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Combating Treatment-Resistant Depression (TRD)

VA Clinician's Guide to Managing TRD (2014)

VA Academic Detailing Service

Real Provider Resources
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Combating Treatment-Resistant Depression

The incidence of treatment-resistant depression (TRD), despite various available treatment options, continues to be common in clinical practice.[1,2] Unsuccessfully treated depressive episodes result in both relapse and chronicity. This is concerning because patients with major depressive disorder (MDD) are more disabled at work, socially, and with their families than patients with most general medical conditions.[1-4] In addition, TRD is often linked to higher rates of comorbidities, particularly with other psychiatric disorders.[5] For these reasons, TRD is a costly illness and has been reported to be the main factor in determining the economic burden of depression.[3] There is no single factor that explains why some patients respond well to standard treatments while others experience TRD, but likely a combination of patient, disease, and environmental factors play important roles.

It is important to strive for remission in our Veterans struggling with depression.

- ➔ Depression is considered "treatment-resistant" when 1–2 adequately delivered treatments do not lead a person to become symptom-free. For example, a Patient Health Questionnaire (PHQ–9) score of ≤4 (remission) for at least one month.[4]
- ➔ After an initial antidepressant treatment course, only 50% of patients will respond and only 33% of those will become symptom-free.[5]
- ➔ Insufficiently treated depression can lead to increased mortality, comorbidity, and suicide attempts.[6-8]
- ➔ Patients who do not achieve remission are 2–3 times more likely to have a relapse of depressive symptoms.[9,10]
- ➔ Other potential consequences for patients who fail to achieve and sustain remission include[11]:
  - ✓ Increased number of chronic depressive episodes
  - ✓ Shorter duration of "wellness" between episodes
  - ✓ Continued suffering and impairment in work and relationships

Veterans may be at greater risk of developing TRD than the general population secondary to the increased incidence of other comorbid Axis I disorders, such as Posttraumatic Stress Disorder and Substance Use Disorder.

Measurement Based Care

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial indicated that use of measurement based tools may be feasible in busy clinical settings and may lead to improved outcomes.[5] Itemized symptom rating scales or measurement based tools, like the PHQ–9, provide more sensitive measures of a patient's clinical status than global judgments made by the clinician or patient, providing a more accurate foundation for clinical decision-making.[12]

- ➔ Several tools can be used in the clinical setting to assess response.
- ➔ The PHQ–9 is available through the Mental Health Assistant found under the Tools menu in CPRS.

PHQ-9 Total Score	Severity
0–4	None
5–9	Mild Depressive Symptoms
10–14	Mild Depression
15–19	Moderate Depression
20–27	Severe Depression

When response to a treatment is not as robust as hoped, it is important to assess for adherence.

- ➔ **Missing three or more doses** in the previous 14 days can be considered a **significant level of nonadherence**.
- ➔ Assess and address side effects and/or reason for nonadherence.[12]
- ➔ Always assess frequency, intensity, and most importantly, the burden of the reported side effects.
- ➔ Adjust medications based on severity of side effects.

PHQ–9[12,13]

Depression Stages

Remission: PHQ–9 score ≤4
Partial response: Five 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

Critical Decision Points

Week 0: Medication Initiation
Baseline PHQ–9

⬇

Week 4–6: Assess Response
Remission: Continue current regimen
Partial response: Continue or increase current dosage
Non-response: Maximize dosage or switch

⬇

Week 8: Assess Response
Remission: Continue current regimen
Partial response: Maximize dosage or use augmentation
Non-response: Switch antidepressant

⬇

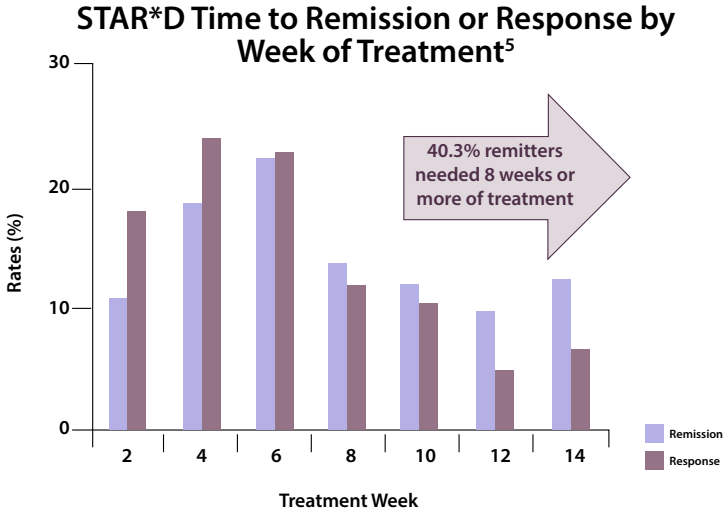
Week 12: Assess Response
Remission: Continue current regimen
Partial response: Maximize dosage, use augmentation or switch antidepressant
Non-response: Switch antidepressant and reassess diagnosis

Side Effect Intolerance: Consider switching antidepressant

Systematic use of the PHQ–9 or similar assessment tool should be used to provide a sensitive and objective measure of response to the current treatment.

Adequate Antidepressant Trial

Adequate dose and duration – Minimum: 6–8 weeks; newer recommendations: 12–14 weeks



Adapted from Trivedi et al.[5] Step one of the STAR*D found 50% of remissions and responses took >6 weeks of therapy. These results indicate that stopping vigorously-dosed treatment may be ill advised especially if a modest improvement (≥25% reduction in symptoms) is observed.

Antidepressant	Theraputic Dose (mg)
Sertraline	100–200
Fluoxetine	20–80
Paroxetine	20–50
Citalopram	20–40*
Venlafaxine IR & XR	150–225
Bupropion SR	200–450
Mirtazapine	15–45

*Max dose 20 mg if age >60, hepatic insufficiency, taking cimetidine, or impaired CYP 2C19 metabolism

A ≥25% decrease in baseline PHQ–9 score by week 6 indicates a patient may benefit from an increase in dose if necessary and should remain on the adjusted dose for 10–12 weeks.[5,14]
Titrate antidepressant to the therapeutic dose based on tolerability and response.

Comparison Among Commonly Used Antidepressants[15,16]*

Class	Drug	Safety						Notes
		Anti-Ach	Sedation	GI	Withdrawal	DDI	OD Risk[1,2]	
SSRI	Citalopram†			N				May cause QT prolongation
	Sertraline			N,D				May cause diarrhea if dose increased quickly
	Paroxetine			N				Dosed at bedtime
	Fluoxetine			N				No need to taper off with discontinuation
	Escitalopram			N				
SNRI	Venlafaxine			N				May increase blood pressure at high doses
	Duloxetine			N				Monitor liver function
TCA	Amitriptyline			C				Dosed at bedtime; postural hypotension; weight gain; overdose can cause seizures and cardiac arrhythmia
	Imipramine			C				
	Nortriptyline***			C				
	Desipramine***			C				
Other	Bupropion							Seizure risk
	Mirtazapine							Can increase appetite and cause weight gain

*Data taken from packet inserts

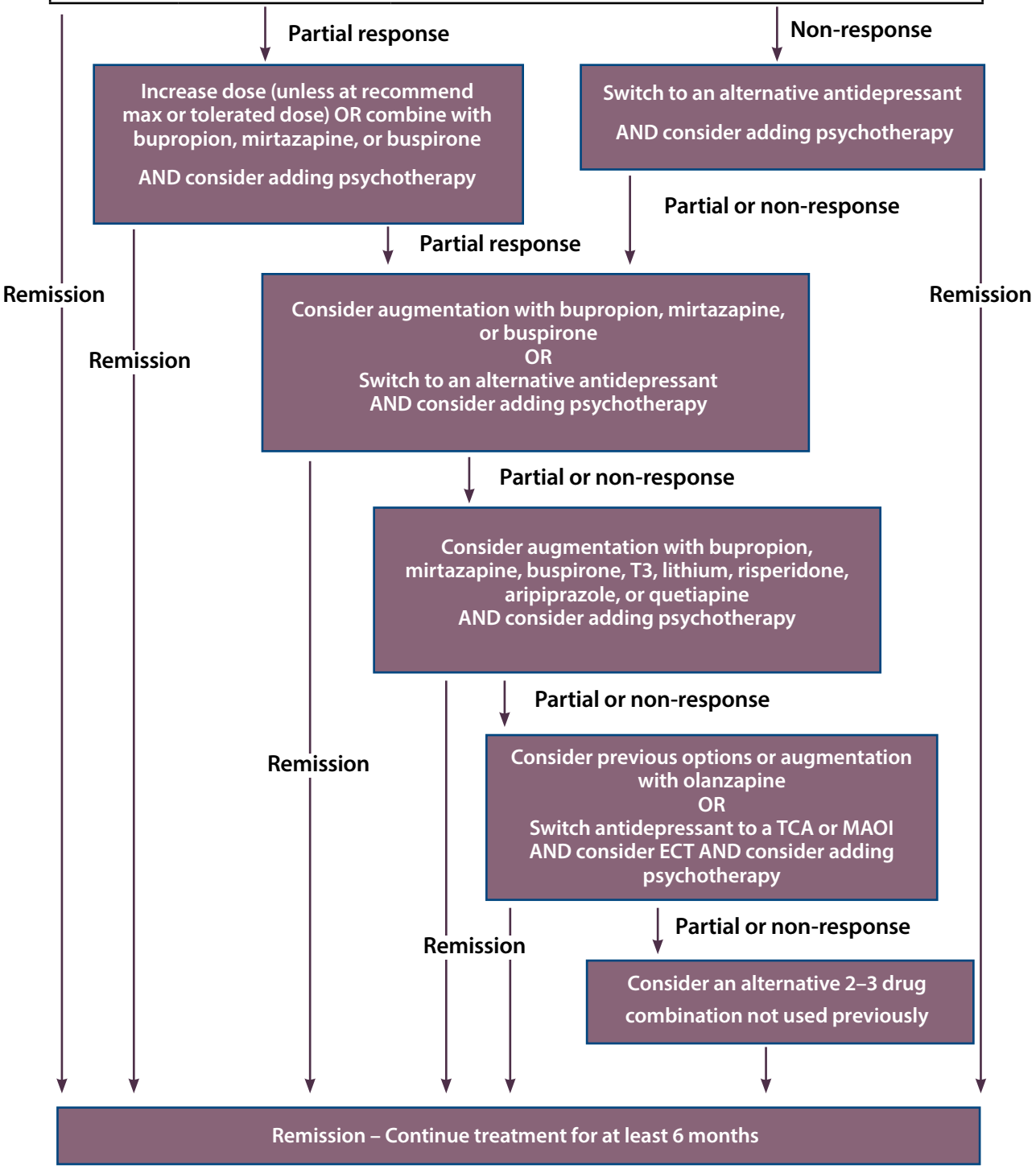
†If >60 y/o, hepatic impairment, poor CYP 2C19 Metabolizer OR on cimetidine -> max dose 20 mg

***These agents may have less anticholinergic, sedating, and hypotensive side effects than other TCAs

Anti-Ach = Anticholinergic; C = Constipation; D = Diarrhea; DDI = Drug-Drug Interactions; GI = Gastrointestinal; N = Nausea/Vomiting; OD = Overdose Risk

= less common
= intermediate
= more common

Treatment Strategies for MDD[4,17]		
PHQ–9 Score	Functional Impairment	Initial Strategy
10–14	Mild	• Watchful waiting, supportive counseling • If no improvement after 1 month, then consider brief psychotherapy or antidepressant monotherapy
15–19	Moderate	• Start antidepressant monotherapy or psychotherapy or combination of both
≥20	Severe	• May start monotherapy antidepressant or psychotherapy • Recommend starting both or multiple drug therapy
Psychoeducation and self-management should be provided for all severity levels		



T3 = Triiodothyronine; TCA = Tricyclic Antidepressant; MAOI = Monoamine Oxidase Inhibitor; ECT = Electroconvulsive Therapy

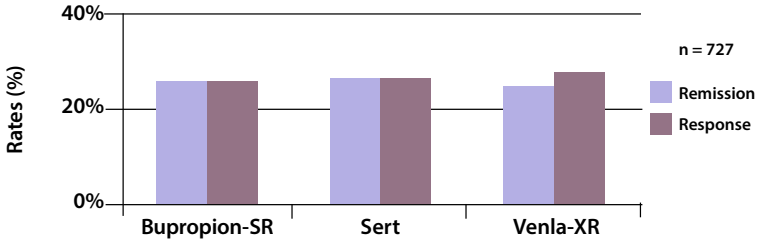
Switching or Augmenting Antidepressants

Switch to, or augment with, another antidepressant if remission is not achieved after an adequate trial of antidepressant monotherapy.[14,18–22]

Non-response or Intolerance to Initial Agent

- ➔ Within-class switch (e.g., citalopram to sertraline)[18,21]
- ➔ Out-of-class switch (e.g., citalopram to bupropion)[18,21]

STAR*D Level 2: Switching Antidepressants[18]



Approximately one in four patients reached remission. Agents did not differ on outcomes, tolerability, or adverse events. Sert = Sertraline, Venla-XR = Venlafaxine XR

Partial Response

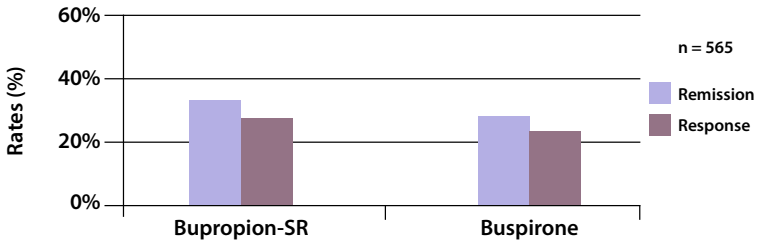
Combination with another antidepressant may offer a synergistic antidepressant effect. In the STAR*D trial, patients who responded to initial treatment with limited side effects preferentially chose combination therapy over switching.[19]

Combination Antidepressant Therapy

Goal: target multiple neurotransmitters

- ➔ Easy to implement
- ➔ No "washout" necessary
- ➔ Excellent choice when patient has partial response and little to no side effects on previous medication trial
- ➔ Inform patients of the signs and symptoms of serotonin syndrome

STAR*D Level 2: Augmenting Antidepressants[19]



Combination with bupropion resulted in greater % decrease in HAM-D (Hamilton Depression rating scale) and QIDS-SR (Quick Inventory of Depression Symptomatology) scores, and fewer patients discontinued due to adverse drug reactions.

Examples of Antidepressant Combinations[19,20,22]
SSRI + Bupropion
SSRI or SNRI + Mirtazapine
SSRI + TCAs*

SSRI = Selective Serotonin Reuptake Inhibitor; SNRI = Serotonin and Norepinephrine Reuptake Inhibitor; TCA = Tricyclic Antidepressant.
*SSRI's may increase serum concentration of TCA's; caution advised

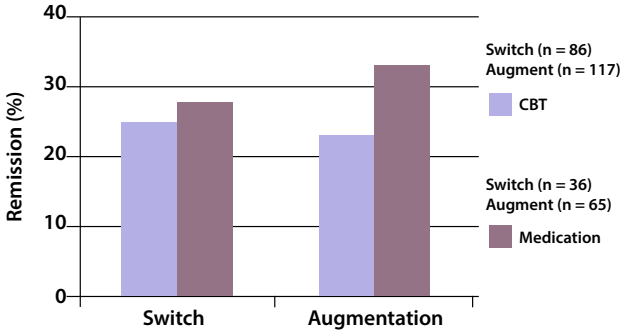
Augmentation Strategies for TRD

Augmenting with Psychotherapies in TRD

Psychotherapies focus on psychosocial stressors and factors that have an impact on the development or maintenance of depressive symptoms.[17]

- ➔ Cognitive behavioral therapy (CBT), interpersonal psychotherapy (IPT), and problem-solving therapy (PST) have the most evidence to support their efficacy in the treatment of MDD.[4]
  - ❖ Effectiveness similar to pharmacotherapy for mild to moderate acute depression.[17]
  - ❖ Only CBT is recommended in conjunction with medication for severe or melancholic MDD.[17]

STAR*D Level 2: Cognitive Therapy vs. Medication: Augmentation and Switch Strategies[23]



Cognitive therapy, was as effective as the various second-step pharmacologic strategies studied. Among participants who opted for an augmentation strategy, the addition of cognitive therapy ultimately resulted in about the same probability of remission as adding sustained release bupropion or buspirone. The benefit of cognitive therapy was slower to emerge, however, with a significant 20-day difference in median time to remission favoring pharmacologic augmentation. Data based on an equipoise-stratified randomization strategy.
CBT = Cognitive Behavioral Therapy

- ➔ The effectiveness of psychotherapies in TRD has not been studied to the same extent as pharmacological strategies.

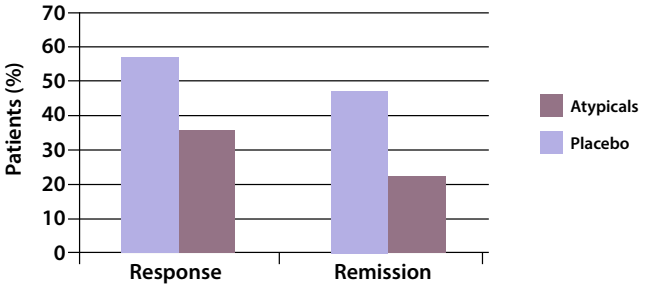
Consider adding CBT to medication therapy as it has been shown to be effective in reducing depressive symptoms in TRD and can lead to better psychosocial functioning.[23,24]

Augmenting with Atypical Antipsychotics

Antipsychotics have been shown to be effective when used as augmenting agents in patients with TRD.[25] Other than ziprasidone, which may not be more effective than placebo, no difference in efficacy among the different atypicals has been found.[25–27]

- ➔ Antipsychotic augmentation in TRD has been shown to lead to symptom reduction within 1–2 weeks of starting therapy.[28]

Atypical Antipsychotics in TRD[25]

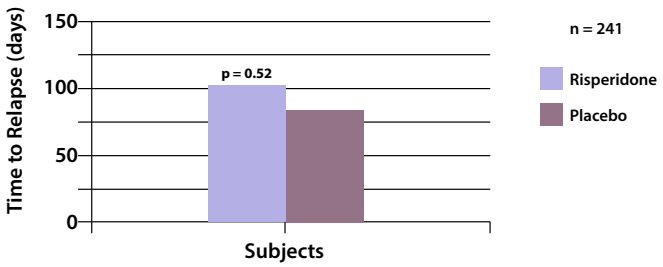


A systematic review and meta-analysis of 10 randomized, double-blind, placebo-controlled trials assessed the efficacy of atypical antipsychotics [olanzapine (5), risperidone (2) and quetiapine (3)] as augmentation agents in patients with TRD. The pooled remission and response rates favored the augmentation of atypical antipsychotics vs. placebo, 47.4% vs. 22.3% and 57.2% vs. 35.4% respectively, with a pooled RR of 1.75 (95% CI 1.36 to 2.24, p<0.0001) and 1.35 (95% CI 1.13 to 1.63, p = 0.001).

Long-term use of Atypical Antipsychotics

- ➔ Atypical antipsychotics are associated with cardiometabolic side effects (weight gain, hyperlipidemia, hypertension, and diabetes).
- ➔ Patients with affective disorders are at greater risk for developing tardive dyskinesia (TD).[29] The number of TD cases caused by atypical antipsychotics is increasing.[30–33]
- ➔ Patients should be informed of, and monitored for, these side effects.
- ➔ Current evidence supports atypical antipsychotic augmentation in TRD only as short-term treatment.[34]

No Difference in Time to Relapse with Risperidone Augmentation[34]



TRD subjects (n = 241) who had previously responded to risperidone augmentationwere randomized to a 24-week double-blind placebo-controlled phase to assess the efficacy of adjunctive risperidone vs. placebo for relapse prevention. Difference in time to relapse was not found to be statistically significant between the risperidone and placebo groups. (102 days vs. 85 days, p = 0.52).

- ➔ Long-term use should be evaluated frequently to assess whether discontinuation of the atypical antipsychotic can be considered.

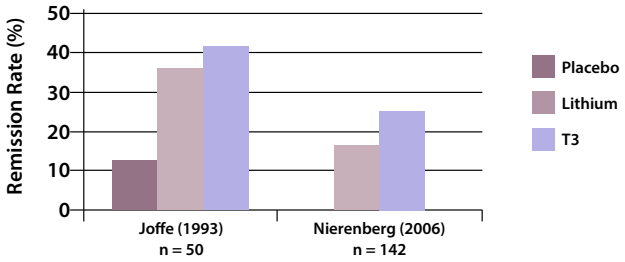
If no response is seen within one month of starting an antipsychotic, consider discontinuing use as risks of side effects may outweigh benefits.

Lithium and Triiodothyronine (T3)

Both lithium and triiodothyronine (T3) may improve remission rates in patients with MDD when added to SSRIs, TCAs, and MAOIs.[35–40]

- ➔ Lithium has been well studied with response rates ranging from 12.5–50% in placebo-controlled trials.[41]
- ➔ Though not as well studied, T3 has demonstrated response rates similar to lithium.[38, 42]
- ➔ The STAR*D trial demonstrated modest remission rates with both lithium and T3 augmentation (15.9% and 24.7%, respectively).[37]

Antidepressant Augmentation with Lithium vs. Triiodothyronine (T3)[36, 37]



Average baseline HAM-D scores = 18–20. In the Joffe trial, all subjects received TCAs and were randomly assigned to augmentation with either lithium, T3 or placebo for 2 weeks. In the Nierenberg trial, patients received a wide variety of antidepressant therapies (mono and combination) prior to randomization to lithium or T3 augmentation for an average of 9.6 weeks. No statistically significant difference in remission rates between the lithium and T3 augmentation were found despite a trend favoring T3. Of note, Joffe, et al. did not find a statistically significant difference for either agent vs. placebo (p = 0.058); this could be secondary to the short duration and small study population.

- ➔ 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).[37]

Medication	Initial Dose	Target Dose	Target Level	Side Effects	Monitoring
Lithium	300–450 mg daily or divided twice daily	N/A	>0.5–1 mEq/L	GI upset, tremor, polyuria, polydipsia, weight gain, hypothyroidism, leukocytosis	EKG, CBC, TFTs, BMP, lithium level
Triiodothyronine (T3)*	25 mcg daily	50 mcg daily	N/A	hyperthyroidism (anxiety, tremor, palpitations, insomnia, ↑risk of osteoporosis and/or atrial arrhythmias);	TFTs

*T3 is the thyroid hormone with the most data to support its use and is likely recommended over thyroxine (T4) due to a faster onset and offset of action

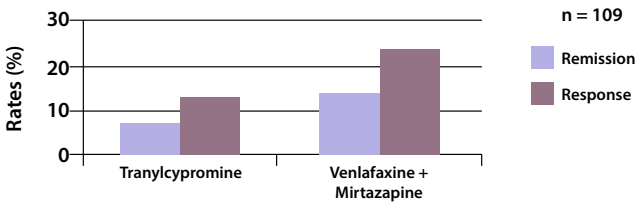
Lithium, triiodothyronine, and atypical antipsychotics are reasonable augmentation options for patients who have failed to achieve remission. Agent selection will need to take into consideration side effects, drug interactions, and clinical characteristics of the patient.

Monoamine Oxidase Inhibitors (MAOIs)

MAOIs may be effective in patients who do not respond to treatment with other antidepressants. In addition, patients with atypical depression may be more likely to respond to MAOIs.[43,44]

- ➔ Requirements for dietary restrictions, adverse effect profile, and propensity for drug interactions limit use.[17]
- ➔ Transdermal selegiline has a more favorable side effect profile and safety margin than orally administered MAOIs.[44]
  - ❖ No dietary restrictions required at the 6 mg/24 hr dose.
- ➔ 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

STAR*D Level 4: Switching Antidepressants[17]



Remission rates were not significantly different between the two treatment groups (6.9% for the tranylcypromine group and 13.7% for the venlafaxine plus mirtazapine group). Tranylcypromine was associated with significantly less symptom reduction and greater attrition due to intolerance.

Monoamine Oxidase Inhibitor Suggested Dosing				
Non-selective MAO Inhibitors	Initial Dose (mg/day)	Dose Titration Increments (mg)	Dosage Range (mg)	Dosing Schedule
Phenelzine (Nardil)	30	15 per week	60–90	TID-QID
Tranylcypromine (Parnate)	30	10 every 1–3 weeks	30–60	BID
Isocarboxazid (Marplan)	20	10 every 2–3 days	40–60	BID-QID
MAO-B selective inhibitors				
Selegiline Transdermal (Emsam)	6†	3 every 2 weeks Increase above 6 mg may not be necessary	6–12	Every 24 hrs

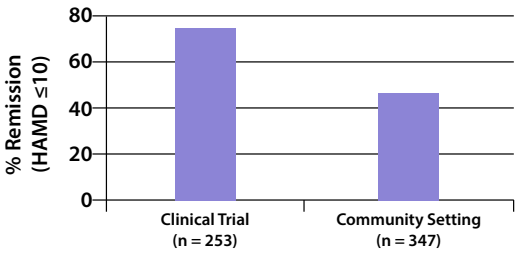
†No dietary restrictions required with 6 mg/day patch BID = Twice a day; TID = Three Times a Day; QID = Four Times a Day

Somatic Treatment of TRD

Somatic treatments include electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), and repetitive transcranial magnetic stimulation (rTMS). However, ECT has the most evidence behind its use. ECT is a rapid and effective treatment that has been shown to quickly decrease or eliminate depressive symptoms.

- ECT remission rates (30–75%) vary on treatment setting, duration of current episode, and comorbid conditions.[17,45,46]
- Depression with psychotic features may have a more rapid and robust response to ECT.[45]
- In a meta-analysis of randomized controlled trials, short-term efficacy of real ECT was shown to be more effective than simulated ECT (effect size -0.91, 95% CI -1.27 to -0.54) and pharmacotherapy (effects size -0.8, 95% CI 1.29 to -0.29).[47]

ECT Remission Rates in Different Treatment Settings[46, 47]

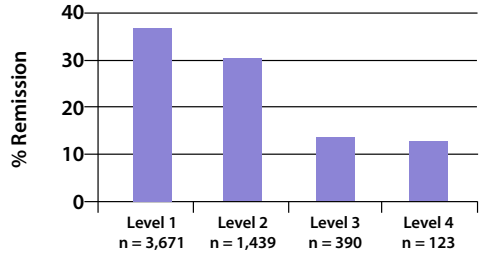


Lower remission rates were observed in the naturalistic community setting. On average, subjects in both trials received a similar number of ECT treatments (inpatient 7.8 vs. community based 7.2) and had similar baseline HAM-D severity.

It is currently recommended that ECT be offered after several adequate treatment trials prove ineffective.[4] However, the number of failed trials remains unspecified and it is unclear if duration of illness plays a role in response to treatment.

- STAR*D trials have shown that lower remission rates and higher relapse rates are seen with increasing treatment steps.[48]
- Greater duration of depressive symptoms may result in decreased effectiveness of ECT, thus reduced rates of remission.[49]

STAR*D Remission Rates by Treatment Step[48]



Total estimated cumulative remission rates are 67%. However, ⅓ of the subjects did not reach remission and with each successive treatment step, minimal additional gain was achieved. Participants that required more treatment steps tended to have greater depressive illness burden and more concurrent psychiatric and general medical disorders.

Not all patients are candidates for ECT and some co-morbid medical conditions could increase the risks of ECT (e.g., recent myocardial infarction or intracerebral hemorrhage, currently taking MAOIs, or retinal detachment).[4]

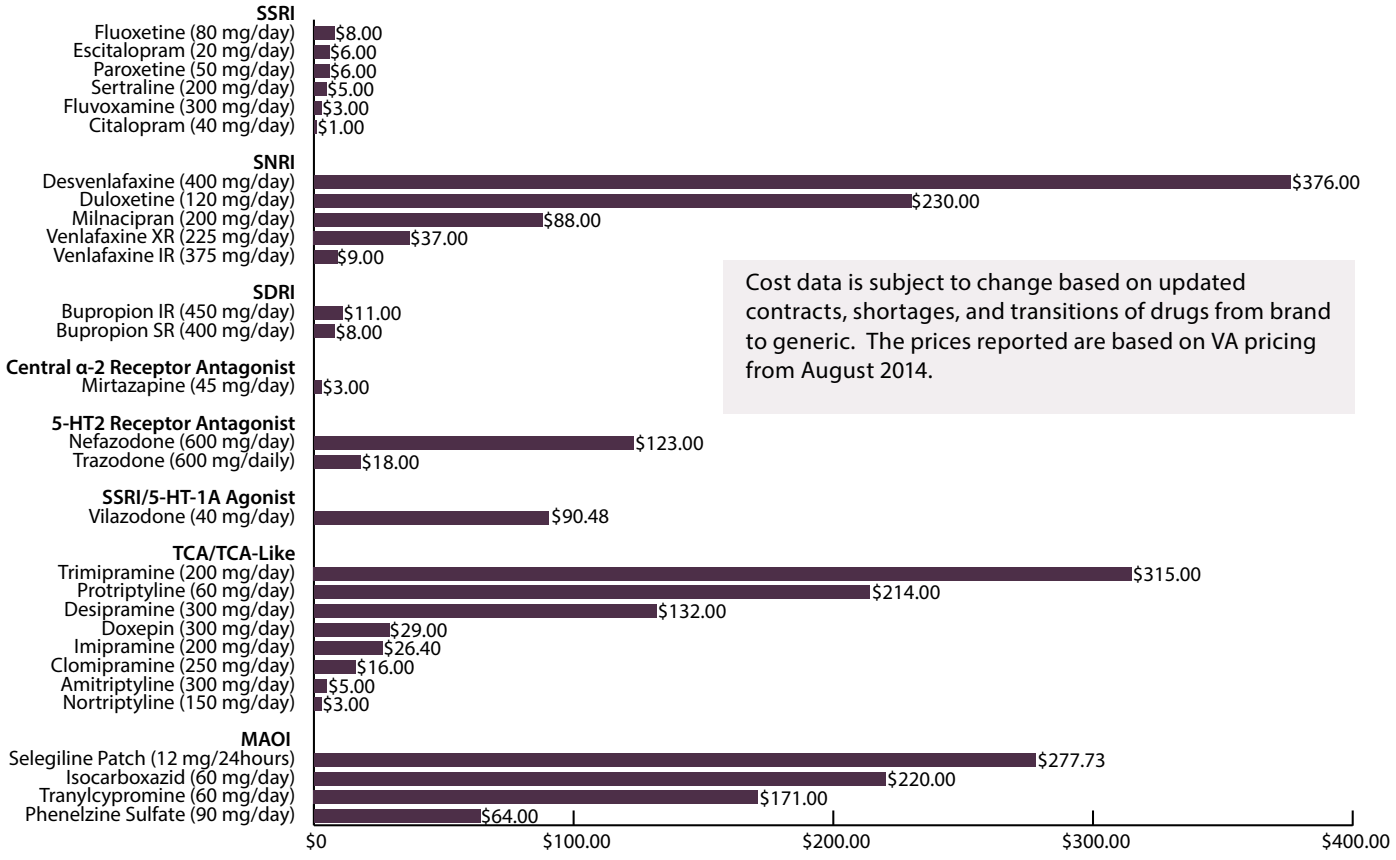
ECT should be considered in patients with TRD who cannot tolerate or have not responded to several trials of antidepressant treatment. Patients may benefit from earlier application of this treatment modality.

Somatic Treatment Interventions for TRD [4,17]			
	Electroconvulsive Therapy (ECT)	**Vagus Nerve Stimulation (VNS)**	**Transcranial Magnetic Stimulation (rTMS)**
Administration	• No difference between bifrontal and right unilateral node placement • Twice weekly ECT shown to have same efficacy as ECT given 3 times per week	• Generator delivers pulses every 5 minutes, 24 hours a day	• Number of pulses per second and number of pulses per session vary ✦ Example: 10 pulses per second with 3000 pulses per session ✦ Sessions 5 times per week for 4–6 weeks
Effect Onset	• 50% respond within 1 week	• Several weeks	• Some respond after 2 weeks
Response, Remission, Relapse	• Relapse rates high within 1st month (maintenance ECT or pharmacotherapy recommended) • 50–70% response rates • Effect size = 0.80 across 18 trials when compared to pharmacotherapy	• Some studies show response rates of 40–50% at 1 and 2 years in initial responders • Not as effective as ECT	• Not well studied; one study reports no effect at 2 week follow-up • Not as effective as ECT • 25–65% response rates • No superiority over placebo in most studies
Side Effects	• Cognitive impairment • Memory loss • Headache • Nausea/Vomiting	• Hoarseness and voice changes • Coughing • Dyspnea • Neck pain	• Headaches • Scalp discomfort

Medication Cost

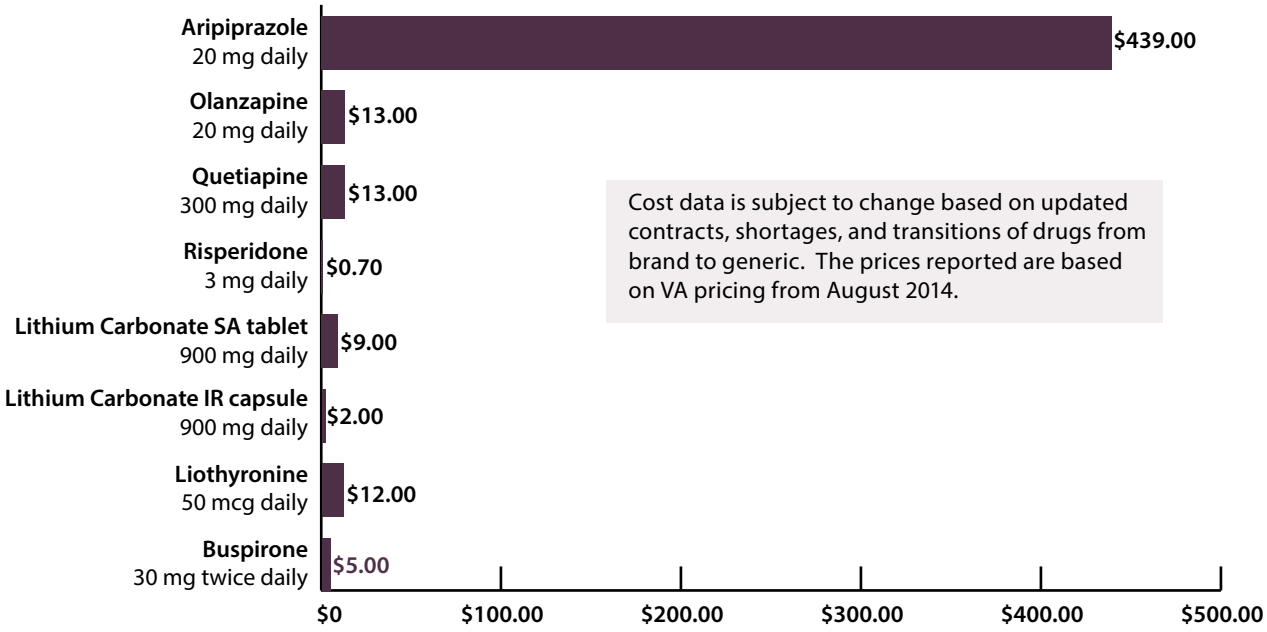
When weighing the value of each medication, it is important to know the relative cost in order to maximize the use of our limited resources.

National Average Antidepressant Maximum Daily Dose Cost/30 Day Supply



Cost data is subject to change based on updated contracts, shortages, and transitions of drugs from brand to generic. The prices reported are based on VA pricing from August 2014.

Augmentation 30 Day Prescription Cost 2014



Indirect Cost

In FY11, atypical antipsychotics were identified as the **most costly outpatient medication class** in the Veterans Health Administration. Even with the increased availability and use of generic antipsychotic agents, we need to assess their true utility in depressed patients and weigh the secondary cost burden associated with managing the metabolic abnormalities.

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

These are general recommendations only; specific clinical decisions should be made by the treating provider based on an individual patient's clinical condition.

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