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How best to manage treatment-resistant depression?

Should you augment the treatment regimen with lithium, thyroxin, or an atypical antipsychotic? This review will help you decide.

PRACTICE RECOMMENDATIONS

- › While lithium produces significant remission rates in augmentation efforts for treatment-resistant depression, it is more likely to cause side effects than many other psychotropic agents. **(A)**
- › Medication and cognitive therapy are equally effective when augmenting antidepressant therapy; cognitive therapy, however, takes longer to achieve remission. **(B)**
- › Since the efficacy of many agents is similar when augmenting treatment, it's important to factor the cost of the medication, side effects, and patient preference into the decision process. **(A)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

The sobering truth about major depression is that too often it goes unrecognized or undertreated.^{1,2} And even when it is treated correctly, up to 34% of patients fail to respond to treatment.³ In the United States alone, the lifetime prevalence of the disease is 16.2%, and more than 6% of adults experience symptoms of major depression in any given year.² Obviously, we need to do more for these patients.

Treatment-resistant depression has been defined as the failure to achieve remission after continuous therapy for about 6 to 12 weeks with an adequate dose of a single antidepressant.⁴ Remission is typically defined as a 50% reduction of scores on depression severity scales, with the 17-item Hamilton Rating Scale of Depression (HRSD17) and the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR16) being the most often used. An adequate dose is the lowest effective dose that doesn't cause intolerable side effects.

What are our best options for treatment-resistant depression?

To answer this question, we reviewed all English language studies in PubMed or Medline that were performed among adults using the search terms “augmentation, antidepressants, major depression.” We excluded studies involving patients with comorbid anxiety, bipolar disorder, or other major mental illnesses.

Based on our review of the literature, we found support for several augmentative treatments for patients with treatment-resistant depression (TABLE). Of note, though: Most of these studies were randomized trials dating back nearly 2 decades and had limitations. Most were not blinded, nor did they have consistent placebo controls. The studies were typically small (albeit frequently still showing efficacy for the agent despite lower statistical power) and of relatively short duration (typi-

TABLE

How these agents compare for treatment-resistant depression

Agent/approach	Remission rate	Starting dose	Titrated to...	Frequency of side effects	SOR rating
Lithium ⁵⁻⁹	53%-60%	300 mg BID-TID	Doses of 800-1500 mg and lithium level of 0.5-1 mmol/L	>25%	A
Thyroid supplementation ¹⁰⁻¹³	25%-59%	20-50 mcg	Often not titrated	11%-25%	A
Aripiprazole ¹⁴⁻¹⁷	25%-37%	2-5 mg	15-20 mg	16%-25%	A
Olanzapine/fluoxetine ¹⁸	25%	Fixed dose	Fixed dose	10%-40%	A
Risperidone ¹⁹⁻²¹	25%-71%	0.25-1 mg	0.5-3 mg	6%-10%	A
Quetiapine ^{22,23}	36%-49%	25-200 mg	100-600 mg	>25%	B
Mirtazapine ²⁴	45%	15 mg	30 mg	6%-10%	B
Cognitive therapy ³⁴	23%	NA	NA	0%-5%	B
Folic acid (Leucovorin) ²⁶	18%	15 mg	30 mg	11%-25%	C
SAMe ²⁷	43%	800 mg	1600 mg	50%	C

NA, not applicable; SAMe, S-adenosyl-L-methionine; SOR, strength of recommendation.

cally 6-14 weeks). There were few studies that looked at treatment approaches over longer periods or that considered indications and timelines for tapering of medications once remission had been achieved. A major exception to the rule was the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, which we'll discuss below.⁵

■ **The research points to several viable options:** Clinicians can switch antidepressants, augment these agents by adding others—usually nonantidepressants—or completely change the therapeutic approach. Since most of the research discusses augmentation, we'll focus on that here. Because the decision to use electroconvulsive therapy, vagus nerve stimulators, or other nonpharmaceutical approaches is made in consultation with a psychiatrist, we will not discuss these options.

Lithium: Good results, but with side effects

Lithium is one of the oldest and most well studied agents.⁶⁻⁹ Most studies used 900 mg divided into 3 daily doses and titrated to lithium plasma levels of 0.5 to 1 mmol/L. Unfortu-

nately, though, lithium is more likely to cause side effects than many other psychotropic agents (>25%).⁵⁻⁹ And while the research has found that lithium produces significant remission rates, it's not very effective in patients who have failed multiple antidepressant trials, with only 12.5% to 15.9% of patients in that cohort achieving remission.^{10,11}

Thyroid hormone has only mild side effects

Low-dose thyroid supplementation has been used for decades in euthyroid patients with treatment-resistant depression; remission rates range from 25% to 59%.¹⁰⁻¹³ Most studies used a low fixed-dose therapy between 25 and 50 mcg daily; side effects were mild and occurred at rates similar to placebo.¹³

Atypical antipsychotics:

Many pluses, but weight gain is an issue

Atypical antipsychotics are an attractive alternative to typical antipsychotics for treatment-resistant depression. They are much less likely to cause extrapyramidal symptoms, tardive dyskinesia, and other motor symptoms, but

What we learned from the STAR*D trial

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study is noteworthy because of its size, duration, design, and impact on the treatment of depression.⁵ This was a multicenter study of 3671 patients with major unipolar depression. Remission was determined by 2 rating scales—HRSD17 and QIDS-SR16*—and side effects were measured at each visit. There was no placebo control, no consideration for atypical antipsychotic medications or other therapies, and randomization was limited.

The **FIGURE** below shows how STAR*D was structured. In Level 1, patients were treated with citalopram (Celexa). If they didn't go into remission, they were encouraged to proceed to Level 2, which involved 3 arms: switching agents, augmenting agents, or cognitive therapy. Patients chose which arm they wanted and were randomized to the specific medications used in that level. Switch agents included bupropion SR (Wellbutrin SR), sertraline (Zoloft), and venlafaxine XR (Effexor XR). Augmentation was with buspirone (BuSpar) and bupropion. Cognitive therapy was with or without continued citalopram with a second augmentation level of bupropion SR or venlafaxine XR. Level 3 also involved switch and augmentation arms using nortriptyline (Aventyl, Pamelor) or mirtazapine (Remeron) for switch agents and lithium or thyroxine for augmentation. Level 4 involved switching to tranylcypromine (Parnate) or venlafaxine XR plus mirtazapine.

Remission rates were 36.8% for those in Level 1, 30.6% in Level 2, 13.7% in Level 3, and 13% in Level 4. The cumulative remission rate was 67%. While remission rates for switch strategies in Levels 2 and 3 appeared to be lower for pharmacologic agents compared with augmentation strategies (27% vs 35% in Level 2 and 10.7% vs 20.5% in Level 3), the sample sizes were too small for the differences to be statistically significant, and the study was underpowered to establish the superiority of switch vs augmentation strategies.

Finally, it's important to mention that patients of primary care physicians had similar remission rates, when compared with psychiatrists' patients.⁴² Keep in mind, however, that the care provided in the STAR*D trial was structured and protocol-driven. After randomization into 1 medication group or another, dose adjustments were standardized at set intervals and based on inadequate response to validated depression severity assessment tools. Outcomes were patient-based and uniformly applied. This study structure may explain why remission rates were identical regardless of the specialty of the treating physician.

*The 17-item Hamilton Rating Scale of Depression and the 16-item Quick Inventory of Depressive Symptomatology–Self Report.

FIGURE
Structure of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D)

Level 1				Citalopram			
Level 2	Switch strategies			Augmentation strategies			
	Level 2a				Cognitive behavioral		
Bupropion SR		Sertraline	Venlafaxine XR	Cognitive therapy	Citalopram + cognitive therapy	Citalopram + bupropion	Citalopram + buspirone
Level 3				If unresponsive, switch to			
				Bupropion SR	Venlafaxine XR		
Level 3	Switch strategies			Augmentation strategies			
	Nortriptyline		Mirtazapine	Lithium augmentation		T3 augmentation	
Level 4	Switch strategies						
	Tranylcypromine			Venlafaxine XR + mirtazapine			

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as a trade-off they often cause weight gain, abnormal glucose metabolism, dyslipidemia, and hyperprolactinemia.

■ **Aripiprazole (Abilify)** is 1 of 2 medications approved by the Food and Drug Administration (FDA) for treatment-resistant depression. Studies have shown remission rates of 25% to 37%, with side effects in 16% to 25% of patients.¹⁴⁻¹⁶ Akathisia, the major side effect, can be reduced by lowering the starting dose to 2.5 mg.¹⁷

■ **Olanzapine, combined with fluoxetine** in a fixed-dose pill (Symbyax), is the other FDA-approved agent for treatment-resistant depression. Trivedi and colleagues showed a remission rate of 25.5% and side effects ranging from 10% to 40%.¹⁸

■ **Risperidone (Risperdal)** rivals the efficacy of the medications previously discussed, but starting doses and titration schedules vary widely, making it difficult to determine which treatment course would be most efficacious.¹⁹⁻²¹

■ **Quetiapine (Seroquel)** has produced mixed results in treatment-resistant patients. That may have been because some studies used lower daily doses—25 to 100 mg—vs 150 to 600 mg in other trials.²² Bauer found higher remission rates compared to placebo (36% vs 24%)²³ while Garakani²² did not (49% for quetiapine vs. 63% for placebo when using an intention-to-treat analysis; a similar lack of efficacy was found if those who dropped out of the study were excluded; $P < 0.29$). Garakani also found that dry mouth, sedation, and other side effects occurred in up to 76% of patients. (Of note: Most studies of atypical antipsychotics are industry funded.)

Mirtazapine has not been well studied

Unfortunately, there are very little data on mirtazapine (Remeron). When the drug was added to ongoing antidepressant therapy, a single double-blind, randomized controlled trial found significantly better response rates compared with placebo.²⁴ One advantage of the drug was that it helped relieve the sexual side effects of ongoing selective serotonin reuptake inhibitor (SSRI) therapy.²⁵

Folic acid and SAME also haven't been well studied

Up to 50% of Americans have low levels

of central nervous system L-methylfolate, which is a key co-factor in monoamine neurotransmitter production. Although lower plasma folate has been linked to depression, folate supplementation as a primary treatment for major depression has not been well studied and its use in treatment-resistant depression is limited to 1 study by Alpert and colleagues.²⁶ Using an open-label, nonplacebo-controlled design in which folinic acid—an activated form of folic acid—was compared with placebo, researchers found remission rates of 18%, which is not significantly higher than the placebo response seen in other studies.

Similarly, there's limited research on S-adenosyl-L-methionine (SAME). Using a similar open-label, nonplacebo-controlled design, Alpert found a 43% remission rate in patients with treatment-resistant depression. Side effects occurred in up to half of patients, prompting 6.6% of patients to leave the study.²⁷

Omega-3 fatty acids:

The news is mixed

Data are contradictory on the value of omega-3 fatty acid for major depression^{28,29} and the evidence to support its use in treatment-resistant depression is likewise limited and contradictory.³⁰ Until the data are more consistent and robust, it's unclear whether omega-3 fatty acid supplementation can benefit patients.

Exercise helps

Some studies suggest that exercise can have a dose-responsive effect on clinical depression.³¹ As a result, the Treatment with Exercise Augmentation for Depression (TREAD) trial is underway to examine whether it can augment drug therapy. Preliminary evidence suggests that 30 minutes of aerobic exercise most days of the week can be effective.^{32,33} (For more on exercise, see "Does exercise alleviate symptoms of depression? Clinical Inquiries, on page 530.)

Cognitive therapy helps patients, and there are no side effects

The STAR*D study showed equivalent efficacy in achieving remission (23% vs. 33%) when comparing augmentation with cogni-

➤ **While lithium produces significant remission rates, it's not very effective in patients who have failed multiple antidepressant trials.**

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tive therapy and augmentation with medications, with a low rate of side effects seen for cognitive therapy.³⁴ Notably, it took longer to achieve remission (55 vs 40 days) when cognitive therapy was added to antidepressants. (For more on the STAR*D trial, see "What we learned from the STAR*D trial" on page 492.) It's also worth mentioning that other researchers did not find similar results for augmentation when they compared cognitive behavioral and brief supportive psychotherapy with medication therapy only.³⁵

These agents don't appear helpful in augmentation efforts

Several other agents have been studied with no effect on remission rates. These include pindolol,³⁶ modafinil,³⁷ buspirone, lamotrigine,³⁸ stimulants, and estrogen replacement.

Consider side effects, cost, and patient preference

Because most studies showed that the efficacy of the tested drugs was similar, how do you decide which augmenting agent to prescribe? The usual standard is lithium, which offers rates of remission that are high, but not statistically significantly better when compared with thyroid supplementation and cognitive therapy. Quetiapine, while not more efficacious, may lower scores on depression rating scales more quickly than lithium.³⁹ Additionally, the STAR*D trial suggests that many agents may be used in augmentation with similar results.

In the final analysis, the family physician has to consider factors other than efficacy.

You also have to factor in the costs of medicines and lab testing, patient preference, and side effects. Lithium is most likely to cause side effects. Atypical antipsychotics seem to have lower short-term side effect profiles with efficacy similar to cognitive therapy. However, the potential drawbacks of antipsychotics, including aberrations in glucose metabolism, weight, and lipid profiles, are not typically seen in short-term studies. Obviously, more long-term studies are necessary before 1 agent can be deemed superior.

When should you stop therapy?

That question still doesn't have a definitive answer. The STAR*D trial found that patients who achieved full remission were less likely to relapse/worsen than those who had only a partial response. The time to relapse ranged from 2.5 to 4.5 months and was shorter for those patients requiring 2 or more levels of treatment. As there was no control of the therapeutic interventions used during this time, we can't be certain about what caused the relapse, but burden of disease, income levels, and ethnicity all played roles in symptom severity, decreasing remission rates, and increasing relapse rates.^{40,41}

While we cannot identify the ideal or even preferred duration of augmentation in patients with treatment-resistant depression, it seems clear that relapse is extremely common and tends to occur relatively early after achieving remission. **JFP**

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Relapse is extremely common and tends to occur relatively early after achieving remission.

INSTANT POLL QUESTION

Which of the following best describes your practice's use of nurse practitioners and/or physician assistants?

- We have 1 NP/PA for every 2 FPs
- We do not employ NPs or PAs
- 1 NP/PA for every 5 FPs
- Other _____
- 1 NP/PA for every 10 FPs

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