

# Treatment Resistant Depression Combating Treatment Resistant Depression (TRD) in Veterans with Major Depressive Disorder



**U.S. Department of Veterans Affairs** 

Veterans Health Administration PBM Academic Detailing Service

# **Treatment Resistant Depression**

Combating Treatment Resistant Depression (TRD) in Veterans with Major Depressive Disorder

A VA Clinician's Guide



U.S. Department of Veterans Affairs Veterans Health Administration PBM Academic Detailing Service

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### Key Messages

Use the PHQ-9 or similar assessment tool to measure depression severity and monitor response to treatment.	7
Provide or refer Veterans to evidence-based psychotherapy for depression.	8
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### **Key Facts**

Major depression is a leading cause of disability and one of the most common mental health disorders in the United States and worldwide.<sup>1</sup>

- According to a recent survey, most adults had severe impairment with a major depressive episode (severity included measurements in 4 domains: home, work, relationships, social life).<sup>1</sup>
- It is estimated that 10 to 30% of adults diagnosed with major depression battle symptoms of depression that don't respond adequately to treatment.<sup>2</sup>

Treatment Resistant Depression	Major depressive episodes that do not remit after $\ge 2$ proven treatments of adequate dose and duration. <sup>3-6</sup>
Treatment Refractory Depression	Major depressive episodes that are resistant to treatment and do not remit after multiple sequential proven treatments of adequate dose and duration. <sup>3-6</sup>

Figure 1. Not Achieving Remission Can Lead to Severe Consequences<sup>2,7–9</sup>



# **Evaluation**

It is important to perform a thorough clinical evaluation of a patient with suspected major depressive disorder.<sup>10</sup> Consider confounders such as certain medications (e.g., opioids) and other conditions (e.g., hypothyroidism) that may be causing or worsening symptoms. Deprescribing and/or treatment of co-morbidities may be necessary.

Figure 2. Evaluating Patients with Suspected Depression<sup>10,11,13</sup>

<b>SAFETY</b> Assess for Acute Safety Risks	Important Diagnostic Considerations	<b>DIAGNOSIS</b> Perform a Diagnostic Evaluation			
Harm to self or others or psychotic features	Changes from DSM-IV-TR to DSM-5 represent a shift in the	Perform a focused clinical interview and review treatment history and relevant family history			
	conceptualization				
Assess during the initial assessment and periodically thereafter as needed	of bipolar disorder from discrete categories (e.g., depressed, manic) to a more commonly encountered dimensional spectrum of symptomatology.	Determine functional status, review medical history, physical examination, and pertinent laboratory and other testing with an eye toward identifying remediable co-occurring conditions, alternative diagnoses, and unrecognized drug or alcohol use disorders			
Screen for, evaluate, and manage suicide risk in patients with depression regardless of the presence or absence of other mental health conditions					
Always in of bipola symptom in patien	nquire about family r symptoms or AN ns of activation/(hy ts presenting with	y history  Y ypo)mania a maior			

depressive episode.<sup>12</sup>



Up to 40% of major depressive episodes are accompanied by 1 or more hypomanic symptoms.<sup>13,14</sup>

Major depressive episodes with mixed features can occur in either MDD or Bipolar Disorder, and some patients with MDD mixed states may never exhibit the euphoria or elation commonly associated with pure hypomania or mania. Careful attention must be paid to assess for activation occurring within motor, behavioral, thought process, and arousal domains.

### Figure 3. DSM-5 Spectrum of Mixed States (Co-occurring Manic and Depressive Symptoms)<sup>\*12</sup>



\*Please see pocket cards for more information on diagnostic criteria for mixed depression.

### **Measurement-based Care**

- Measurement-based tools, like the PHQ-9, provide a more consistent measure of a patient's clinical status and a foundation for clinical decision-making.<sup>15</sup>
- Use of measurement-based tools is feasible in busy clinical settings and can lead to improved outcomes.<sup>16,17</sup>

Figure 4. Measurement-based Care Results in Higher Response and Remission Rates<sup>17</sup>



Outpatients with moderate to severe major depression were randomized to 24 weeks of either measurement-based care (guideline- and rating scale-based decisions; n = 61), or standard treatment (clinicians' choice decisions; n = 59). Time to response and remission was shorter and more treatment adjustments occurred in the measurement-based care group.



### Table 1. Initial Treatment Selection and Severity of Depression<sup>11,18</sup>

Initial Treatment Selection and Severity of Depression						
Severity	Mild Moderate Severe Persistent or Recurrent*					
PHQ-9 Score	10–14	15–19	≥20	n/a		
	Psychoeducational Strategies (e.g., exercise, bibliotherapy)					
Treatment**	Psychotherapy <b>OR</b> Pharmacotherapy		Psychotherapy <b>AND</b> Pharmacotherapy			

\*Chronic MDD is characterized as MDD with duration greater than two years and recurrent MDD is defined by three or more episodes; DSM-5 eliminated use of "chronic" and combined it with dysthymia to become persistent depressive disorder; recurrent MDD is ≥3 episodes. \*\*Treatment selection should be based on patient preference, safety and side effect profile, personal/family history of response to a specific medication, concurrent medical illnesses and medications, cost of medication and provider training/competence.

Use the PHQ-9 or similar assessment tool to measure depression severity and monitor response to treatment.

### **Evidence-based Psychotherapy (EBP)**

EBPs are recovery-oriented and time-limited with Veterans and therapists working together to identify and reach personal goals. Unlike pharmacotherapy, EBPs have been shown to maintain effectiveness after treatment ends.

### Figure 5. EBP for Depression Reduces Severity of Depression and Suicidal Ideation<sup>19–21,22</sup>



Veterans participating in EBP for depression experience a **41%** 

average reduction in depression severity



When the Veteran prefers psychotherapy, one of the following evidence-based interventions can be offered based on Veteran preference and availability:

#### Table 2.Evidence-based Psychotherapy for Depression

Evidence-based Psychotherapy for Depression			
<ul> <li>Acceptance and commitment therapy (ACT)*</li> <li>Cognitive behavioral therapy (CBT)*</li> <li>Interpersonal therapy (IPT)*</li> </ul>	<ul> <li>Behavioral therapy/behavioral activation (BT/BA)</li> <li>Mindfulness-based cognitive therapy (MBCT)</li> <li>Problem-solving therapy (PST)</li> </ul>		

\*EBPs for depression disseminated by the VA National EBP Training Program.

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Provide or refer Veterans to evidence-based psychotherapy for depression.

### **Evidence-based Pharmacotherapy**

There is no evidence to suggest that one antidepressant drug class is superior to another for all patients with depression. A recent meta-analysis found that all antidepressants were more effective at achieving a response or remission than placebo in adults with moderate to severe depression.<sup>11,23</sup>

### Table 3. VA/DoD Guideline Recommended 1st Line Antidepressants<sup>11,24</sup>

Medication	Usual Dose Range (mg)	Medication	Usual Dose Range (mg)
Bupropion XR	150-450	Mirtazapine	30-45
Citalopram	20-40*	Paroxetine	20–50
Duloxetine	60-120**	Sertraline	50–200
Escitalopram	10–20	Venlafaxine XR	75–225
Fluoxetine	20-80		

\*Max dose 20 mg if age >60, hepatic insufficiency, taking certain medications (e.g., cimetidine, omeprazole), impaired CYP 2C19 metabolism. \*\*Limited data to support doses above 60 mg. Please see QRG for information on other antidepressant options.

Both dose and duration must be considered to provide an "adequate" antidepressant trial. In the past, a duration of at least 6–8 weeks was recommended as the minimum duration, but newer literature recommends as many as 12–14 weeks <u>for maximum</u> <u>effect</u> on an adequate dose.<sup>16</sup>

Note: Sexual side-effects occur commonly with antidepressants but may not be spontaneously reported.

### **Re-evaluating Depression**

If the patient has received an adequate trial of pharmacotherapy or psychotherapy but did not respond as expected, it is important to re-evaluate.<sup>11</sup>

If the patient's clinical state worsens after being placed on an antidepressant, evaluation for emergent mixed features and consideration of alternative treatment strategy are warranted.<sup>12</sup>

### Using the PHQ-9 to Evaluate Response<sup>15,25</sup>

#### **Remission:**

■ PHQ-9 score ≤4

#### **Partial Response:**

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

#### Non-response:

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

#### Figure 6. Considerations During Thorough Re-evaluation of Depression<sup>4,12,15,16,26,27</sup>



\*Common symptoms in patients with mixed depression include: irritability, anxiety, distractibility, psychomotor agitation, anger, emotional lability/ tearfulness, and several others. In patients with MDD with mixed features, antidepressants may not alleviate depressive symptoms and may exacerbate subthreshold mania symptoms.

Once a thorough re-evaluation has been completed and a diagnosis of MDD is confirmed, treatment should be adjusted to achieve remission.<sup>10</sup>

### Treatment Strategies for TRD: Switching or Augmenting Antidepressants

Augmenting antidepressants can be considered after it is confirmed that there is a partial response to the initial medication. It is important to continually evaluate and remove unnecessary mental health medications. Consider referring to an evidence-based psychotherapy provider, even if it was offered previously, for recommendations on other psychotherapy options (e.g., ACT, CBT, IPT, BT/BA, MBCT, PST).

Figure 7. Considerations When Switching Antidepressants<sup>11,28-31</sup>



MAOI = monoamine oxidase inhibitor; MDD = major depressive disorder; SNRI = serotonin norephinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

### Tricyclic Antidepressants<sup>11</sup>

- Effectiveness shown to be similar to other classes of antidepressants
  - According to STAR\*D, nortriptyline response and remission rates did not differ significantly when compared to mirtazapine (nortriptyline 16.5% and 19.8%, mirtazapine 13.4% and 12.3%).<sup>32</sup>

Note: Tricyclic antidepressants are associated with more sedation, anticholinergic side effects, and greater lethality in overdose.

### Monoamine Oxidase Inhibitors (MAO-Is)

- Requirements for dietary restrictions, adverse effect profile, and propensity for drug interactions limit use.<sup>34</sup>
- Selegiline patch has a favorable side effect profile and dietary restrictions are not required at the 6 mg/24-hour dose.<sup>29</sup>
- When switching to or from an MAOI, washout periods are required.
  - MAOI to antidepressant = 2 weeks
  - Antidepressant to MAOI = 2 weeks
  - Fluoxetine to MAOI
     = 5 weeks

Switch to or augment with another antidepressant if remission is not achieved after an adequate trial of antidepressant monotherapy.<sup>26,33,35-38</sup> Figure 8. Modest Remission Rates and Lower Side Effect Burden with Venlafaxine/Mirtazapine Combo vs. Tranylcypromine<sup>33</sup>



Patients who did not achieve remission in three previous medication trials were randomized to tranylcypromine (n = 58) or venlafaxine plus mirtazapine (n = 51). Remission rates were modest for both treatment arms with a lower side effect burden seen with the venlafaxine plus mirtazapine combination.

### Table 4. Antidepressant Treatment Strategies for TRD<sup>33,35–39</sup>

Response to Initial Agent	Treatment Choice	Next Step Antidepressant Examples	Key Points
Non-response or Intolerance to Initial Agent	In-class Switch Out-of-class Switch	SSRI to SSRI SSRI to Bupropion	Outcomes are similar among antidepressants, so selection is based more on patient factors and potential side effects.
Partial Response	Augment Therapy	SSRIs + Bupropion SSRIs + Buspirone SSRIs or SNRIs + Mirtazapine SSRIs + TCAs	<ul> <li>May have synergistic antidepressant effect</li> <li>Educate on the signs and symptoms of serotonin syndrome</li> </ul>

Avoid combinations with monoamine oxidase inhibitors due to risk of hypertensive crisis or serotonin syndrome.

### Augmentation Strategies for TRD: Atypical Antipsychotics

Atypical antipsychotics are effective in reducing depressive symptoms in patients with TRD and have been shown to reduce symptoms within 1 to 2 weeks.<sup>40-45</sup> **Please note, antipsychotics are associated with various side effects and discussions with the patient about the risks versus benefits is important before starting one of these medications.** 

 Aripiprazole, brexpiprazole, cariprazine, olanzapine, olanzapine + fluoxetine, quetiapine, risperidone, and ziprasidone have evidence to support their use.<sup>4,45-47</sup> If no response is seen within 1 month of starting an antipsychotic, consider discontinuing use as risks of side effects may outweigh benefits.

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- Patients with affective disorders are at greater risk for developing tardive dyskinesia (TD) and the number of cases of TD caused by atypical antipsychotics is increasing.<sup>48-53</sup>
  - Patients should be informed of and monitored for these side effects (monitor at regular intervals using a rating scale such as the Abnormal Involuntary Movement Scale (AIMS)).

### Augmentation Strategies for TRD: Lithium and Triiodothyronine (T3)

Both lithium and T3 improve remission rates in patients with MDD when added to SSRIs, TCAs, and MAOIs.<sup>54–61</sup>

- Lithium
  - Well studied with response rates ranging from 12.5–50% in placebo-controlled trials.<sup>62</sup>
  - Anti-suicidal effects.<sup>60</sup>
  - Effective treatment option for older adult patients.<sup>63</sup>

Figure 9. Modest Remission Rates Seen with Both Lithium and T3 Augmentation but Less Side Effects with T3 (STAR\*D Step 3)<sup>54</sup>



The STAR\*D trial (Step 3) demonstrated modest remission rates with both lithium and T3 augmentation. The difference between treatment arms was not statistically significant. Patients receiving lithium augmentation experienced more side effects (35.9 vs. 15.9%, p = 0.045) and were more likely to discontinue treatment due to side effects (23.2 vs. 9.6%, p = 0.027).

- Triiodothyronine (T3)
  - Not as well studied
  - Demonstrated response rates similar to lithium.<sup>57,64</sup>
  - Can be considered in patients who are euthyroid

Consider augmenting antidepressants with lithium, triiodothyronine, or atypical antipsychotics in Veterans who have failed to achieve remission. Agent selection will need to take into consideration side effects, drug interactions, and clinical characteristics of the patient.

### Augmentation Strategies for TRD: Stimulant Agents<sup>4,34,65-67</sup>

In patients with depression, fatigue can be a residual symptom that inhibits functionality. For some patients with MDD, augmentation with a stimulant may be considered to improve depressive symptoms, remission rates, and fatigue.<sup>4</sup>

- Stimulant medications can be tapered over several days and stopped after the patient is in remission.
- Patients with chronic depressive symptoms may relapse when the stimulant is decreased, so restarting the stimulant at the lowest effective dose may be necessary.

### Figure 10. Stimulant Considerations in Patients with TRD<sup>9,65–69</sup>



\*Seek cardiology consultation before prescribing stimulants in patients with comorbid cardiovascular disease. Medications with limited evidence for use include: modafinil, methylphenidate, dextroamphetamine.

### Treatment Strategy for TRD: Glutamatergic Agents<sup>70-74</sup>

Ketamine is a non-selective, non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. Esketamine is the S-enantiomer of racemic ketamine.

> To date, there are no clinical trials comparing intravenous (IV) ketamine to intranasal (IN) esketamine.

Both IV ketamine and IN esketamine are associated with sedation, dissociation, abuse and misuse, and suicidal thoughts and behaviors.

### Intravenous (IV) Ketamine

IV Ketamine is FDA-approved as an anesthetic agent and has been used off-label for the management of major depression. There is limited data evaluating longer-term IV ketamine use.<sup>75</sup>

The use of a single IV infusion (0.5 mg/kg), as monotherapy or as an augmenting agent to an antidepressant, has been shown to produce a rapid antidepressant effect that may last up to seven days.<sup>76,77</sup>

#### Figure 11. IV Ketamine<sup>10,70,75–77</sup>

Dose	<ul> <li>Single IV infusion (0.5 mg/kg)</li> <li>Monotherapy or as an augmenting agent to an antidepressant</li> </ul>
Response	<ul> <li>Provides rapid antidepressant effect that may last up to 7 days</li> <li>Long-term data is limited</li> </ul>
Role in Treatment	<ul> <li>Not a first-line treatment option for any severity level of depressive episode</li> <li>Adjunctive treatment for short-term reduction in suicidal ideation in patients with MDD</li> </ul>
Considerations	• The risk of each ketamine infusion should be balanced with the risk of long-term exposure, including neurotoxicity, cystitis, and abuse potential

#### Intranasal (IN) Esketamine

IN Esketamine is approved in conjunction with an oral antidepressant, for the treatment of TRD in adults.

- Long-term efficacy and safety data are lacking.
- Current VA criteria for use do not support the use of IN esketamine in Veterans >65 years of age given the absence of statistically significant benefit over placebo

#### Table 5. Summary of Key Esketamine (ESK) Literature<sup>73,74,78</sup>

Study	Duration	Key Study Population Info	Dose	Outcome**
TRANSFORM-1	4 weeks	18–64 yo with TRD*; median age of 47; 62% female, 93% Caucasian	<ul> <li>Placebo + AD</li> <li>ESK 56 mg + AD</li> <li>ESK 84 mg + AD</li> </ul>	Did not meet the pre-specified statistical tests for demonstrating effectiveness.
TRANSFORM-2	4 weeks	18–64 yo with TRD*; median age of 47; 62% female, 93% Caucasian	<ul> <li>Placebo + oral AD</li> <li>ESK (56 mg or 84 mg) + oral AD</li> </ul>	Esketamine demonstrated statistically significant effect compared to placebo on the severity of depression.
TRANSFORM-3	4 weeks	≥65 years of age	<ul> <li>Placebo + AD</li> <li>ESK (56 mg or 84 mg) + oral AD</li> </ul>	Did not meet the pre-specified statistical tests for demonstrating effectiveness.
<b>SUSTAIN-1</b> (longer -term maintenance-of- effect trial)	Variable***	Achieved treatment response to ESK in 1 of 2 short-term double-blind, active-controlled studies	<ul> <li>Placebo + AD</li> <li>ESK (56 mg or 84 mg) + oral AD</li> </ul>	Statistically significantly longer time to relapse of depressive symptoms than patients on placebo nasal spray plus an oral antidepressant.

AD = antidepressant; TRD = treatment resistant depression; yo = years old. \*In the current depressive episode, has not responded adequately to at least 2 different antidepressants of adequate dose and duration. \*\*Primary efficacy measure was the change from baseline on the Montgomery-Åsberg Depression Rating Scale (MADRS) total score at the end of the 4-week double-blind induction phase. \*\*\*Study continued until requisite number of relapses occurred (up to 84 weeks for remission and 88 weeks for response).

#### Table 6. IV Ketamine and IN Esketamine Comparison

	IV Ketamine*	IN Esketamine <sup>#</sup>	
FDA-Approved Indication	Induction and maintenance of general anesthesia	Treatment resistant depression (in conjunction with an oral antidepressant)	
DEA Schedule	Ш	Ш	
Onset of Action	Rapid	Rapid	
Comparator Drug	Midazolam	Only compared to placebo	
When to Use	In patients who do not achieve remission from at least four adequate antidepressant trials	In patients who do not achieve remission from at least four adequate antidepressant trials	
Administration	Twice weekly	Twice weekly x 4 weeks (induction)	
Duration	Individualized	Individualized	
Restrictions	Requires Ketamine Safety Form to be completed after every treatment session and submitted to VAMedSAFE online	Requires Esketamine Safety Form to be completed after every treatment session and submitted to VAMedSAFE online	
REMS	No	Yes	
Cost/patient/year (\$)	\$	\$\$\$\$	

\*See National Protocol Guidance for intravenous ketamine infusion for TRD for additional information. #See National Protocol Guidance for intranasal esketamine for TRD for additional information. Please see VA PBM criteria for use and national protocol guidance for more detailed information regarding patient selection and use (e.g., inclusion criteria, exclusion criteria, administration considerations, dosing, monitoring, etc.).

Consider using ketamine or esketamine in Veterans who have treatment resistant depression and have not responded to several past treatment options.

### **Treatment Strategy for TRD: Brain Stimulation**

Brain stimulation treatments include electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS). They differ in terms of invasiveness and how well they work acutely versus over the long-term.



### Figure 12. ECT is the Most Effective Acute Treatment Available

Cervical VNS takes months or years to reach full effectiveness and is thus not useful acutely.

### Electroconvulsive Therapy (ECT)

Amongst the existing brain stimulation treatments, ECT has the most evidence behind its use and has been shown to quickly decrease or eliminate depressive symptoms.

- ECT is the most effective acute treatment for depression.
  - Also effective for bipolar depression, catatonia, psychotic depression, acute mania, Parkinson's Disease (PD), and status epilepticus.<sup>79</sup>

ECT remission rates range between 30 to 75% and vary based on treatment setting, duration of current episode, and comorbid conditions.<sup>34,79,80</sup>

### Safety Considerations

ECT is a medical procedure involving repeated sessions of general anesthesia and is estimated to have a mortality rate similar to minor surgery or childbirth.<sup>81</sup>

### Figure 13. Safety Considerations with ECT



\*Patients with preexisting cardiac disease are at greatest risk for developing irregular rhythms.

#### ECT Continuation and Maintenance Considerations:

While ECT has remarkable acute efficacy, there is a risk for relapse after treatment is discontinued. Continuation of depression treatment (e.g., maintenance ECT, medication) after the initial course of ECT should be considered to reduce risk of relapse.<sup>82,83</sup>

ECT should be considered in patients with MDD who cannot tolerate or have not responded to several trials of antidepressant treatment; patients with more severe symptoms may benefit from earlier application of this treatment modality.

#### Repetitive Transcranial Magnetic Stimulation (rTMS)

Repetitive Transcranial Magnetic Stimulation (rTMS) is approved for the treatment of MDD in adults who have failed to achieve satisfactory improvement from at least one prior course of antidepressant medication.<sup>11,84</sup>

- Shown to be effective for both response and remission of MDD and is well tolerated.<sup>85-88</sup>
- Compared to ECT, rTMS has fewer side effects but lower remission rates and longer time to response.<sup>87–90</sup>
- According to a 2018 study in a Veteran population, at the end of the acute treatment phase, there was no statistically significant difference in remission rates

Common Side Effects from rTMS:

- Headache
- Discomfort at treatment site
- Light-headedness
- Facial tingling

between those in the treatment group versus those in the sham treatment group (33 of 81 (40.7%) active treatment versus 31 of 83 (37.4%) sham treatment group, p-value = 0.67).<sup>91</sup>

### Figure 14. rTMS is Superior to Sham for Both Response and Remission for TRD<sup>87,88</sup>



O'Reardon et al. (Neuronetics) randomized 301 medication free patients to active or sham treatment. Participants were treated with 10Hz rTMS at 120% of their motor threshold (MT) for 3000 pulses per session, 5 days a week for a total of 4–6 weeks. Patients showed high tolerance for treatment and only mild adverse events were reported; MADRS remission rates (total score <10) at week 6 were 14.2% with active TMS versus 5.5 with sham TMS (p < 0.05 vs. sham). George et al. (OPT-TMS) randomized 190 medication free patients who were treated 5 days a week using 10Hz rTMS at 120% MT. They received a total of 3000 pulses per session for 3 weeks and non-remitters continued for an additional 3 weeks. Remission was defined as a HAM-D score of  $\leq$ 3 or 2 consecutive scores <10. Active rTMS group improved depressive symptoms (p = 0.02 vs. sham) with minimal side effects.

#### Figure 15. rTMS Administration<sup>84,87,92,93</sup>



#### Table 7.Treatment Considerations for ECT vs. rTMS<sup>11,87,88,94,95</sup>

	Pros	Cons	Relative Contraindications	Discussion
ECT	• Higher remission rates	<ul> <li>More side effects</li> <li>Need for sedation / anesthesia</li> <li>Higher risk, more complex procedure</li> </ul>	<ul> <li>Cardiovascular disease</li> <li>Space-occupying intracranial lesion with the evidence of elevated intracranial pressure</li> <li>Recent cerebral hemorrhage or stroke</li> <li>Bleeding or otherwise unstable vascular aneurysm</li> <li>Severe pulmonary disease</li> </ul>	Appropriate for acute and severe MDD including psychotic depression or catatonia

\*Should a clinician decide to treat individuals who are on one of these medications, it is recommended that careful monitoring and regular re-determination of the motor threshold be considered.

### Table 7. Treatment Considerations for ECT vs. rTMS<sup>11,87,88,94,95</sup></sup>

	Pros	Cons	Relative Contraindications	Discussion
rTMS	• Fewer side effects	<ul> <li>Lower remission rates</li> <li>Longer time to response</li> <li>Minimal risks and side effects</li> <li>Daily administration</li> </ul>	<ul> <li>Epilepsy or history of seizures</li> <li>Active substance use disorder</li> <li>Tumor or other neuroanatomical abnormality near treatment site</li> <li>Cochlear implants</li> <li>Deep brain stimulators</li> <li>Pacemakers / implantable medical devices</li> <li>Presence of any ferromagnetic material in the head</li> <li>Medications that decrease seizure threshold*</li> </ul>	Appropriate for patients with severe, persistent or recurrent MDD who are treatment resistant to and/ or intolerant of pharmacotherapies

\*Should a clinician decide to treat individuals who are on one of these medications, it is recommended that careful monitoring and regular re-determination of the motor threshold be considered.

Consider offering rTMS for treatment during a major depressive episode in patents with treatment resistant depression.

#### Vagus Nerve Stimulation (VNS)

Although VNS is FDA approved for treatment resistant depression, there is no current evidence that supports its routine use in the treatment of MDD and it is not widely available.<sup>11</sup>

When discussing this as a treatment option it's important to indicate that the risk of harm is high with a 5% chance of serious side effects (e.g., voice alteration, dysphagia, dyspnea, infection, dizziness, asthenia, chest pains, palpitations, and vocal cord paralysis) and lack of evidence showing benefit.<sup>11</sup>

# **Treatment Strategies for MDD**<sup>11,34</sup>

#### Table 8.Treatment Strategies for MDD\*11,18



### **Important Resources**

- Suicide Risk Identification and Management SharePoint Page: https://vaww.visn19.portal.va.gov/sites/ECHCS/srsa/SitePages/Home.aspx
- Veterans Crisis Line: https://www.veteranscrisisline.net/

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This reference guide was created as a tool for VA providers and is available from the Academic Detailing Service SharePoint.

These are general recommendations only. The treating provider should make clinical decisions based on an individual patient's clinical condition.

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