

**Penn State College of Medicine  
Continuing Education**

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## Antidepressants: Mechanisms, Treatment, and Side Effects

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## OBJECTIVES:

- ❖ State standard antidepressants available for use.
- ❖ State common adverse drug reactions, drug interactions, and contraindications of antidepressants.

3

## DISCLOSURE

No Conflicts of Interest

There will be some discussion of off-label use

4

## WHAT IS DEPRESSION? <sup>3</sup>

- DSM-5-TR requires at least 5 of 9 symptoms, one of which must be either #1 or #2, nearly every day and most of the day for at least two weeks **and causing significant distress or impairment** in social, occupational, or other important areas of functioning.
- Additionally, the symptoms must **not** be due to a substance or another medical condition.

Depressed mood

Anhedonia (loss of interest or pleasure)

Significant unintended weight loss/gain

Sleep changes (insomnia or hypersomnia)

Psychomotor agitation or retardation observable by others

Fatigue or loss of energy

Feelings of worthlessness/excessive guilt

Diminished ability to concentrate or indecisiveness

Recurrent thoughts of death (not fear of dying), SI, or SA

## DEPRESSION PREVALENCE, TRENDS, AND IMPACTS <sup>14, 31</sup>

April 2025: CDC released depression prevalence data

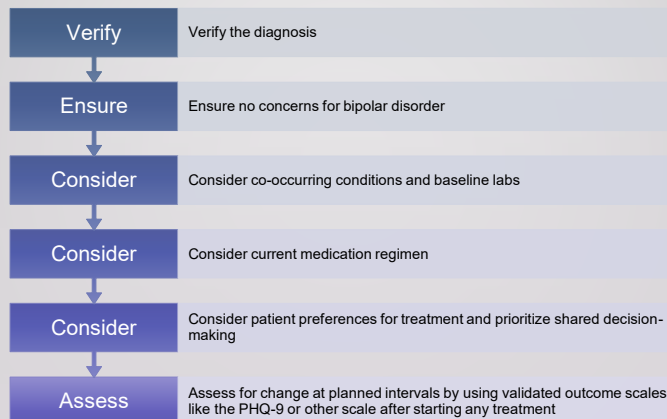
- Increased by 60% in the last decade
- Women have higher rates of depression, but are also more likely to seek therapy
- Depression rates decrease with age, but adults aged 18-44 are also least likely to take medications

This also included information on antidepressant prescribing

## SCREENING AND EARLY IDENTIFICATION IN PRIMARY CARE <sup>42, 43</sup>

- Routine screening improved the detection of mood and anxiety disorders
  - Supports early treatment initiation
  - Improves suicide risk detection
  - Screening supports measurement-based care
- Use validated tools
  - Improved chance of remission and treatment adherence
- PHQ-9
  - Minimal (0-4)
  - Mild (5-9)
  - Moderate (10-14)
  - Moderately severe (15-19)
  - Severe (20+)

## BEFORE STARTING AN ANTIDEPRESSANT <sup>25</sup>



## MONOAMINE THEORY OF DEPRESSION <sup>37</sup>

- What are Monoamines?
- Classic biological etiology theory of depression
  - Depression is due to deficiency of monoamine neurotransmitters
- Current theory indicates all 3 monoamines are important in different brain circuits and symptoms may indicate the neurotransmitters involved
  - Also consider nature vs nurture, stress and BDNF

## ANTIDEPRESSANT CLASSES <sup>37</sup>

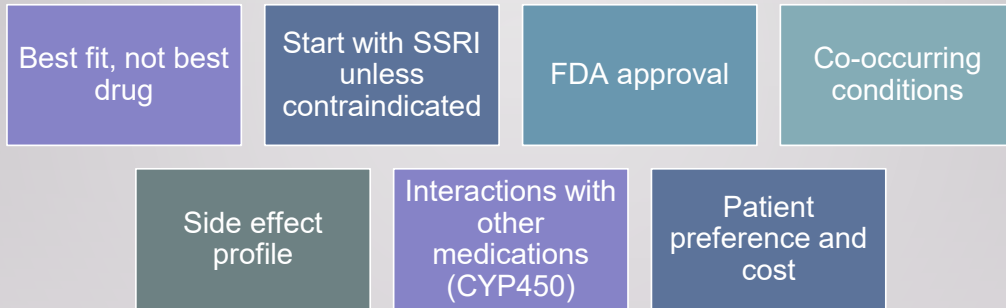
### First-generation antidepressants

- TCAs
  - Tricyclic antidepressants
  - Amitriptyline, nortriptyline
- MAOIs
  - Monoamine oxidase inhibitors
  - Phenelzine

### Second-generation antidepressants

- SSRIs
  - Selective serotonin reuptake inhibitors
- SNRIs
  - Serotonin norepinephrine reuptake inhibitors
- NDRI
  - Norepinephrine dopamine reuptake inhibitors
- SARI
  - Serotonin agonist reuptake inhibitors
- NaSSA
  - Noradrenaline and specific serotonergic agent
- Multimodals

## CHOOSING THE ANTIDEPRESSANT 9, 10, 25, 36



## ANTIDEPRESSANTS FDA-APPROVED FOR DEPRESSION AND ... 36

Drug Class	Generic Name	Brand Name	Other FDA-Approved Indications
<b>SSRI</b>	Fluoxetine	Prozac	OCD, Bulimia Nervosa, Panic Disorder, PMDD
	Sertraline	Zoloft	OCD, Panic Disorder, PTSD, Social Anxiety Disorder, PMDD
	Paroxetine	Paxil	OCD, Panic Disorder, Social Anxiety Disorder, PTSD, GAD, PMDD
	Escitalopram	Lexapro	GAD
	Citalopram	Celexa	—
<b>SNRI</b>	Duloxetine	Cymbalta	GAD [Diabetic Neuropathy, Fibromyalgia, Chronic Pain]
	Venlafaxine	Effexor XR	GAD, Social Anxiety Disorder, Panic Disorder, Separation Anxiety Disorder
	Desvenlafaxine	Pristiq	—
	Levominlacipran	Fetzima	—
<b>NDRI</b>	Bupropion	Wellbutrin	Seasonal Affective Disorder (SAD) [Smoking Cessation]
<b>SARI</b>	Trazodone	Desyrel	—
<b>SMS / Multimodal</b>	Vortioxetine	Trintellix	—
	Vilazodone	Viibryd	—
<b>NaSSA</b>	Mirtazapine	Remeron	—

Review prior to prescribing

#### Common versus Serious

- Common: Appetite and GI impacts, sleep/wakefulness, and sexual side effects
- Serious: Manic switch, serotonin syndrome, cardiac arrhythmias, bruising/bleeding, reduced seizure threshold

Minimize side effects by starting with a low dose and titrating as needed

Make the side effects work for you

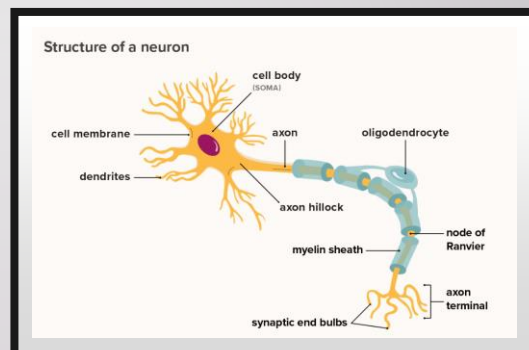
They may improve once adjusting to the medication

- Can try a lower starting dose if usually sensitive to medications or particularly anxious

## SIDE EFFECTS OF SEROTONERGIC ANTIDEPRESSANTS <sup>25, 28, 36, 37</sup>

## SSRI THEORETICAL MECHANISM OF ACTION <sup>35, 37</sup>

- MOA as best understood today
- Old theory vs. New theory
- Receptor desensitization mediates side effects and benefits
- Consider secondary pharmacological actions
- Efficacy of different SSRIs is often patient-specific



## WHICH SSRI? <sup>37</sup>

- Fluoxetine/Prozac
  - Can be activating due to 5HT<sub>2C</sub> antagonism
- Sertraline/Zoloft
  - Mild activation
- Paroxetine/Paxil
  - Calming/sedating early in treatment but commonly causes sexual side effects and withdrawal symptoms
- Citalopram/Celexa
  - R and S enantiomer
- Escitalopram/Lexapro
  - S enantiomer only
  - Best-tolerated with least CYP450 interactions

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## SSRI PRESCRIBING <sup>36, 37</sup>

### SSRI Dosing and Titration Table

Medication (Generic/Brand)	Starting Dose (Daily)	Typical Titration Increment	Maximum Dose (Daily)
Sertraline (Zoloft)	50 mg	25 – 50 mg	200 mg
Escitalopram (Lexapro)	10 mg	5 – 10 mg	20 mg
Fluoxetine (Prozac)	20 mg	10 – 20 mg	80 mg
Citalopram (Celexa)	20 mg	10 – 20 mg	40 mg
Paroxetine (Paxil)	20 mg	10 mg	50 mg
Fluvoxamine (Luvox)	50 mg	50 mg	300 mg

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## SSRI VERSUS SNRI <sup>36</sup>

SSRI usually first line

SNRI versus SSRI efficacy unclear

SNRIs have efficacy for multiple pain syndromes

Consider the patient

- SSRIs work better in the presence of estrogen for women
- SNRIs with more consistent efficacy whether pre- or post-menopausal regardless of estrogen replacement
- May improve vasomotor symptoms of perimenopause

## SNRI THEORETICAL MECHANISM OF ACTION <sup>37</sup>

- SERT inhibition seen with SSRIs plus norepinephrine transporter (NET) inhibition
  - Boost serotonin and norepinephrine throughout the brain
  - Also boosts dopamine in prefrontal cortex

## WHICH SNRI? <sup>37</sup>

### Venlafaxine/Effexor

- Sweating and BP elevations, especially as the dose increases

### Desvenlafaxine/Pristiq

- Venlafaxine converts into desvenlafaxine
- More predictable NET inhibition, less need for titration

### Duloxetine/Cymbalta

- Depression without pain, pain without depression, cognitive and painful physical symptoms of depression

### Levomilnacipran/Fetzima

- Positive: energizing, benefit to fatigue and cognitive symptoms
- Negatives: more sweating and urinary hesitancy possible

## SNRI PRESCRIBING <sup>36, 37</sup>

Medication (Generic/Brand)	Starting Dose (Daily)	Typical Titration Increment	Maximum Dose (Daily)
<b>Venlafaxine ER</b> (Effexor XR)	37.5mg x 1 week, then increase to 75mg daily if tolerating	37.5 – 75 mg	225 mg
<b>Duloxetine</b> (Cymbalta)	40mg/day (divided)	20-30 mg/day	120 mg
<b>Desvenlafaxine</b> (Pristiq)	50 mg	25 mg	400 mg but max recommended 100mg
<b>Levomilnacipran</b> (Fetzima)	20 mg (for 2 days)	40 mg	120 mg

- Current hypothesis
  - Bupropion inhibits reuptake of both dopamine and norepinephrine
  - No other significant pharmacologic actions have been consistently identified currently

## NDRI (BUPROPION) THEORETICAL MECHANISM OF ACTION <sup>37</sup>

## OTHER CONSIDERATIONS WITH BUPROPION <sup>36, 37</sup>

Can reduce  
seizure  
threshold

Preference for  
once-daily XL  
formulation

Can be a helpful  
adjunct to  
serotonergic  
antidepressants

Less likely than  
serotonergic  
antidepressants  
to cause sexual  
side-effects

## SARI (TRAZODONE) MECHANISM OF ACTION <sup>37</sup>



**Serotonin 2A and 2C receptor antagonist  
AND serotonin reuptake inhibitor**

Also H<sub>1</sub>-histaminic and alpha1-adrenergic antagonism  
More specific serotonin receptor actions than SSRI/SNRI



**Primarily used for insomnia**

## NASSA (MIRTAZAPINE) THEORETICAL MECHANISM OF ACTION <sup>36</sup>

Mirtazapine/Remeron

Noradrenaline and specific  
serotonergic agent

- Acts more specifically at serotonin receptors than SSRIs and SNRIs

Two main actions

Insomnia benefit, less GI side-effects

Weight gain, daytime drowsiness

## MULTIMODAL AGENT MECHANISM OF ACTION <sup>36, 37</sup>

### Vilazodone (Viibryd)

- SERT inhibition and 5HT<sub>1A</sub> partial agonist
- May have less sexual side effects
- Fewer CYP450 interactions than vortioxetine
- Must be taken with food

### Vortioxetine (Trintellix)

- SERT inhibition, 5HT<sub>1A</sub> and 5HT<sub>1B/D</sub> partial agonist, antagonist at 5HT<sub>7</sub> and 5HT<sub>3</sub>, plus possible additional effects
- May have less sexual side effects

## NDRI, SARI, NaSSA, AND MULTIMODAL AGENT PRESCRIBING <sup>36</sup>

Medication (Generic/Brand)	Starting Dose (Daily)	Typical Titration Increment	Maximum Dose (Daily)
<b>Bupropion XL</b> (Wellbutrin XL)	150 mg	150 mg	450 mg
<b>Mirtazapine</b> (Remeron)	15 mg	15 mg	45 mg
<b>Vortioxetine</b> (Trintellix)	10 mg	10 mg	20 mg
<b>Vilazodone</b> (Viibryd)	10 mg (for 7 days)	10 – 20 mg	40 mg
<b>Trazodone</b> (Desyrel)	150 mg	50 mg	400 mg

## WHAT IS THE GOAL? <sup>3, 37</sup>

- Goal used to be 50% reduction of symptoms
  - Now considered a response
- 20% improvement in early treatment is encouraging
- What is the goal?
  - Full remission!!
- Why do we want it??
  - Avoids relapse and recurrence
    - Remission usually not achieved with first antidepressant

## ACHIEVING THE GOAL <sup>12, 34</sup>

Measure response with validated scales like the PHQ-9 at each visit

Adequate trial, adequate dose prior to considering switching

Switch versus augmentation

## PHQ-9: DEPRESSION SEVERITY AND TREATMENT RESPONSE <sup>25, 27, 34, 40</sup>

### Depression Severity

Minimal PHQ-9= 0-9	Mild PHQ-9=10-14	Moderate PHQ-9=15-19	Severe PHQ-9= ≥ 20
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Effective antidepressant dose 6-8 weeks. A ≥ 25% reduction in baseline PHQ-9 by week 6 indicates a patient may benefit from an increase in dose (if tolerated) or further exposure for as many as 12 weeks.

### Monitoring Treatment Response

**Remission:**  
PHQ-9 score ≤4 for at least one month

**Partial Response:**

- 5-point score reduction or
- A score of >4 and >10 on PHQ-9 or
- >25% decrease from baseline

**Non-response:**

- Less than 5-point score reduction or
- ≤25% decrease from baseline

*Continue current regimen*

*Continue or increase current dosage*

*Maximize dosage or switch*

## SWITCHING ANTIDEPRESSANTS <sup>15, 33, 38</sup>

+ (direct switch safe)

++ (cross taper recommended)

+++ (washout period)

Initial Medication	SSRI's and Vortioxetine	SNRI's	Mirtazapine	Bupropion	TCA's	MAOI's^	Equivalent doses (mg)!
Citalopram	+	+	++	++	++	+++	20
Escitalopram	+	+	++	++	++	+++	10
Fluoxetine*	+	+	+	+	+++	+++	20
Paroxetine*	+	+	++	++	++	+++	20
Sertraline	+	+	++	++	++	+++	50
Vilazodone	+	+	++	++	++	+++	10
Vortioxetine	+	+	++	++	++	+++	10

## SWITCHING ANTIDEPRESSANTS <sup>15, 33, 38</sup>

+ (direct switch safe)

+ + (cross taper recommended)

+++ (washout period)

Initial Medication	SSRI's and Vortioxetine	SNRI's	Mirtazapine	Bupropion	TCA's	MAOI's <sup>^</sup>	Equivalent doses (mg)!
Duloxetine	+	+	++	++	++	+++	30
Venlafaxine	+	+	++	++	++	+++	75
Desvenlafaxine	+	+	+	+	++	+++	50
Levomilnacipran	+	+	++	++	++	+++	20
Mirtazapine	++	++		++	++	+++	15
Bupropion XR*	+	++	++		++	+++	150
TCA's	++	++	++	++		+++	
MAOIs <sup>^</sup>	+++	+++	+++	+++	+++	+++	

## ANTIDEPRESSANT SWITCHING PEARLS <sup>15, 33, 38</sup>



Cross taper generally takes one to two weeks.



\* May increase serum concentration of TCA's, SSRI's, bupropion, and vortioxetine; therefore start at low dose to avoid toxicity.



! Equivalent doses are approximate and may vary based on patient specific factors such as sensitivity to medication side effects and concomitant medications.



<sup>^</sup> MAOI's- wait two weeks before discontinuation of an MAOI before starting another antidepressant; wait two weeks after discontinuing an antidepressant before starting an MAOI, except fluoxetine which needs a washout period of at least five weeks.

## IDENTIFYING DISCONTINUATION SYMPTOMS BY SYSTEM <sup>19, 21</sup>

System	Symptoms
General	Chills, malaise, flu-like symptoms, fatigue, lethargy, fever, dizziness, diaphoresis
Eyes, Ears, Nose, Mouth, Throat	Blurred vision, eye movement abnormalities, sore eyes, eye twitch, tinnitus, rhinorrhea, sinus congestion, nasal congestion, increased salivation
Respiratory	Shortness of breath
Cardiovascular	Palpitations, tachycardia, elevated blood pressure
Gastrointestinal, Genitourinary	Nausea, vomiting, diarrhea, abdominal pain, stomach cramps, abdominal bloating, genital hypersensitivity, premature ejaculation
Musculoskeletal	Sore muscles, myalgia, arthralgia, muscle cramps
Skin and Hair	Pruritus
Neurological	Disequilibrium, sensory disturbances (usually sensitive to sound, electric shock-like sensations, paresthesia, dysgeusia, and brain zaps), neuromuscular symptoms (acute dystonia, myoclonus, tremor, shaking, akathisia) cognitive symptoms (delirium, amnesia, memory impairments, disorientation, confusion)
Psychiatric	Worsening of mood, exacerbation of anxiety, sleep disruption, perceptual impairments (depersonalization, hypnagogic hallucinations auditory and visual hallucinations)

## EDUCATION IS KEY: REDUCING ANTIDEPRESSANT DISCONTINUATION SYNDROME <sup>19, 21, 38</sup>

Half-life	Taper Duration	Recommendations
≥24 hours (escitalopram, fluoxetine, mirtazapine, sertraline)	2-4 weeks	<ul style="list-style-type: none"> <li>➢ Mild symptoms that occur despite a gradual taper can be managed with reassurance and watchful waiting.</li> <li>➢ Moderate to severe symptoms that occur during taper Decrease pace of taper.</li> <li>➢ Moderate to severe symptoms that occur after discontinuation Restart at the dose at which there were no symptoms and decrease pace.</li> </ul>
<24 hours (duloxetine, paroxetine, venlafaxine)	2-3 months	<ul style="list-style-type: none"> <li>➢ Switching to fluoxetine (10-20mg) may be a reasonable option for those who cannot tolerate a slow taper.</li> </ul>

- Fluoxetine and bupropion not generally associated with discontinuation syndrome.
- Vortioxetine 10mg no taper needed; higher doses taper over a week.
- Monoamine Oxidase Inhibitors (MAOI's) need to be tapered over 1-6 months depending on duration of use.

## ANTIDEPRESSANTS AND SEXUAL DYSFUNCTION 18, 22, 26

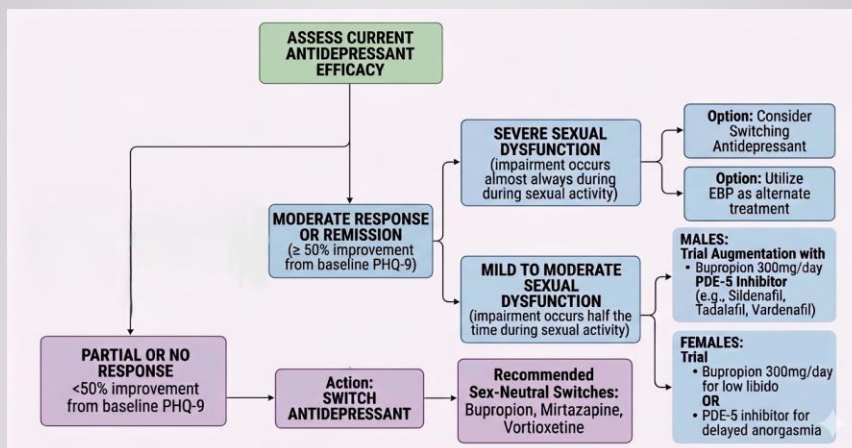
Baseline sexual dysfunction: "Have you noticed any problems in sexual desire, orgasms/ejaculations, or arousal capacity since you started taking the medication?"

Treatment strategies:

WAIT: generally within 6 months, 10% of patients have remission in sexual dysfunction, 15-20% report symptom improvement.

Decrease dose: Higher doses have been associated with higher rates of dysfunction and may lead to reduced antidepressant effect.

## MANAGING SEXUAL SIDE EFFECTS OF ANTIDEPRESSANTS 18, 23, 26, 39



## ANTIDEPRESSANTS AND HYPONATREMIA 23, 24, 38

Risk Factors for Hyponatremia					
Demographic	Co-medications		Medical Comorbidities		
Old age	Antipsychotics	Omeprazole	Diabetes	Glomerular filtration rate <50ml/min	Recent hx of pneumonia
Female	Carbamazepine	Oxcarbazepine	Hypothyroidism	Low baseline sodium	Hx of hyponatremia
Living in a warm weather climate	Chemotherapy	Thiazide Diuretics	Low Body Weight	Various cancers Head injury or CVA	Hypertension/ heart failure
	NSAIDs Tramadol	Trimethoprim			

## RESTARTING AN ANTIDEPRESSANT AFTER HYPONATREMIA HAS RESOLVED 23, 24

01

Select an agent from a different class

- Fewer reports of recurrence with a different mechanism of action is selected

02

Consider withdrawing other medications associated with hyponatremia

- Thiazide diuretics, carbamazepine, NSAIDs, tramadol, proton pump inhibitors

03

Start low, go slow, and monitor serum sodium closely

04

Consider long-term maintenance strategies if antidepressant still needed

- Fluid restriction, careful use of oral demeclocycline

## SEROTONIN REUPTAKE INHIBITORS AND GI BLEEDING <sup>4, 5, 6, 20</sup>

### Risk Factors

History of GI bleed	Active peptic ulcers
Elderly	Liver disease
Drugs that increase bleeding ( warfarin, ASA)	Surgical procedures
Drugs that cause GI injury (NSAIDs)	

### Management Strategies:

- Risk is present for as long as the serotonin reuptake inhibitor is present.
  - Consider switching to a non-serotonergic antidepressant
  - Mirtazapine, bupropion, and/or MAOI are recommended in patients at risk for bleeding.
  - Nortriptyline and protriptyline may be safe alternatives
- Consider adding acid-suppressing agents (PPI or H2 blocker) to reduce risk

## SEROTONIN SYNDROME <sup>1, 16, 44</sup>

Signs and Symptoms of Serotonin Syndrome		Medications Associated with Serotonin Syndrome		
Neurologic	Confusion, agitation, ataxia, akathisia	Most antidepressants	Linezolid	Metoclopramide
		Lithium	Reserpine	Dextromethorphan
Neuromuscular	Clonus, hyperreflexia tremor	Valproate	Sibutramine	Ginseng
		Triptans	Tramadol	St. John's Wort
Autonomic		Buspar	Fentanyl	Ondansetron
		Methadone	Amphetamines	Cocaine

### Strategies for Prevention/ Treatment

Augment: use of non-serotonergic medication, i.e., Bupropion

Education: signs and symptoms of serotonin syndrome

Treatment: If serotonergic medication is required, restart after symptoms of serotonin syndrome are absent

\*\* Titrate: LOW and SLOW\*\*

## TCA MECHANISM OF ACTION AND OFF- LABEL USE <sup>17</sup>

Blocks reuptake of 5-HT and NE

Blocks receptors: M,  $\alpha$ , H(Autonomic)

Off-label use:

- Migraine prevention
- Insomnia
- Irritable bowel syndrome
- Anxiety
- Chronic pain, especially neuropathic pain conditions and fibromyalgia
- Bedwetting (nocturnal enuresis)
- Bulimia nervosa

## ADVERSE EFFECTS AND DOSING FOR TRICYCLIC ANTIDEPRESSANTS <sup>29</sup>

	Reuptake mechanism <sup>B</sup>	Sedation	Hypotension	Seizure	Weight gain	Cardiac	Initial/maximum dosing (MDD)
<b>Tertiary amine TCAs</b>							
<b>Amitriptyline</b>	5-HT > NE	+++	+++	++	++	+++	25-75mg/200 mg daily
<b>Clomipramine</b>	5-HT > NE	++	++	+++	+	++	25 mg/250 mg daily
<b>Doxepin<sup>C</sup></b>	5-HT = NE	+++++	+	++	++	+	50-75 md/300 mg nightly
<b>Imipramine</b>	5-HT = NE	++	+++	++	++	+++	50-100mg/200 mg daily
<b>Secondary amine TCAs</b>							
<b>Desipramine</b>	NE > 5-HT	+	+	+	+	++	100-200 mg/300 mg daily
<b>Maprotiline</b>	NE > 5-HT	++	+	+	++	+	25-50 mg/225 mg nightly
<b>Nortriptyline</b>	NE > 5-HT	+	+	+	+	++	25-50 mg/150 mg daily

A Plus sign (+) indicates the potential severity of an adverse effect.

B Tertiary amine TCA's tend to preferentially inhibit serotonin reuptake, resulting in greater synaptic serotonin levels, whereas secondary amine TCA's tend to preferentially inhibit norepinephrine uptake, resulting in greater synaptic norepinephrine levels.

C FDA approved, 2010 for insomnia MDD = depressive disorder; NE = norepinephrine; 5-HT = serotonin

## CAUTION: TCA's AND DRUG INTERACTIONS <sup>12</sup>

TCA- Drug Interaction	Potential Effects
Monoamine oxidase inhibitors (MAOIs)	Concurrent use of MAOIs with TCAs may cause serotonin syndrome or hypertensive crisis, a life-threatening condition caused by excessive levels of serotonin or norepinephrine in the body.
Selective serotonin reuptake inhibitors (SSRIs)	Concurrent use of SSRIs with TCAs may lead to serotonin syndrome or elevated TCA levels in the body due to the inhibitory effect of certain SSRIs on the CYP2D6 enzyme.
Serotonin-norepinephrine reuptake inhibitors (SNRIs)	Concurrent use of SNRIs with TCAs can result in serotonin syndrome or elevated TCA levels in the body due to the inhibitory effect of certain SNRIs on the CYP2D6 enzyme.
Anticholinergic drugs	Concurrent use of anticholinergic drugs, such as antihistamines, antipsychotics, or anti-Parkinsonian drugs, with TCAs may cause additive anticholinergic effects, including dry mouth, constipation, urinary retention, blurred vision, confusion, or delirium.
Anticoagulants	Concurrent use of anticoagulants, such as warfarin or heparin, with TCAs could potentially heighten the risk of bleeding. This might result from either the inhibition of platelet aggregation by certain TCAs or the displacement of warfarin from plasma proteins by specific TCAs.
Lithium	Concurrent use of lithium with TCAs can lead to neurotoxicity, serotonin syndrome, or neuroleptic malignant syndrome. These severe conditions are marked by altered mental status, muscle rigidity, fever, and autonomic instability.
Clonidine	TCAs could potentially diminish the antihypertensive effects of clonidine, as they obstruct the presynaptic alpha-2 receptors that regulate the feedback inhibition of norepinephrine release.
Blood pressure medications	TCAs can interact with blood pressure medications, such as beta-blockers, calcium channel blockers, or clonidine, causing additive or antagonistic effects on blood pressure or heart rate.
Cimetidine	Cimetidine can elevate the levels of TCAs in the body and increase the likelihood of adverse effects.

## MAO-I AND TYRAMINE <sup>11, 38</sup>

Selected Foods with High Tyramine Content	
Tap beers, red wine	Smoked meat or fish
Pickled/fermented	Meat tenderizer
Aged cheese	Fermented sauces
	Soybeans
	Dried fruit
	Dried meats
Selected MOA-I Mental Health Medication Interactions	
Amphetamines	↑ risk of hypertensive episode
Atomoxetine	↑ risk of hypertensive episode
Bupropion	↑ risk of neurotoxic episode
Serotonergic Medications	↑ risk of serotonin syndrome
Methadone, Tramadol, Meperidine	↑ risk of serotonin syndrome

MAOI Toxicity Symptoms	
<b>Mild</b>	Agitation, diaphoresis, tachycardia, mild temperature elevation
<b>Moderate</b>	Altered mental status, tachypnea, vomiting, dysrhythmias, hyperthermia, hypertension
<b>Severe</b>	Severe hyperthermia, seizure, central nervous system depression, cardiorespiratory depression, muscle rigidity, myoclonus

## MONOTHERAPY AGENTS IN TREATMENT-RESISTANT DEPRESSION: MONOAMINE OXIDASE INHIBITORS (MAO-I) 32, 33

- MAOIs require a low tyramine diet, except the Selegiline 6 mg/day patch.
  - Increases above 6 mg may not be necessary.

	INITIAL DOSE (MG/DAY)	DOSE TITRATION INCREMENTS (MG)	DOSAGE RANGE (MG/DAY)
<b>Non-selective MOA Inhibitors</b>			
Phenelzine (Nardil®)	15 three times daily	15 per week	Initial dose: 60-90* Maintenance: 15
Tranylcypromine (Parnate®)	10-30 twice daily	10 every 1-3 weeks	30-60
Isocarboxazid (Marplan)	20 BID BID-QID two to four times daily	10 every 2-4 days	40-60
<b>MOA-B Inhibitors</b>			
Selegiline patch+ (Esmam)	6 every 24 hours	3 every 2 weeks	6-12

\* Maintain doses at 60 to 90 mg daily until maximum benefit is obtained, then slowly reduce dose over several weeks.

## MAINTAINING THE GOAL 21

- Preventing recurrence is ultimate goal
  - Medications for at least 6-12 months after remission
  - Medications for 2 years or longer if higher risk



## DOSE REDUCTION AND MEDICATION DISCONTINUATION <sup>21</sup>

No clear consensus

Consider the situation

- Rapid versus gradual

Monitor for return of depression symptoms and antidepressant discontinuation symptoms

## WHAT ABOUT GENETIC TESTING? <sup>7, 8</sup>

- No clear evidence of the benefit of pharmacogenetic genetic testing
- Only gives information on possible metabolism of CYP450 pathways and medications
- Starting low and increasing as needed should be general practice regardless of pharmacogenetic testing status

## NUTRITIONAL AUGMENTATION STRATEGIES <sup>2, 13</sup>

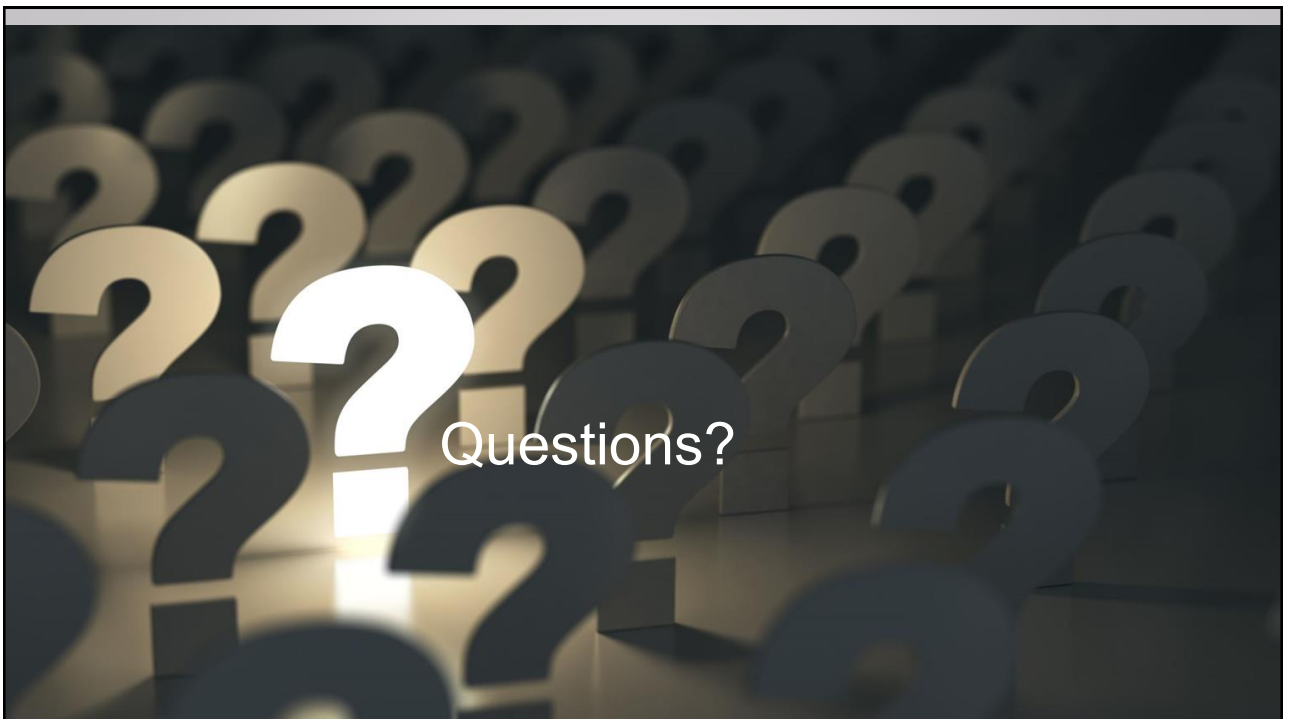
L-methylfolate may improve antidepressant response

- Particularly useful in partial responders

Vitamin D improves depressive symptoms in deficient patients

N-acetylcysteine boosts glutathione levels-OCD

Useful as an adjunctive not monotherapy



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