

Managing Partial Response or Nonresponse: Switching, Augmentation, and Combination Strategies for Major Depressive Disorder

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Despite the multitude of agents approved for the treatment of major depressive disorder, approximately 50% of patients experience no response to treatment with a first-line antidepressant. Clinicians have 4 broad pharmacologic strategies to choose from for treating antidepressant nonresponders: increasing the dose of the antidepressant, switching to a different antidepressant, augmenting the treatment regimen with a nonantidepressant agent, and combining the original antidepressant with a second antidepressant. To date, the most comprehensively studied treatment strategy for nonresponse or partial response to antidepressants is augmentation with atypical antipsychotic agents, including aripiprazole, olanzapine, quetiapine, and risperidone. However, augmentation or combination with other agents such as mirtazapine, mianserin, and omega-3 fatty acids is also supported by considerable efficacy data. Lithium, desipramine, triiodothyronine, and modafinil have mixed data. While more studies are needed, agents such as bupropion, desipramine, mecamlamine, and testosterone look promising. Switching antidepressants, especially to the newer agents, including selective serotonin reuptake inhibitors, bupropion, mirtazapine, and venlafaxine, is also supported by considerable efficacy data. Clinicians should carefully reevaluate patients with major depressive disorder who are nonresponders to treatment, particularly those who have had several adequate trials. When choosing the best treatment strategy for antidepressant nonresponders, clinicians should take into account the efficacy and tolerability of treatment as well as patient preference and treatment history. Finally, the risk of potential loss of partial therapeutic benefit from the first-line antidepressant, as well as the risk of withdrawal symptoms, should be taken into account when considering switching antidepressants, while the risk of drug interactions and poor adherence should be taken into account when considering combination and augmentation treatments.

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With more than 180 randomized, double-blind, placebo-controlled trials published since 1980,¹ contemporary antidepressants have been firmly established as safe and effective treatments for adults with nonpsychotic major depressive disorder (MDD). However, similar to all other medical interventions, antidepressants have limitations in terms of their efficacy, safety, and tolerability. For

example, a meta-analysis¹ of randomized, double-blind, placebo-controlled trials published between 1980 and mid-2007 reported pooled response rates (50% or greater reduction in symptoms) of 53.8% for adults receiving antidepressant treatment versus 37.3% for those receiving placebo, yielding a relative efficacy margin of antidepressants versus placebo of 16.5% and a number needed to treat (NNT) of, roughly, 1 in 6.

Regardless of which antidepressant is chosen, the ultimate goal of therapy for MDD is remission of the major depressive episode followed by the resolution of residual depressive symptoms, outcomes that are considerably more stringent than clinical response. Lack of attaining these goals has been associated with a number of adverse outcomes. Specifically, compared with patients who achieve full remission, those with residual symptoms have a greater risk of relapse and recurrence,^{2–4} more chronic depressive episodes,² a shorter duration between episodes,² and continued impairment in work and relationships.⁵ In addition, the presence or persistence of a major depressive episode has been linked to increased overall mortality,⁶ as well as increased mortality and morbidity from a number of comorbid medical disorders, including stroke,⁷ diabetes,^{8,9} myocardial infarction,¹⁰ cardiovascular disease,¹¹ congestive heart failure,¹² and human immunodeficiency virus.¹³ Furthermore, residual

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- ◆ Choose evidence-based treatment strategies for antidepressant-resistant depression such as raising the dose of the initial antidepressant, switching to a different antidepressant, and augmentation and combination therapies.
- ◆ Evaluate patients with treatment-resistant depression by confirming the diagnosis, ensuring the adequacy of and adherence to the first-line treatment trial, assessing for comorbid medical and psychiatric diagnoses, and differentiating between nonresponse to therapy and depressive relapse.
- ◆ Consider the tolerability of the first-line agent and the potential loss of partial benefit (if any) from the first-line antidepressant when choosing between switching and augmentation and combination strategies.

symptoms of depression may confer an ongoing increased risk of suicide.¹⁴

EVALUATING PARTIAL RESPONSE OR NONRESPONSE TO TREATMENT WITH ANTIDEPRESSANTS

Clinicians should evaluate for several possible contributing factors when faced with nonresponse or inadequate symptom improvement in patients with MDD, particularly for patients who have had several treatment trials. Initially, clinicians should differentiate between a depressive relapse while taking an antidepressant and nonresponse to an antidepressant by obtaining a detailed history to ascertain whether the patient achieved near or full remission of their major depressive episode at some point during the course of the most recent antidepressant treatment trial. Clinicians should then establish that the antidepressant regimen was, in fact, adequate in terms of dose and duration. Adequate duration of treatment may range from 6 to 12 weeks, depending on whether the patient experiences nonresponse or partial improvement of symptoms during the first 4 to 6 weeks of therapy. It has also been reported¹⁵ that less than 20% of patients prescribed an antidepressant followed treatment guidelines consistently for 6 months. Therefore, treatment adherence, particularly among patients experiencing a heavy burden of side effects or patients on a complex polypharmacy regimen, should be assessed when patients exhibit little to no response to antidepressant treatment, or when there is a loss of therapeutic benefit.

Following the differential assessment of relapse versus resistance, ruling out nonadherence, and establishing the adequacy of treatment, clinicians should then conduct a diagnostic reassessment in order to confirm whether, indeed, the correct diagnosis is nonpsychotic MDD by ruling out alternative diagnostic possibilities that would require a different treatment approach (ie, a major depressive episode in the setting of bipolar disorder or MDD accompanied by psychotic symptoms). Clinicians should also reassess for psychiatric comorbidities, including substance use disorders,

anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), and eating disorders. The presence of Axis I comorbidity can contribute to patient discomfort and disability and has been found to confer a risk of poor acute treatment outcome among patients with MDD.¹⁶ In addition, a modified treatment approach may be required in the presence of Axis I comorbidity, since agents proven effective for MDD may not necessarily be effective in treating various comorbid Axis I disorders that may be present. Finally, medical comorbidities, including cardiovascular disease¹⁷ and chronic pain,¹⁸ may also impede response to antidepressants, and should be carefully reevaluated.

TREATMENT APPROACHES FOR ANTIDEPRESSANT-RESISTANT DEPRESSION

Four broad pharmacologic approaches are available for treating patients who have experienced insufficient symptom response to a first-line antidepressant: (1) increasing the dose of the antidepressant, (2) switching to a different antidepressant, (3) augmenting the treatment regimen with a nonantidepressant agent, and (4) combining the initial antidepressant with a second antidepressant. Each of these strategies has advantages and disadvantages, and treatment decisions should be based on several factors, including efficacy, safety, tolerability, treatment history, and patient preference. The following paragraphs will review evidence focusing on comparing the efficacy and tolerability of various switch strategies from randomized clinical trials, followed by evidence from randomized, double-blind, placebo-controlled studies examining the use of various augmentation and combination strategies for antidepressant nonresponders.

Switching Strategies

Switching medications has certain advantages over augmenting or combining medications, including a lower risk of drug interactions and, potentially, better patient compliance, since fewer medications are involved. Switching may also prove less costly than augmentation, although this is not always the case (eg, switching from a generic to a brand

antidepressant versus augmentation with a generic compound). Most importantly, switching may be favorable over augmentation and combination therapies for patients who experience intolerable side effects from the first-line therapy while demonstrating little or no symptom improvement.

There are 2 major types of switch studies in the literature: studies evaluating whether there is any difference between switching selective serotonin reuptake inhibitor (SSRI) nonresponders to a different SSRI (within-class switch) versus a non-SSRI antidepressant (across-class switch) and crossover studies that randomly assign patients to begin treatment with 1 of 2 antidepressants and then allow antidepressant nonresponders to switch to the alternative agent. These types of studies are reviewed below, along with levels 3 and 4 of the multicenter Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,¹⁹ which examined switching to nortriptyline, mirtazapine, tranylcypromine, or the combination of venlafaxine and mirtazapine for patients who were nonresponders following several sequential therapeutic trials.

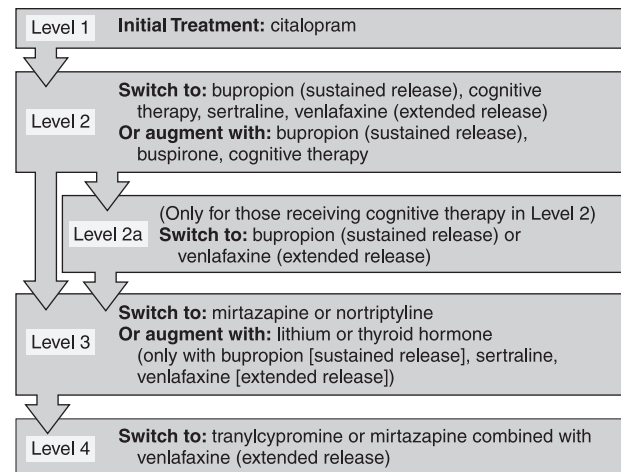
Across-class versus within-class switching strategies for SSRI nonresponders. The greatest amount of evidence on the efficacy of switching antidepressants to achieve resolution of symptoms focuses on the use of newer agents. For example, switching from an SSRI to either the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine or another SSRI has been studied in 2 randomized, double-blind trials.^{20,21}

In the first such study,²⁰ patients who had not responded to 2 successive antidepressants (most had previously taken SSRIs) were randomly assigned to treatment with either venlafaxine or the SSRI paroxetine. Response rates were 52% for venlafaxine and 33% for paroxetine ($P = .044$), while remission rates were 42% for venlafaxine and 20% for paroxetine ($P = .01$). The second study²¹ focused on patients who had not responded to treatment with an SSRI other than citalopram, who were then randomly assigned to take either venlafaxine extended release (ER) or citalopram. The primary analysis showed no statistical difference in depressive symptom outcome between these 2 treatment groups.

Thase and colleagues²² studied switching from an SSRI to the serotonin and norepinephrine receptor antagonist (SNRA) mirtazapine versus switching to the SSRI sertraline. The results of the study showed no statistical difference in remission rates or rates of discontinuation due to intolerance between the 2 treatment groups.

The STAR*D¹⁹ trial, the largest clinical trial ever conducted in the field of psychiatry, was a multisite study designed to assess the relative efficacy, safety, and tolerability of different treatment strategies for antidepressant nonresponders with MDD. The first level of STAR*D¹⁹ was an open-label trial of citalopram, and patients with inadequate depressive symptom response advanced to successive levels of treatment involving open-label randomization to a series of different augmentation, combination, and switch strategies in levels 2, 3, and 4 (Figure 1). Level 2 of the STAR*D trial²³ compared

Figure 1. STAR*D (Sequenced Treatment Alternatives to Relieve Depression) Treatment Algorithm^a



^aReprinted with permission from Rush et al.¹⁹

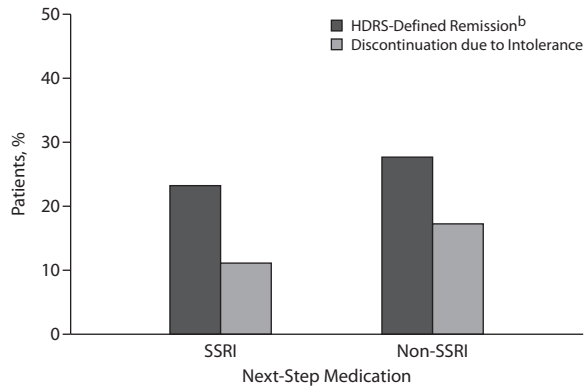
switching patients with no remission of symptoms from citalopram to bupropion, a norepinephrine-dopamine reuptake inhibitor (NDRI), or to sertraline or venlafaxine. No differences in efficacy or tolerability were found between the 3 treatment groups, with remission rates across treatments of, approximately, 25%.

A meta-analysis²⁴ of the above studies²⁰⁻²³ found a numerically small (NNT = 1 in 22) but statistically significant ($P = .007$) advantage in remission rates when comparing SSRI nonresponders switched to a non-SSRI antidepressant versus a second SSRI (Figure 2). In addition, a nonsignificant trend favoring tolerability for the within-class switch was reported in the meta-analysis (ie, lower discontinuation rates due to intolerance for the within-class switching group than the across-class switching group).

Crossover studies. Three such trials have been conducted to date. McGrath and colleagues^{25,26} conducted 2 studies involving a crossover from the tricyclic antidepressant (TCA) imipramine to the monoamine oxidase inhibitor (MAOI) phenelzine and vice-versa for nonresponders to the initial treatment. Both studies demonstrated that switching imipramine nonresponders to phenelzine was superior to switching phenelzine nonresponders to imipramine. Finally, in a separate study, Thase and colleagues²⁷ compared sertraline nonresponders switched to imipramine versus imipramine nonresponders switched to sertraline. Significantly higher response rates in the intent-to-treat sample were reported for patients switched from imipramine to sertraline than vice versa (60% versus 44%, respectively; $P = .03$). Sertraline was also reported to be better tolerated than imipramine, with discontinuation rates due to intolerance of 10% versus 25%, respectively.

Levels 3 and 4 of STAR*D. Level 3 of the STAR*D trial²⁸ compared switching to mirtazapine with switching to the

Figure 2. Meta-Analysis Pooled Remission and Discontinuation Rates for Switch to SSRI Versus Non-SSRI Following SSRI-Resistance^a



^aData from Papakostas et al.²⁴

^b $P < .05$.

Abbreviations: HDRS = Hamilton Depression Rating Scale, SSRI = selective serotonin reuptake inhibitor.

TCA nortriptyline for patients who did not respond to 2 previous antidepressant trials. The study found no statistical differences for response and remission rates or for tolerability between the 2 treatments, with remission rates notably low (< 20%).

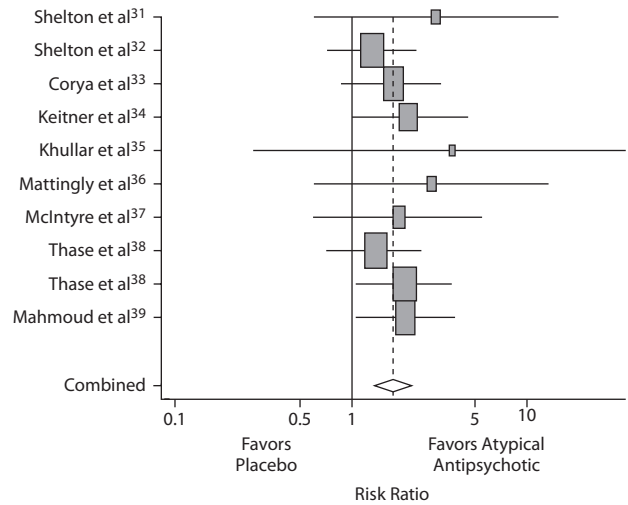
Finally, Level 4 of the STAR*D trial²⁹ compared switching to the MAOI tranylcypromine versus switching to the combination of mirtazapine and venlafaxine for patients who had not responded to 3 previous trials. Although treatment outcomes were not significantly different (remission rates of 6.9% versus 13.7%, respectively), switching to mirtazapine and venlafaxine was found to be significantly better tolerated than switching to tranylcypromine ($P < .05$).

Augmentation Strategies

The potential advantages of augmentation and combination strategies versus switching include minimizing the risk of loss of any therapeutic benefit from the first-line agent as well as avoiding the risk of withdrawal symptoms that may occur upon switching. Additionally, it may be possible to choose an augmenting agent that will not only help resolve the major depressive episode overall, but also target side effects of the first-line therapy. For example, a clinician may choose to augment with a stimulating augmenting agent for patients with inadequate response to an antidepressant who are also experiencing somnolence and fatigue, or a sedating agent for patients with inadequate response and insomnia. However, the possibility also exists for side effects from the first-line agent to persist and to perhaps even be compounded by the augmenting agent if, for example, a sedating agent is added to the treatment regimen of a patient experiencing antidepressant-induced somnolence.

Atypical antipsychotics. Presently, the treatment strategy with the largest evidence base for antidepressant

Figure 3. Risk Ratios for Remission in Studies of Olanzapine, Risperidone, and Quetiapine Augmentation of Antidepressants^a



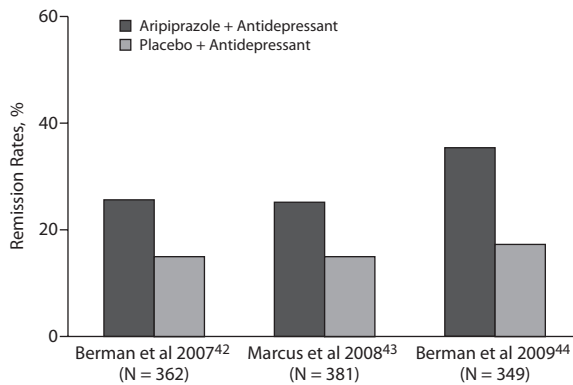
^aAdapted with permission from Papakostas et al.³⁰

nonresponders with MDD is the use of adjunctive atypical antipsychotic agents. At least 15 randomized, double-blind studies have been conducted to date. The results of an early meta-analysis³⁰ comprised of the first 10 such trials³¹⁻³⁹ (involving olanzapine, quetiapine, and risperidone) indicated that these agents were more effective than adjunctive placebo in helping resolve depressive symptoms, with pooled remission rates of, approximately, 47% versus 22%, respectively (NNT = 1 in 4; Figure 3). However, these agents were also found to be significantly less well tolerated than adjunctive placebo, with more than a 3-fold higher discontinuation rate due to adverse events ($P < .0001$).

Since this meta-analysis was conducted, 2 additional placebo-controlled trials^{40,41} have demonstrated superior efficacy for quetiapine augmentation versus placebo augmentation in antidepressant nonresponders with MDD. In both studies, patients taking antidepressants were randomly assigned to receive adjunctive placebo, quetiapine 150 mg/d, or quetiapine 300 mg/d. Both trials reported the 300-mg dose to be significantly superior to placebo ($P < .05$), while 1 trial⁴⁰ also found the 150-mg dose to be significantly superior to placebo in resolving depressive symptoms ($P < .01$).

Finally, a total of 3 randomized, double-blind placebo-controlled trials⁴²⁻⁴⁴ have also been conducted to determine whether aripiprazole is more effective than placebo as augmentation in antidepressant nonresponders with MDD. Antidepressants augmented in those trials included fluoxetine, sertraline, paroxetine, escitalopram, and venlafaxine. Each of these 3 trials demonstrated that remission rates were higher with adjunctive aripiprazole than adjunctive placebo (Figure 4), while discontinuation rates due to adverse events were very low (less than 10% of the total sample).

Figure 4. Aripiprazole Augmentation: Comparison of 3 Randomized, Double-Blind, Placebo-Controlled Trials^a



^aTreatment included an 8-week prospective phase followed by a 6-week double-blind treatment phase. $P < .05$ for all comparisons.

As a result, aripiprazole was approved by the US Food and Drug Administration (FDA) in 2008 as adjunctive therapy to antidepressants for patients with antidepressant-resistant MDD.

In summary, atypical antipsychotic augmentation has the advantage of being the best-studied augmentation strategy. However, atypical antipsychotics, depending on the agent chosen, have the potential for adverse events that include neuroendocrine side effects such as hyperprolactinemia; metabolic side effects such as weight gain, dyslipidemia, and glucose dysregulation; and extrapyramidal side effects such as akathisia, parkinsonism, and dystonic reactions, as well as rare but serious extrapyramidal side effects such as tardive dyskinesia and neuroleptic malignant syndrome.

Lithium. Lithium augmentation for TCA nonresponders with MDD has also been extensively studied. Seven randomized, double-blind, placebo-controlled studies⁴⁵⁻⁵¹ have been published to date, with 3 studies showing lithium augmentation being superior to placebo in resolving depressive symptoms, and 4 showing an equivalence in antidepressant efficacy between the 2 treatment groups. However, those studies that demonstrated the superiority of lithium augmentation over placebo were of very short duration—from 1 to 3 weeks—bringing into question whether lithium is, indeed, more effective than placebo as an augmenting agent when used for longer treatment durations. Nevertheless, a meta-analysis of randomized, double-blind, placebo-controlled trials of lithium augmentation of antidepressants for antidepressant nonresponders with MDD demonstrated greater antidepressant efficacy for lithium (NNT = 1 in 3.7).⁵²

A second limitation of the lithium augmentation literature is the relative paucity of randomized, double-blind, placebo-controlled studies focusing on adjunctive use with agents that are commonly used as first, second, or third-line treatments (ie, SSRIs, SNRIs, the NDRI bupropion). In fact, only 2 randomized, double-blind, placebo-controlled studies

have been conducted of lithium augmentation of SSRIs. The first was a small (N = 24) study⁵³ of 1 week's duration that found lithium to be superior to placebo ($P < .05$) when added to citalopram. However, a longer (6 weeks) and slightly larger (N = 62) study⁵⁴ found no significant differences in antidepressant efficacy between patients who received lithium or placebo augmentation of fluoxetine or lofepramine.

A third limitation of the lithium augmentation literature is the limited relative efficacy of lithium augmentation compared to other strategies for antidepressant nonresponders with MDD. For instance, Fava and colleagues^{55,56} conducted 2 identical, randomized, double-blind studies that compared increasing the SSRI dose versus lithium augmentation or desipramine combination for SSRI nonresponders with MDD. Pooling these 2 studies revealed a greater resolution of depressive symptoms for patients who had their SSRI dose increased than for those who received either lithium augmentation or desipramine combination. Taken together, these studies suggest that increasing the SSRI dose is superior in efficacy to either augmentation with lithium or combination with desipramine.

Disadvantages of lithium augmentation include the risk of cardiotoxicity, nephrotoxicity, thyrotoxicity, and weight gain, as well as the need for monitoring of blood lithium levels due to its narrow therapeutic index.

Pindolol. Pindolol is a β -blocker and serotonin-1A receptor antagonist. To date, at least 4 randomized, double-blind, placebo-controlled studies⁵⁷⁻⁶⁰ have focused on the use of adjunctive pindolol for antidepressant nonresponders with MDD. In the first such study, Maes and colleagues⁵⁷ compared the adjunctive use of pindolol or placebo with trazodone for a total of 4 weeks (N = 33). These investigators reported a response rate of about 73% for patients who received adjunctive therapy with pindolol versus 20% for those who received adjunctive placebo. A second study⁵⁸ conducted by the same investigators that compared pindolol versus placebo augmentation of fluoxetine also demonstrated pindolol to be superior to placebo in efficacy (N = 31). A criticism of these 2 studies, however, is that not all patients randomly assigned to pindolol versus placebo augmentation had failed at least 1 adequate antidepressant treatment trial. In fact, 2 subsequent randomized, double-blind, placebo-controlled studies^{59,60} focusing on the use of pindolol augmentation in populations that exclusively consisted of patients who had not experienced sufficient symptom improvement to antidepressant therapy did not demonstrate the superiority of pindolol over placebo. Therefore, although there is some evidence that the use of pindolol may accelerate response to standard antidepressants when used concomitantly,⁶¹ there is little evidence to suggest the utility of adjunctive pindolol for antidepressant nonresponders. Side effects reported with this treatment combination include somnolence, nausea, postural hypotension, sweating, and dry mouth.

Omega-3 fatty acids. Major omega-3 fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid

(DHA). These essential fatty acids cannot be synthesized by humans, and must be obtained from their diet. Randomized, double-blind, placebo-controlled studies⁶²⁻⁶⁴ support the use of adjunctive omega-3 fatty acids (EPA and DHA) for patients with MDD who do not experience sufficient symptom improvement following antidepressant therapy. One disadvantage to the strategy is that the optimal dose of omega-3 fatty acids has not been established, with some conflicting findings in the literature. For example, 1 study⁶³ found 2 g/d of ethyl-EPA to be superior to placebo as adjunctive therapy, another study⁶² reported 1 g/d but not 2 or 4 g/d of EPA to be superior to placebo, while a third study⁶⁴ found 660 mg/d of an EPA-DHA mix to be superior to placebo.

A second disadvantage of this strategy is cost, since insurance programs do not typically cover treatment with omega-3 fatty acids. The major advantage of this strategy is that it is relatively well tolerated and very acceptable to patients. In addition, treatment with omega-3 fatty acids may provide other health benefits, such as promoting cardiovascular health.

Triiodothyronine. Triiodothyronine (T_3) is the active form of thyroid hormone in the human body. Three randomized, double-blind, placebo-controlled studies^{50,65,66} have focused on the use of T_3 as augmentation to TCAs in TCA nonresponders. Two of those studies^{50,65} reported T_3 to be superior to placebo, while the third study⁶⁶ did not. Similar to lithium, limitations of this literature include the relatively short duration of most studies (ie, 2 weeks), as well as the use of TCAs rather than more contemporary antidepressants such as the SSRIs, SNRIs, and bupropion. A meta-analysis pooling randomized, double-blind, placebo-controlled trials of adjunctive T_3 for antidepressant nonresponders did not demonstrate greater symptom resolution for adjunctive T_3 than placebo.⁶⁷

Finally, Level 3 of STAR*D examined the use of adjunctive lithium versus adjunctive T_3 for patients who had not achieved remission after 2 optimal antidepressant trials.⁶⁸ The results of this study demonstrated a large numerical but not statistically significant advantage in remission rates for T_3 over lithium augmentation, and a statistically significant advantage in favor of T_3 augmentation over lithium augmentation in terms of tolerability ($P = .027$ for discontinuation due to side effects). Although doses of T_3 used in MDD (25 μ g or 50 μ g) appear to be well tolerated during the acute phase of treatment (ie, the first few months or so), the long-term safety and tolerability of this treatment strategy, particularly with respect to the impact of T_3 on bone density in women, has not been adequately studied.

Modafinil. Modafinil is an agent of unclear mechanism of action, although it may potentiate histaminergic tone in the human brain.⁶⁹ To date, 2 randomized, double-blind, placebo-controlled studies^{70,71} have focused on the adjunctive use of modafinil for antidepressant nonresponders with MDD who also experience sleepiness and fatigue, whether as a side effect of antidepressant therapy or a residual

symptom of depression. Although both studies found that modafinil lessened fatigue and improved daytime wakefulness early on, modafinil was not significantly superior to placebo at endpoint in terms of resolving depressive symptoms, sleepiness, or fatigue. However, a pooled analysis⁷² of patients enrolled in these 2 studies who also met certain criteria (most notably, significant somnolence as evidenced by a score ≥ 10 on the Epworth Sleepiness Scale⁷³) demonstrated that modafinil augmentation of SSRI therapy was superior to placebo in improving wakefulness and depressive symptoms ($P < .05$).

Advantages for modafinil include a relatively low abuse potential compared with other stimulating agents and its usefulness in treating residual symptoms such as hypersomnia. However, whether modafinil is effective for patients with antidepressant nonresponse who do not have sleepiness, or for those with prominent insomnia, is unclear. Side effects reported during modafinil augmentation of antidepressants include headache, nervousness, irritability, nausea, insomnia, diarrhea, dizziness, and dry mouth.

Buspirone and bupropion. Buspirone is a serotonin-1A agonist that is approved by the FDA for the treatment of generalized anxiety disorder, while the NDRI bupropion is approved as monotherapy for adults with MDD. As an adjunct for antidepressant nonresponders with MDD, buspirone has been studied at doses ranging between 7.5 mg/bid and 30 mg/bid. Although buspirone may be helpful in treating SSRI-induced sexual dysfunction, especially among women,⁷⁴ 2 placebo-controlled studies^{75,76} have not demonstrated buspirone augmentation to be superior to placebo in alleviating depressive symptoms among antidepressant nonresponders with MDD.

Finally, a treatment arm of Level 2 of STAR*D involved adding bupropion versus buspirone to citalopram among citalopram nonresponders.⁷⁷ Patients treated with adjunctive bupropion had lower Quick Inventory of Depressive Symptomatology–Self-Report (QIDS–SR)⁷⁸ scores at endpoint than patients treated with adjunctive buspirone ($P < .05$). In addition, a numerical but not statistically significant advantage in terms of QIDS–SR remission rates was found for bupropion (39% versus 32.9%, respectively). Furthermore, a significant tolerability advantage was found for bupropion, with a dropout rate due to intolerance of about 13% versus about 21% for buspirone ($P < .009$). Side effects reported with buspirone augmentation include somnolence, headache, nausea, and sweating. Bupropion is contraindicated in patients with eating disorders, as well as patients with epilepsy or a history of head injury.

Methylphenidate. Methylphenidate, which is FDA-approved for the treatment of ADHD, is a psychostimulant thought to block the reuptake of dopamine and, to some extent, increase the presynaptic release of dopamine. To date, 2 randomized, double-blind, placebo-controlled trials^{79,80} have focused on the adjunctive use of osmotic-release oral system (OROS) methylphenidate for patients with MDD

who were antidepressant nonresponders. Neither of these 2 trials demonstrated superior efficacy for OROS methylphenidate augmentation versus placebo for depressive symptoms overall. However, specific symptoms, such as apathy and fatigue, were more likely to be resolved with adjunctive methylphenidate than placebo, a potential advantage of this treatment strategy. Also, as depression and ADHD are often comorbid, methylphenidate can be used as a treatment strategy to target residual ADHD symptoms in antidepressant nonresponders. Disadvantages regarding the use of stimulants include their appetite-suppressing effects, irritability, insomnia, and the risk of dependence and abuse.

Lamotrigine. Lamotrigine is an anticonvulsant that has demonstrated efficacy in treating major depressive episodes in patients with bipolar disorder.⁸¹ However, when evaluated in 2 randomized, double-blind, placebo-controlled studies^{82,83} as adjunctive therapy for antidepressant nonresponders with MDD, lamotrigine was not found to be significantly superior than adjunctive placebo. Both studies had small sample sizes ($N < 35$) that may have contributed to the lack of significance in the results. A disadvantage to lamotrigine therapy is the slow titration required to minimize the risk of Stevens-Johnson syndrome, a rare but potentially lethal side effect.

Testosterone. An 8-week, randomized, placebo-controlled trial⁸⁴ evaluated the efficacy of a testosterone patch in hypogonadal men with refractory depression ($N = 22$). A greater resolution of depressive symptoms was reported among patients who received adjunctive therapy with testosterone in that trial. Disadvantages of testosterone treatment include the risk of erythrocytosis, irritability, and, in women, hirsutism.

Mecamylamine. Mecamylamine, a cholinergic agent and neuronal nicotinic receptor antagonist, was compared with placebo as an augmentor of citalopram in citalopram nonresponders.⁸⁵ Patients receiving mecamylamine augmentation achieved significantly better results than those taking adjunctive placebo in terms of reduction of depressive symptoms ($P = .04$). Significant improvement was also found on a secondary scale measuring irritability ($P \leq .001$). Mecamylamine's novel mechanism of action may represent an alternative treatment strategy for depression, but the data are limited. Possible side effects include constipation and dizziness.

Inositol. Inositol is a carbohydrate involved in the phosphatidylinositol second messenger system. A randomized, double-blind, placebo-controlled study⁸⁶ focusing on inositol as an augmentor of SSRIs for SSRI nonresponders did not demonstrate efficacy.

Combination Strategies

Mirtazapine and mianserin. Mirtazapine and mianserin are antidepressants with similar mechanism of action; specifically, they are antagonists of the serotonin-2 and

Table 1. Relative Strength of Evidence Supporting Efficacy of Augmentation, Combination, and Switching Strategies in Treatment-Resistant Depression^a

Strategy	Evidence Grade ^b
Augmentation/Combination	
Atypical antipsychotics ³⁰⁻⁴⁴	A
Mirtazapine/mianserin ^{58,87-90}	A-
Omega-3 fatty acids ⁶²⁻⁶⁴	A-
Modafinil ⁷⁰⁻⁷²	B
Lithium ⁴⁵⁻⁵⁴	
T ₃ ^{50,65-68}	
Bupropion ⁷⁷	
Testosterone ⁸⁴	B-
Mecamylamine ⁸⁵	
Desipramine ⁹¹	
Pindolol ⁵⁷⁻⁶¹	C
Buspiron ⁷⁴⁻⁷⁶	
Inositol ⁸⁶	
Lamotrigine ^{82,83}	C
Methylphenidate ^{79,80}	
Switching	
SSRI to bupropion, venlafaxine, or mirtazapine ²⁴	A
SSRI to SSRI ²⁴	A
TCA to MAOI ^{25,26} or SSRI ²⁷	B
MAOI or SSRI to TCA ^{25,26}	C

^aThe efficacy grades were derived by reviewing all randomized, double-blind, placebo-controlled studies for these compounds, in addition to data from STAR*D, which was not placebo-controlled.

^bA = good efficacy data, B = mixed efficacy data, C = weak efficacy data. Abbreviations: MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, STAR*D = Sequenced Treatment Alternatives to Relieve Depression, TCA = tricyclic antidepressant, T₃ = triiodothyronine.

serotonin-3 receptors and of the α_2 -adrenergic inhibitory autoreceptor. To date, 3 studies^{58,87,88} have compared treatment with an SSRI alone versus an SSRI plus mianserin for patients with treatment-resistant depression. Combination therapy was found superior in efficacy to SSRI monotherapy in 2 of those studies.^{58,87}

A double-blind, placebo-controlled trial⁸⁹ of mirtazapine augmentation of an antidepressant in 26 patients with resistant depression showed response and remission rates of 64% and 45%, respectively, for the mirtazapine group versus 20% and 13%, respectively, for the placebo group. Mirtazapine augmentation was also associated with improvement in overall functioning and quality of life. A more recent 6-week study⁹⁰ ($N = 61$) compared monotherapy with mirtazapine or paroxetine versus combination therapy with both mirtazapine and paroxetine. The remission rate for the combination therapy was 43%, compared with 19% for mirtazapine alone and 26% for paroxetine alone ($P < .05$).

The dosages prescribed in these studies generally ranged between 15 mg/d and 30 mg/d at bedtime. In addition to the strong efficacy data for these agents in helping patients to achieve remission from depression, their use as adjuncts may also help target insomnia, whether as a symptom of depression or a side effect of the first-line antidepressant

treatment. Disadvantages to using these antidepressants include the risk of weight gain and sedation, as both of these agents have potent antihistaminic and anticholinergic properties, and a rare risk of agranulocytosis.

Bupropion. The use of bupropion as adjunctive therapy for antidepressant nonresponders with MDD was studied in STAR*D and, therefore, was reviewed with buspirone in the augmentation section of this article.

Desipramine. In a double-blind study,⁹¹ 38 inpatients were randomly assigned to 6 weeks of desipramine monotherapy, fluoxetine monotherapy, or the combination of the 2 agents. Patients receiving the combination therapy were significantly more likely to achieve remission than patients receiving either agent alone ($P = .001$). This positive result may be due to the synergistic effect of combining serotonergic and noradrenergic mechanisms of action; however, as discussed earlier (see Lithium), the relative efficacy of this treatment strategy versus alternative treatment strategies (eg, dose increase) in SSRI nonresponders remains in question.^{55,57} Disadvantages of this strategy include sedation, weight gain, and the risk of drug interactions via the cytochrome P450 enzyme system.

Relative Efficacy of Treatment Strategies

Table 1 lists relative grades representing the relative evidence base supporting the efficacy of various switching, augmentation, and combination treatment strategies for antidepressant nonresponders with MDD. These evidence grades were derived from reviewing randomized, double-blind, placebo-controlled studies focusing on augmentation/combination strategies and randomized, double-blind studies for switching strategies. Grading criteria were based on the number of studies that demonstrated superiority versus equivalence for each intervention against placebo (for augmentation/combination) or alternative antidepressant monotherapy (for switch strategies). Data from STAR*D were also taken into consideration when grading the evidence base for a particular intervention.

CONCLUSION

While many antidepressants are available for the treatment of MDD, they have limitations in terms of their efficacy, safety, and tolerability. In fact, about half of all MDD patients fail to experience clinical response following treatment with a first-line antidepressant. When evaluating antidepressant nonresponders, clinicians should reevaluate the patient's diagnosis, ensure the adequacy of their antidepressant treatment trial, rule in or rule out the presence of comorbid medical and psychiatric diagnoses, assess patient adherence to treatment, and differentiate between nonresponse to therapy and depressive relapse. Clinicians have 4 broad pharmacologic treatment strategies to choose from for antidepressant nonresponders: increasing the dose of the antidepressant, switching to another antidepressant, augmenting

with a nonantidepressant agent, or combining the original treatment regimen with a second antidepressant.

The most comprehensively studied treatment strategy for antidepressant nonresponders is augmentation with atypical antipsychotic agents. However, augmentation or combination with other agents such as mirtazapine, mianserin, and omega-3 fatty acids also possesses considerable efficacy data. Lithium, T_3 , and modafinil augmentation have mixed data, while agents such as testosterone, bupropion, mecamylamine, and desipramine appear promising but require further study. Finally, switching SSRI nonresponders to a different SSRI or to a newer non-SSRI antidepressant such as bupropion, mirtazapine, or venlafaxine, has also been well studied. Several factors should be considered when choosing between strategies, including the tolerability of the first-line treatment trial and the potential loss of partial benefit from the first-line antidepressant, the risk of withdrawal symptoms when switching agents, and the risk of drug interactions and compliance problems with combination and augmentation treatments.

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), desipramine (Norpramin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), mecamylamine (Inversine), methylphenidate (Metadate, Ritalin, and others), mirtazapine (Remeron and others), modafinil (Provigil), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), quetiapine (Seroquel), risperidone (Risperdal and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, buspirone, lamotrigine, mecamylamine, methylphenidate, modafinil, quetiapine, risperidone, inositol, lofepramine, mianserin, pindolol, and triiodothyronine are not approved by the US Food and Drug Administration for the treatment of major depressive disorder.

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