Depression Pharmacotherapy Review

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Disclosure

- Chris Paxos has no actual or potential conflict(s) of interest in relation to this presentation.

Objectives

1. Compare and contrast the pharmacologic properties of modern antidepressants

2. Describe adverse effects and drug interactions associated with modern antidepressants

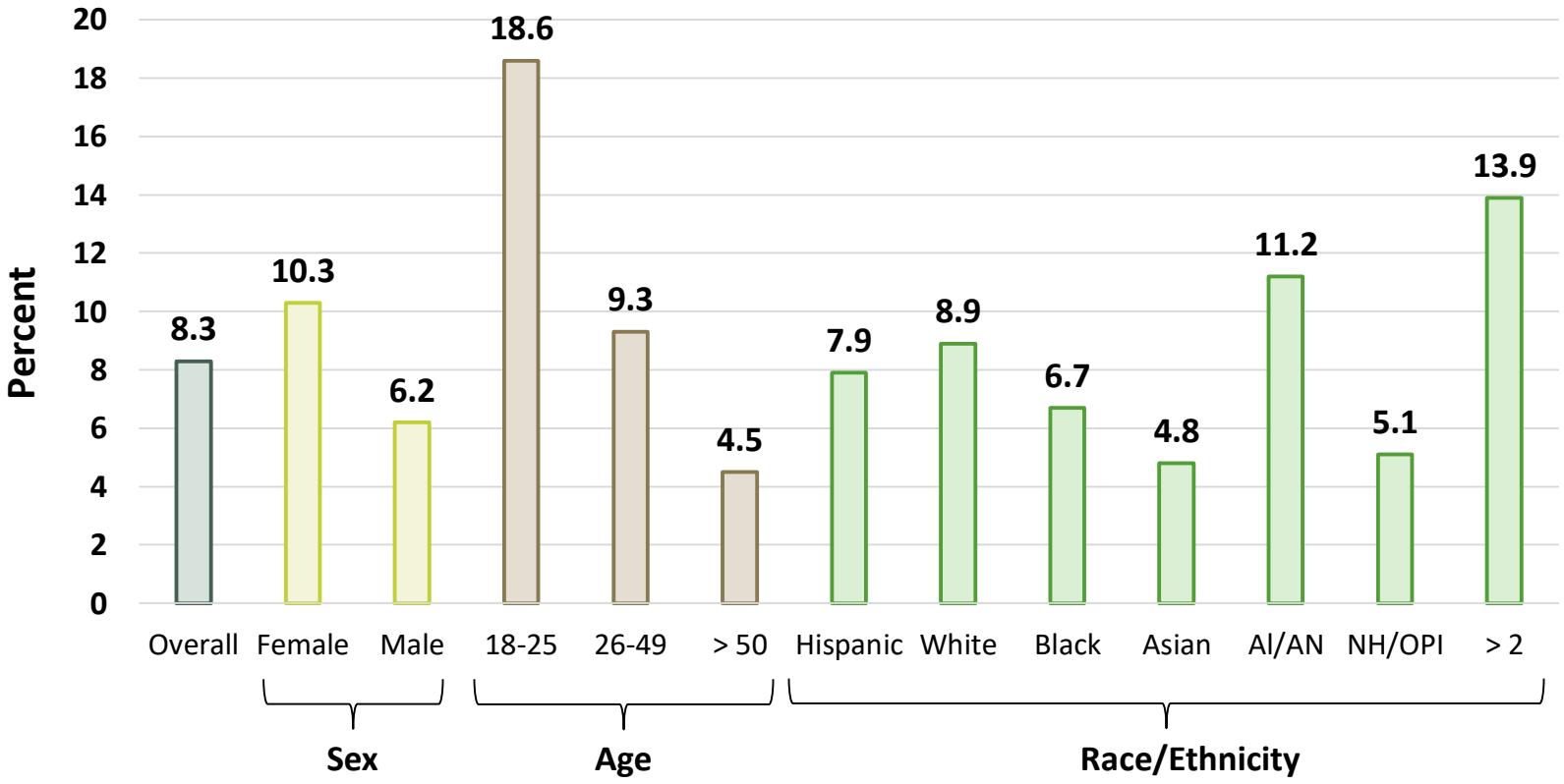
3. Describe principles associated with antidepressant use for the management of major depressive disorder

Psychopharmacology Trivia

Which antidepressant was the first to be FDA approved for the treatment of depression in the United States?

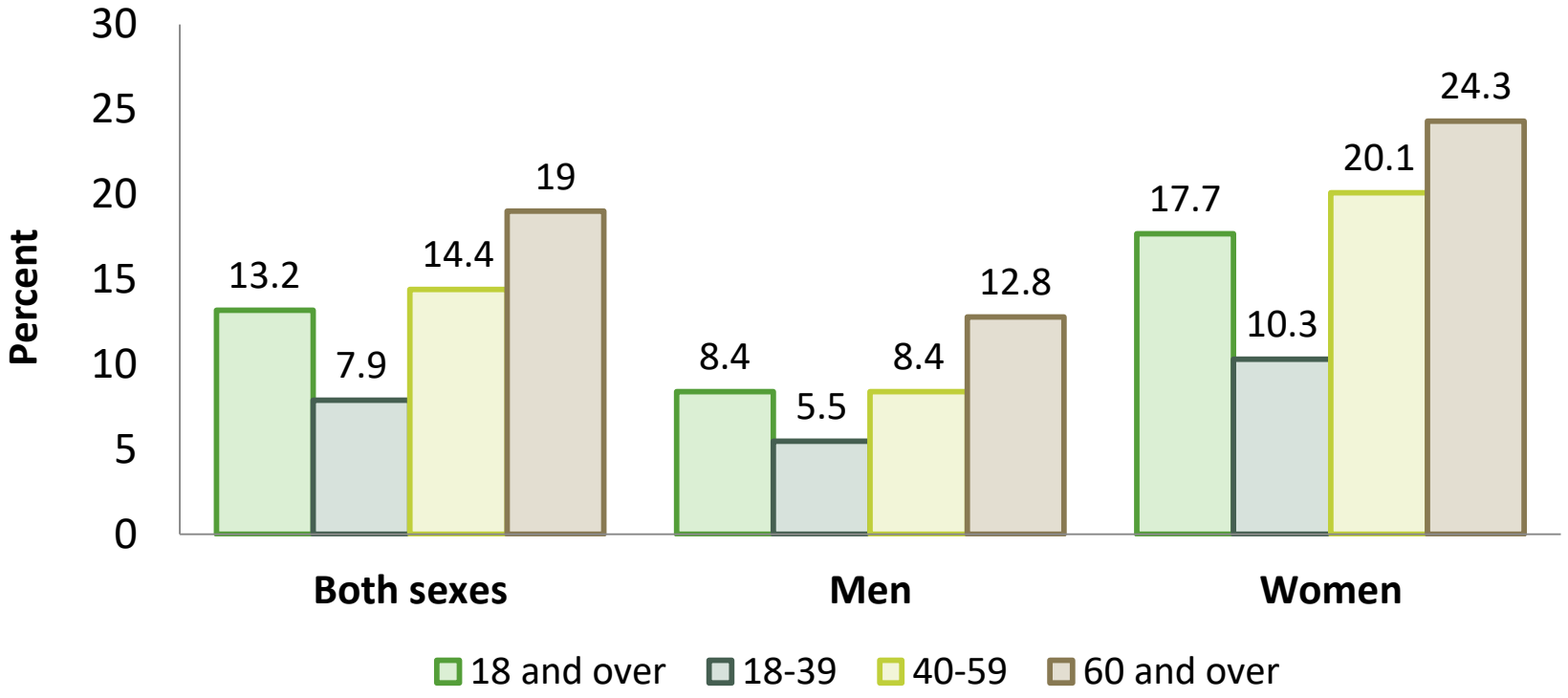
Major Depressive Disorder

- Americans ≥ 18 years experiencing a major depressive episode, 2021



Antidepressants

- Americans ≥ 18 years taking antidepressants between 2015-2018



Centers for Disease Control and Prevention, 2020.

Modern Antidepressants

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Assessment Question

A patient is started on citalopram 20 mg once daily. After three weeks of treatment, the patient complains of difficulty achieving orgasm and decreased overall libido. The prescriber would like to switch medications. Which antidepressant is least likely to cause sexual side effects?

A. Sertraline
B. Bupropion
C. Venlafaxine
D. Escitalopram

SSRIs

- Fluoxetine (Prozac®)
  - Activating, take in AM
  - Long half-life (4–16 days)
- Paroxetine (Paxil®)
  - Weight gain, mildly antiACh
  - Discontinuation syndrome
- Sertraline (Zoloft®)
  - GI distress (diarrhea)
- Fluvoxamine (Luvox®)
  - Not approved for MDD
  - Sedating, take at bedtime
- Citalopram (Celexa®)
  - QT interval prolongation
  - Max 20 mg (liver dx, > 60 yo)
- Escitalopram (Lexapro®)
  - Enantiomer of citalopram

GI distress	Activating effects	Sexual dysfunction	Sleep disturbances

Pharmacotherapy, 2022.
N Engl J Med. 2019;380(6):559-68.

SSRIs

	MDD	GAD	OCD	SAD	PTSD	PD	BN	PMDD	VSM
Fluoxetine	X		X			X	X	X	
Paroxetine	X	X	X	X	X	X		X	X
Sertraline	X		X	X	X	X		X	
Citalopram	X								
Escitalopram	X	X							
Fluvoxamine			X						

MDD, major depressive disorder; **GAD**, generalized anxiety disorder; **OCD**, obsessive-compulsive disorder; **SAD**, social anxiety disorder; **PTSD**, posttraumatic stress disorder; **PD**, panic disorder; **BN**, bulimia nervosa; **PMDD**, premenstrual dysphoric disorder; **VSM**, vasomotor symptoms of menopause

SNRIs

- Adverse effects
  - Similar adverse effects to SSRIs; hyperhidrosis more common
  - SNRIs may increase **blood pressure** in a dose-dependent manner

- Venlafaxine (Effexor®)
  - NE reuptake at high doses
  - Discontinuation syndrome
- Duloxetine (Cymbalta®)
  - Constipation, dry mouth
  - Several pain indications
  - Hepatotoxicity
- Desvenlafaxine (Pristiq®)
  - Venlafaxine metabolite
  - Tablet may appear in stool
- Levomilnacipran (Fetzima®)
  - Enantiomer of milnacipran
  - Most noradrenergic SNRI
  - Urinary hesitancy (4-6%)

Pharmacotherapy, 2022.
N Engl J Med. 2019;380(6):559-68.

Other Antidepressants

- Bupropion (Wellbutrin®)
  - Activating (take in AM)
  - Low sexual dysfx, weight gain
  - **Contraindications**
- Trazodone (Desyrel®)
  - Sedating (take at bedtime)
  - Orthostatic hypotension
  - Priapism (rare)
- Vilazodone (Viibryd®)
  - Nausea (23%), diarrhea (26%)
  - Food enhances absorption
- Mirtazapine (Remeron®)
  - Sedating (take at bedtime)
  - Appetite stimulation, weight gain
  - Agranulocytosis (rare)
- Nefazodone (Serzone®)
  - Sedation, orthostatic hypotension
  - Strong CYP3A4 inhibitor
  - Hepatotoxicity
- Vortioxetine (Trintellix®)
  - Nausea (21-32%)
  - Improves SSRI sexual dysfx

Pharmacotherapy, 2022.
N Engl J Med. 2019;380(6):559-68.

SNRIs & Other Antidepressants

	MDD	GAD	SAD	PD	FM	DPN	CMP	SC	WL
Venlafaxine	X	X	X	X					
Desvenlafaxine	X								
Duloxetine	X	X			X	X	X		
Levomilnacipran	X								
Bupropion	X							X	X
Mirtazapine	X								
Trazodone	X								
Nefazodone	X								
Vilazodone	X								
Vortioxetine	X								

MDD, major depressive disorder; **GAD**, generalized anxiety disorder; **SAD**, social anxiety disorder; **PD**, panic disorder; **FM**, fibromyalgia; **DPN**, diabetic peripheral neuropathy; **CMP**, chronic musculoskeletal pain; **SC**, smoking cessation; **WL**, weight loss (with naltrexone)

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A. Sertraline
B. Bupropion
C. Venlafaxine
D. Escitalopram

Select Adverse Effects

Discontinuation Syndrome

- Discontinuation syndrome
  - Occurs with routine antidepressant use
  - Often involves short half-life agents
  - Onset typically occurs in 1-3 days
  - Onset with fluoxetine may take weeks
- Management
  - Patient education
  - Taper over weeks to months
  - Restart agent, slow taper rate

F	Flu-like symptoms
I	Insomnia
N	Nausea
I	Instability, dizziness
S	Sensory disturbances
H	Hyperarousal

Lancet Psychiatry. 2019;6(6):538-46.
Am Fam Physician. 2006;74:449-57.

Hyponatremia

- Considerations/risk factors
  - SSRIs, SNRIs
  - Older age
  - Females
  - Thiazide diuretics
  - Low baseline Na^+
- Management
  - Monitor Na^+
  - Fluid restriction
  - Discontinue antidepressant
  - Use lower risk antidepressant

Headache	Weakness	Unsteadiness	Poor concentration	Confusion
	Hallucinations	Seizures	Coma	

J Psychosom Res. 2021;151:110654.
Ann Pharmacother. 2006;40:1618-22.

Pharmacokinetic Interactions

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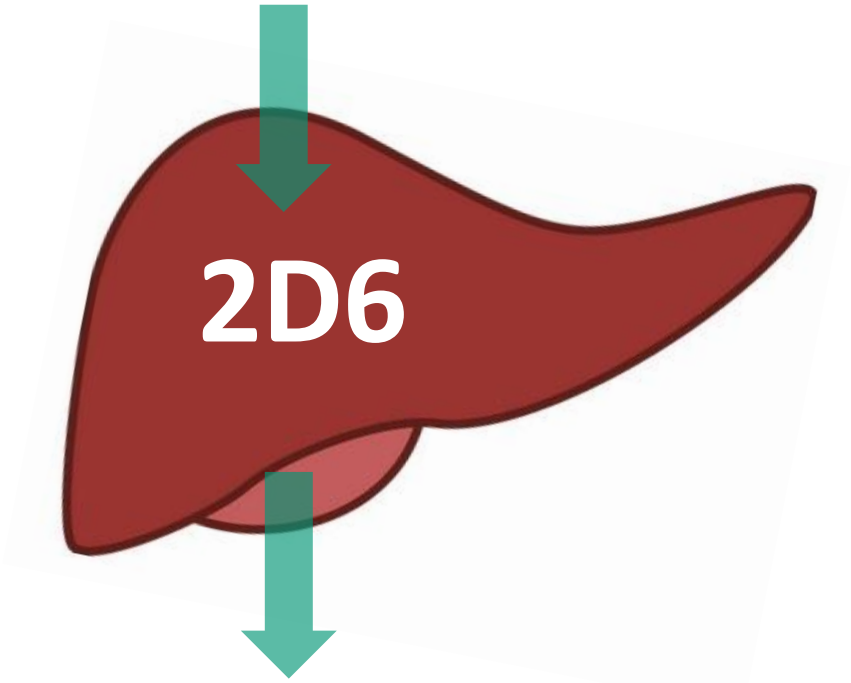
Assessment Question

A patient is newly diagnosed with major depressive disorder and started on fluoxetine 20 mg once daily. After one week of treatment, the dose is increased to 40 mg once daily. Past medical history includes migraines and seasonal allergies. Current medications include metoprolol 50 mg twice daily, sumatriptan 50 mg once daily PRN, and loratadine 10 mg once daily. Labs are unremarkable. At today's appointment, the patient reports dizziness and falling at home yesterday. Vital signs show the patient is hypotensive with a heart rate of 52 beats per minute. What issue has emerged with the patient's pharmacotherapy?

Pharmacokinetic Interactions

Metoprolol (Lopressor®)



inactive metabolites

Inhibiting the activity of the 2D6 enzyme would result in:

1. Slower metoprolol metabolism
2. Increased metoprolol levels
3. Lower blood pressure, pulse

Many modern antidepressants are inhibitors of these types of drug metabolizing enzymes

Pharmacokinetic Interactions

Inhibitory CYP potential of select antidepressant medications

	Bupropion	Citalopram	Duloxetine	Fluoxetine	Fluvoxamine	Mirtazapine	Nefazodone	Paroxetine	Sertraline	Venlafaxine
CYP1A2	—	weak	—	mod	**strong**	weak	—	weak	weak	—
CYP2C19	—	weak	—	mod	mod	—	—	weak	mod	—
CYP2D6	**strong**	weak	Mod	**strong**	weak	—	—	**strong**	mod	weak
CYP3A4	—	—	—	weak	weak	weak	**strong**	weak	mod	weak

U.S. National Library of Medicine, 2023.
American Psychiatric Association, 2010.

Assessment Question

A patient is newly diagnosed with major depressive disorder and started on **fluoxetine** 20 mg once daily. After one week of treatment, the dose is increased to 40 mg once daily. Past medical history includes migraines and seasonal allergies. Current medications include **metoprolol** 50 mg twice daily, sumatriptan 50 mg once daily PRN, and loratadine 10 mg once daily. Labs are unremarkable. At today's appointment, the patient reports dizziness and falling at home yesterday. Vital signs show the patient is hypotensive with a **heart rate** of 52 beats per minute.

Recent FDA Approvals

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Assessment Question

A patient with major depressive disorder is started on gepirone 18.2 mg once daily with food and increased to 36.3 mg once daily on day 4 of treatment. Current medications include furosemide, diltiazem, lisinopril, and fexofenadine. Which medications interact with gepirone treatment?

A. Lisinopril
B. Diltiazem
C. Furosemide
D. Fexofenadine

Gepirone

Gepirone (Exxua®)

Pharmacology
- Serotonin-1A (5HT1A) receptor agonism

Indication
- Major depressive disorder

Adverse effects
- Dizziness, nausea, abdominal pain, insomnia, dyspepsia

Dosage form
- XR tablets: 18.2 mg, 36.3 mg, 54.5 mg, 72.6 mg

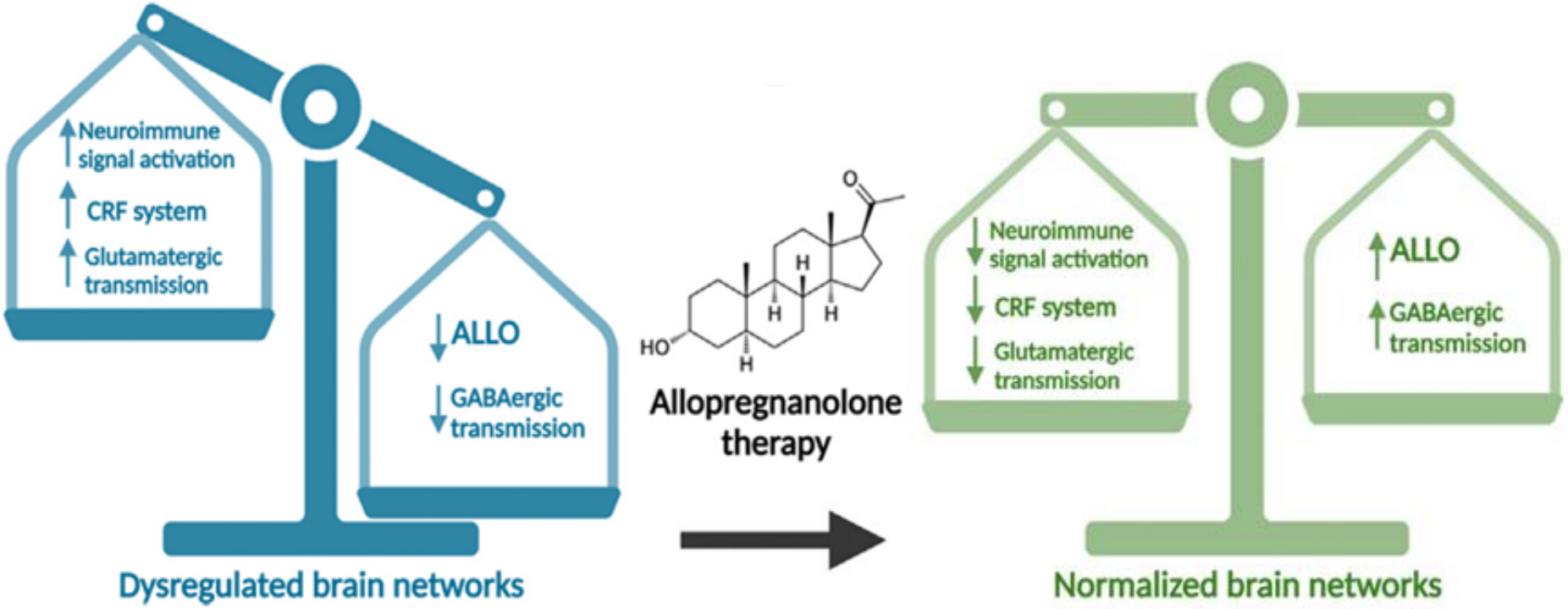
- Contraindications
  - Prolonged QT interval (> 450 msec)
  - Congenital long QT syndrome
  - Severe hepatic impairment
  - Strong CYP3A4 inhibitors
- Dosing
  - **Initial**: 18.2 mg once daily with food
  - **Maximum**: 72.6 mg once daily with food
- Monitoring
  - **Electrolytes**: correct prior to starting
  - **ECG**: during titration, then periodically

Gepirone (Exxua®)

Moderate CYP3A4 Inhibitors	Strong CYP3A4 Inhibitors	QT Prolonging Medications
Amiodarone (Pacerone®)	Clarithromycin (Biaxin®)	Antiarrhythmics
Dronedarone (Multaq®)	Voriconazole (Vfend®)	Antipsychotics
Diltiazem (Cardizem®)	Posaconazole (Noxafil®)	Antibiotics
Verapamil (Calan®)	Itraconazole (Sporanox®)	Methadone
Cyclosporine (Neoral®)	Nefazodone (Serzone®)	Loop diuretics*
Fluconazole (Diflucan®)	Ritonavir*	Corticosteroids*
Imatinib (Gleevec®)	Cobicistat*	
Grapefruit juice		
50% dose reduction	Contraindicated	Electrolytes, ECG

Lexicomp Online, 2023.
U.S. National Library of Medicine, 2023.

Brexanolone & Zuranolone



GABA-A Receptor Positive Modulators

Biol Psychiatry. 2022;91(3):252-3.

Brexanolone (Zulresso®)

DEA schedule: **C-IV**

Pharmacology
- Neuroactive steroid
- Proprietary allopregnanolone
- GABA-A receptor modulation

Indication
- Postpartum depression
- Patients ≥ 15 years of age

REMS program
- Excessive sedation
- Sudden loss of consciousness
- Monitor with pulse oximetry
- Monitor patient-child interactions

- Dosage and administration
  - 60-hour (2.5 day) IV infusion

Hours	Dosage
0–4	30 mcg/kg/hour
4–24	60 mcg/kg/hour
24–52	90 mcg/kg/hour
52–56	60 mcg/kg/hour
56–60	30 mcg/kg/hour

Zuranolone (Zurzuvae®)

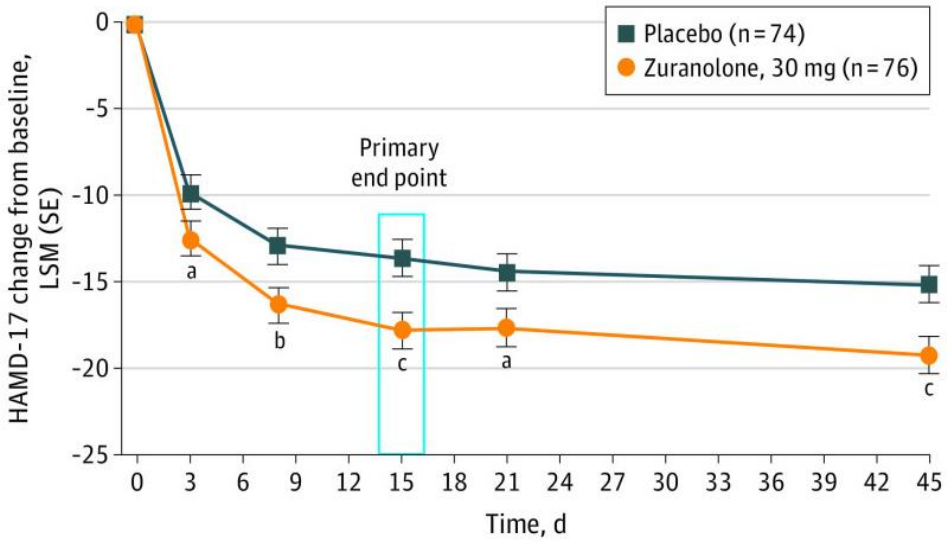
DEA schedule: **pending**

Pharmacology
- Neuroactive steroid
- GABA-A receptor modulation

Indication
- Postpartum depression
- Only indicated in adults

Warning
- CNS depression
- Sedation or confusion
- Avoid driving for 12 hours

- Dosage and administration
  - **50 mg in the evening x 14 days**
  - Take with or without antidepressant
  - Take with fat-containing food



U.S. National Library of Medicine, 2023.
JAMA Psychiatry. 2021;78(9):951-9.

a: p=0.03; **b**: p=0.01; **c**: p=0.003

Intranasal Esketamine

Esketamine (Spravato®)

DEA schedule: **C-III**

Pharmacology
- S-enantiomer of ketamine
- NMDA receptor antagonism

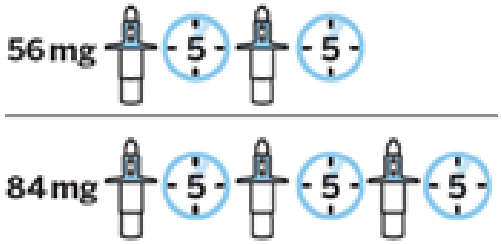
Indications
- Treatment-resistant depression
- MDD with acute suicidal ideation

Continue oral antidepressant treatment with esketamine

Monitoring
- Blood pressure before and after
- Observe ≥ 2 hours after use

- Treatment-resistant depression

Weeks	Dose	Frequency
1 – 4	56 mg (first dose) 56 – 84 mg	Twice weekly
5 – 8	56 – 84 mg	Once weekly
≥ 9	56 – 84 mg	Once weekly, or every 2 weeks



U.S. National Library of Medicine, 2023.
J Clin Psychiatry. 2020;81(3):19m12891.

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A. Lisinopril
B. Diltiazem
C. Furosemide
D. Fexofenadine

MDD Pharmacotherapy

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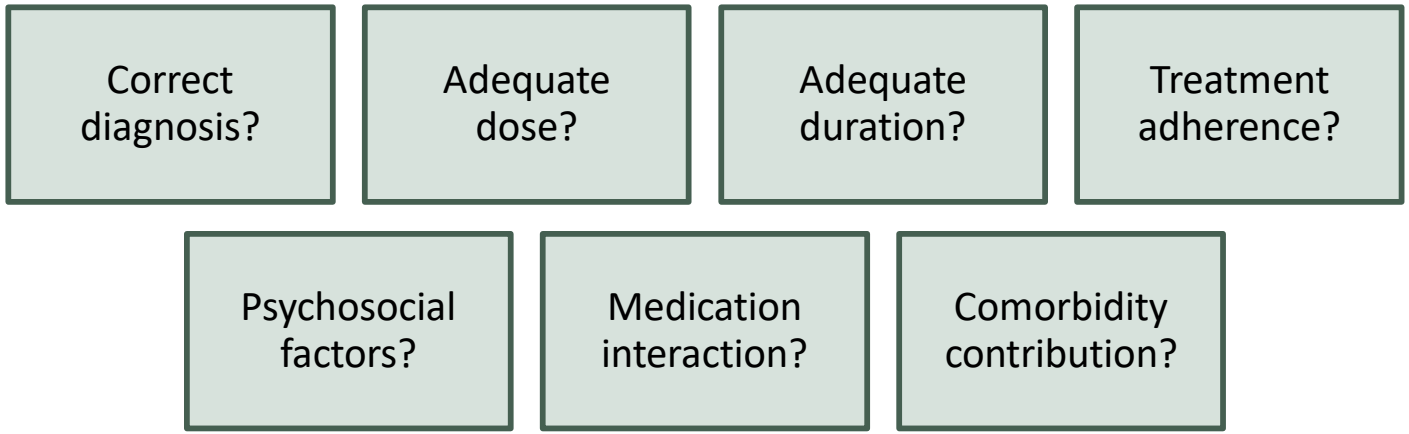
Assessment Question

A patient recently diagnosed with major depressive disorder (MDD) is started on escitalopram 10 mg once daily and titrated to 20 mg after one week. Following an 8-week trial, the patient experiences minimal-to-no response and continues to report depressed mood, anhedonia, and sleep disturbances. Other causes of MDD are ruled out. Which medication is the next best monotherapy trial to consider for this patient?

A. Sertraline
B. Phenelzine
C. Zuranolone
D. Aripiprazole

Pharmacotherapy Initiation

- Antidepressant initiation
  - Start at recommended dose, with titrations every 1-2 weeks
  - Consider lower initial doses for older adults and patients with anxiety
  - At least 4-8 weeks of treatment needed to assess response
  - With nonresponse, consider several factors:



American Psychiatric Association, 2010.
Am Fam Physician. 2009;80(2):167-72.
J Clin Psychiatry. 2007;68[suppl 8]:17-25.

Treatment Guidelines

VA/DoD Guidelines (2022)			
1st line	**Uncomplicated MDD**: ▪ Psychotherapy or Pharmacotherapy ▪ Pharmacotherapy ➢ SSRI ➢ SNRI ➢ Bupropion ➢ Mirtazapine ➢ Trazodone ➢ Vilazodone ➢ Vortioxetine **Severe MDD:** ▪ Psychotherapy + Pharmacotherapy ▪ Electroconvulsive therapy	2nd line	**Partial response/No response**: ▪ Alternative first-line agent ▪ Alternative pharmacotherapy ➢ Tricyclic antidepressant ➢ Monoamine oxidase inhibitor ➢ Esketamine/ketamine ➢ Nefazodone ▪ Switch to psychotherapy ▪ Augment with psychotherapy ▪ Augment with **atypical antipsychotic**

Veterans Health Administration and Department of Defense, 2022.

Additional MDD guidelines:
Canadian Network for Mood & Anxiety Treatments, 2016.
American Psychiatric Association, 2010.

Adjunctive Medications

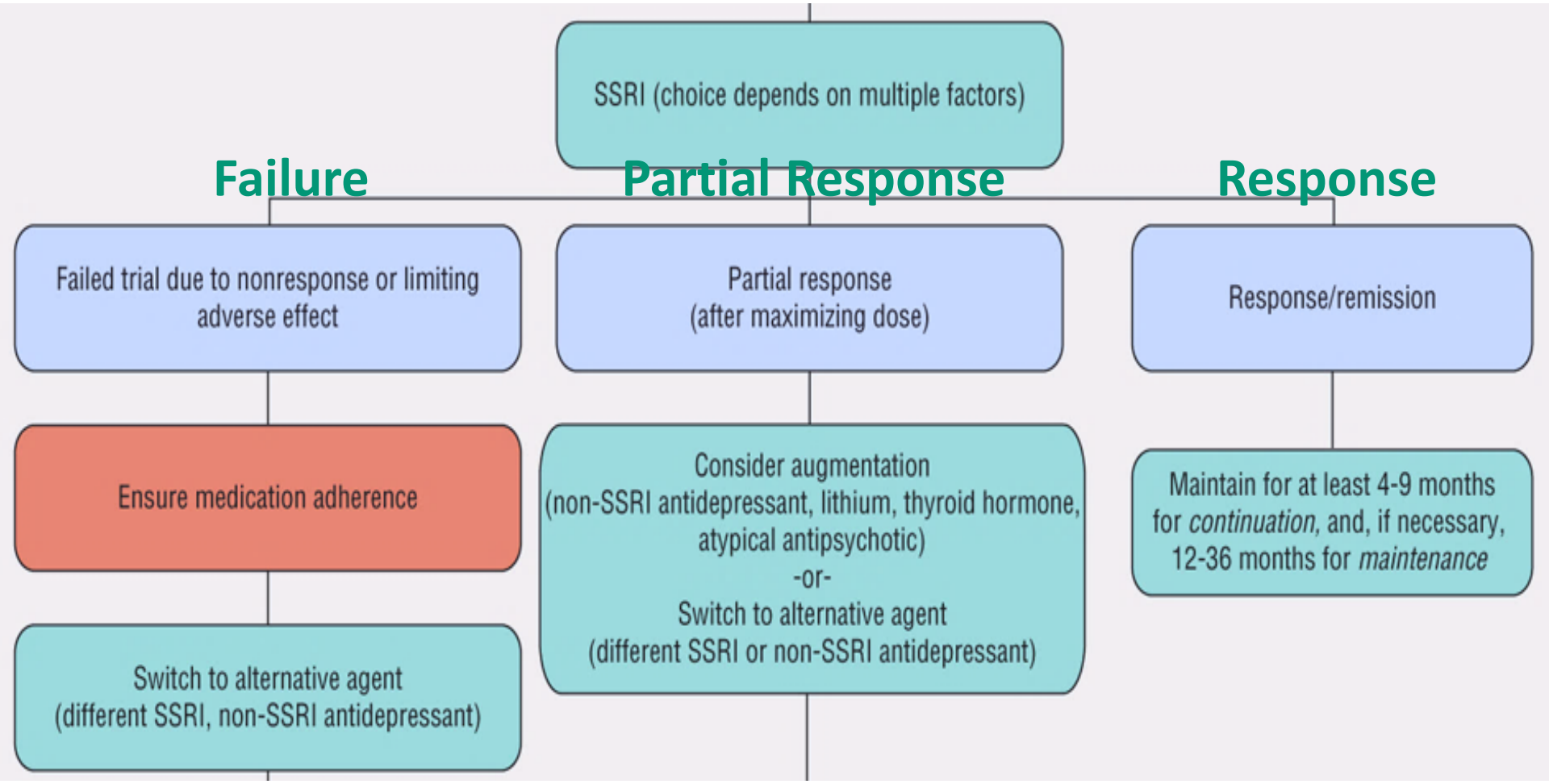
- Second generation (atypical) antipsychotics
  - FDA approved as adjuncts to antidepressant treatment
  - Mechanisms: 5HT2A antagonism, NE reuptake inhibition, 5HT1A agonism

	Aripiprazole	**Brexpiprazole**	**Quetiapine**	**Cariprazine**
Brand Name	Abilify®	Rexulti®	Seroquel XR®	Vraylar®
U.S. Approval	2007	2015	2009	2015
Starting Dose	2–5 mg	0.5–1 mg	50 mg	1.5 mg
Maximum Dose	15 mg	3 mg	300 mg	3 mg
Adverse Effects	Akathisia (25%)	Akathisia (≤ 14%)	Sedation (≤ 43%)	Akathisia (≤ 10%)
Weight Gain*	5.2%	2–5%	5%	2–3%

*Percentage of patients with MDD with weight gain ≥ 7% of body weight

U.S. National Library of Medicine, 2023.
Stahl's Essential Psychopharmacology, 2021.

Treatment Algorithm



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