

C, Y, P.... it's as Easy as 450!

Assessing the Clinical Significance of Common Drug-Drug Interactions in SUD Care

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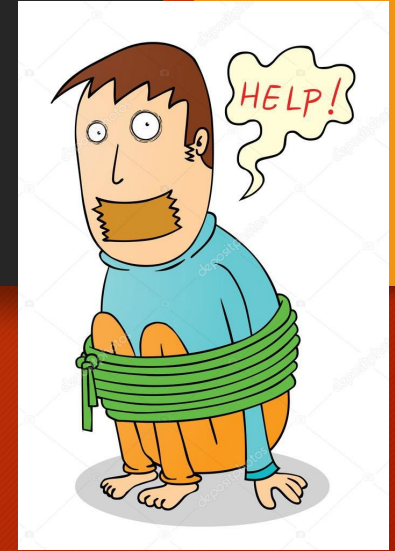
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Learning Objectives

- Describe how pharmacokinetic (PK) parameters are used to assess medication interactions in SUD care
- Describe the CYP450 enzymes including common substrates, inhibitors, and inducers and expected timeframe of CYP450 enzyme interactions
- Identify key psych/SUD medications involved in CYP450 enzyme and P-glycoprotein interactions
- Apply PK and medication interaction knowledge to a patient scenario involving SUDs

Important Terms: we'll dive into each in more detail, but here's the first seed.

- Substrate: medication (substance) that uses a specific enzyme for metabolism
 - E.g., methadone is a CYP450 3a4 substrate so it is metabolized by 3a4
- Inhibitor: a medication (substance) that inhibits a specific enzyme so that it becomes much less active, which reduces metabolism of any substrates
 - E.g., ketoconazole is a 3a4 inhibitor so when it is combined with simvastatin, the levels will increase and can cause fatal overdose
 - Example: methadone and ketoconazole
- Inducer: a medication (substance) that causes a specific enzyme to become expressed more, which increases the metabolism of any substrates
 - E.g., rifampin is a 3a4 inducer so when it is combined with methadone, the levels of methadone will lower and can cause acute opioid withdrawal



Types of drug interactions

- **Pharmacokinetic**: What the body does to the drug
 - Traditionally ADME; now ADME-T
 - Majority are CYP450 enzyme interactions
- **Pharmacodynamic**: What the drug does to the body
 - Receptor binding and cellular influence
 - Must be considered for additive effects, synergy, and oppositional effects

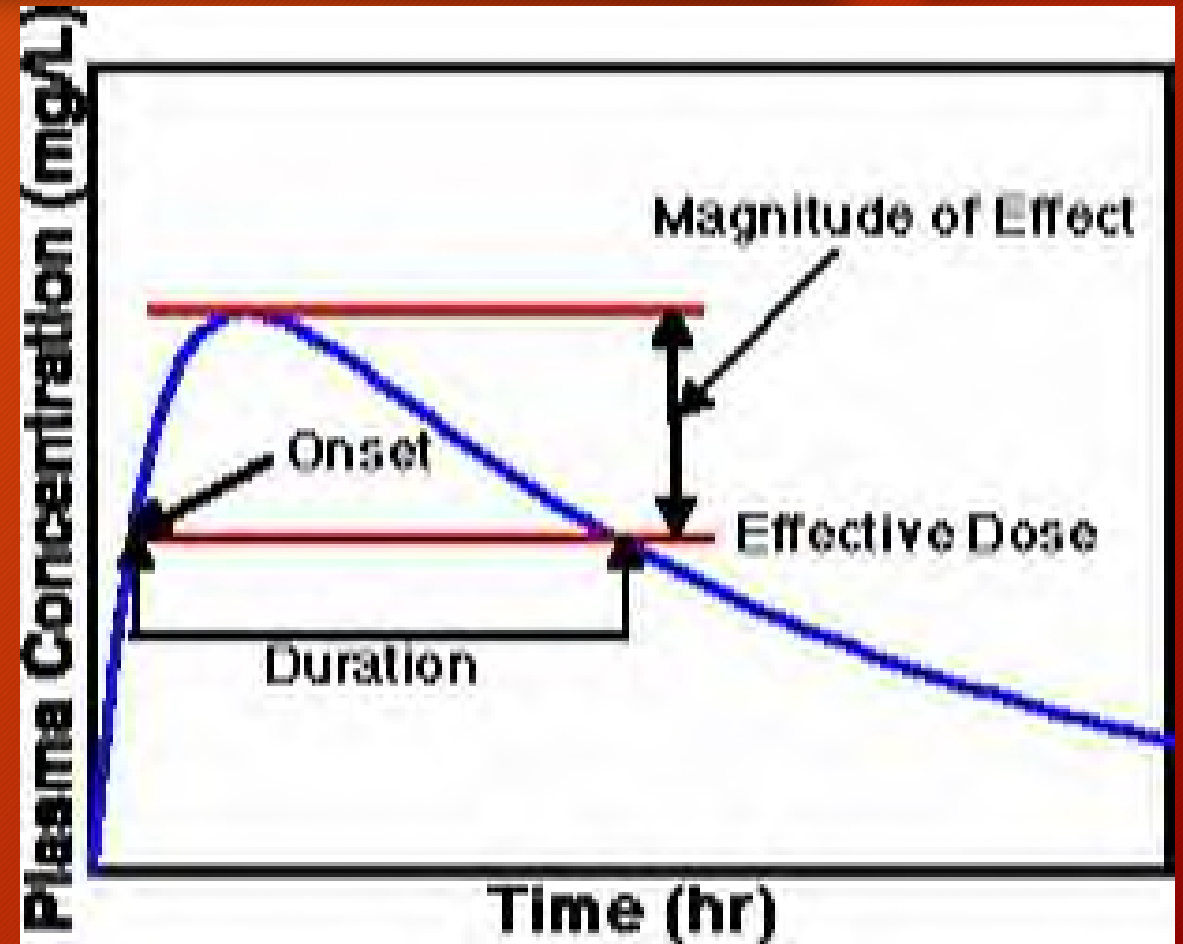


Focus for today

Pharmacokinetics and PK interactions

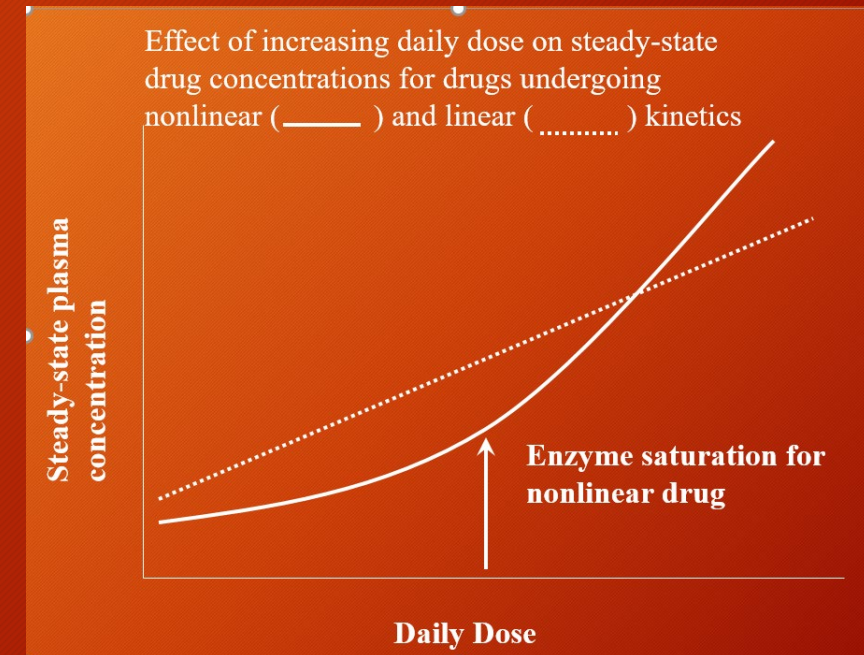
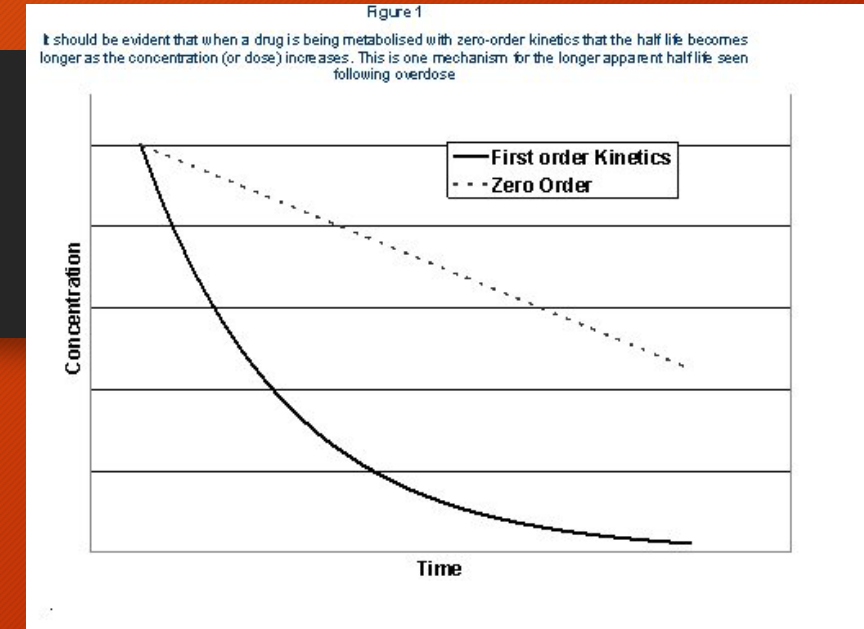
Classic time concentration curve for a single dose

- Where is C_{max} on this curve?
- Where is T_{max} on this curve?
- Why is knowing each of these important for assessment of drug-drug interactions (DDIs)?



First order (linear) vs zero order kinetics

- Almost all drugs follow 1st order kinetics, except in overdose
- First order kinetics
 - Levels increase proportionally to dose increases
 - Constant fraction of total drug stores eliminated per unit time
 - We can then determine when 50% will be gone and name this a half life ($T_{1/2}$)
- Zero order
 - Constant amount (vs %) eliminated per unit time regardless of drug stores
 - No proportionality of dose with serum level
 - Often due to saturation of transporters or metabolic enzymes so kinetics switch from 1st to 0 order
 - E.g., phenytoin 50% dose increase -> 300% increase in level

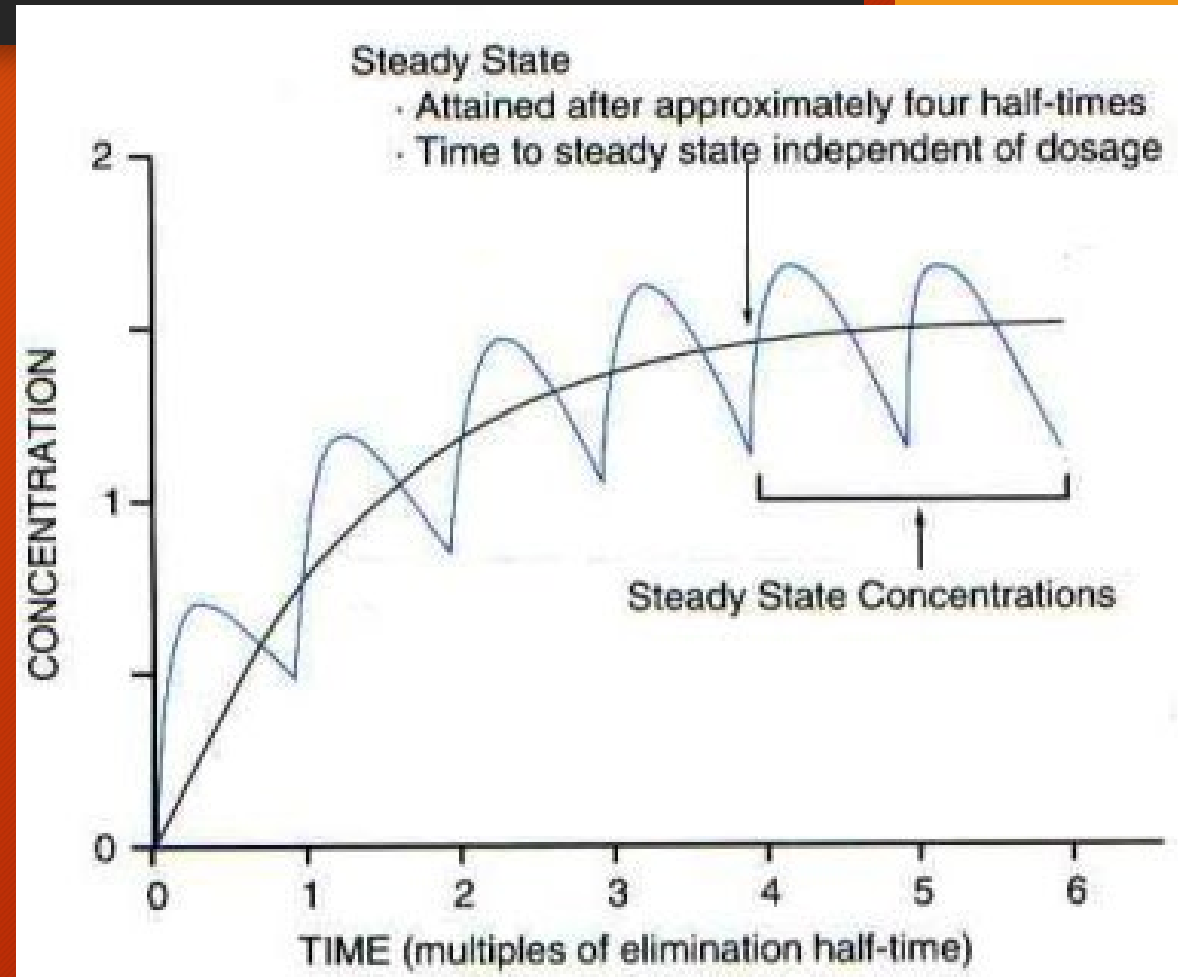


Half-life

- Time it takes for half of an administered drug to be eliminated
 - only for medications which follow first order kinetics
 - *Regardless* of starting amount
 - Doesn't apply to some drugs or many toxicology cases
- Defines the time needed for equilibrium in levels (steady-state) to occur after initiation and dose changes
- Defines the time needed for complete elimination of drug from the body after discontinuation (4-5 half-lives)
- Critically important to help understand and predict the outcomes of medication interactions

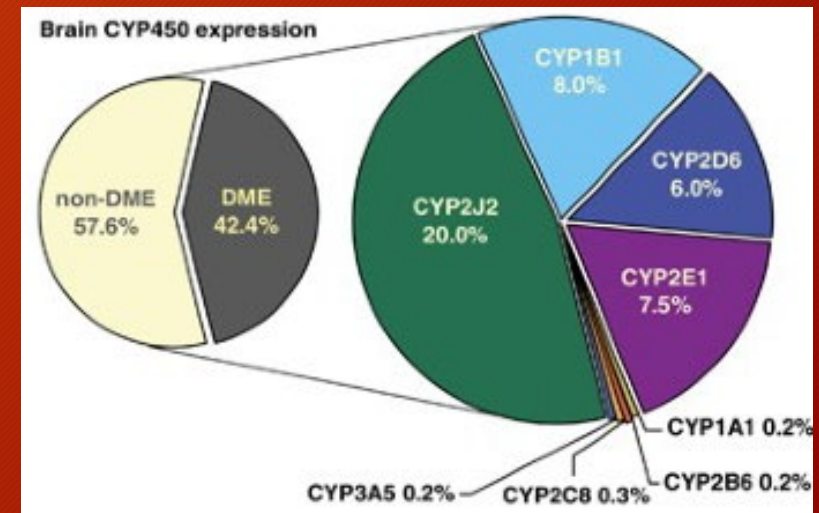
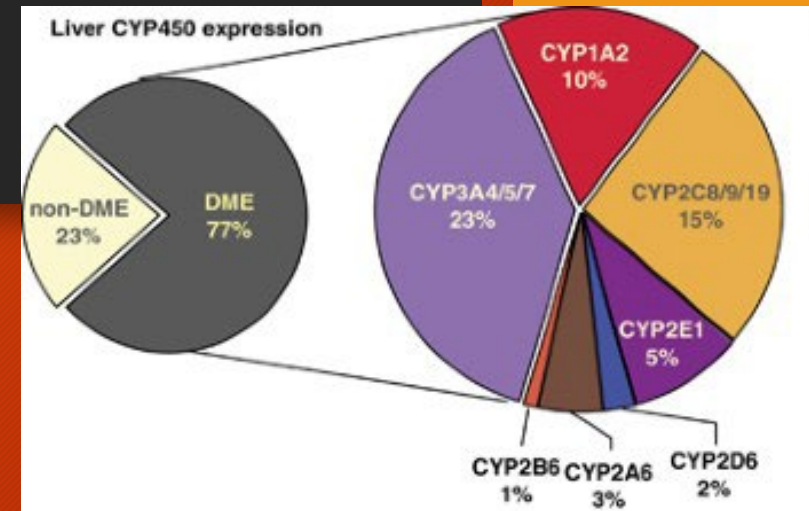
Pharmacokinetic Principles: Steady State

- Steady state (SS):
 - drug amount eliminated equals drug amount administered (equilibrium)
 - relatively constant serum drug level
 - occurs after 4-5 half-lives
- The full extent of medication inhibition usually occurs at the new SS of the substrate
- Sometimes the inhibitor must be at SS to become clinically significant (varies by medication), for others it is a specific dose (e.g., sertraline vs valproic acid)



Metabolism

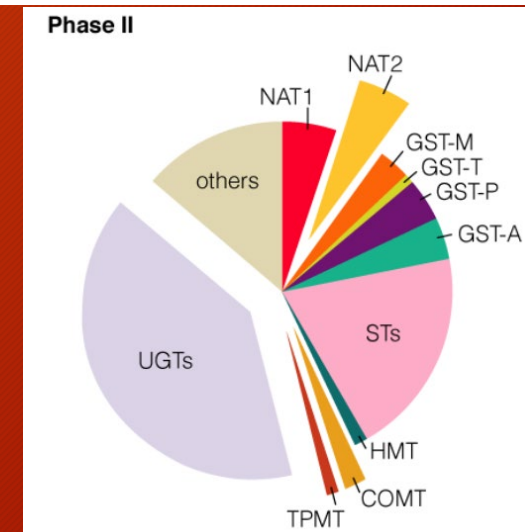
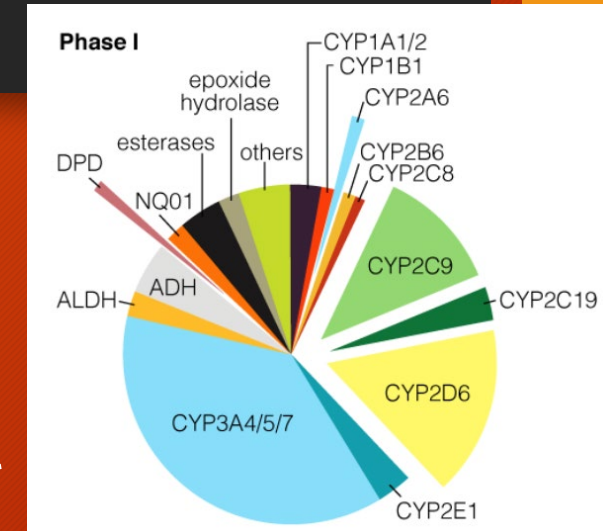
- Mostly occurs in the liver, but also in the intestines, brain, blood, etc
- Purpose: to rid the body of toxins (drugs), usually by making them water soluble (polar)
 - Sometimes a prodrug is activated or other active metabolites are formed



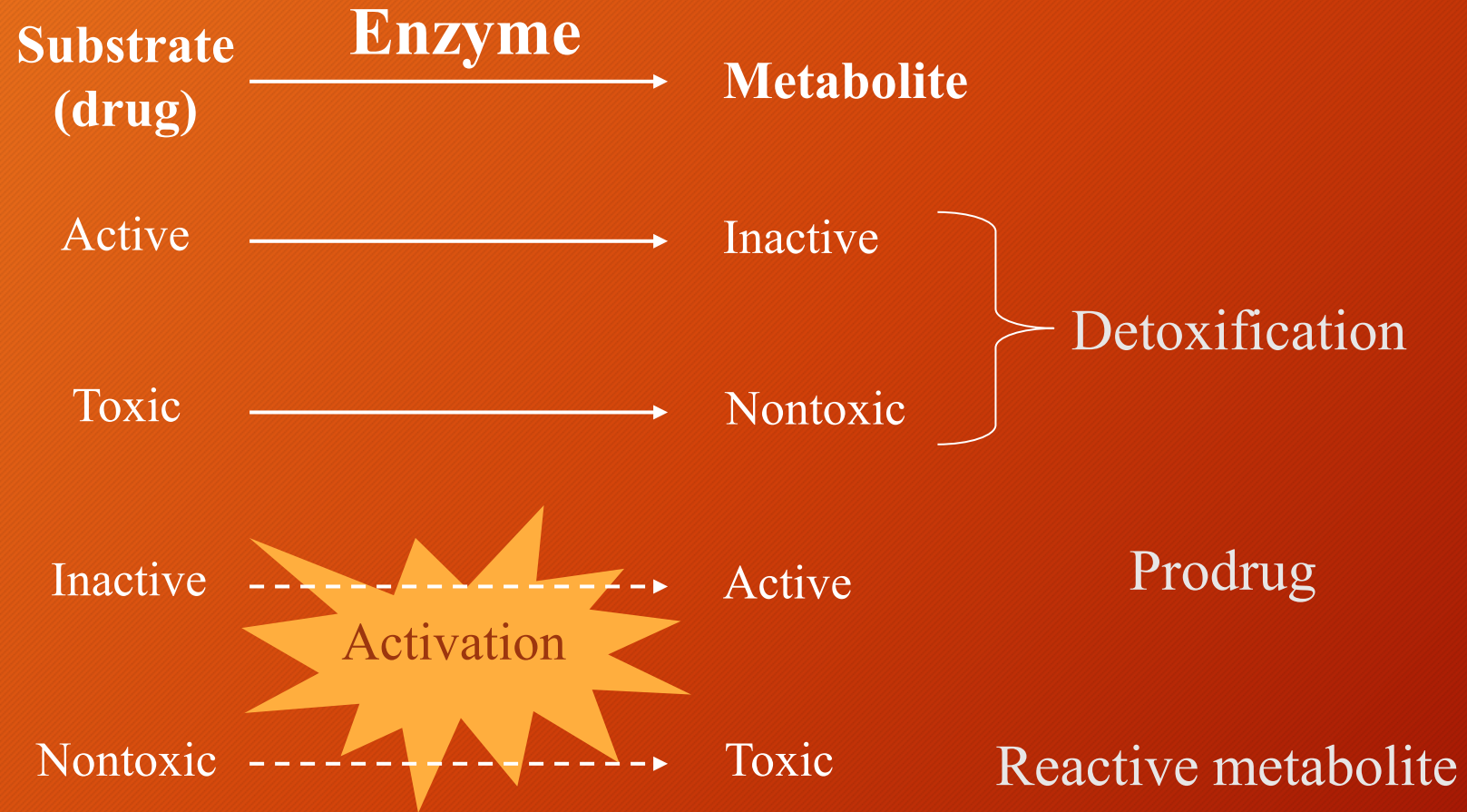
Drug Metabolism

Graphics: Percentage of each enzyme contribution to phase I and II metabolism (note: based on medications available in 1999)

- Phase I reactions: hydrolysis, oxidation, reduction, dealkylation, deamination, etc
 - May be inhibited
 - May be induced (e.g., barbiturates, carbamazepine, phenytoin, rifampin, smoking, St John's wort)
 - Genetic differences in functionality of many Phase I reactions (CYP 2D6, 2C9, 2C19, etc)
- Phase II reactions: glucuronidation, acetylation
 - Generally preserved with liver dysfunction
 - Important interaction story: lamotrigine phenobarbital and valproic acid



Most Outcomes of Drug Metabolism



Parent	Metabolite vs. Parent	Example
Active	↑ Activity	Bupropion
Active	↔ Activity	Venlafaxine Risperidone Fluoxetine
Active	↓ Activity	Quetiapine
Active	Opposite activity	Nefazodone
Active	Inactive	Duloxetine
Inactive	Active	Tamoxifen

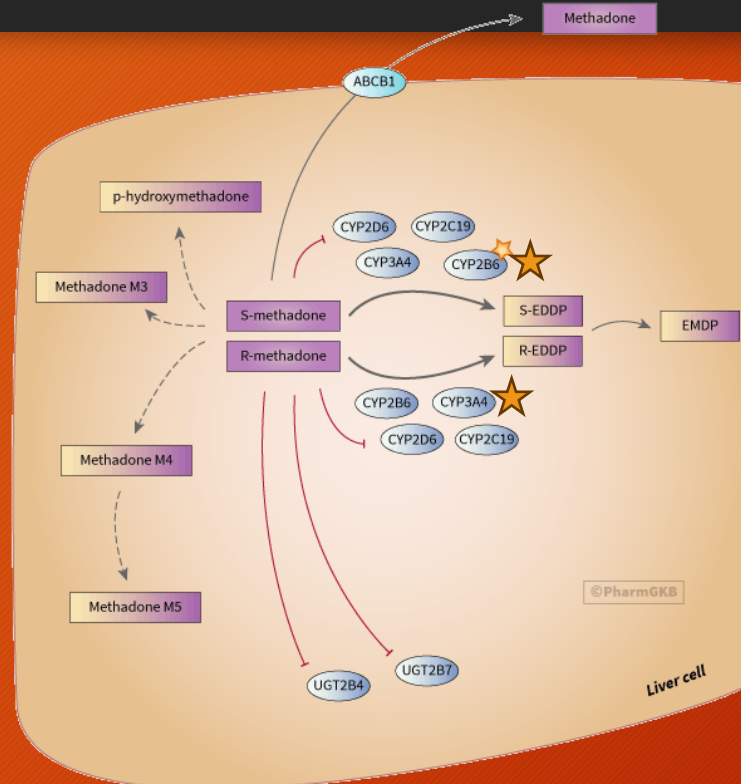
Examples of Active Metabolites

- Diazepam (desmethyl and nor metabolites) $T_{1/2} = 100-200$ h
- Venlafaxine (desvenlafaxine)
- Bupropion (hydroxybupropion)
- Tramadol (M2)
- Risperidone (paliperidone)
- Fluoxetine (norfluoxetine)
- Acetaminophen (NAPQI)
- Heroin (morphine)

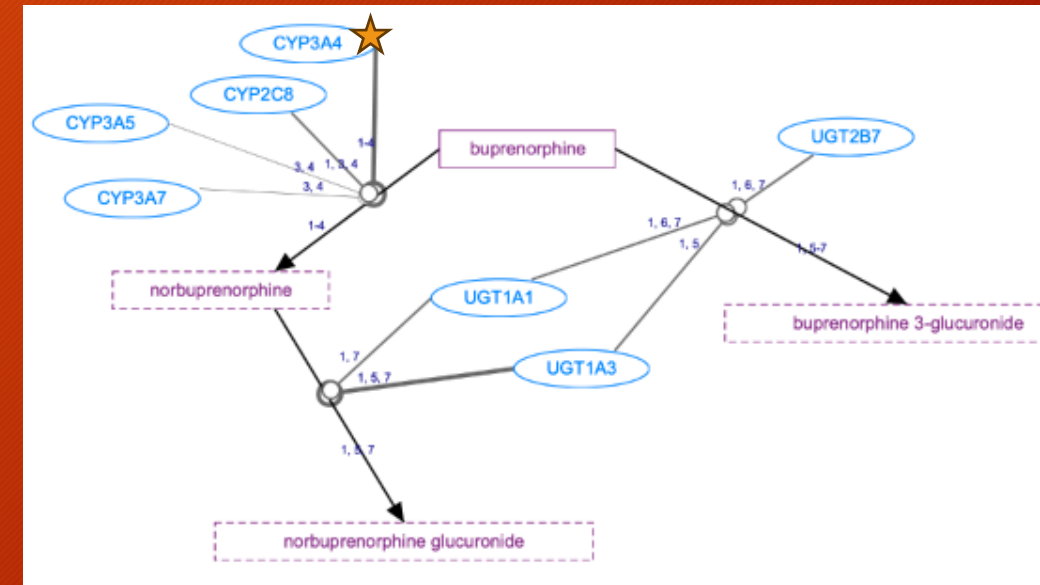
	SUD indication	Substrate of	Inhibits	Induces
methadone	OUD	2B6, 3A4 (major w/ 3A4 ind) Minor: 2C9/19, 2D6, 3A4 (w/ 3A4 inh)	2D6 (weak)	-
buprenorphine	OUD	3A4	-	-
naltrexone	OUD, AUD, StUD	-	-	-
acamprosate	AUD	-	-	-
topiramate	AUD, StUD	-	-	3A4 (>200mg/d)
gabapentin	AUD	OCT2	-	-
disulfiram	AUD	Minor: 1A2, 2A6, 2B6, 2D6, 2E1, 3A4	2E1 (strong), 1A2 (weak)	-
valproic acid	AUD (w/d)	Minor: 2A6, 2B6, 2C9/19, 2E1	UGTs (strong)	-
diazepam	AUD (w/d)	3A4, 2C19 Minor: 1A2, 2B6, 2C9	-	-
phenobarbital	AUD (w/d)	2C19 (major w/ 2C19 inh) Minor: 2C9, 2E1, 2C19 (w/ 2C19 ind)	-	Mod: 3A4, UGT1A1, PGP Weak: 1A2, 2A6, 2B6, 2C9
baclofen	StUD	-	-	-
bupropion	TUD, StUD	2B6 Minor: 1A2, 2A6, 2C9, 2D6, 2E1, 3A4	2D6 (strong)	-
N-acetylcysteine	CanUD	-	-	-
varenicline	TUD	OCT2, MATE1/2-K	-	-
mirtazapine	StUD	3A4 Minor: 1A2, 2C9, 2D6	-	-
smoking	Active TUD/CanUD	1A2	-	1A2

Metabolic Pathway for Medications for Opioid Use Disorder (MOUD)

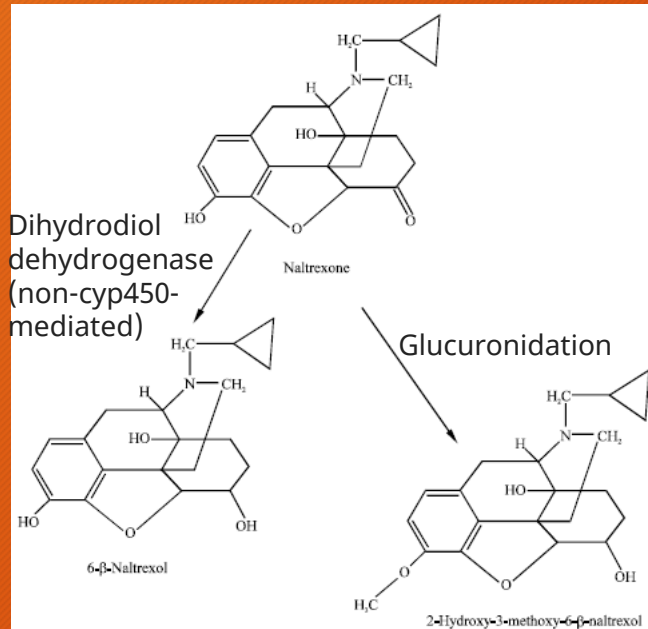
- Methadone
- Buprenorphine
- Naltrexone



<https://www.clinpgx.org/pathway/PA166247541>

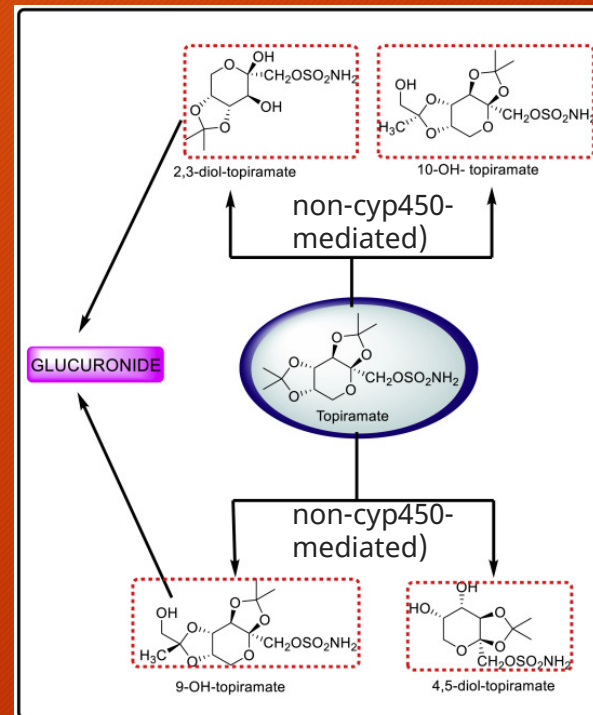


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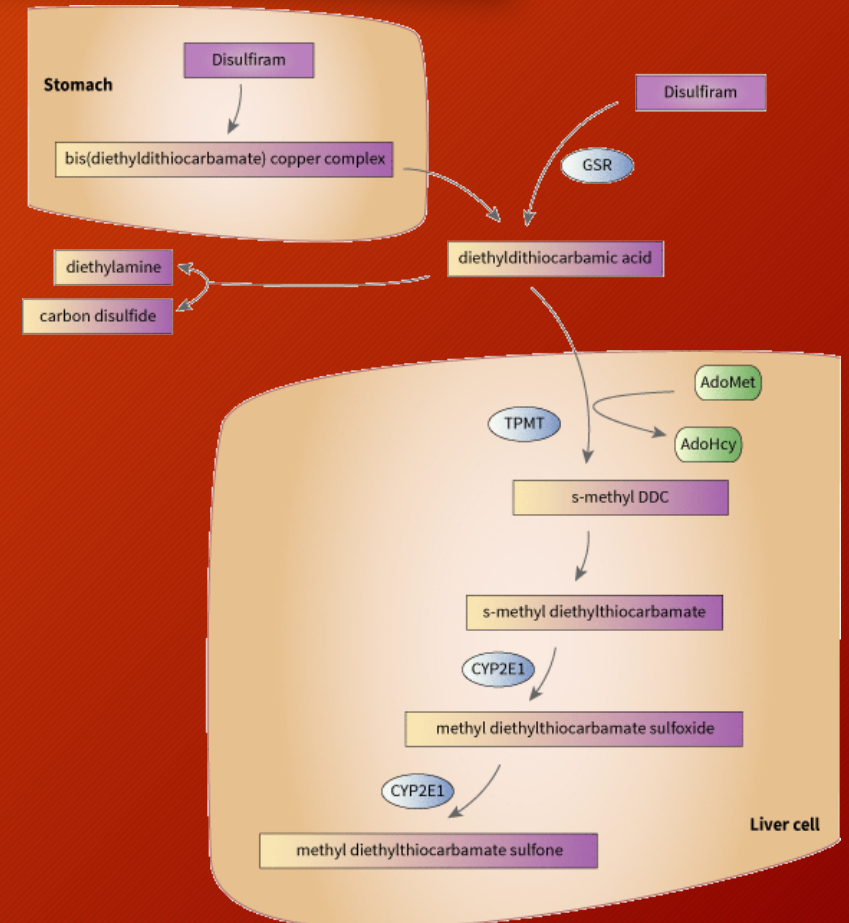


Metabolic Pathway for Medications for Alcohol Use Disorder (MAUD)

- Naltrexone (see MOUD)
- Acamprosate (no metabolism)
- Disulfiram
- Topiramate
- Gabapentin (no metabolism)



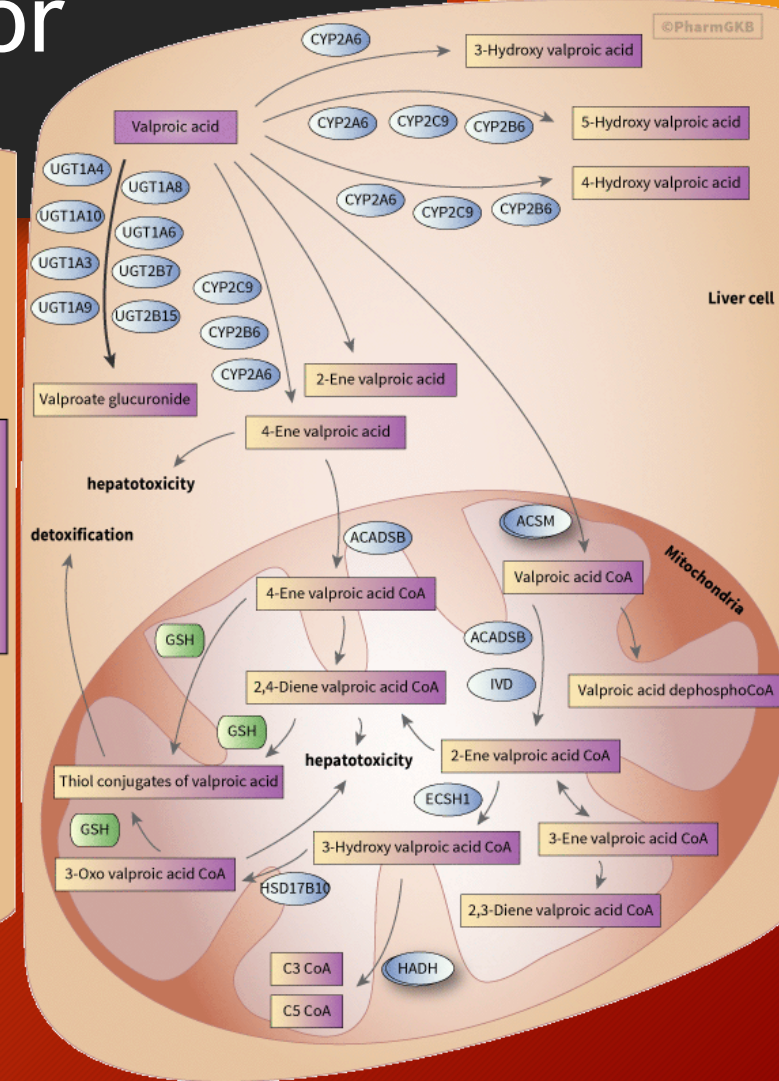
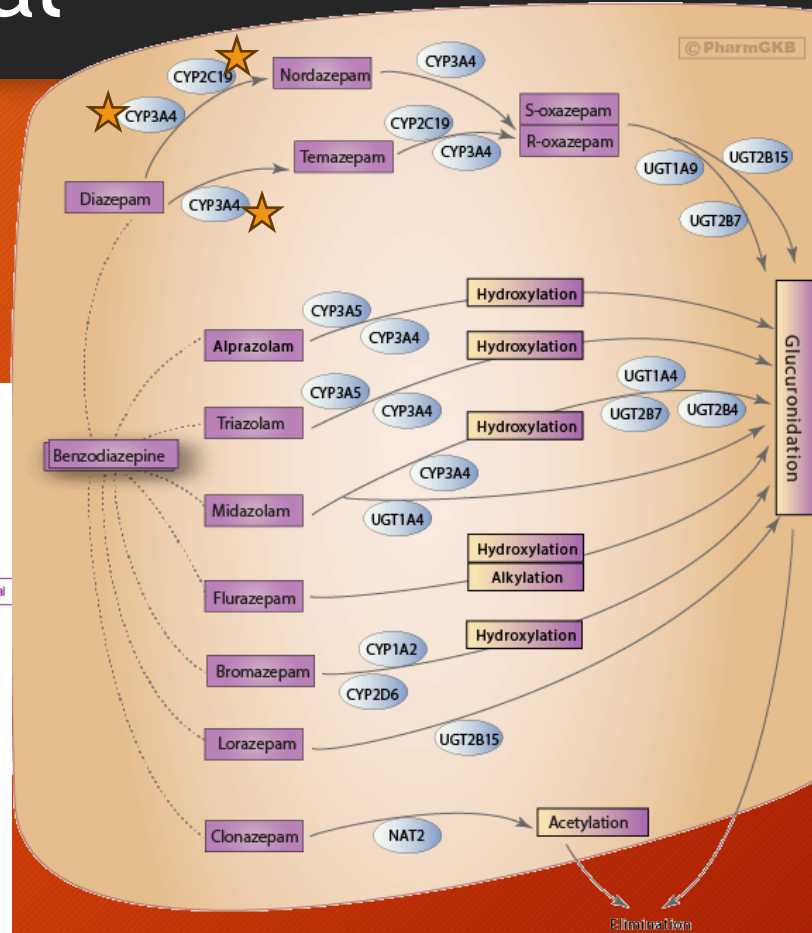
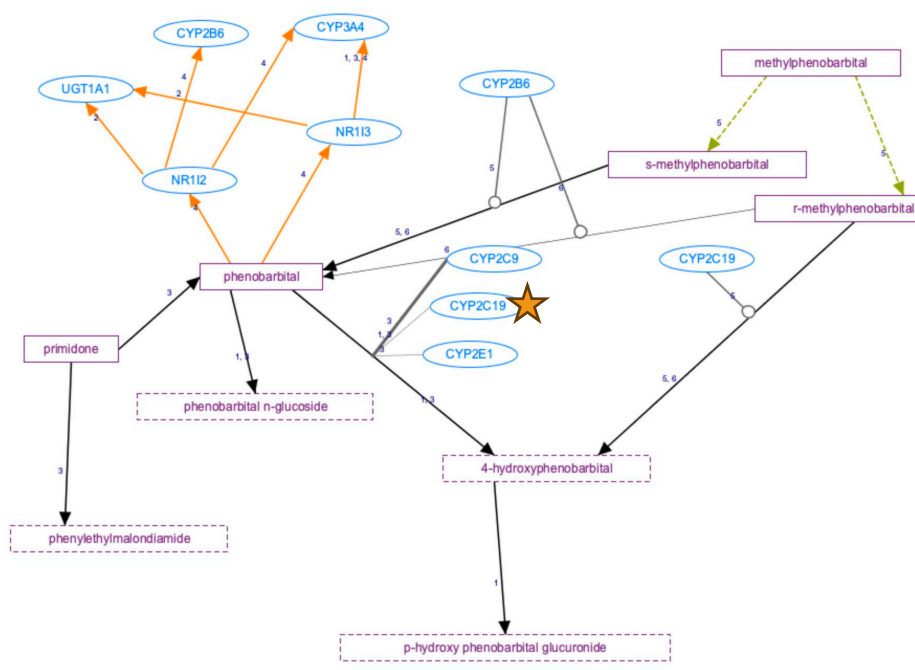
<https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/phentermine-topiramate>



<https://www.clinpgx.org/pathway/PA166287601>

Metabolic Pathway for Medications for Alcohol Withdrawal

- Valproic acid
- Benzodiazepines
- Phenobarbital



<https://www.clinpgx.org/pathway/PA165111375>

<https://www.clinpgx.org/pathway/PA165964265>

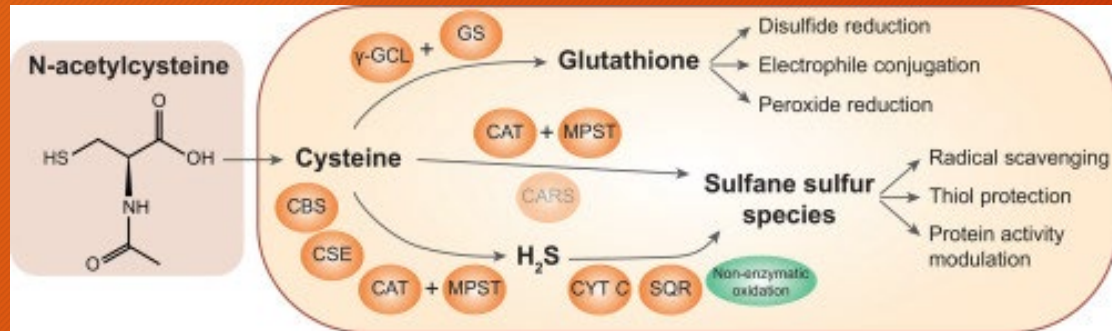
<https://www.clinpgx.org/pathway/PA166348361>

- Baclofen (only ~15% metabolism)
- Bupropion
- Naltrexone (see MOUD)
- Mirtazapine



Metabolic Pathway for Medications for Tobacco Use Disorder (MTUD) and Cannabis Use Disorder (MCanUD)

- Bupropion (see StUD)
- Varenicline (only ~8% metabolism)
- N-acetylcysteine



<https://www.sciencedirect.com/science/article/pii/S0163725821001182>

Essence of CYP450 interactions: active to inactive

Substrate
(drug)

P450
enzyme

Metabolite

Active

Inactive

Normal

Fentanyl, norfentanyl
Inh: grapefruit inhibits lurasidone
Ind: rifampin, induces methadone

Active

P450
enzyme

Inactive

Inhibition

What
happens to
the
medication
effect with
inhibition?

Active

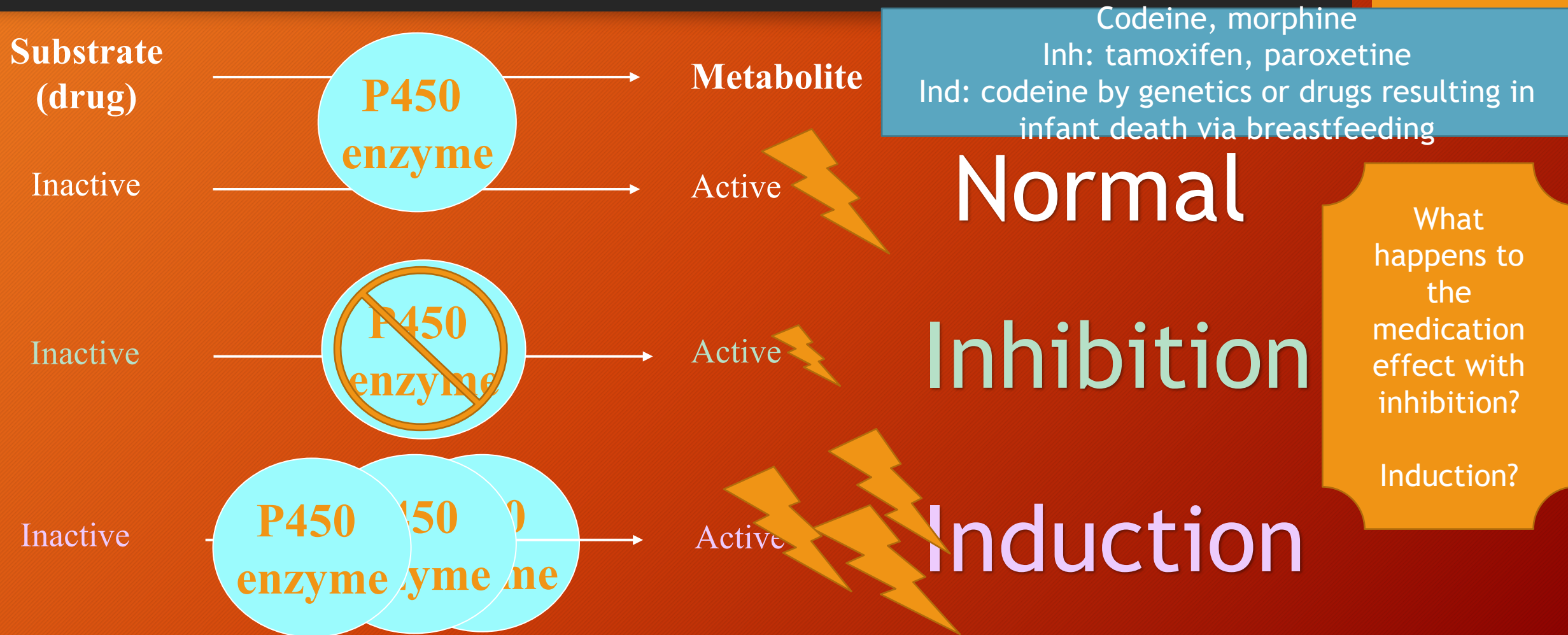
P450 P450 P450
enzyme enzyme enzyme

Inactive

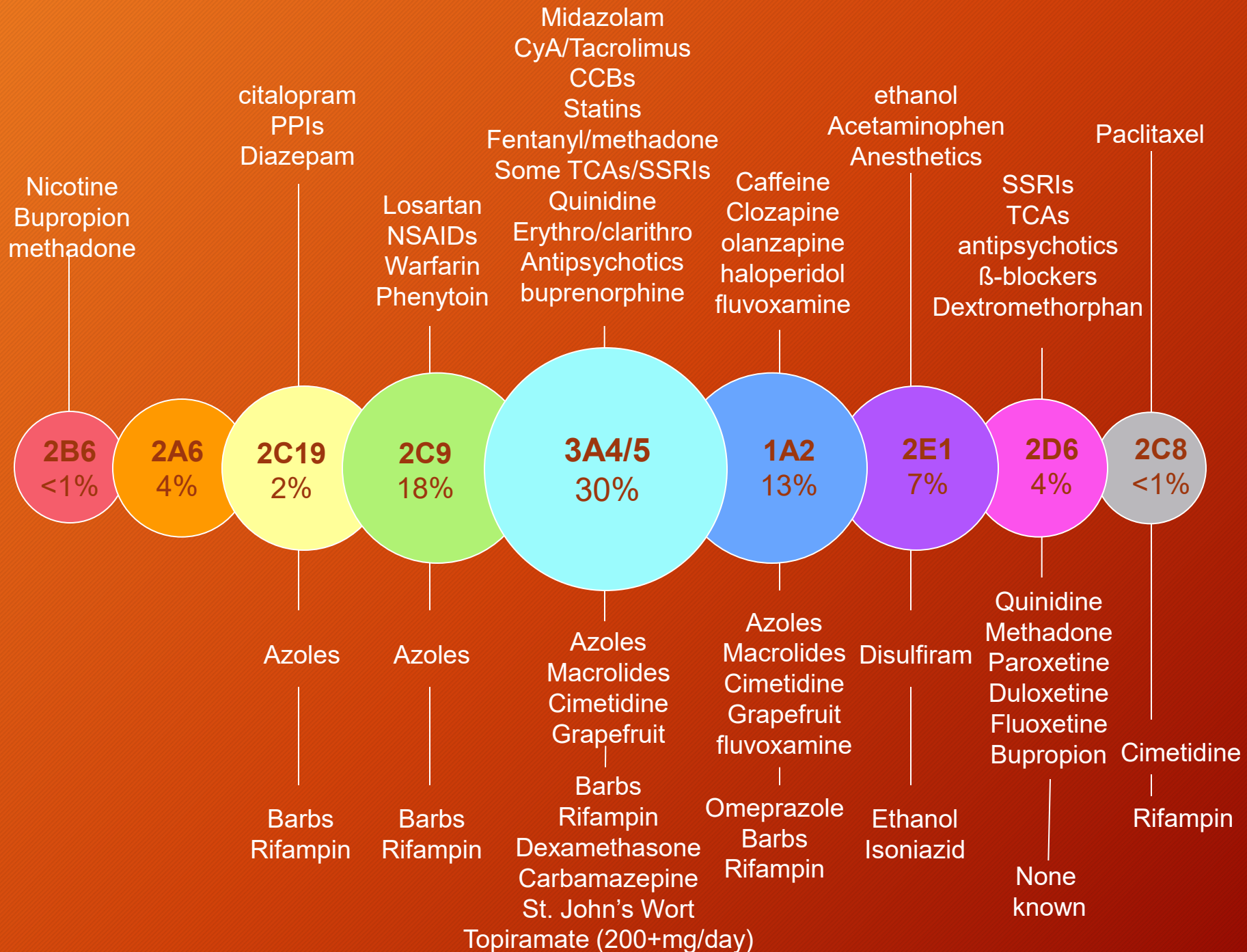
Induction

Induction?

Essence of CYP450 interactions: inactive to active



CYP450 Substrates



Patient Scenario 1: MOUD

- 45 yo male with a history of hypertension, OUD, and hyperlipidemia
 - Presents with symptoms of muscle weakness/pain and excessive sedation
 - No unusual or strenuous activity and continues to receive his usual methadone dose at his clinic. No other opioids have been taken.
 - Medications include amlodipine and atenolol for hypertension, methadone for OUD, and simvastatin for elevated cholesterol
 - The only change the patient reports is a new “grapefruit diet” that he has been trying. The diet consists of one large grapefruit in the AM and grapefruit juice several times during the day and at mealtimes.
-
- What is going on here?
 - Would you expect the same outcome if this patient was taking buprenorphine?

- *Methadone is a major 3A4 and 2B6 substrate and simvastatin is 3A4. Grapefruit juice is inhibiting CYP 3A4 metabolism in the gut, concurrent grapefruit juice consumption allows for more simvastatin and methadone to be absorbed, leading to excess serum levels of these drugs.*
- *Risk of OD - monitor carefully and ensure take home naloxone is available. Stop the grapefruit and switch.*
- *Buprenorphine is safer due to partial agonism and reduced risk of OD. Still recommend switch juices.*

Grapefruit

- One whole grapefruit or 200 mL of grapefruit juice is sufficient to cause clinically relevant DDIs
 - Most profound 4 hours after ingestion (50% at 10 hours and 25% at 24 hours)
 - DDIs also occur with sufficient quantities of Seville oranges (often used in marmalades), limes, and pomelos
 - Does not occur with sweet oranges (e.g., navel or Valencia)
- CYP450-3A4 inhibition by furanocoumarins
 - Mainly Intestine (so most applicable to PO administration)
 - Markedly increased absorption via inhibition of 3a4-mediated intestinal metabolism (increases C_{max})
 - Much lesser extent in the Liver:
 - Decreased hepatic 3A4 metabolism, increasing duration of effect (increases $T_{1/2}$) for some medications
 - Furanocoumarins are metabolized by CYP3A4 to reactive intermediates that bond covalently to the active site of the enzyme, causing irreversible inactivation
 - CYP3A4 activity in the small intestine is impaired until de novo synthesis returns the enzyme to its previous level (about 3 - 7 days)
- Can also cause mild P-GP and OATP inhibition

Intestinal metabolism

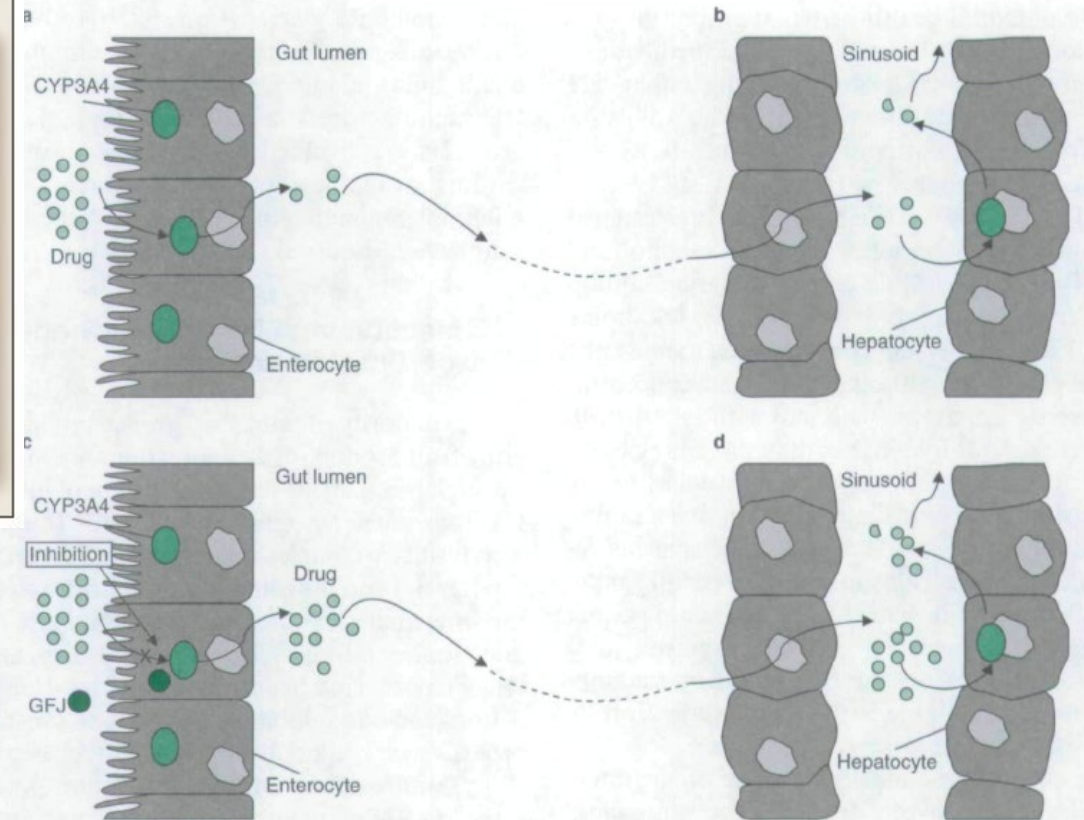
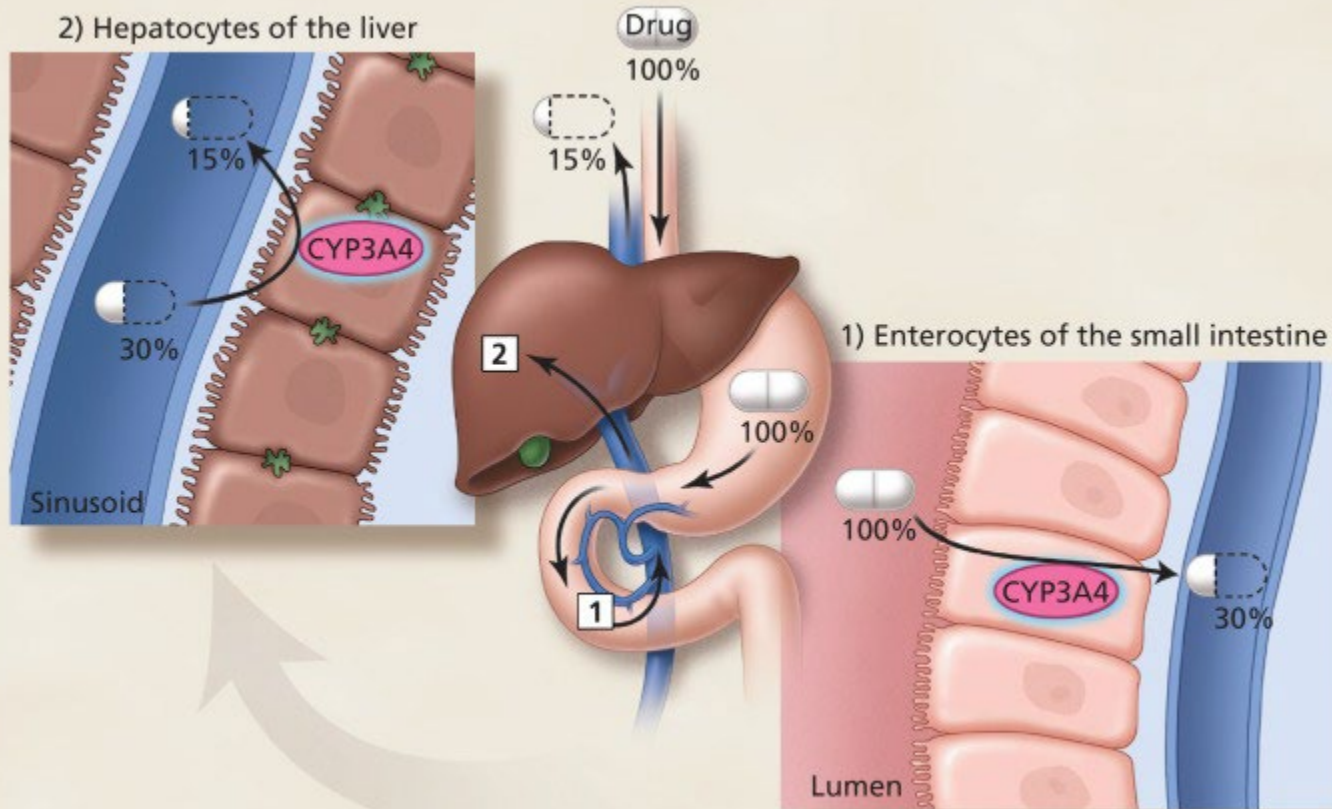


Fig. 1. Schematic representation of the first-pass metabolism of a cytochrome P450 (CYP) 3A4 substrate (e.g. felodipine) in the absence of grapefruit juice (GFJ) in (a) the intestine and (b) the liver, and in the presence of GFJ in (c) the intestine and (d) the liver. CYP3A4 substrates with a high first-pass metabolism are extensively metabolized in the epithelium of the intestine before passage into the liver, where further metabolism takes place, thus lowering bioavailability. GFJ or grapefruit-containing products specifically inhibit intestinal CYP3A4-mediated metabolism. Therefore, in the presence of GFJ, CYP3A4 metabolism is reduced and more substrate is available to pass to the liver. Although metabolism is unaffected here, more substrate is bioavailable and free to enter the systemic circulation, e.g. felodipine.

- Buspirone
- Dextromethorphan
- Lurasidone
- Oxycodone
- Quetiapine
- Diazepam, triazolam
- Ziprasidone
- Domperidone
- Carbamazepine
- Methadone
- Buprenorphine

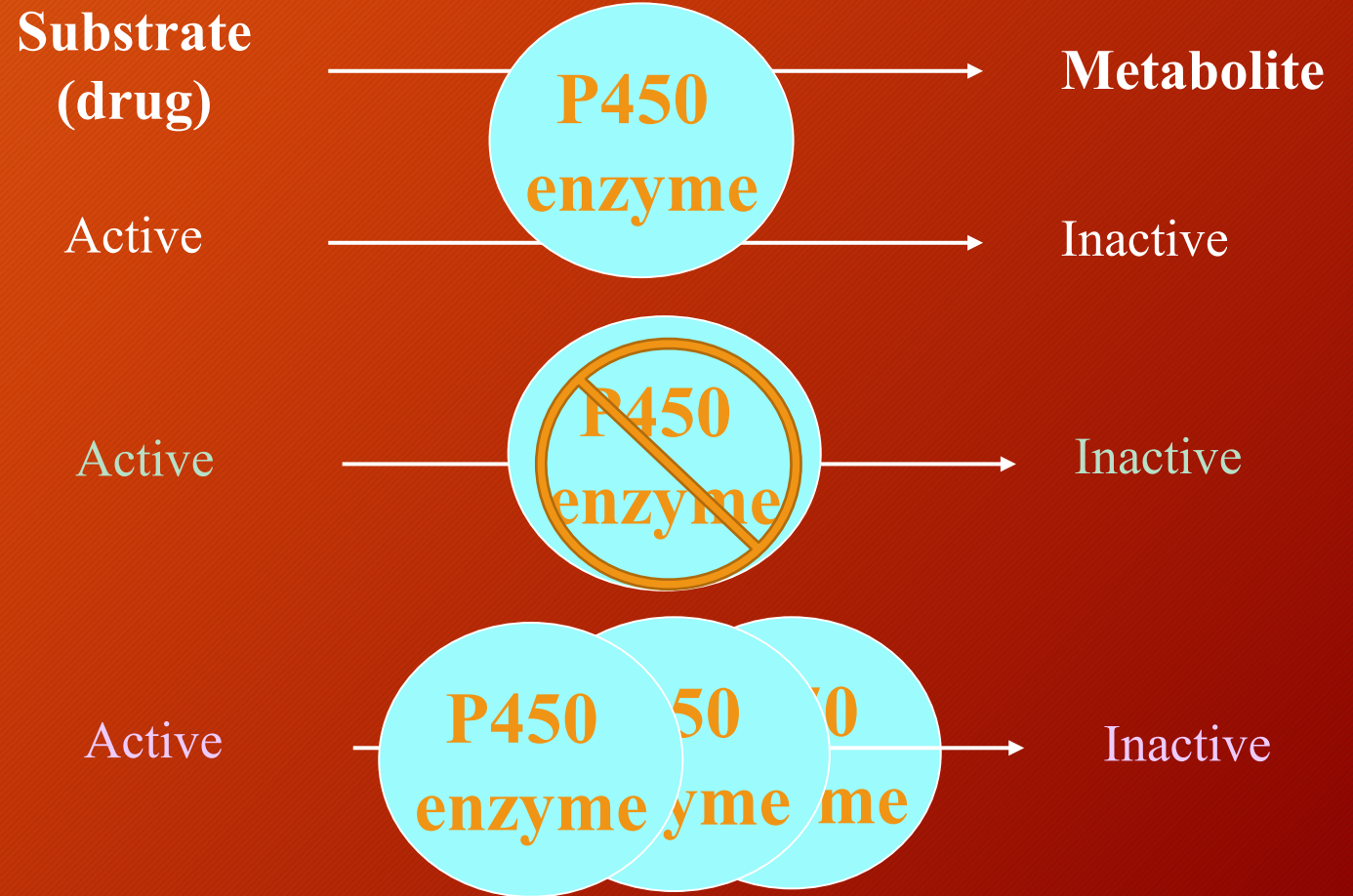
Range of significance: usually mod and strong are important

- Substrates:
 - AUC values of sensitive index substrates increase 5-fold with inhibition or poor metabolism
 - AUC values of moderately sensitive index substrates increase 2- to <5-fold
- Inhibitors:
 - Strong increase the AUC of substrates ≥ 5 -fold
 - moderate increase AUC by 2 to <5-fold
 - Mild increase by AUC 1.25 to <2
- Inducers:
 - Strong decrease the AUC of substrates $\geq 80\%$
 - moderate decrease AUC by 50 - <80%
 - Mild decrease by AUC by 20 - <50%

-----DRUG INTERACTIONS -----	
Factors	Dosage Adjustments for REXULTI (2.5)
Strong CYP2D6* or CYP3A4 inhibitors	Administer half of usual dose.
Strong/moderate CYP2D6 with Strong/moderate CYP3A4 inhibitors	Administer a quarter of usual dose.
Known CYP2D6 poor metabolizers taking strong/moderate CYP3A4 inhibitors	Administer a quarter of usual dose.
Strong CYP3A4 inducers	Double the usual dose and further adjust based on clinical response.

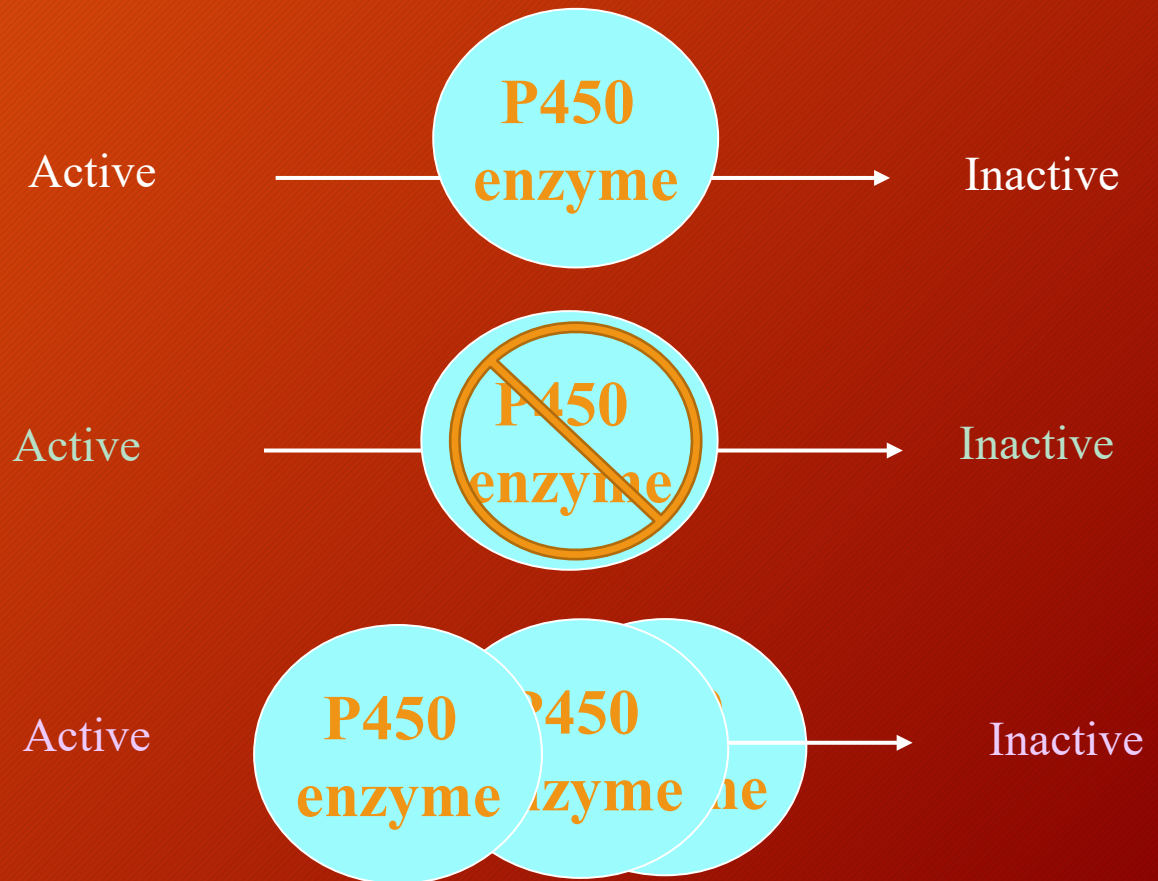
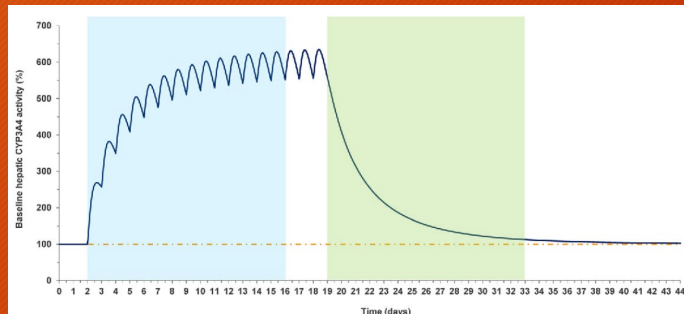
Making it a tiny bit more complicated...

- Let's think on this for 1m and then chat with a partner.....
- What happens when both inhibition and induction are present?
 - a. Substrate levels are equalized to be normal
 - b. Substrate levels are lower
 - c. Substrate levels are higher
- Clozapine -> smoking -> ciprofloxacin
- Lamotrigine + phenobarbital -> valproic acid



Time course of drug interactions matters

- Inhibition starts when inhibitor levels are high enough and peak at inhibitor SS
 - When can we expect to reach max inhibition if half life of inhibitor is 6h?
- Induction is a bit more delayed
 - Rifampin $T_{1/2}$ = 4h but takes about 10 - 14 days for new SS enzyme function
 - Phenobarbital can take up to 3 weeks
 - Why is the onset of induction longer than inhibition?



Other considerations

Metabolism/Transport Effects

Substrate of CYP3A4 (major), OATP1B1/1B3 (SLCO1B1/1B3); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

- Medications can be a substrate for only one enzyme or transporter or multiple enzymes/transporters
 - If it has multiple pathways, it has more wiggle room, but that is where mild inhibitors can sneak up on you
 - Amitriptyline and the Fryeburg fair
 - Note the location of this information in Lexicomp (for methadone) - you will need it for clinical assessment

Metabolism/Transport Effects

Substrate of CYP1A2 (minor), CYP2B6 (minor), CYP2C19 (minor), CYP2C9 (minor), CYP2D6 (major), CYP3A4 (minor); **Note:** Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential

The screenshot shows a web interface for drug interactions. On the left, a sidebar menu has 'Interactions' expanded, with 'Metabolism/Transport Effects' selected. Below it are 'Drug Interactions', 'Food Interactions', and 'Test Interactions'. At the bottom of the sidebar is 'Pharmacogenomics'. The main content area shows a list with 'Opioids' selected. Below this, the heading 'Metabolism/Transport Effects' is followed by text: 'Substrate of CYP2B6 (major), CYP2C19 (minor), CYP2C9 (minor), CYP2D6 (minor), CYP3A4 (major); Note: Assignment of Major/Minor substrate status based on clinically relevant drug interaction potential; Inhibits CYP2D6 (weak)'. Below this text are two buttons: 'Drug Interactions' and 'Open Interactions'.

- Consider % renal vs hepatic for anticipated outcome of interactions

Metabolism: Extensively metabolized by CYP3A4 and, to a lesser extent, by CYP2D6 to active metabolites (desmethyl cariprazine [DCAR] and didesmethyl cariprazine [DDCAR]). DCAR is further metabolized into DDCAR by CYP3A4 and CYP2D6. DDCAR is then metabolized by CYP3A4 to a hydroxylated metabolite.

Half-life elimination: Cariprazine: 2 to 4 days; DCAR: 1 to 2 days; DDCAR: 1 to 3 weeks

Time to peak, plasma: Cariprazine: 3 to 6 hours

Excretion: Urine (21%; 1.2% as unchanged drug cariprazine)

Purposeful inhibition

- Ritonavir + many antiretrovirals
- Cobicistat + many antiretrovirals
- Quinidine/bupropion + dextromethorphan
- Clozapine + fluvoxamine
- Caffeine and smoking?

P glycoprotein (PGP)

- Prevalent and non-discriminant ATP dependent efflux transport system
- Protective mechanism against a wide variety of toxic substances
- Location: intestine, renal tubule, biliary system, CNS, WBC, testes, tumor cell
- Relevance: limits absorption & distribution, and expedites elimination of toxins
- Inhibitors include verapamil, quinidine, ketoconazole, amiodarone, clarithromycin
- Can be functionally inhibited with excessive substrate
 - Loperamide story

Case Reports > J Addict Med. May/Jun 2019;13(3):245-247.

doi: 10.1097/ADM.0000000000000472.

Loperamide-Associated Opioid Use Disorder and Proposal of an Alternative Treatment With Buprenorphine

Lee A Wolfrum ¹, Aimee S Nordmeyer, Christopher W Racine, Stephanie D Nichols

Affiliations + expand

PMID: 30379781 DOI: 10.1097/ADM.0000000000000472

Patient Scenario 2 part 1

- A patient (they/them) presents to the clinic asking about medication for AUD.
- They are currently prescribed ethinyl estradiol as an oral contraceptive and sumatriptan as needed for migraines.
- They have uterine fibroids and require frequent surgical treatments involving opioid therapy.
- What are some MAUD considerations?

Patient Scenario 2 Part 2

- For AUD, they are prescribed topiramate 25mg nightly and titrated up to 300mg per day.
- Six months later, they present to the clinic with amenorrhea and breast tenderness.
- What test should be performed next and how does this new presentation relate to their medication regimen?

Topiramate Dose Dependent Enzyme Induction

- Clinically significant mild-mod 3A4 induction at doses greater than 200mg per day, with higher induction at higher doses (ie. 800mg/day)
- Reduces oral contraceptive exposure (AUC) by 30% in clinical trials
- Not as potent as inducer as carbamazepine, rifampin, or phenobarbital, but still potentially clinically significant in a given patient

TABLE 2. *Fold-increase (compared with untreated control) in the CYP3A4 activity, immunoreactive protein, and mRNA levels in human hepatocytes after 72-h treatment with various drugs*

	Rifampicin ^b 10 μ M	Phenobarbital ^b 2 mM	Topiramate					
			10 μ M	25 μ M	50 μ M	100 μ M	250 μ M	500 μ M
CYP3A4 activity ^a	14.5 $\pm$ 3 ^c	11.9 $\pm$ 4 ^c	1.5 $\pm$ 0.3	1.4 $\pm$ 0.3	1.6 $\pm$ 0.3	3.6 $\pm$ 1.7 ^c	5.1 $\pm$ 2.5 ^c	8.2 $\pm$ 6.2 ^c

	SUD indication	Substrate of	Inhibits	Induces
methadone	OUD	2B6, 3A4 (major w/ 3A4 ind) Minor: 2C9/19, 2D6, 3A4 (w/ 3A4 ind)	2D6 (weak)	-
buprenorphine	OUD	3A4	-	-
naltrexone	OUD, AUD, StUD	-	-	-
acamprosate	AUD	-	-	-
topiramate	AUD, StUD	-	-	3A4 (>200mg/d)
gabapentin	AUD	OCT2	-	-
disulfiram	AUD	Minor: 1A2, 2A6, 2B6, 2D6, 2E1, 3A4	2E1 (strong), 1A2 (weak)	-
valproic acid	AUD (w/d)	Minor: 2A6, 2B6, 2C9/19, 2E1	UGTs (strong)	-
diazepam	AUD (w/d)	3A4, 2C19 Minor: 1A2, 2B6, 2C9	-	-
phenobarbital	AUD (w/d)	2C19 (major w/ 2C19 inh) Minor: 2C9, 2E1, 2C19 (w/ 2C19 ind)	-	Mod: 3A4, UGT1A1, PGP Weak: 1A2, 2A6, 2B6, 2C9
baclofen	StUD	-	-	-
bupropion	TUD, StUD	2B6 Minor: 1A2, 2A6, 2C9, 2D6, 2E1, 3A4	2D6 (strong)	-
N-acetylcysteine	CanUD	-	-	-
varenicline	TUD	OCT2, MATE1/2-K	-	-
mirtazapine	StUD	3A4 Minor: 1A2, 2C9, 2D6	-	-
smoking	Active TUD/CanUD	1A2	-	1A2

Take Home Points

- CYP450-mediated drug interactions can be unlikely/impossible (eg gabapentin), relatively simple (eg buprenorphine), or complex (eg methadone, bupropion)
- Understanding metabolic pathways and meaning of terminology around degree of enzyme inhibition and induction (eg strong/weak and major/minor) can help a clinician avoid, monitor for, predict, anticipate, and mitigate clinically significant drug interactions
- In SUD care, most medications are either not metabolized or are victims of interactions rather than perpetrators
 - Exceptions which are perpetrators: VPA, high dose topiramate, PHB, bupropion, disulfiram, and smoking itself
- Generally, from a CYP450 perspective, most psychotropic medications will not impact levels of most MSUD
 - Most psychotropic/MSUD interactions are pharmacodynamic involving CNS or resp depression risk
 - Watch 2D6 inhibiting antidepressants with general opioid therapy (not bupr nor methadone): fluoxetine, paroxetine, duloxetine, bupropion

Thank you! Questions?

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Penny