Augmentation Strategies to Increase Antidepressant Efficacy

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Augmentation strategies for the treatment of major depressive disorder (MDD) are needed when patients with MDD have not tolerated or responded to antidepressant monotherapies. Clinicians can employ sequenced treatment steps, preferably coupled with the use of a treatment algorithm, to utilize augmentation strategies that will enable patients to achieve remission. The focus of augmentation therapy has been combining an antidepressant medication with another antidepressant; however, atypical antipsychotics are becoming commonly used to augment antidepressants. Beyond antidepressants and antipsychotics, alternative augmentation strategies include emerging pharmacologic treatments and nonpharmacologic strategies. *(J Clin Psychiatry 2007;68[suppl 10]:18–22)*

Clinicians need augmentation or combination strategies for the treatment of major depressive disorder (MDD) because many patients do not tolerate or respond to initial antidepressant monotherapies, much less attain the treatment goal of remission. Among outpatients who receive first-time treatment for MDD, only about 50% respond to treatment, and about 50% to 70% of those patients achieve remission.[1] New strategies are needed to help patients not only reach remission but also maintain sustained recovery, without relapse and recurrence.

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D)[2–4] study used equipoise-stratified randomization to evaluate the relative efficacy and tolerability of various treatments for adult outpatients aged 18 to 75 years (N = 4000) who had nonpsychotic, treatment-resistant MDD. After an initial monotherapy stage with the selective serotonin reuptake inhibitor (SSRI) citalopram, in which remission rates were 28% to 33% (depending on the rating scale used),[5] STAR*D compared a variety of augmentation/combination or monotherapy treatment strategies. At levels 2, 3, and 4 of the study, patients could choose whether to switch from one monotherapy to another or to augment monotherapy with another treatment. The goal of the trial was remission, and the trial results raised the question of whether augmentation/combination therapy might help patients with MDD achieve remission more effectively than monotherapy does.[6,7]

This article will focus on augmentation and combination strategies described in STAR*D or other research. Atypical antipsychotics have been prescribed as augmentation agents for treatment-resistant MDD, but as with all treatments, atypical antipsychotics carry the risk of adverse effects.[8] Beyond antidepressants and antipsychotics, clinicians are employing alternative augmentation strategies that include pharmacologic agents and nonpharmacologic strategies such as cognitive-behavioral therapy (CBT).

STAR*D AUGMENTATION AND COMBINATION STRATEGIES

If antidepressant monotherapy proves ineffective for patients with MDD, sequenced treatment steps utilizing augmentation strategies may be beneficial. After level 1 of STAR*D,[5] patients who did not achieve remission or did not tolerate citalopram were encouraged to participate in level 2, in which they chose whether to switch to a different monotherapy or augment/combine citalopram with another agent. Augmentation/combination options were the antianxiety agent buspirone, the non-SSRI antidepressant bupropion, or cognitive therapy, while switch options were bupropion, the SSRI sertraline, the serotonin-norepinephrine reuptake inhibitor venlafaxine, or cognitive therapy. The sustained-release formulation of bupropion and the extended-release formulation of venlafaxine were used. According to Rush et al.,[9] a 67% rate of remission was expected in patients who adhered to sequenced treatment steps. The doses and durations of treatments

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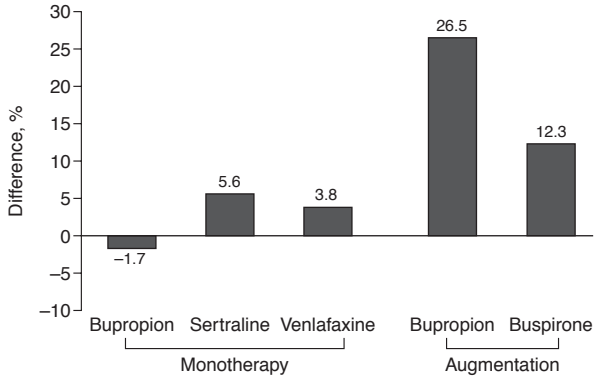
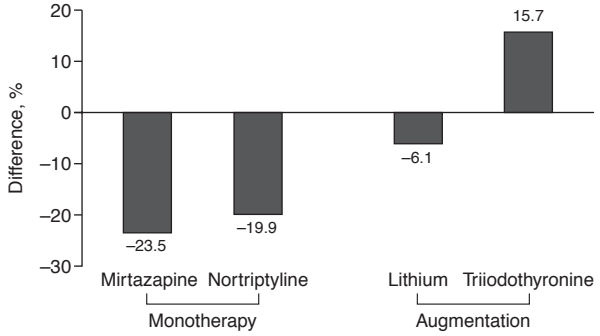
Figure 1. Remission Rates Minus Intolerance Rates in Level 2 of STAR*D[a]



[a]Data from Rush et al.[9] Negative results indicate patients were more likely to be intolerant of treatment; positive results indicate patients were more likely to remit with treatment.
Abbreviation: STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

Figure 2. Remission Rates Minus Intolerance Rates in Level 3 of STAR*D[a]



[a]Data from Rush et al.[9] Negative results indicate patients were more likely to be intolerant of treatment; positive results indicate patients were more likely to remit with treatment.
Abbreviation: STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

throughout the study were similar to those commonly prescribed in clinical practice.

In level 2 of STAR*D,[9] bupropion augmentation showed a 39.0% remission rate. Interestingly, intolerance (discontinuation because of side effects) of bupropion was greater among patients who used it as monotherapy following citalopram discontinuation (27.2%) than among patients who were treated with the combination of citalopram and bupropion (12.5%). The difference between the intolerance rates of bupropion monotherapy and bupropion augmentation therapy may indicate that patients switching monotherapies experienced some rebound and loss of therapeutic effect from discontinuing citalopram.

Subtracting level 2 intolerance rates from level 2 remission rates[9] provides a comparison of whether outpatients were more likely to adhere to treatment and go into remission or more likely to discontinue treatment because of an adverse effect. Of the monotherapies, bupropion was less likely to result in remission than discontinuation (25.5% vs. 27.2%, respectively), while sertraline and venlafaxine were slightly more likely to yield remission than discontinuation (26.6% vs. 21.0% and 25.0% vs. 21.2%, respectively). Patients treated with the combination of citalopram plus either bupropion or buspirone were considerably more likely to experience remission than to discontinue treatment (39.0% vs. 12.5% and 32.9% vs. 20.6%, respectively) (Figure 1).

At level 3 of STAR*D,[1] patients could augment the agent they had switched to at level 2 with either lithium or triiodothyronine, or they could switch to mirtazapine or nortriptyline monotherapy. The differences between remission and intolerance rates at level 3 show that augmentation with triiodothyronine was more likely to lead to remission than to discontinuation (25.7% vs. 10.0%), unlike any of the other options (Figure 2).[9] While lithium augmentation offered a higher remission rate than either monotherapy, the discontinuation rate was higher than the remission rate (remission = 14.5%, discontinuation = 20.6%).

At level 4 of STAR*D,[10] outpatients could switch to either tranylcypromine monotherapy or the combination of venlafaxine and mirtazapine. Combination therapy resulted in remission in 16.0% of subjects, while tranylcypromine treatment had a 14.5% remission rate. The intolerance rate of the monotherapy was twice as high (40%) as that of the combination strategy (20%); no treatment at this level was more likely to lead to remission than to discontinuation. STAR*D researchers concluded that more effective treatment options are needed to help patients achieve and sustain remission from MDD.[9]

AUGMENTATION STRATEGIES WITH ATYPICAL ANTIPSYCHOTICS

The increasingly common use of atypical antipsychotics to augment SSRIs in treating MDD has met with success, but clinicians should be aware of adverse effects.

Olanzapine and Fluoxetine

One small pilot study[8] combined the atypical antipsychotic olanzapine with the SSRI fluoxetine. Patients (N = 28) with MDD without psychotic features who had not responded to at least 2 previous antidepressant trials (1 with an agent other than an SSRI) and who were treated unsuccessfully during a screening period with fluoxetine monotherapy were included. These nonresponders were randomly assigned to 1 of 3 treatments:

fluoxetine plus placebo, olanzapine plus placebo, or the combination of fluoxetine and olanzapine. Combination therapy produced a robust response that was sustained for the full 8 weeks of the trial. The combination therapy demonstrated greater efficacy for outpatients with treatment-resistant MDD than did either agent as a monotherapy.[8] A larger study (N = 500)[11] found that the combination of olanzapine and fluoxetine provided the most rapid antidepressant response versus the other treatments (fluoxetine alone, olanzapine alone, or nortriptyline alone), but at the end of the 8-week trial the efficacy was not statistically significantly different among the groups.

Risperidone and SSRIs

One trial[12] used risperidone as an augmentation treatment for patients who had partially responded to SSRI treatment. Low-dose risperidone was added to the original SSRI treatment (either fluoxetine or paroxetine). The size of the trial was small, but all 8 outpatients remitted within 1 week of the risperidone augmentation. Sleep disturbance and sexual dysfunction were improved as well.

Side Effects of Antipsychotics

Atypical antipsychotics can disturb glucose regulation and lead to such serious metabolic disorders as reversible hyperglycemia and diabetic ketoacidosis.[13] The studies[8,11] of combined olanzapine and fluoxetine found that increased appetite and weight gain were both statistically significantly more frequent in either group that received olanzapine than in the fluoxetine group.

On the other hand, atypical antipsychotics carry a lower risk of the serious side effect tardive dyskinesia than typical antipsychotics. According to a review[14] of 11 long-term studies in adult populations (N = 1419), about 5% of adults treated with typical antipsychotics per year will develop tardive dyskinesia, but the risk of tardive dyskinesia with second-generation, or atypical, antipsychotics is less than 1% in adults (aged 53 years or less). Despite the lower risk, a clinically significant case of tardive dyskinesia in a patient whose condition does not require antipsychotic medication would be a catastrophic outcome. More benign alternatives than antipsychotics should be considered first for augmentation in patients with resistant MDD.

AUGMENTATION STRATEGIES WITH NONPHARMACOLOGIC AND NON-ANTIPSYCHOTIC

Clinicians have employed alternative augmentation strategies using pharmacologic and nonpharmacologic methods. These methods include cognitive therapy, dopaminergic agents, psychostimulants, anticonvulsants, and dietary supplements.

Table 1. Emerging Augmentation Therapies for Depression

Dopaminergic Agents
Pergolide
Amantadine
Pramipexole
Stimulants
Methylphenidate
Amphetamines
Modafinil
Anticonvulsant
Lamotrigine
Other
Opioids
Omega-3 fatty acids
Dehydroepiandrosterone
Folate

Cognitive Therapy

Keller et al.[15] showed that a nonpharmacologic treatment could be an effective augmentation to an antidepressant. The cognitive-behavioral analysis system of psychotherapy (CBASP) is a version of CBT specifically designed for treatment-resistant depression. Subjects were treated with nefazodone, CBASP, or both. Among patients who completed the study (N = 519), those treated with nefazodone augmented with CBASP had a 42% remission rate, whereas the rates of remission were 24% with CBASP alone and 22% with nefazodone alone ($p < .001$). The 3 groups had similar rates of discontinuation.

In STAR*D,[9] cognitive therapy was used as an augmentation strategy at level 2, and a remission rate of 29.4% resulted, with a 10.6% discontinuation rate. In fact, when cognitive therapy was used as a monotherapy switch in level 2, a 41.9% remission rate was found, which was higher than the remission rates of all other treatment strategies used in STAR*D. However, the discontinuation rate was 16.1%. Rush[6] noted that few subjects chose treatment options that involved cognitive therapy and suggested that inconvenience and cost were factors.

Emerging Treatments

Emerging pharmacologic and nonpharmacologic augmentations are proving beneficial for treatment-resistant MDD (Table 1). Of course, the safety of any drug combinations should be weighed against the benefit. Dopaminergic agents, such as pergolide[16] and amantadine,[17] have shown some beneficial effects, and the data from pramipexole[18] also support the efficacy of dopaminergic agents. Stimulants, such as methylphenidate and amphetamines, are frequently prescribed, although data[19–21] concerning the efficacy for stimulants combined with antidepressants for treating depression are limited. Patient response to modafinil as an antidepressant augmentation has been positive in terms of relieving fatigue and excessive sleepiness associated with residual symptoms of depression, which improved mood.[22–24] The anticonvulsant lamotrigine has prolonged remission in women with

treatment-resistant depression,[25] and a chart review[26] concluded that lamotrigine was both tolerable and efficacious as an augmentation strategy for treatment-resistant depression. Opiates, used to treat MDD in past decades, have returned with the arrival of opioids that carry lower risks of dependence and abuse than traditional opiates.[27] Evidence[28] suggests omega-3 fatty acids may be a well-tolerated and effective augmentation strategy for MDD in patients with a deficiency of omega-3 fatty acids, due to either inadequate dietary intake or genetic disposition. Dehydroepiandrosterone, or DHEA, may have promise as an augmentation agent.[29] Finally, folate is a relatively benign augmentation treatment that has been shown to improve the antidepressant effect of fluoxetine,[19,30] as well as the effects of other antidepressant medications.[31,32]

CONCLUSION

Helping patients achieve and sustain remission from MDD is more difficult than obtaining a response, but remission is the goal of treatment. Clinicians can employ systematic, sequenced treatment steps that will ultimately lead to remission for patients who stay in treatment. A number of combination or augmentation strategies appear to be effective when monotherapy is not entirely effective, although safety should always be considered. Using benign combinations earlier in treatment rather than using one monotherapy after another may be the best strategy to enable patients to achieve remission.

Drug names: amantadine (Symmetrel and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), methylphenidate (Ritalin, Daytrana, and others), mirtazapine (Remeron and others), modafinil (Provigil), nortriptyline (Pamelor, Aventyl, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), pramipexole (Mirapex), risperidone (Risperdal), 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, amantadine, bupropion, buspirone, lamotrigine, lithium, methylphenidate, modafinil, nortriptyline, pramipexole, risperidone, tranylcypromine, dehydroepiandrosterone, folate, and pergolide are not approved by the U.S. Food and Drug Administration for the treatment of treatment-resistant depression.

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