MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Drug Interactions

Mechanisms and Clinical Relevance

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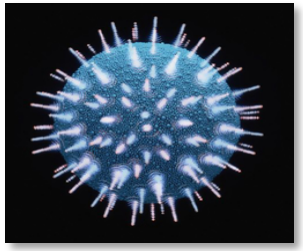
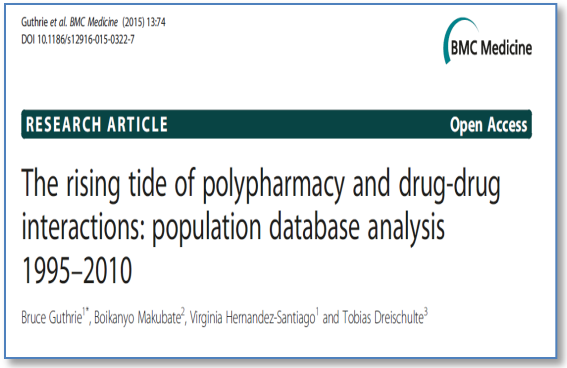
Drug Interactions



- Ubiquitous polypharmacy
- Treatment of psychiatric conditions among medically ill
- Use of dietary health supplements/OTCs
- Focus on preventable drug errors
- Advances in pharmacokinetics and pharmacodynamics and in bioinformatics
- Application of bioinformatics to large populations
- Clinical decision support software in EHRs
- Combinatorial pharmacogenetic decision support tools


Guthrie et al. BMC Medicine (2015) 13:74
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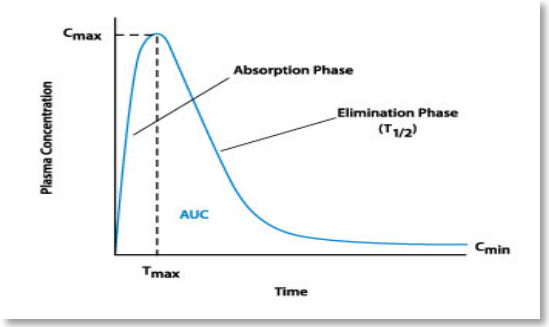
BMC Medicine

RESEARCH ARTICLE Open Access

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

Bruce Guthrie[1*], Boikanyo Makubate[2], Virginia Hernandez-Santiago[1] and Tobias Dreischulte[3]



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) -> potential misdiagnosis and unnecessary medical work-ups
  - Poor tolerability -> risk 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), lamotrigene (Lamictal), lithium** and **hydrochlorothiazide.**

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

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

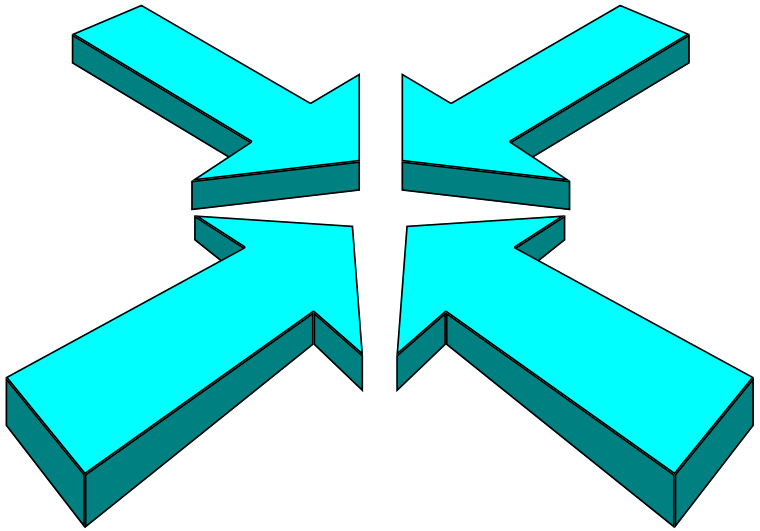
Interactions are ubiquitous but…

- 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 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 2020 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

Studies Range Widely in Rigor and Relevance

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
- 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 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
- 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" (Monteith S, Glenn T *Psychiatry Research* 275:366-372, 2019)
Good practice to check more than one of the resources + consider lit search of original references

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
- 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 α_2-adrenergic receptor; pramipexol [Mirapex] and risperidone at D2 receptor; naltrexone and buprenorphine at the μ 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 ("ADME"):

- **A**bsorption
- **D**istribution
- **M**etabolism
- **E**xcretion

Mixed Drug Interactions

Interactions believed to involve both a pharmacokinetic *and* pharmacodynamic component:

Examples:

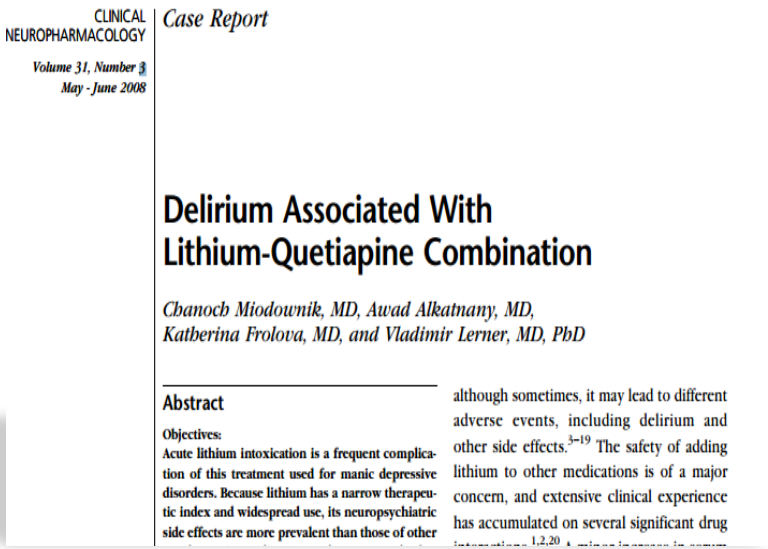
Serotonin toxicity on paroxetine and dextromethorphan: paroxetine inhibits metabolism of dextromethorphan leading to increased levels of dextromethorphan (**pharmacokinetics**) plus both drugs exert serotonergic effects (**pharmacodynamics**).

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



CLINICAL NEUROPHARMACOLOGY
Volume 31, Number 3
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Case Report

Delirium Associated With Lithium-Quetiapine Combination

Chanoch Miodownik, MD, Awad Alkatnany, MD, Katherina Frolova, MD, and Vladimir Lerner, MD, PhD

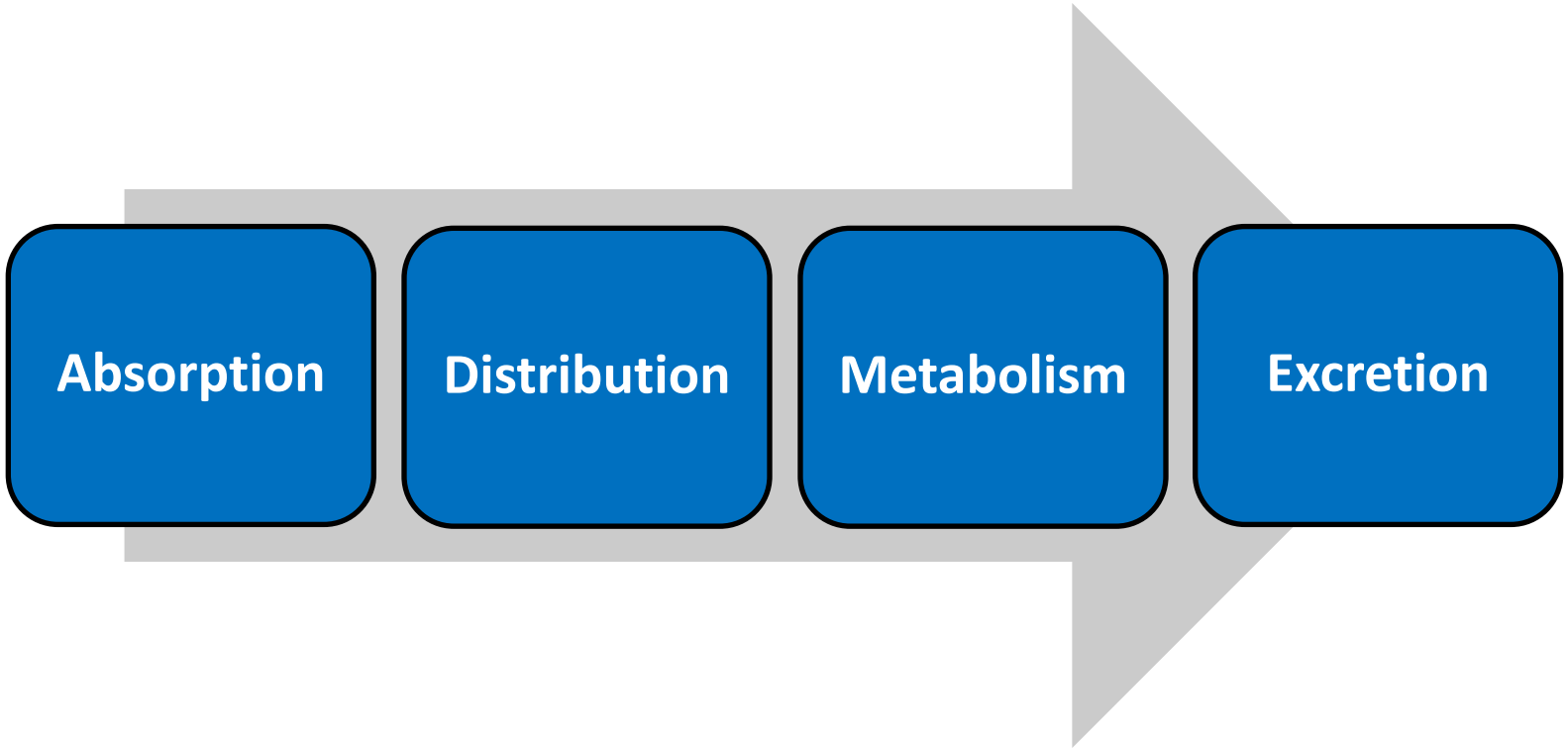
Abstract

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.[3–19] 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

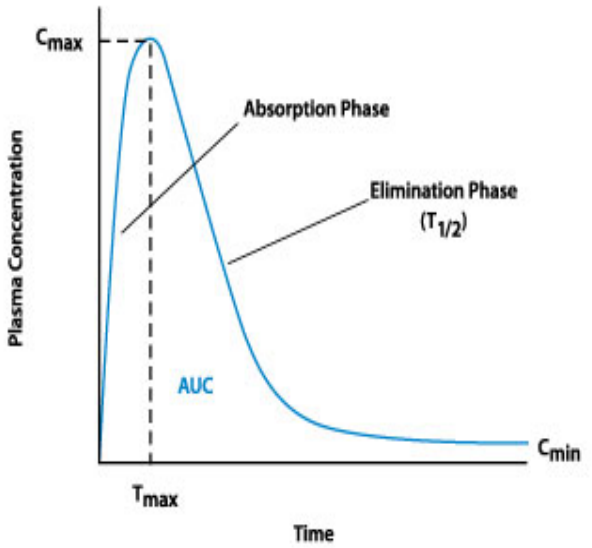
More about the four key pharmacokinetic mechanisms (**ADME**)…



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.

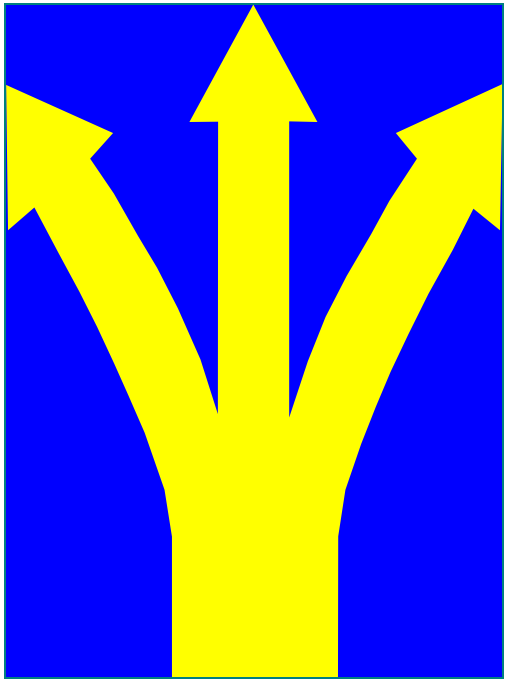
- ***Drugs that Inhibit gut enzymes*** (including MAO and P450 3A4 enzymes) may increase amount of relevant substrate (e.g. tyramine) reaching portal circulation.

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

Distribution

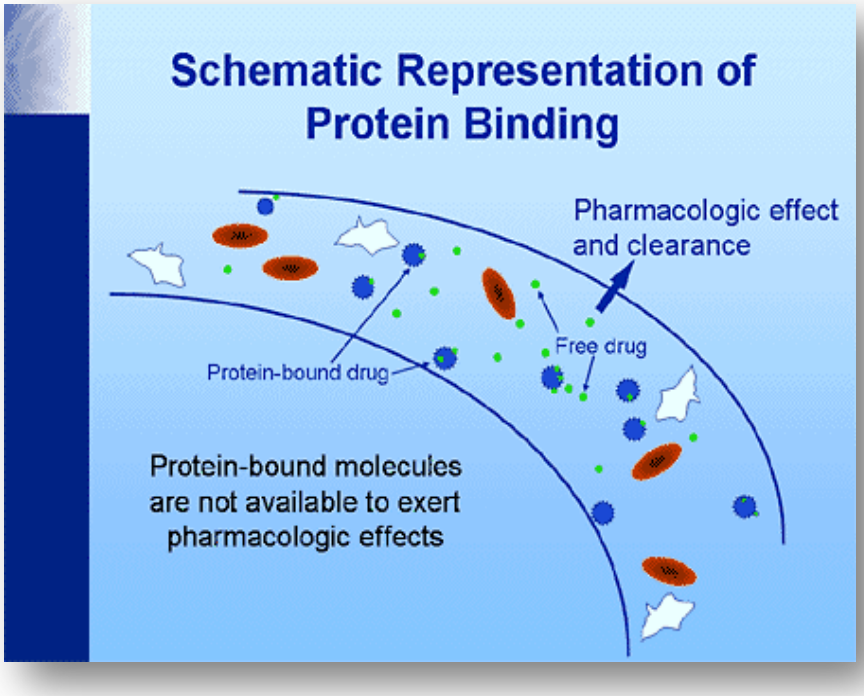
- Regional blood flow
- Lipophilicity
- Adipose/ lean body mass
- Protein binding
- Drug transport proteins (e.g. P-glycoprotein [Pgp])



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%
Lamotrigene [Lamictal]	< 60%

*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

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

"Red Flags": Think Induction When You See ...

Clinically Relevant Inducers

Carbamazepine	Rifampin
Phenobarbital	*Chronic* alcohol
Phenytoin	Chronic smoking
Primidone	Charbroiled meats
Prednisone	Cruciferous vegetables
Ritonavir (chronic)	St. John's Wort

"Red Flags": Think Inhibition When You See...

Clinically Relevant Inhibitors

Antifungals (azoles)	SSRIs	*Acute* alcohol
Macrolide antibiotics	Phenothiazines	Cimetidine
Fluoroquinolones	Valproic acid	Quinidine
Antiretrovirals	Nefazodone	Ca++ ch. blockers
Isoniazid	Duloxetine	Grapefruit juice
Antimalarials	Bupropion	Propafenone
Disulfiram	β-blockers	Amiordarone

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**
- **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)

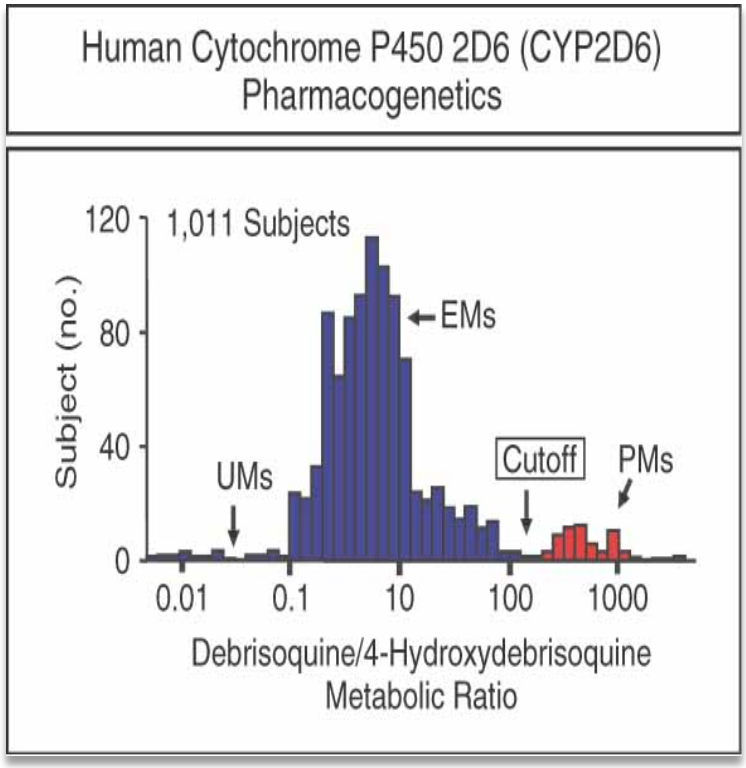
Steadily evolving knowledge on hundreds of alleles for common P450 isoenzymes (cf. www.imm.ki/CYPalleles/)

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

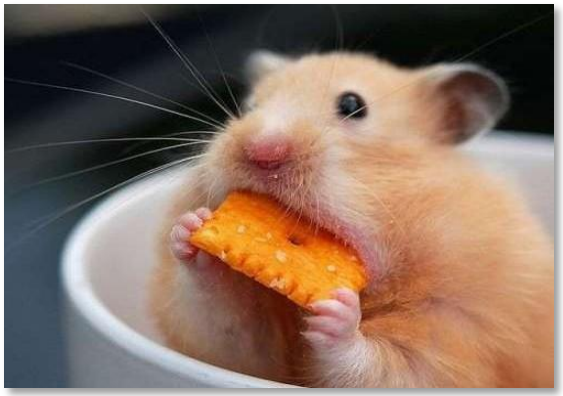
Extensive *(Normal)*

- Susceptible to **normal degrees of induction or inhibition** with inducers and inhibitors
- Convert to poor metabolizers functionally in 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

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 10 Drug Interactions involving Psychotropic Medications

#1 MAOI Interactions

Hypertensive Crises:

- *With **sympathomimetics***
  - includes OTCs (pseudoephedrine, phenylephrine, oxymetazoline [Afrin]
  - Involves **inhibition of MAO-A** primarily (hence selegiline [Emsam] at ≤ 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 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

Serotonin Syndrome: Hunter Criteria

Hunter Serotonin Toxicity Criteria: Decision Rules

In the presence of a serotonergic agent:

1. IF (spontaneous clonus = yes) THEN serotonin toxicity = YES
2. ELSE IF (inducible clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
3. ELSE IF (ocular clonus = yes) AND [(agitation = yes) OR (diaphoresis = yes)] THEN serotonin toxicity = YES
4. ELSE IF (tremor = yes) AND (hyperreflexia = yes) THEN serotonin toxicity = YES
5. ELSE IF (hypertonic = yes) AND (temperature > 38°C) AND [(ocular clonus = yes) OR (inducible clonus = yes)] then serotonin toxicity = YES
6. ELSE serotonin toxicity = NO

ANY OF THE FOLLOWING SETS (A-E)

(A) Spontaneous clonus

(B) Inducible clonus plus agitation or diaphoresis

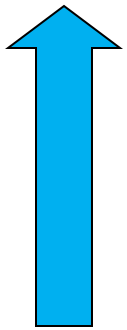
(C) Ocular clonus plus agitation or diaphoresis

(D) Tremor plus hyperreflexia

(E) Hypertonicity plus fever plus ocular clonus or inducible clonus

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

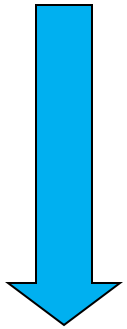
#2 Lithium Interactions



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 alkalinization (acetazolaminde, sodium bicarbonate)
- Sodium chloride
- Osmotic diuretics (mannitol)

#3 P450 2D6 Inhibition

Potential consequences...

- Increased levels of TCAs, β-blockers (lipophilic – including proprolol 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

SSRIs, SSNRIs and P450 2D6 Inhibition

SSRI/SNRI	1A2	2C	2D6	3A
Fluoxetine	-	++	++++(++++)	+ (++)
Sertraline	-	+ (+)	+	+ (+)
Paroxetine	-	-	++++	-
Fluvoxamine	++++	++	-	+++
Escitalopram	-	-	-	-
Citalopram	-	-	+	-
Vilazodone	-	+	+	-
Venlafaxine	-	-	(+)	-
Desvenlafaxine	-	-	+	-
Duloxetine	-	-	+++	-
Levomilnacipran	-	-	-	-
Vortioxetine	-	-	-	-

+ = inhibition

() = metabolite effect

Other Antidepressants and P450 Inhibition

Drug	1A2	2C	2D6	3A
Bupropion	-	-	++++	-
Nefazodone	-	-	-	++++
Mirtazapine	-	-	-	
Reboxetine	-	-	-	
St. John's Wort	-	-	-	---

--- = suspected induction

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, cimeditine, 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, cyclosporine, opiates, calcium channel blockers, pimozide, ketamine, statins, OCPS, valbenazine, THC and cannibidiol (CBD), some director oral anticoagulants (rivaroxaban and apixaban)
- Increased pimozide may cause arrhythmias;
- Increased carbamazepine may cause delirium, seizures
- Increased methdone, 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)

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, diazepam, disopyramide, efavirenz, estradiol, eszopiclone, fentanyl, guanafacine, iloperidone, indinavir, HMG-CoA reductase inhibitors (lovastatin, simvastatin), ketamine, levomilnacipran, lidocaine, loratadine, 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, 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, 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, cruciferous vegetables, insulin, omeprazole, modafinil, ritonavir, smoking (cigarettes, marijuana)

#7 TCAs, Low Potency and Some Atypical Antipsychotics

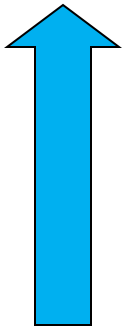
Potential for…

- Additive/synergistic anti-histamine, anti-muscarinic, anti-α_1-adrenergic and quinidine-like effects

#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 lamotrigene and valproate, thereby reducing levels of these anticonvulsants by as much as 50%**
  - Anticipated dose increase for lamotrigene; possibly for valproate (therapeutic drug monitoring is needed after OCP added)

#9 Valproate Inhibition of Metabolism

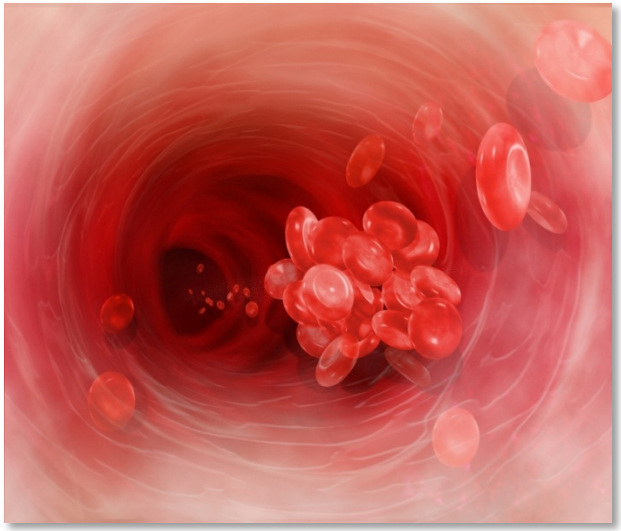


Increased levels of:

- 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: Increased Bleeding Risk with SSRIs and Other Agents

- 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
- Interference of metabolism (increased levels) of warfarin by P450 2C9 inhibitors (e.g., fluoxetine)
- Interference of metabolism (increased levels) of several direct oral anticoagulants (apixaban – Eliquis; rivaroxaban – Xarelto) by P3A inhibitors (e.g., fluoxetine, fluvoxamine)



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), 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 **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 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**

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**