Optimizing Strategies and Approaches for Treatment-Resistant Depression

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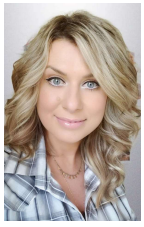
Meet the Speaker



Dr. Marvanova serves as the Professor and Dean of the Pacific University School of Pharmacy in Hillsboro, Oregon. She is a Board-Certified Psychiatric and Geriatric Pharmacist, as well as a Fellow of the American Society of Consultant Pharmacists (ASCP). She holds an M.S. (Pharm), Pharm.D., and a Ph.D. in Pathological Neurobiochemistry from Charles University in the Czech Republic, along with a Ph.D. in Neuropharmacology from the University of Eastern Finland. She also completed a medical research fellowship in neuropharmacology at Vanderbilt University School of Medicine and a Parkinson's disease traineeship at Northwestern University.

Her clinical expertise lies in geriatrics and neuropsychiatry, and she has extensive experience practicing in both inpatient and outpatient team-based clinical settings. Since 2013, she has served on the editorial board of *Continuum: Lifelong Learning in Neurology* (published by the American Academy of Neurology) and acts as a clinical pharmacy specialist consultant in neurology and psychiatry for Lexicomp, Wolters Kluwer. As a clinician, educator, and scholar, Dr. Marvanova is deeply committed to advancing training in geriatrics and neuropsychiatry while working to improve health outcomes for older adults.

Disclosure

Marketa Marvanova does not have relevant financial relationships with ineligible companies.

None of the planners for this activity have relevant financial relationships to disclose with ineligible companies.

This presentation will include discussion of off-label, experimental, and/or investigational use of drugs or devices: ketamine, lithium, risperidone, cariprazine, ziprasidone, liothyronine (T3), modafinil.

Learning Objectives

- Define treatment-resistant depression (RPh, CPT)
- Recognize and differentiate pseudoresistance from true TRD, and identify factors contributing to inadequate treatment response (RPh)
- Recognize common reasons why depression treatments may not work as expected (CPT)
- Evaluate and apply evidence-based strategies and treatment approaches for managing TRD (RPh)
- Discuss basic treatment strategies and approaches for management of TRD (CPT)

Pre-Test Question #1 (RPh, CPT)

Which of the following best defines treatment-resistant depression (TRD) according to the Food and Drug Administration (FDA) definition?

A. Major depressive disorder that does not respond to at least one adequate trial of an antidepressant

B. Depression that requires augmentation with a second medication for symptom relief

C. Failure to achieve an adequate response after at least two trials of different antidepressants at appropriate doses and durations

D. Depression that recurs after initial improvement with antidepressant therapy

Pre-Test Question #2 (RPh)

A 55-year-old female with recurrent major depressive disorder (MDD) presents for follow-up with persistent symptoms of anhedonia, poor concentration, excessive guilt, somnolence, and decreased appetite. Her PHQ-9 score today is 12, with an initial score of 13 before starting her current treatment. She has been on venlafaxine 300 mg daily for the past six weeks with good adherence, but her symptoms have not significantly improved.

Relevant medical history & previous trials:

- CBC, CMP, TSH, vitamin B12, and folic acid levels are all within normal limits
- Duloxetine 60 mg daily – ineffective after 3 months (good adherence)
- Paroxetine 50 mg daily – ineffective after 3 months (good adherence)

Pre-Test Question #2 (RPh)

What is the best next step to address her lack of response?

A. Perform CYP450 genotyping
B. Increase the dose of venlafaxine
C. Reevaluate for possible bipolar depression
D. Switch to bupropion

Pre-Test Question #2 (CPT)

A 50-year-old male with major depressive disorder has been on venlafaxine 225 mg daily for the past six weeks without significant improvement. He reports persistent low mood, fatigue, and poor concentration. Upon further questioning, you discover that he often forgets to take his medication and has missed multiple doses each week. His medical history includes untreated obstructive sleep apnea and hypothyroidism, and he is currently taking levothyroxine 50 mcg daily for thyroid function. **Which of the following is the most likely reason for his lack of response to treatment?**

A. True treatment resistance requiring a switch to another antidepressant class
B. Pseudoresistance due to nonadherence and untreated medical conditions
C. Inadequate venlafaxine dosage requiring an increase in medication strength
D. Pharmacokinetic failure due to CYP2C19 ultra-rapid metabolism phenotype

Pre-Test Question #3 (RPh)

A 31-year-old female with a 5-year history of major depressive disorder presents for follow-up after multiple failed treatment attempts. She reports persistent feelings of hopelessness, insomnia, loss of appetite, severe anhedonia, worsening suicidal ideation, and inability to engage in daily activities. Her PHQ-9 score is 23, indicating severe depression. She is currently taking venlafaxine XR 225 mg daily for the past 12 weeks, with augmentation of aripiprazole 5 mg daily for the past 4 weeks.

Past Medical and Psychiatric History:

- No history of psychosis or substance use disorder
- Medical history is unremarkable
- Adherent to medications and engaged in psychotherapy

Past Medication History:

- Mirtazapine 45 mg daily for 12 weeks – no response
- Fluoxetine 60 mg daily for 10 weeks – no response
- Escitalopram 30 mg daily for 10 weeks – minimal response

Pre-Test Question #3 (RPh)

Which of the following is the most appropriate next step in treatment?

A. Continue venlafaxine and increase aripiprazole dose to 10 mg daily
B. Discontinue venlafaxine and initiate monoamine oxidase inhibitor (MAOI) therapy
C. Initiate esketamine treatment in combination with an oral antidepressant
D. Continue current therapy and add bupropion

Pre-Test Question #3 (CPT)

Which of the following augmentation options in treatment-resistant depression (TRD) can provide both a rapid onset of antidepressant effects and an antisuicidal benefit?

A. Lithium
B. Buspirone
C. Esketamine
D. Bupropion

Major Depressive Disorder (MDD)

- A complex illness including a group of highly heterogenous disorders with different courses of illness and treatment response
- Usually **chronic or recurrent**
- Up to 20% lifetime prevalence

Greden JF. J Clin Psychiatry. 2001;62(suppl 22):5-9.; Kessler RC, et al. JAMA. 2003;289:3095-3105.; Keller MB, et al. Biol Psychiatry. 1998;44:348-360. 4. Keller MB, et al. Am J Psychiatry. 1982;139:438-442.; Mueller TI, et al. Psychiatr Clin North Am. 1996;19:85-102.; Fava M, et al, for the STAR*D Investigators Group. Psychiatr Clin North Am. 2003;26:457-494; Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press, Ltd.; 1995:1082-1097; American Pharmaceutical Association Web site. Accessed December 18, 2004; Russell JM, et al. J Clin Psychiatry. 2004;65:341-347.; Lépine J-P, et al, on behalf of the DEPRES Steering Committee. Int Clin Psychopharmacol. 1997;12:19-29.; Crown WH, et al. J Clin Psychiatry. 2002;63:963-971.

MDD First-Line Pharmacologic Treatment

1. **Assessment via standardized tool** (e.g., PHQ-9)
2. **Adequate Dose**
3. **Adequate trial: 6-12 weeks**

MDD

SSRIs	SNRIs	MIRT	BUP	VTX	VLZ
○ Sertraline ○ Citalopram ○ Escitalopram ○ Fluoxetine ○ Paroxetine	○ Venlafaxine XR ○ Duloxetine ○ Desvenlafaxine ○ Levomilnacipran				

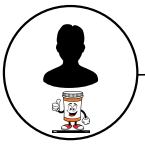
4. **Assessment via standardized tool** (e.g., PHQ-9)

Comparable efficacy when given in comparable doses

SSRI = selective serotonin reuptake inhibitor; SNRI = serotonin norepinephrine reuptake inhibitor; MIRT = mirtazapine; BUP = bupropion; VTX = vortioxetine; VLZ = vilazodone; PHQ = Patient Health Questionnaire

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; Quaid JR, Buelt A, Capaldi V, et al. *Ann Intern Med*. 2022;175(10):1440-1451; American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, Virginia: American Psychiatric Association, 2010.

Response Assessment to an Antidepressant Trial



4-8 (12) weeks

No Response	< 25% improvement
Partial Response	25% to < 50% improvement
Response	≥ 50% improvement
Remission	PHQ-9 score <5
AEs/Intolerance	

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687 Quaid JR, Buelt A, Capaldi V, et al. *Ann Intern Med*. 2022;175(10):1440-1451; American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, Virginia: American Psychiatric Association, 2010.

Response Assessment to an Antidepressant Trial

SUBJECTIVE SSESMENT			OBJECTIVE ASSESSMENT
"I feel the same"	No Response	PHQ-9 score reduction from 25 to 23 (8%)	
"I feel better but still depressed"	Partial Response	PHQ-9 score reduction from 25 to 18 (28%)	
"I feel much better but still not like myself"	Response	PHQ-9 score reduction from 25 to 11 (56%)	
"I feel like my old self again"	Remission	PHQ-9 score reduction from 25 to 2	

Treatment-Resistant Depression (TRD)

- As many as **1/3 of people diagnosed with MDD** are classified as TRD
  - Increased disability, decreased quality of life, increased morbidity and mortality, high risk of suicide, greater healthcare utilization and costs
- No consensus how to define TRD
- Most commonly accepted TRD definition:

"Lack of an adequate clinical response to two or more different treatments on an adequate dose for an adequate duration in the current episode"

  - With antidepressants of **same or different class**
  - In patients **adherent** to therapy
- After 2 treatment steps, chance of achieving remission is reduced to 13.7%

The US Food and Drug Administration (FDA) and the European Medicines Agenc (EMA) adopted definition for TRD.

McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Gold- berg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; Thase ME, Rush AJ. Treatment-resistant depression. In: Bloom FE, Kupfer DJ, eds. Psychopharmacology: The Fourth Generation of Progress. New York, NY: Raven Press, Ltd.; Amos et al. *J Clin Psychiatry*. 2018;79: pii:17m11725; Feldman et al. *J Med Econ*. 2013;16:62; Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry; Rush AJ, Trivedi MH, Wisniewski SR, et al. *Am J Psychiatry*. 2006;163(11):1905–1917; Rush AJ, Trivedi MH, Wisniewski SR, et al. *Am J Psychiatry*. 2006;163(11):1905-1917.

Self-Assessment Question #1

74-year-old female with recurrent MDD, presents to the provider with complaints of fatigue, low mood, anhedonia, poor concentration and excessive guilt that increased in intensity in the past 2 months. Today's PHQ-9 score is 11 (moderate depression). She started sertraline 25 mg one week ago that she has to discontinue due to severe diarrhea.

Past medication trials:

- Escitalopram 20 mg daily (on therapy for 30 days that deemed to be ineffective)

Does this patient most-likely suffer from TRD?

A. Yes
B. No

Strategies for Management TRD: Rule-out Pseudoresistance

Confirm diagnosis of MDD/TRD

TRD?

Response to antidepressant monotherapy and patient factors

1. **MISDIAGNOSIS (need for accurate diagnosis)**
2. **NONADHERENCE**
3. **UNDER-TREATMENT (treatment optimization)**

Confirm Diagnosis

- Detailed review of medical, treatment, current and past treatment (including doses, duration), medication reconciliation, pharmacogenomics testing (if available or if necessary), adherence and AEs and complications
- Physical examination and basic lab testing (CBC, CMP, TSH, vitamin B12 and folic acid)
  - *Anemia, renal or liver insufficiency, B12 and folic acid deficiency*: **depressive symptoms**, fatigues, dizziness, somnolence, weight gain or weight loss, memory and/or concentration issues
  - *Hypothyroidism*: **depressive symptoms**, fatigue, weight gain, somnolence, memory and/or concentration issues, muscle weakness
  - *Obstructive sleep apnea*: excessive daytime sleepiness, **depressive symptoms**, insomnia, concentration issues
- Neuropsychiatric evaluation: *bipolar disorder, PTSD, depression secondary due to substance use disorder, medication-induced depression*

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Gold- berg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry;

Under-Treatment

Etiology	Solution/Intervention
Subtherapeutic dose	Increase dose (if tolerated)
Low therapeutic dose	Increase dose to upper limit (if tolerated)
Inadequate treatment trial time	Ensure treatment period of 6-12 weeks
Phenoconversion	Identify and resolve
Allelic variation: CYP2D6 (1-20%) and CYP2C19 (2-5%) ultra-rapid metabolizer	Consider or recommend pharmacogenomic testing to help guide treatment

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Gold- berg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry; Knöchel C et al., *Curr Neuropharmacol*. 2015;13(5):577-591.; Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494; Rush AJ, et al, for the STAR*D Investigators Group. *Control Clin Trials*. 2004;25:119-142.; American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, Virginia: American Psychiatric Association, 2010.

Major Substrates for CYP450 Isoforms

CYP2D6	CYP2C19	CYP3A4	CYP1A2
Fluoxetine	Citalopram	Vilazodone	Olanzapine
Paroxetine	Escitalopram	Levomilnacipran	
Venlafaxine	Sertraline	Mirtazapine	
Duloxetine	Quetiapine	Aripiprazole	
Bupropion		Brexpiprazole	
Mirtazapine		Buspirone	
Vortioxetine			Vortioxetine
TCAs			TCAs
Aripiprazole			

Antidepressants
Antipsychotics
Miscellaneous

Tricyclic antidepressants = TCAs

van Westrhenen R, Aitchison KJ, Ingelman-Sundberg M, Jukić MM. *Front Psychiatry*. 2020;11:94.

Self-Assessment Question #2

A 32-year-old female with recurrent Major Depressive Disorder (MDD) presents to the provider with complaints of fatigue, low mood, anhedonia, poor concentration, and heightened feelings of excessive guilt, which have intensified over the past two months. Today's PHQ-9 score is 11 (moderate).

For the past three months, she has been treated with venlafaxine XR 225 mg daily, with good adherence. Her initial PHQ-9 score was 12 (moderate). Laboratory results, including CBC, CMP, TSH, and vitamin B12 and folic acid levels, are all within normal limits.

Past medication trials:

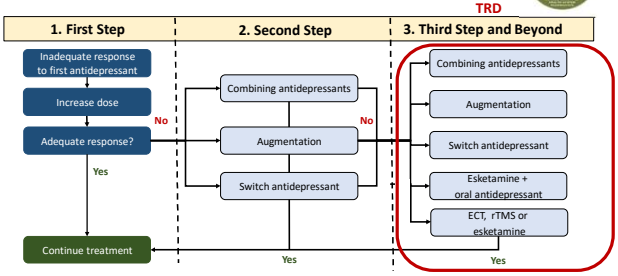
- Paroxetine 50 mg daily (deemed ineffective after 3 months with good adherence)
- Duloxetine 60 mg daily (deemed ineffective after 3 months with good adherence)

Self-Assessment Question #2

Which of the following would be best to recommend at this time?

A. Increase dose of venlafaxine
B. Diagnosis of bipolar depression
C. Switch to bupropion
D. CYP450 genotyping

Strategies and Approaches for Management TRD



Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Gold- berg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Kasper et al. *World J Biol Psychiatry*. 2021;22:468; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry; Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494; Rush AJ, et al, for the STAR*D Investigators Group. *Control Clin Trials*. 2004;25:119-142.; American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, Virginia: American Psychiatric Association, 2010.

Commonly Used Treatments for TRD

Antidepressant Switch Options

Safer Antidepressants	TCAs	MOAIs
Older antidepressants **SSRIs, SNRIs, mirtazapine; bupropion,** vortioxetine, vilazodone Other newer antidepressants: Levomilnacipran		

Adjunctive Treatment Options

Antidepressant	Other Agents	Non-pharmacologic
Mirtazapine **Bupropion** Low dose of nortriptyline	**AAs (e.g., aripiprazole)** **Lithium** **Liothyronine (T3)** Buspirone Modafinil **Esketamine** Ketamine	Cognitive behavioral therapy (CBT) Electroconvulsive therapy (ECT) Repetitive transcranial magnetic stimulation (rTMS)

Atypical antipsychotics = AAs; Monoamine oxidase inhibitors = MOAIs; Selective serotonin reuptake inhibitors = SSRIs; serotonin and norepinephrine reuptake inhibitors = SNRIs; tricyclic antidepressants = TCAs.

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Gold- berg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Marvanova M, McGrane I. *Sr Care Pharm*. 2021, 36:11-21; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry; Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494; Rush AJ, et al, for the STAR*D Investigators Group. *Control Clin Trials*. 2004;25:119-142.; American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, Virginia: American Psychiatric Association, 2010.

Guiding Characteristics and Clinical Profile	Antidepressant Switch	Adjunctive Treatment (Augmentation or Combination)
Type of therapy	Monotherapy (decreased medication/cost burden)	Combination therapy (increase medication/cost burden)
Who is a good candidate (tolerability of antidepressant)?	Poor tolerability	Good tolerability or inability to further increase
Who is a good candidate (response to an antidepressant)?	No response or partial response	Partial response
Who is a good candidate (time, urgency)?	Non-urgent: More time to wait for a response (< functional impairment)	More urgent: less time to wait for a response (symptoms severity/functional impairment)
Who is a good candidate (other)?		Presence of targeted specific residual symptom or improvement of tolerability

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Switching Antidepressants

- In-class or out-of-class switch
- Variety of strategies for switch depending on tolerability, safety, symptoms severity, comorbidities, and drug interactions

Direct switch	Cross titration	A taper followed by an immediate switch	Tapering of antidepressants, allowing a washout period

- Risk for serotonin syndrome (SS), adverse effects and complications (hypertensive crisis)
  - 5-week washout period when switching from fluoxetine
  - 2 week washout period from MAOI (e.g., phenelzine, tranylcypromine) or when switching to MAOI

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Gold- berg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Marvanova M, McGrane I. *Sr Care Pharm*. 2021, 36:11-21; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry; Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494; Rush AJ, et al, for the STAR*D Investigators Group. *Control Clin Trials*. 2004;25:119-142.; American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, Virginia: American Psychiatric Association, 2010.

Antidepressant Combination

- Combing antidepressants with different pharmacodynamic profile= intention of creation a synergistic effect
  - SSRI or SNRI plus mirtazapine or bupropion
  - SSRI plus low dose TCA such as nortriptyline
- Do not combine SSRI, SNRI, vortioxetine or vilazodone
- Do not combine MAOIs with other antidepressants due to risk of hypertensive crisis and SS: 2 weeks washout period
- Educate on the signs and symptoms of SS

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Gold- berg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Marvanova M, McGrane I. *Sr Care Pharm*. 2021, 36:11-21; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry; Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494; Rush AJ, et al, for the STAR*D Investigators Group. *Control Clin Trials*. 2004;25:119-142.; American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, Virginia: American Psychiatric Association, 2010.

Adjunctive Therapy Selection Guidance

Selection can be guided by safety, evidence, and also clinical presentation and remaining bothersome symptoms due to depression or antidepressant

- **Suicidality**: lithium, esketamine, ECT
- **Need for fast-onset:** esketamine (rapid-onset), ECT
- **Sexual dysfunction**: bupropion, mirtazapine, buspirone
- **Fatigue, apathy, low energy, weight gain, tiredness, somnolence**: bupropion, T3, modafinil
- **Anhedonia and demotivation:** aripiprazole
- **Weight loss/decreased appetite:** mirtazapine
- **Somatic pain, migraine, neuropathic pain**: TCAs (e.g., nortriptyline), duloxetine, venlafaxine XR
- **Insomnia:** quetiapine, mirtazapine

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Gold- berg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Nuñez NA, Joseph B, Pahwa M, et al. *J Affect Disord*. 2022;1;302:385-400; Quaid JR, Buelt A, Capaldi V, et al. *Ann Intern Med*. 2022;175(10):1440-1451; Marvanova M, McGrane I. *Sr Care Pharm*. 2021, 36:11-21; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry; Fava M, et al, for the STAR*D Investigators Group. *Psychiatr Clin North Am*. 2003;26:457-494; Rush AJ, et al, for the STAR*D Investigators Group. *Control Clin Trials*. 2004;25:119-142.; American Psychiatric Association (APA). Practice guideline for the treatment of patients with major depressive disorder, 3rd ed. Arlington, Virginia: American Psychiatric Association, 2010.

Self-Assessment Question #3

66-year-old male with recurrent MDD presents to the provider with complaints of fatigue, somnolence, and anhedonia. Today's PHQ-9 score is 9 (mild depression). For the past 8 weeks, he was treated with venlafaxine XR 225 mg daily with good adherence and tolerance except for some reports of sexual dysfunction. He still suffers from residual somnolence, and fatigue. His initial PHQ-9 score was 16 (moderately severe). His BMI is 35 kg/m^2

Past medication trials:

- Sertraline 150 mg daily (deemed ineffective after 3-month with good adherence)
- Duloxetine 60 mg daily (deemed ineffective after 3-month with good adherence)

Self-Assessment Question #3

What therapeutic recommendation would you suggest at this time?

A. Add mirtazapine

B. Switch to vortioxetine

C. Add bupropion

D. Increase dose of venlafaxine XR

Augmentation with Atypical Antipsychotics

- Symptom reduction in 1-2 weeks (if no response in a month, consider to discontinue)
- 4 antipsychotics FDA-approved for augmentation
  - **Aripiprazole:** akathisia
  - **Brexpiprazole:** weight gain, akathisia
  - **Quetiapine XR:** sedation, dry mouth, metabolic AEs
  - **Olanzapine** (with fluoxetine): sedation, weight gain, metabolic AEs, anticholinergic AEs
- Off-label use: risperidone, cariprazine, ziprasidone
- **Note:** acute and long-term AEs/complications

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Nuñez NA, Joseph B, Pahwa M, et al. *J Affect Disord*. 2022;302:385-400; Quaid JR, Buelt A, Capaldi V, et al. *Ann Intern Med*. 2022;175(10):1440-1451; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; *Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry.*

Augmentation with Lithium

- **Place in therapy:** Augmentation agent for MDD (off-label); significant reduction of risk of suicide
- **Initial dosing:**
  - Use empirical titration with target serum concentration of 0.3-0.6 mEq/L (monitor every 6-12 months)
  - Evaluate therapy after minimum of 2 weeks and if response is seen continue therapy for at least 12 months
- **Onset:** response seen in 2-6 weeks
- **Monitoring and AEs/complications:**
  - Narrow therapeutic index and renal clearance and frequent drug interactions require frequent monitoring
  - Interactions with salt content in diet, HCTZ, ACE inhibitors, ARBs, furosemide, NSAIDs
  - Long-term use associated with risk of hypothyroidism, weight gain
  - Check at baseline and at least every 12 months: TSH, serum creatinine and weight/BMI

Lam RW, Kennedy SH, Adams C, et al., *Can J Psychiatry*. 2024;69(9):641-687; McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, et al. *World Psychiatry*. 2023;22(3):394–412; Quaid JR, Buelt A, Capaldi V, et al. *Ann Intern Med*. 2022;175(10):1440-1451; Voineskos D, Daskalakis ZJ, Blumberger DM. *Neuropsychiatr Dis Treat*. 2020;16:221-234; *Shapero, B.G., Mischoulon, D., & Cusin, C. (2019). The Massachusetts General Hospital Guide to Depression. Current Clinical Psychiatry; Buspavanich P, Behr J, Stamm T, et al. J Affect Disord. 2019;251:136-140.*

Esketamine (Spravato™)

- Active isomer of ketamine (NMDA receptor antagonist/glutamate system)
- CIII drug: dissociation, sedation, misuse/abuse
- **Dosage form:** Nasal spray
- **Place in therapy:**
  - TRD in adults, as monotherapy or in conjunction with an oral antidepressant.
  - Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior in conjunction with an oral antidepressant
- **Onset:** within 24 hours (rapid-acting antidepressant)
- **Treatment:**
  - In-office treatment: administered at clinic/hospital under REMS program
  - Monotherapy or in conjunction with antidepressant therapy
  - Two-hour post dose monitoring due to dissociation, sedation and blood pressure
  - Consider to use if patient has TRD and failed multiple therapies or suffers from severe symptoms and suicidal ideation/behavior
  - Long-term safety and efficacy date (4.5 years)

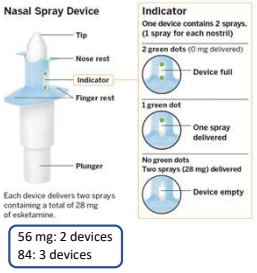
Zaki N, Chen LN, Lane R, Doherty T, et al. *Neuropsychopharmacology*. 2023;48(8):1225-1233;.
SPRAVATO® (esketamine). [Prescribing Information]. 2025. Janssen Pharmaceuticals, Inc., Titusville, NJ. January 2025.
Kasper et al. *World J Biol Psychiatry*. 2021;22:468.
Jalloh M. *Am Fam Physician*. 2020 Mar 15;101(6):339-340.

Esketamine (Spravato™)

- **Comments:**
  - Contraindicated in history of cerebral hemorrhage
  - Avoid food 2 h before/after and liquids 30 min before
  - If you take a nasal corticosteroid or nasal decongestant medicine take these medicines at least 1 hour before

- **Adverse Effects (AEs):**
  - Dissociation (41%)
  - Nausea and vomiting (28%)
  - Dizziness (29%)
  - Vertigo (23%)
  - Sedation (23%)
  - Headache (20%)
  - Taste disturbance (19%)
  - Hypertension/increased BP (10%)

SPRAVATO® (esketamine). [Prescribing Information]. 2025. Janssen Pharmaceuticals, Inc., Titusville, NJ. January 2025.
Kasper et al. *World J Biol Psychiatry*. 2021;22:468.
Jalloh M. *Am Fam Physician*. 2020 Mar 15;101(6):339-340.



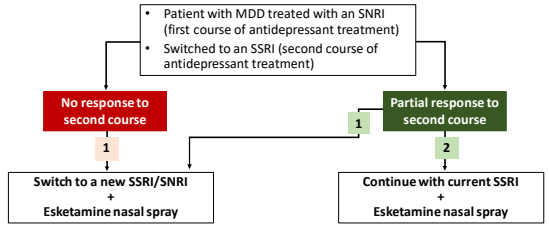
56 mg: 2 devices
84: 3 devices

Dosing (18-65 years old):

- Induction Phase (week 1-week 4): 56-84 mg twice weekly
- Maintenance Phase A (week 5-week 8): 56-84 mg once weekly or every other week
- Maintenance Phase B (week 9-thereafter): 56-84 mg once weekly or every other week

SPRAVATO® (esketamine). [Prescribing Information]. 2025. Janssen Pharmaceuticals, Inc., Titusville, NJ. January 2025.

Esketamine Integration in Clinical Practice



Adapted from: Kasper et al. *World J Biol Psychiatry*. 2021;22:468.

Neurostimulation

Repetitive Transcranial Magnetic Stimulation (rTMS)

- **Place in therapy**: MDD after ≥1 failed antidepressant treatment
- **Onset:** 4-6 weeks
- **Setting:** office/outpatient
- **Treatment:** once daily, 5 days/week
  - 20 sessions should be delivered before deemed as a treatment failure
  - Extension to 30-36 session if improvement occurs (different protocols/TMS method)
- **Maintenance:** use as needed to maintain response
- **Note:** monotherapy or combination with antidepressants; tolerability advantage over ECT; less effective than ECT

Electroconvulsive Therapy (ECT)

- **Place in therapy:** 2nd line for MDD, 1st-line for catatonia, psychosis or acute suicidal thoughts/behaviors, and for severe TRD
- **Onset**: after 6 treatments (~2 weeks)
- **Setting:** inpatient
- **Treatment:** 3 times/week for 3-4 weeks
- **Maintenance:** monthly or as needed
- **Note:** use of antidepressant post ECT reduces risk for relapse; no absolute contraindications but careful in recent cerebro/cardio-vascular issues (e.g., MI, cerebral hemorrhage, brain aneurysm, stroke, atrial fibrillation)

Key Points

- TRD is common and associated with significant morbidity and mortality
- First step in management of TRD to rule-out misdiagnosis (pseudoresistance)
- There are many options but preferred strategies are not well-defined and strength of evidence is currently lacking to recommend one over the other
- Switch or adjunctive treatment is tailored based on clinical profile of patient ("tailored" add-on treatment)
- Esketamine is a rapid-onset therapy that offers option for severe cases or situations where quick therapeutic effects are required
- Neurostimulation such as ECT and rTMS plays an increasing role in TRD

Post-Test Question #1 (RPh, CPT)

Which of the following best defines treatment-resistant depression (TRD) according to the Food and Drug Administration (FDA) definition?

A. Major depressive disorder that does not respond to at least one adequate trial of an antidepressant
B. Depression that requires augmentation with a second medication for symptom relief
C. Failure to achieve an adequate response after at least two trials of different antidepressants at appropriate doses and durations
D. Depression that recurs after initial improvement with antidepressant therapy

Post-Test Question #2 (RPh)

A 55-year-old female with recurrent major depressive disorder (MDD) presents for follow-up with persistent symptoms of anhedonia, poor concentration, excessive guilt, somnolence, and decreased appetite. Her PHQ-9 score today is 12, with an initial score of 13 before starting her current treatment. She has been on venlafaxine 300 mg daily for the past six weeks with good adherence, but her symptoms have not significantly improved.

Relevant medical history & previous trials:

- CBC, CMP, TSH, vitamin B12, and folic acid levels are all within normal limits
- Duloxetine 60 mg daily – ineffective after 3 months (good adherence)
- Paroxetine 50 mg daily – ineffective after 3 months (good adherence)

Post-Test Question #2 (RPh)

What is the best next step to address her lack of response?

A. Perform CYP450 genotyping
B. Increase the dose of venlafaxine
C. Reevaluate for possible bipolar depression
D. Switch to bupropion

Post-Test Question #2 (PT)

A 50-year-old male with major depressive disorder (MDD) has been on venlafaxine 225 mg daily for the past six weeks without significant improvement. He reports persistent low mood, fatigue, and poor concentration. Upon further questioning, you discover that he often forgets to take his medication and has missed multiple doses each week. His medical history includes untreated obstructive sleep apnea (OSA) and hypothyroidism, and he is currently taking levothyroxine 50 mcg daily for thyroid function. **Which of the following is the most likely reason for his lack of response to treatment?**

A. True treatment resistance requiring a switch to another antidepressant class
B. Pseudoresistance due to nonadherence and untreated medical conditions
C. Inadequate venlafaxine dosage requiring an increase in medication strength
D. Pharmacokinetic failure due to CYP2C19 ultra-rapid metabolism phenotype

Post-Test Question #3 (RPh)

A 31-year-old female with a 5-year history of major depressive disorder presents for follow-up after multiple failed treatment attempts. She reports persistent feelings of hopelessness, insomnia, loss of appetite, severe anhedonia, worsening suicidal ideation, and inability to engage in daily activities. Her PHQ-9 score is 23, indicating severe depression. She is currently taking venlafaxine XR 225 mg daily for the past 12 weeks, with augmentation of aripiprazole 5 mg daily for the past 4 weeks.

Past medical and psychiatric history:
- No history of psychosis or substance use disorder
- Medical history is unremarkable
- Adherent to medications and engaged in psychotherapy

Past medication history:
- Mirtazapine 45 mg daily for 12 weeks – no response
- Fluoxetine 60 mg daily for 10 weeks – no response
- Escitalopram 30 mg daily for 10 weeks – minimal response

Post-Test Question #3 (RPh)

Which of the following is the most appropriate next step in treatment?

A. Continue venlafaxine and increase aripiprazole dose to 10 mg daily
B. Discontinue venlafaxine and initiate monoamine oxidase inhibitor (MAOI) therapy
C. Initiate esketamine treatment in combination with an oral antidepressant
D. Continue current therapy and add bupropion

Post-Test Question #3 (CPT)

Which of the following augmentation options in treatment-resistant depression (TRD) can provide both a rapid onset of antidepressant effects and an antisuicidal benefit?

A. Lithium
B. Buspirone
C. Esketamine
D. Bupropion

What questions do you have?

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