TCAs,  $\beta$ -blockers (lipophilic – including propranolol and metoprolol but NOT atenolol or nadolol), antiarrhythmics, phenothiazines (e.g., thioridazine), atypical antipsychotics (e.g., aripiprazole, iloperidone), valbenazine
- **Inhibited conversion of pro-drugs including tamoxifen, codeine and tramadol** to active forms

# Cytochrome P450 Inhibitory Effects of Antidepressants

Drug	1A2	2C9/19	2D6	3A4
Fluoxetine		++	+++	++
Paroxetine			+++	
Duloxetine			+++	
Bupropion			+++	
Fluvoxamine	+++			
Nefazodone and St. John's Wort				+++
Sertraline		+	++	+
Citalopram/ Escitalopram			+	
Vilazodone		+	+	

**+++ = Marked; ++ = Moderate; + = Minor Inhibition**

# CYP450 2D6

## Substrates

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

## Inhibitors

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

## Inducers

Dexamethasone, rifampin

# #4 P450 3A Inhibition and Induction

## Potential consequences...

- **Altered levels of numerous key substrates**
    - e.g., carbamazepine, clozapine, cyclosporine, opiates, calcium channel blockers, pimozide, ketamine, statins, OCPS, valbenazine, THC and cannibidiol (CBD), some direct oral anticoagulants (rivaroxaban and apixaban), dual orexin receptor antagonists (suvorexant, lemborexant, daridorexant)
  - **Increased pimozide or hydroxychloroquine may cause arrhythmias;**
  - **Increased carbamazepine may cause delirium, seizures**
  - **Increased methadone, oxycodone, fentanyl may cause respiratory depression**
  - **Increased direct oral anticoagulants can cause bleeding**
  - **Decreased methadone, buprenorphine may cause withdrawal**
- Common inhibitors include fluvoxamine, fluoxetine and nefazadone (increase levels of 3A substrates), ritonavir**
- Common inducers include carbamazepine, modafinil and armodafinil, St. John's Wort (decrease levels of 3A substrates)**

# CYP450 3A Subfamily

## Substrates

Alfentanil, alprazolam, amiodarone, amprenavir, apixaban, aripiprazole, brexpiprazole, bromocriptine, buprenorphine, buspirone, calcium channel blockers, caffeine, cannabidiol, carbamazepine, cisapride, cocaine, clozapine, cyclosporine, daridorexant, dexamethasone, diazepam, disopyramide, efavirenz, estradiol, eszopiclone, fentanyl, guanafacine, hydroxychloroquine, iloperidone, indinavir, HMG-CoA reductase inhibitors (lovastatin, simvastatin), ketamine, lemborexant, levomilnacipran, lidocaine, lopinavir, loratadine, lumateperone, lurasidone, methadone, midazolam, nimodipine, pimozide, prednisone, progesterone, propafenone, quetiapine, quinidine, ramelteon, rivavoxaban, ritonavir, sildenafil, suvorexant, tacrolimus, testosterone, tertiary TCAs, THC, trazodone, triazolam, valbenazine, 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, nirmatrelvir, norfloxacin, ritonavir

## Inducers

Armodafinil, carbamazepine, efavirenz (also inhibitor), glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, ritonavir (chronic), St. John's Wort, troglitazone

## #5 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
- Oxcarbazepine and topiramate can also induce metabolism of other agents, generally to lesser extent

# #6 P450 1A2 Inhibition by Fluvoxamine

## 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, procarcinogens, ramelteon, riluzole, ropinirole, tacrine, tertiary tricyclic antidepressants, theophylline, R-warfarin, zileuton, zolmitriptan

## Inhibitors

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

## Inducers

Armodafinil, charbroiled meats, cruciferous vegetables, insulin, omeprazole, modafinil, ritonavir, smoking (cigarettes, marijuana)



# #7 TCAs, Low Potency and Some Atypical Antipsychotics

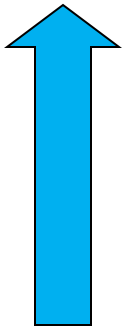
## Potential for...

- Additive/synergistic anti-histamine, anti-muscarinic, anti- $\alpha_1$ -adrenergic and quinidine-like effects (QTc prolongation)

# #8 Oral Contraceptives

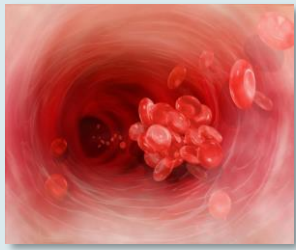
- **Many psychotropics induce metabolism of OCPs (estrogen component) including carbamazepine, oxcarbazepine, phenobarbital, phenytoin, and high dose topiramate, St. John's Wort and modafinil and armodafinil**
  - Second form of contraception required and/or dose increase if used for other purposes when 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)

# #9 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)



## #10: Bleeding Risks -Pharmacodynamic and Pharmacokinetic Components

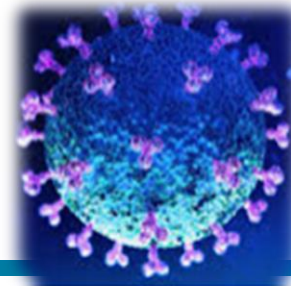
Serotonergic agents interfere with hemostatic mechanisms including platelet aggregation and vasoconstriction, and may increase gastric acid secretion (pharmacodynamic effects)

Increased risk of upper GI bleeds on SSRIs + high dose NSAIDs as well as SSRIs + Warfarin; proton pump inhibitors and H2 blockers may be protective

Some antidepressants also interfere with Cytochrome P450 metabolism of anticoagulants (pharmacokinetic effects) including:

- Elevated levels of warfarin with fluoxetine
- Elevated levels of several direct oral anticoagulants (apixaban – Eliquis; rivaroxaban – Xarelto) with fluoxetine and fluvoxamine

# COVID-19: Potential Drug Interactions



**Remdesivir** – no significant interactions

**Ritonavir/nirmatrelvir (Paxlovid)** – inhibits P450 3A and p-glycoprotein causing multiple substrate levels to rise (cf. Resources: Cytochrome tables), including increased levels of alprazolam, midazolam, zolpidem, methadone, ziprasidone, clozapine, pimozide, valbenazine,

**Azithromycin** – may increase QT (use with caution with other agents that prolong QT)

**Hydroxychloroquine** – may increase QT; drug levels may rise with P450 3A inhibitors (e.g., fluoxetine) and fall with inducers (e.g., carbamazepine; modafinil); hydroxychloroquine also inhibits P450 2D6 causing other substrate levels to rise (e.g., many antipsychotics and TCAs)

**Steroids** – P450 3A substrates susceptible to induction/inhibition

# CYP450 2C Subfamily

## Substrates

Barbiturates, bortezomib, cannabidiol, 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

# 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 desvenlafaxine (Pristiq) from the covering MD. Presents with confusion, diarrhea, fever and brisk reflexes. *Current* meds are: aripiprazole (Abilify), lamotrigine (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 **desvenlafaxine (Pristiq)**

# 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), *quetiapine* (Seroquel), and the vilazodone (Viibryd). Recreational *cannabis*. She **was recently started on clarithromycin** (Biaxin) for sinusitis.

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

**Rapidly rising levels of multiple P450 3A substrates** (alprazolam, eszopiclone, quetiapine, cannabidiol/THC) 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

# Parting Reflections

- **Maintain perspective:** Psychopharmacological drug interactions are ubiquitous, though few absolute contraindications. Many factors influence drug response; drug interactions are among them.
- **Become familiar with key interactions:** numerous resources exist for looking up others
- **Navigate between denial and therapeutic paralysis:**
  - Patients rely on us to minimize risk of side-effects and toxicity though also count on our resourcefulness to promote their best outcomes
- **Celebrate the fire hose: integral part of the lifelong learning and expertise we bring to patient care**

