

# MINIMIZING DRUG-DRUG INTERACTIONS & POLYPHARMACY

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# DISCLOSURES

Relevant to the content of this educational activity, we do not have a financial relationship with an ineligible company; however, we intend to discuss the off-label use of a commercial product or device and agree to inform learners. All relevant financial relationships have been mitigated.

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# OBJECTIVES

Devise an appropriate dose, route, and duration for current medications in an individual patient's treatment plan.

Predict drug-drug interactions based on a medication's mechanism of action and pharmacokinetic profile.

Construct an effective and safe medication regimen based on individual patient characteristics.

**DEVISE AN APPROPRIATE DOSE, ROUTE, AND  
DURATION FOR CURRENT MEDICATIONS IN AN  
INDIVIDUAL PATIENT'S TREATMENT PLAN**

# PATIENT CASE

WT is a 49-year-old cisgender female admitted to the hospital for pneumonia. While this is being treated, a behavioral health consult is ordered. Her past medical history is significant for major depressive disorder with psychotic features, generalized anxiety disorder, insomnia, obesity, and chronic neuropathic pain because of an injury sustained in an MVA one year prior. WT verbalizes frustration with her medication list. She stated that the pharmacist informed her that a few of her medications “are supposed to do the same thing.” She would like her medication to be consolidated, as she is tired of taking “handfuls of pills” every day.

# CURRENT MEDICATION LIST

Amitriptyline 25 mg daily at 6pm

Duloxetine 90 mg daily at 8am

Escitalopram 5 mg twice a day – 8am and bedtime

Esomeprazole 40 mg daily at 8am

Mirtazapine 15 mg daily at 6pm

Multivitamin daily at 8am

Paliperidone 9 mg daily at 6pm

Pregabalin 150 mg twice a day – 8am and bedtime

Topiramate 100 mg daily in the morning

Trazodone 200 mg at bedtime

# QUESTIONS

**What are the overlapping mechanisms of action?**

**What potential adverse effects concern you?**

What potential drug interactions are present in this patient?

Which medications might be able to be consolidated?

**PREDICT DRUG-DRUG INTERACTIONS BASED  
ON A MEDICATION'S MECHANISM OF ACTION  
AND PHARMACOKINETIC PROFILE**

**CANADIAN NETWORK FOR MOOD AND ANXIETY  
TREATMENTS (CANMAT) 2023 UPDATE ON CLINICAL  
GUIDELINES FOR MANAGEMENT OF MAJOR DEPRESSIVE  
DISORDER IN ADULTS**

# CANMAT 2023

## Mild

- Psychotherapy OR pharmacotherapy
  - Psychotherapy preferred
- Exercise, certain complimentary & alternative medicine (CAM) treatments, or guided digital health interventions (DHI)

## Moderate

- Pharmacotherapy
- Psychotherapy
- Combination of pharmacotherapy + psychotherapy
- Exercise, certain CAM treatments, and/or DHIs used as adjuncts to pharmacotherapy or psychotherapy

## Severe

- For severe episodes without psychotic symptoms, pharmacotherapy + psychotherapy
- For severe episodes with psychotic symptoms, antidepressant + antipsychotic
- For very severe and/or life-threatening situations, consider electroconvulsive therapy (ECT)

# CANMAT 2023 – SUMMARY RECOMMENDATIONS FOR ANTIDEPRESSANTS

## 1<sup>st</sup> line

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Bupropion
- Mirtazapine
- Vilazodone
- Vortioxetine

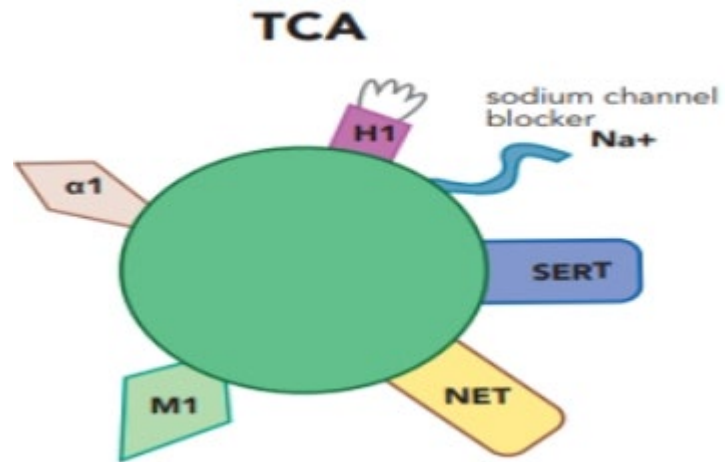
## 2<sup>nd</sup> line

- Tricyclic antidepressants (TCAs)
- Trazodone
- Quetiapine
- Dextromethorphan-bupropion
- Selegiline transdermal

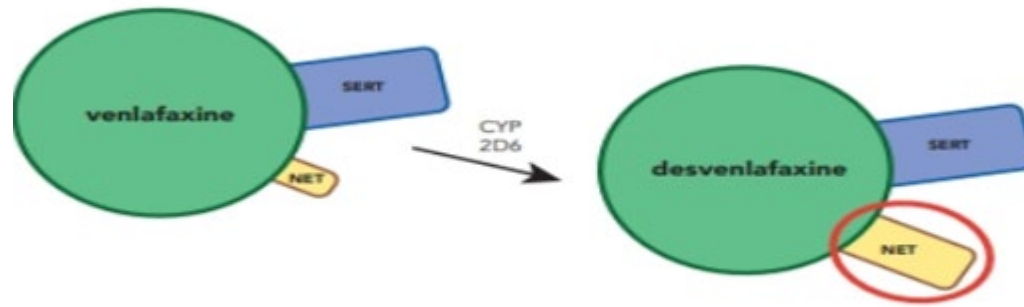
## 3<sup>rd</sup> line

- Phenelzine
- Tranylcypromine

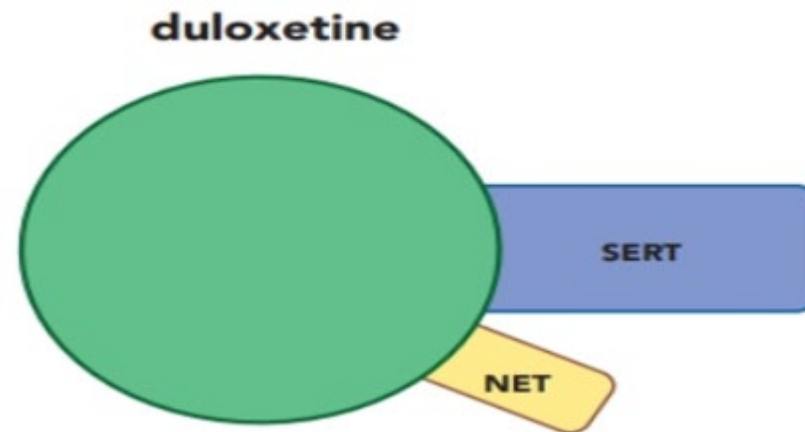
# TCA MECHANISM OF ACTION



# SNRI MECHANISM OF ACTION - VENLAFAXINE

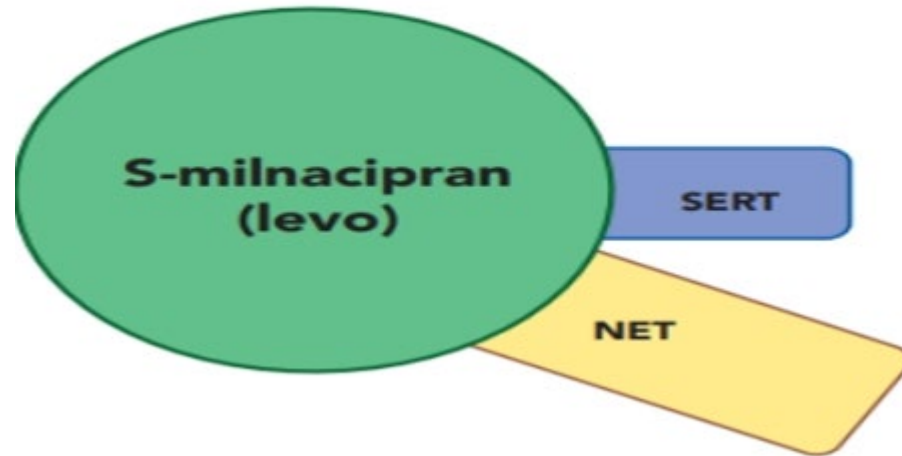


# SNRI MECHANISM OF ACTION - DULOXETINE

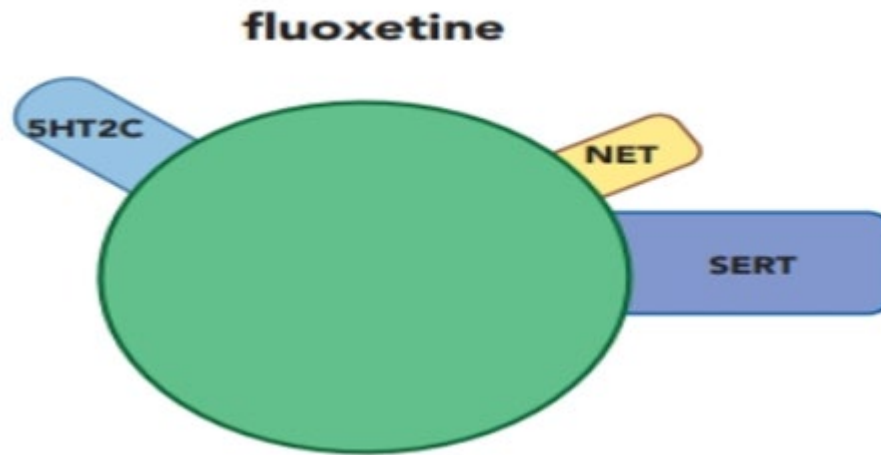


# SNRI MECHANISM OF ACTION - LEVOMILNACIPRAN

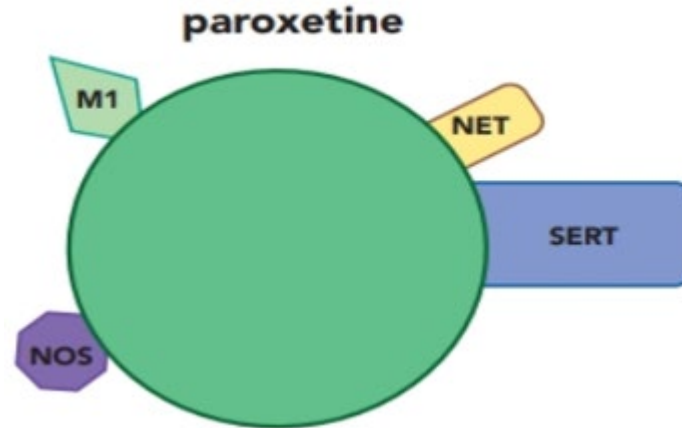
**levomilnacipran: S-milnacipran**



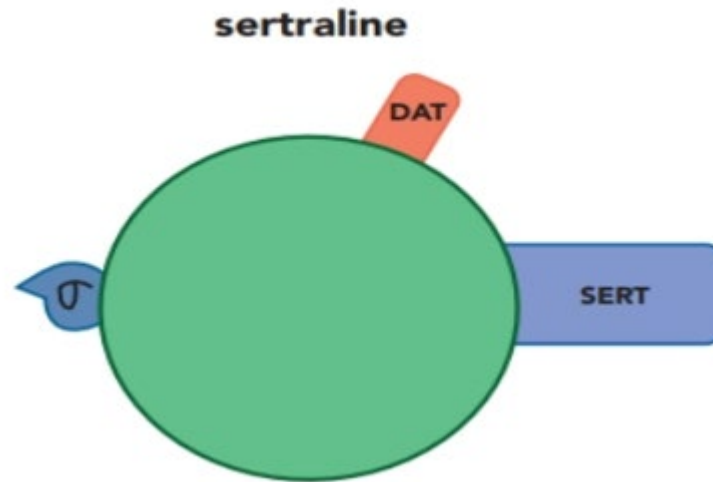
# SSRI MECHANISM OF ACTION - FLUOXETINE



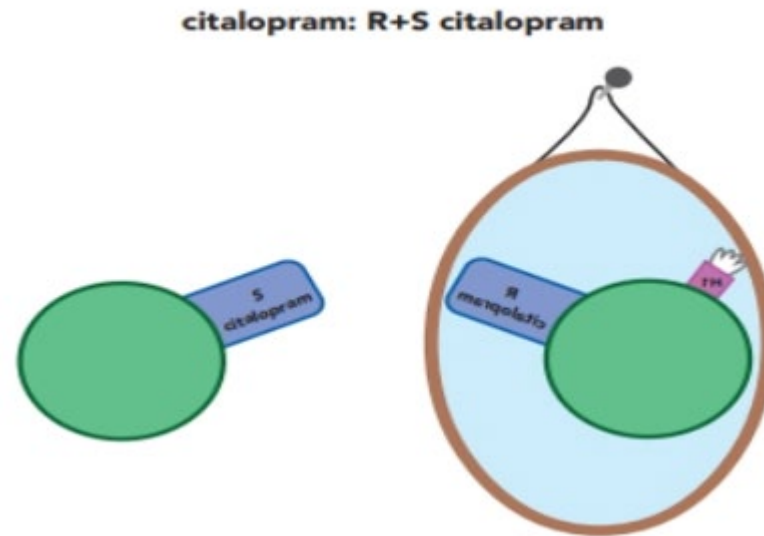
# SSRI MECHANISM OF ACTION - PAROXETINE



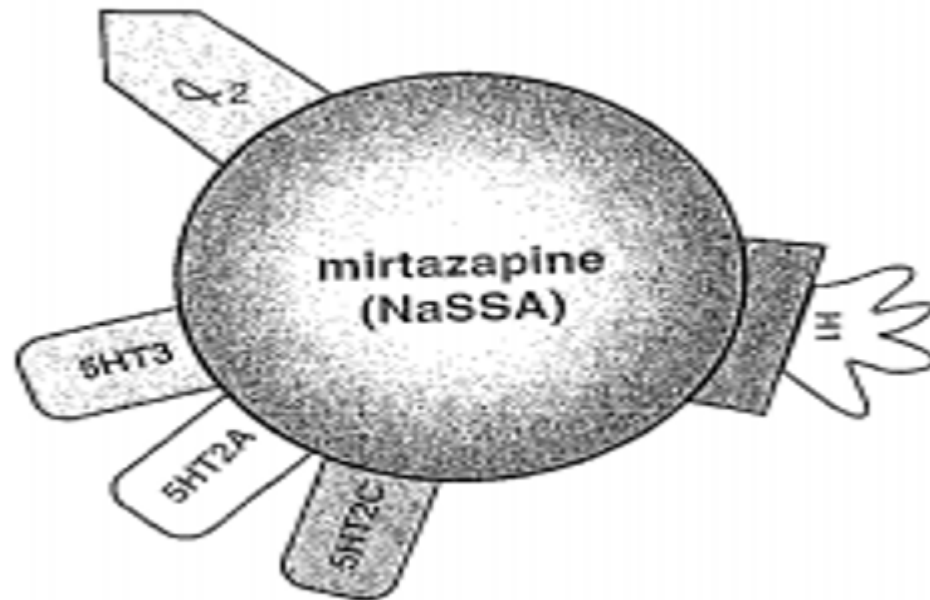
# SSRI MECHANISM OF ACTION - SERTRALINE



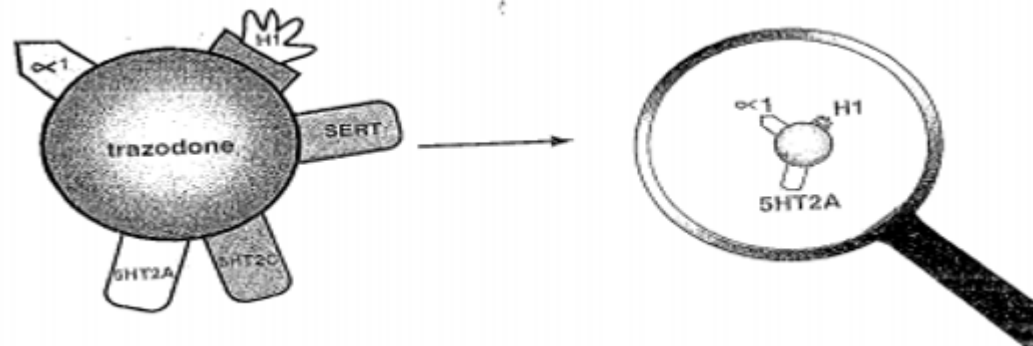
# SSRI MECHANISM OF ACTION – CITALOPRAM & ESCITALOPRAM



# MIRTAZAPINE MECHANISM OF ACTION



# TRAZODONE MECHANISM OF ACTION



# STRATEGIES TO IMPROVE PARTIAL RESPONSE

Partial response definition

Ensure adequate adherence, dose, & duration

1. Extend medication trial and/or increase dose if patient is tolerating medication

2. Augmentation:

- Lithium
- Buspirone
- Triiodothyronine
- Second generation antipsychotics
- Stimulants
- Lamotrigine

3. Combination:

- Another antidepressant is added to 1<sup>st</sup> antidepressant

# COMBINATION ANTIDEPRESSANTS

SSRI or SNRI + bupropion

SSRI or SNRI + mirtazapine

Use of multiple mechanisms of action recommended

Using 2 agents from the same class is NOT recommended

**PREDICT DRUG-DRUG INTERACTIONS BASED ON A  
MEDICATION'S MECHANISM OF ACTION AND  
PHARMACOKINETIC PROFILE**



# DRUG-DRUG INTERACTIONS

## Pharmacokinetics

- ❖ What the body does to a drug
- ❖ Movement into and out of the body.
  
- ❖ Generally manifest as changes of blood levels.

## Pharmacodynamics

- ❖ What a drug does to the body.
- ❖ Based on drugs mechanisms of action.
  
- ❖ Do not involve alteration in blood levels of either interacting drug.

# PHARMACODYNAMICS INTERACTIONS

- Additive/Synergistic
  - Enhanced Effects by adding medications with complementary effects.
- Antagonistic
  - Incompatible effects.

# PHARMACOKINETIC INTERACTIONS

- ❖ Absorption: more or less in a system.

  - ❖ Changes in GI motility, etc.

- ❖ Elimination:

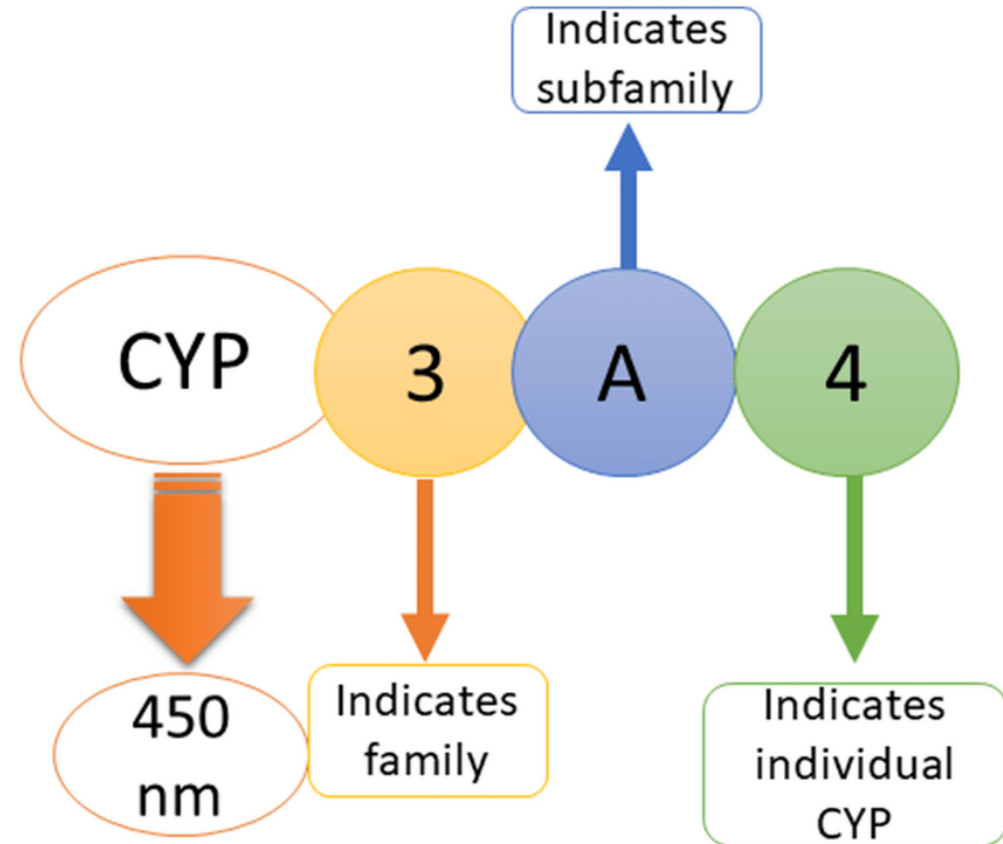
  - ❖ Phase I: **CYP450 Enzymes.**

  - ❖ Phase II: UGT Enzymes.

  - ❖ Renal clearance.

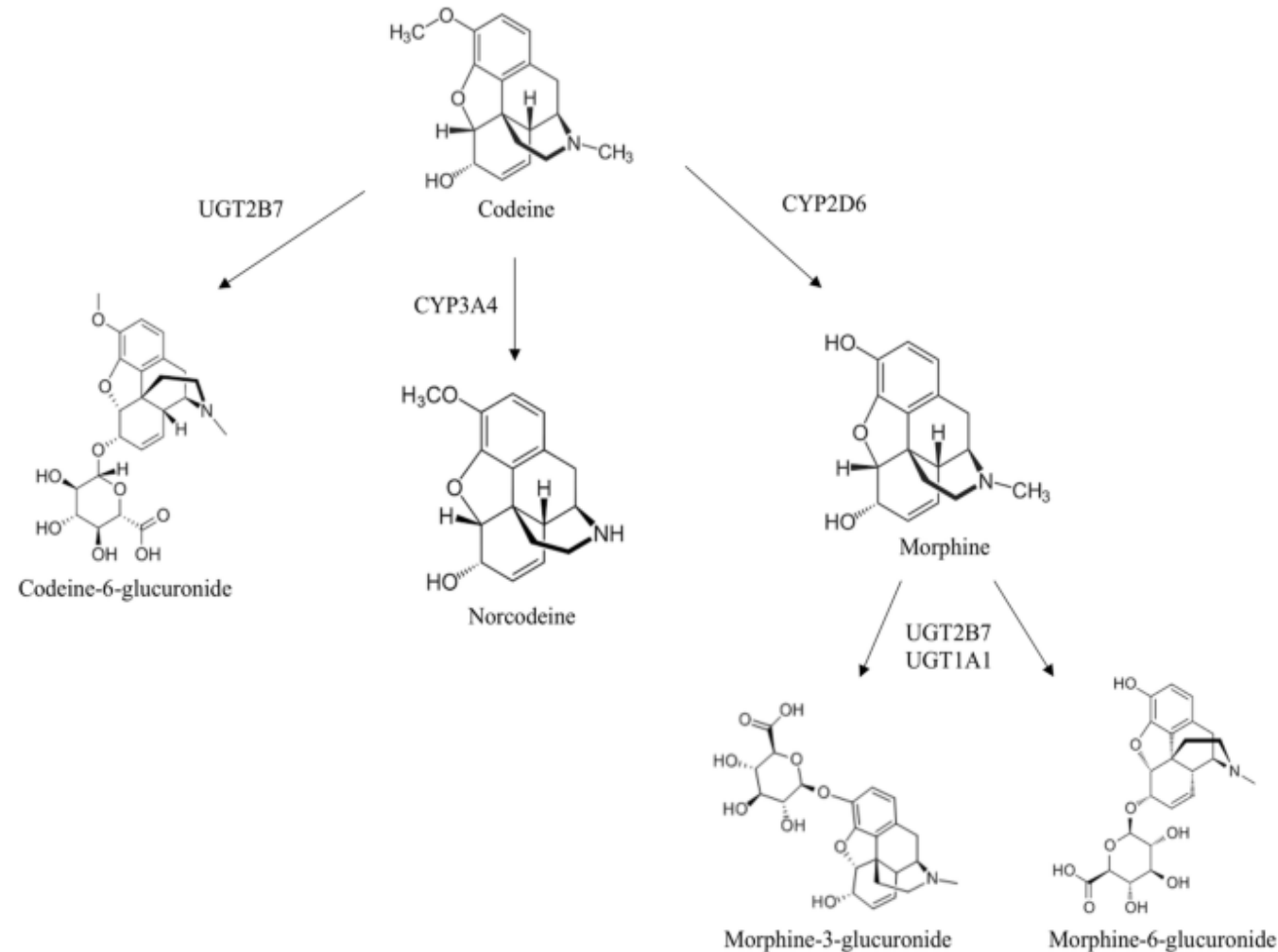
# CYP450 ENZYMES

- ❖ Mediated by the liver.
- ❖ Fifty enzymes in total.
  - ❖ Six important for medications.
  - ❖ 1A2, 2D6, 3A4 most important.



# SUBSTRATES

- ❖ A drug that is transformed by an enzyme is a substrate of that enzyme.
- ❖ When a substrate is transformed, it is a metabolite.
- ❖ Each CYP can metabolize several substrates.
- ❖ Medications influence inhibition or induction, usually.



# CYP 3A4 SUBSTRATES

Vilazodone,  
buspirone,  
trazodone

Zolpidem,  
eszopiclone,  
suvorexant,  
lemobrexant

THC, CBD, heroin

Valbenazine

Donepezil

Buprenorphine,  
codeine, fentanyl,  
hydrocodone,  
methadone,  
oxycodone, tramadol

# INHIBITION AND THE FLUFFERS

## Inhibition

- ❖ Inhibition: substrate is not metabolized.
- ❖ Generally, the plasma level of the substrate increases.
  - ❖ Takes effect quickly (hours).
  - ❖ May not take effect for two to four days.
  - ❖ Influenced by number of CYP pathways.
- ❖ Mild/moderate/strong inhibitors.

## Fluffers (Strong Inhibitors).

Fluvoxamine

Fluoxetine

Fluconazole

Ketoconazole.

# INDUCTION AND THE SHREDDERS

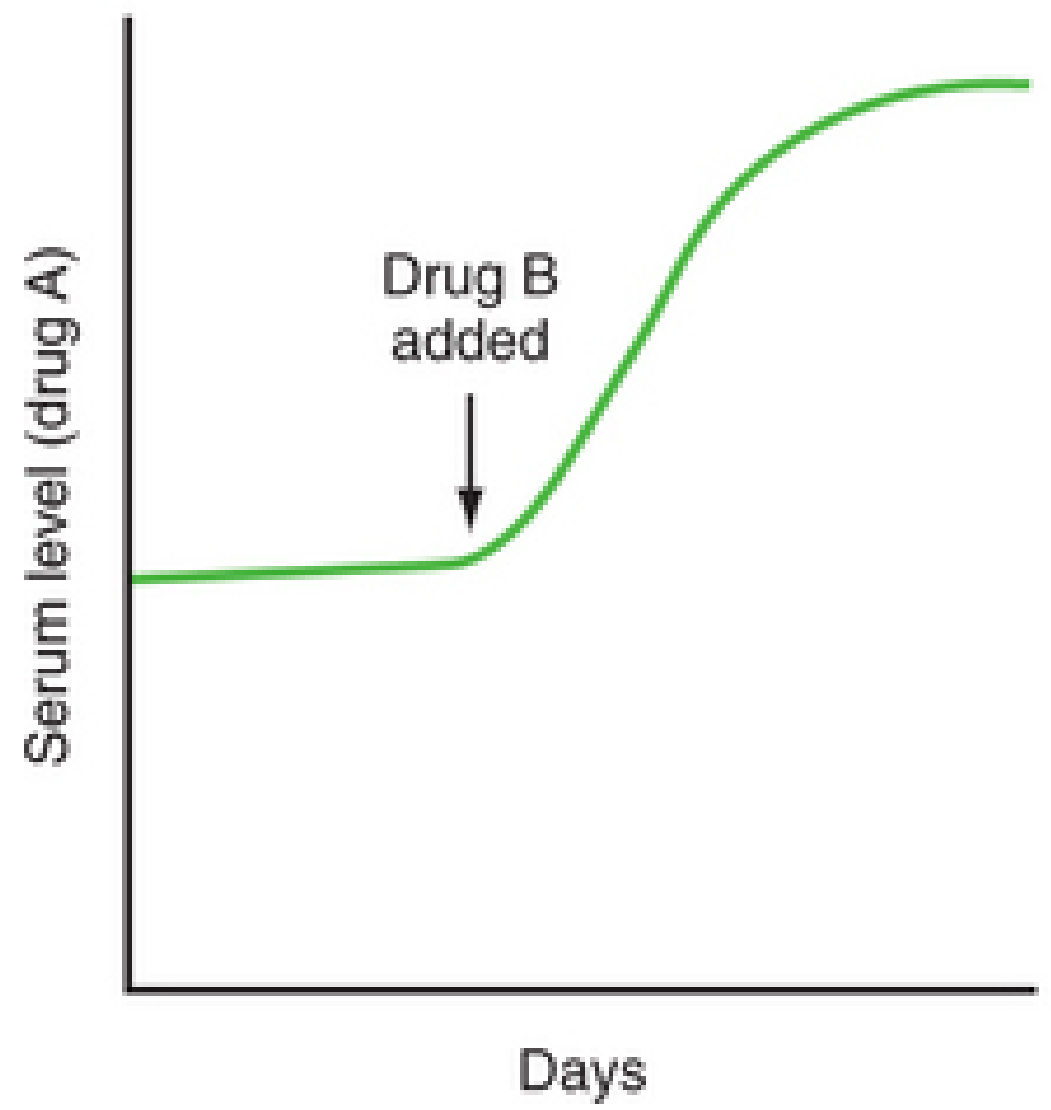
## Induction

- ❖ Drug stimulates the liver to produce more enzymes.
  - ❖ Allows for enhanced metabolism of substrates.
- ❖ Generally, decreased serum levels of substrates.
- ❖ Is delayed, takes two to four weeks, generally.
  - ❖ Requires gene expression.

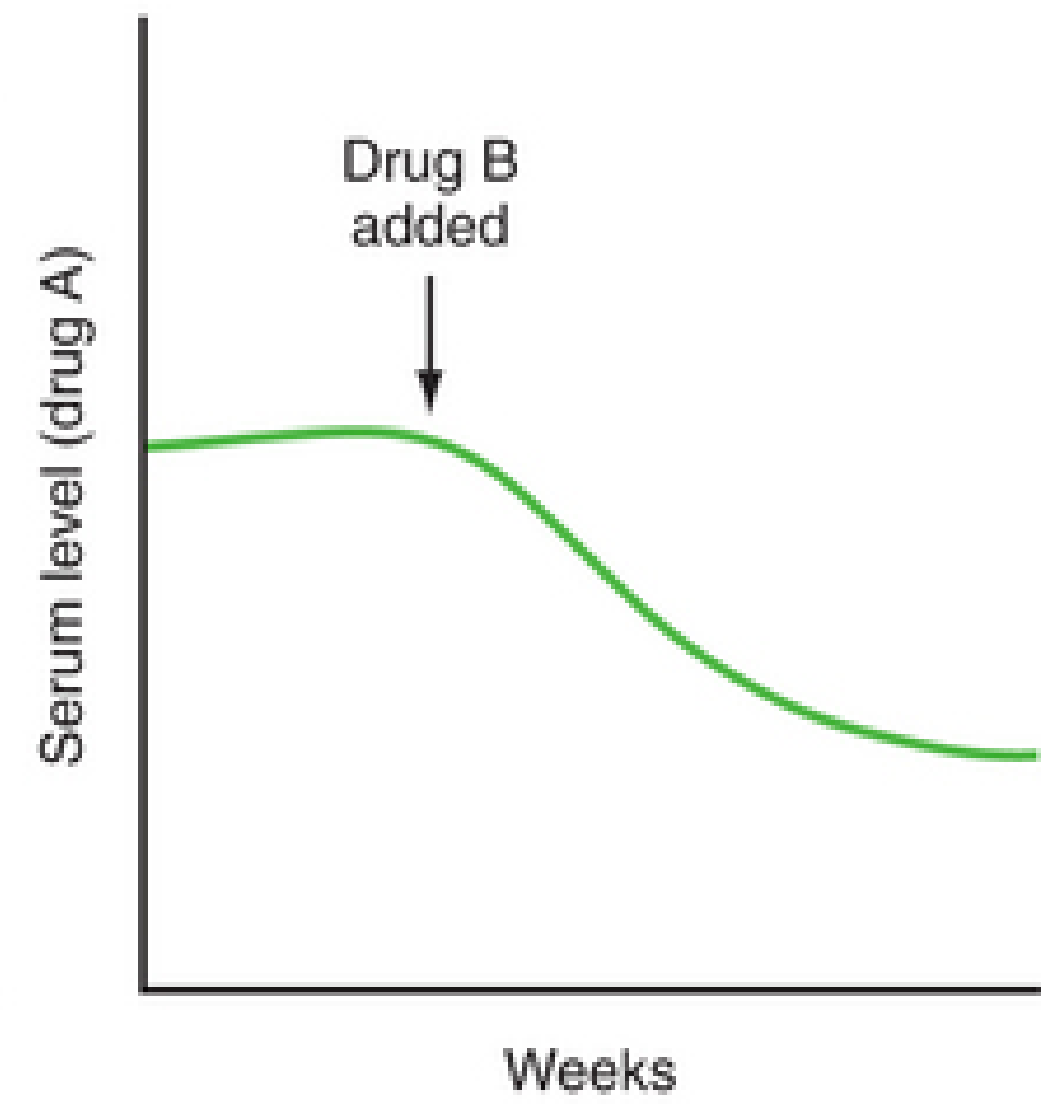
## Shredders (Strong Inducers)

- ❖ Carbamazepine
- ❖ Phenobarbital
- ❖ Phenytoin
- ❖ Rifampin

### INHIBITION



### INDUCTION



**DIPIRO'S PHARMACOTHERAPY:  
A PATHOPHYSIOLOGIC  
APPROACH, 13<sup>TH</sup> EDITION >  
DEPRESSIVE DISORDERS**

**Antidepressants and Cytochrome (CYP) P450 Enzyme Inhibitory Potential**

Medication	CYP Enzyme Inhibition			
	1A2	2C	2D6	3A4
Bupropion	0	0	+++	0
Citalopram	0	0	+	NA
Duloxetine	0	0	+++	0
Escitalopram	0	0	+	0
Fluoxetine	0	++	++++	++
Fluvoxamine	++++	++	0	+++
Mirtazapine	0	0	0	0
Nefazodone	0	0	0	++++
Paroxetine	0	0	++++	0
Sertraline	0	++	+	+
(des)-Venlafaxine	0	0	0/+	0
Vilazodone	0	0	0	0
Vortioxetine	0	0	0	0

# ANOTHER TWIST

- ❖ Take away an inducer, concentration of substrate increases.
  - ❖ Occurs over a few weeks (extra CYP enzymes are degraded).
  
- ❖ Take away an inhibitor, concentration of substrate decreases.
  - ❖ Occurs over four to five half-lives (steady state)
  - ❖ Takes that long to clear the inhibitor.
  - ❖ Fluoxetine has a half life of seven days (within system for forty-five days).

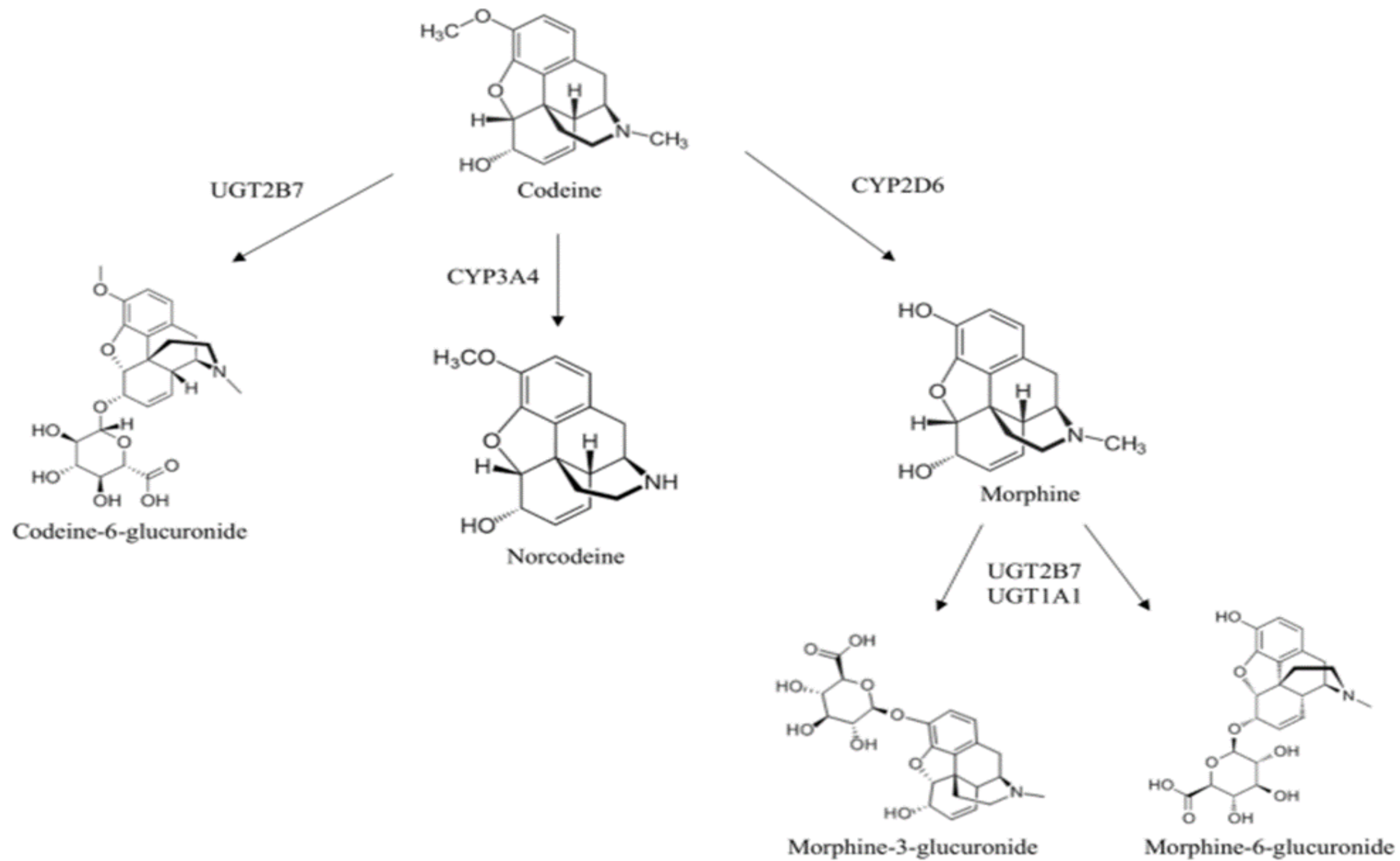
# EVEN MORE TWISTS!

- ❖ Phase I metabolism

- ❖ Transform an active drug to a more/less active chemical.
- ❖ Some medications require transformation into more active metabolites
- ❖ Substrate (aka prodrug) is bioactivated.

- ❖ Related to inhibition/induction as noted.

- ❖ Inhibitors increase the levels of the substrate.
- ❖ Inducers decrease the levels of the substrate.



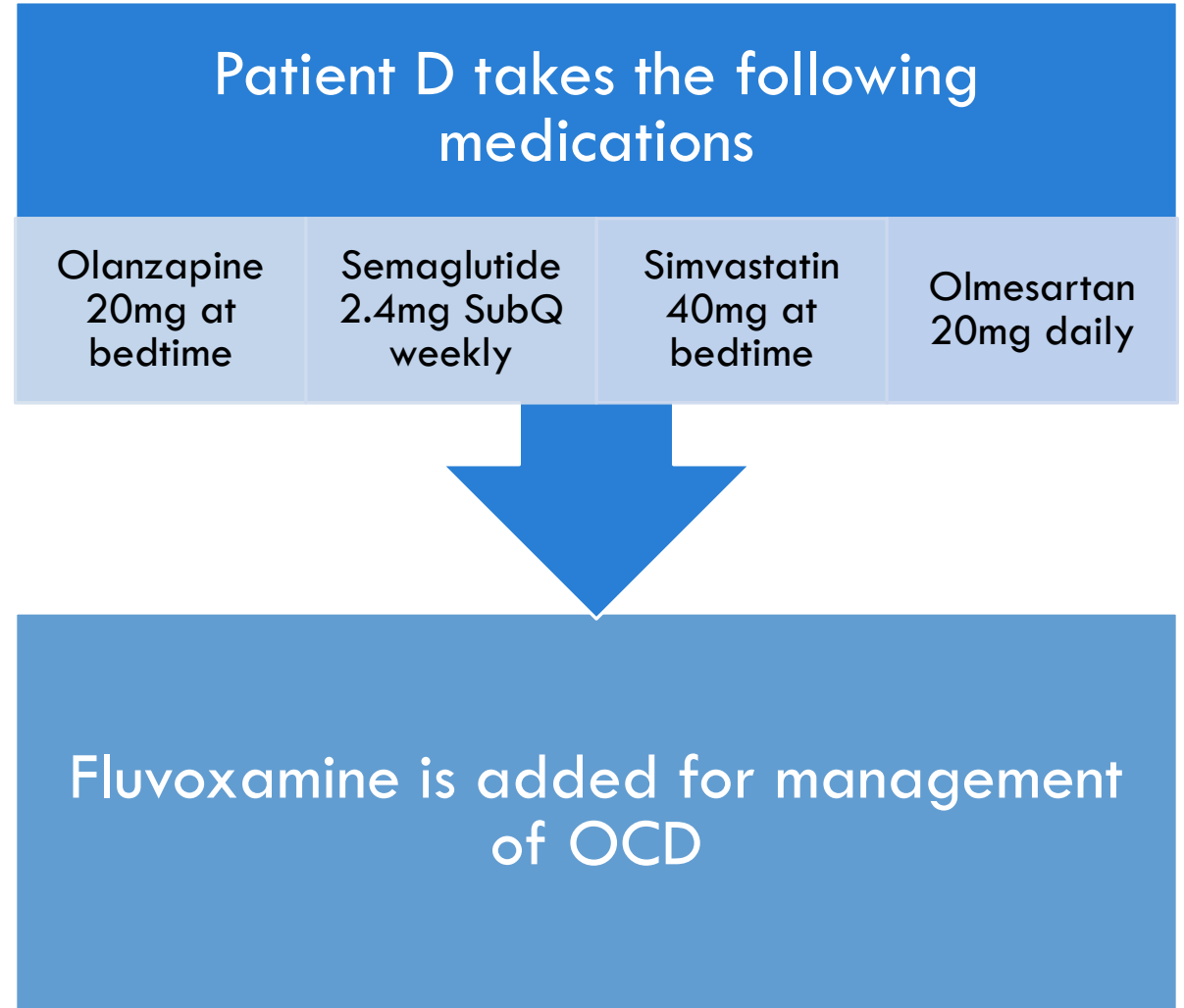


**LET'S PRACTICE**



WHAT IMPACT COULD  
THE ADDITION OF  
FLUVOXAMINE HAVE  
ON THE PATIENT'S  
MEDICATION REGIMEN?

HOW SHOULD THIS  
PATIENT BE  
MONITORED?





WHAT ARE YOUR  
THOUGHTS ON THIS  
REGIMEN?

HOW SHOULD THIS  
PATIENT BE  
MONITORED?

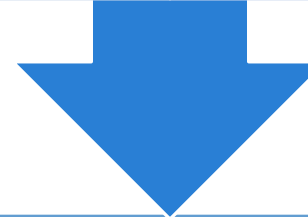
Patient C takes the following  
medications

Vortioxetine  
20mg daily

Trazodone  
75mg at  
bedtime

Naproxen  
500mg twice  
daily PRN (uses  
twice weekly)

Multivitamin  
daily



Patient C is diagnosed with H. Pylori  
and is prescribed a course of  
omeprazole, clarithromycin, and  
amoxicillin

**WHAT IF I WANT TO TAKE THINGS AWAY?**

# DEPRESCRIBING

- ❖ US Deprescribing Research network

- ❖ Has Deprescribing Guidelines/Algorithms

- ❖ PPIs, Benzodiazapines, Antihyperglycemics.

- ❖ Deprescribing.org

- ❖ Provide information on deprescribing groups, internationally (UK, Australia, Canda, Northern Europe)



### Why is patient taking a BZRA?

If unsure, find out if history of anxiety, past psychiatrist consult, whether may have been started in hospital for sleep, or for grief reaction.

- Insomnia on its own OR insomnia where underlying comorbidities managed  
For those ≥ 65 years of age: taking BZRA regardless of duration (avoid as first line therapy in older people)  
For those 18-64 years of age: taking BZRA > 4 weeks

- Other sleeping disorders (e.g. restless legs)
- Unmanaged anxiety, depression, physical or mental condition that may be causing or aggravating insomnia
- Benzodiazepine effective specifically for anxiety
- Alcohol withdrawal

**Engage patients** (discuss potential risks, benefits, withdrawal plan, symptoms and duration)

### Recommend Deprescribing

### Continue BZRA

- Minimize use of drugs that worsen insomnia (e.g. caffeine, alcohol etc.)
- Treat underlying condition
- Consider consulting psychologist or psychiatrist or sleep specialist

### Taper and then stop BZRA

(taper slowly in collaboration with patient, for example ~25% every two weeks, and if possible, 12.5% reductions near end and/or planned drug-free days)

- For those ≥ 65 years of age (strong recommendation from systematic review and GRADE approach)
- For those 18-64 years of age (weak recommendation from systematic review and GRADE approach)
- Offer behavioural sleeping advice; consider CBT if available (see reverse)

If symptoms relapse:

Consider

- Maintaining current BZRA dose for 1-2 weeks, then continue to taper at slow rate

Alternate drugs

- Other medications have been used to manage insomnia. Assessment of their safety and effectiveness is beyond the scope of this algorithm. See BZRA deprescribing guideline for details.

### Monitor every 1-2 weeks for duration of tapering

Expected benefits:

- May improve alertness, cognition, daytime sedation and reduce falls

Withdrawal symptoms:

- Insomnia, anxiety, irritability, sweating, gastrointestinal symptoms (all usually mild and last for days to a few weeks)

Use non-drug approaches to manage insomnia

Use behavioral approaches and/or CBT (see reverse)

**CONSTRUCT AN EFFECTIVE AND SAFE MEDICATION  
REGIMEN BASED ON INDIVIDUAL PATIENT  
CHARACTERISTICS**

# CURRENT MEDICATION LIST

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# QUESTIONS

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**Which medications might be able to be consolidated?**

# REFERENCES

Cafer Jason MD, Link Julianna PA-C. Cafer's Psychopharmacology: Visualize to Memorize 270 Medication Mascots. 2020. 1<sup>st</sup> Edition.

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Stahl SM. Essential psychopharmacology: Neuroscientific basis and practical applications, 5th ed. New York: Cambridge University Press, 2021.

# PHARMACOGENOMICS

- ❖ Testing of genes in individuals which may be a sign of altered metabolism.
  - ❖ Hope to reduce adverse drug reactions, lead to more precise prescribing.
- ❖ Classification based upon gene polymorphisms.
- ❖ There are commercial tests which does not require provider approval.
- ❖ Age/sex/concurrent use of medications/illness(es)/diet/weight are not included with PGx testing.
  - ❖ Influences pharmacodynamics/pharmacokinetics.