Update on Partial Response in Depression

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Full symptomatic remission is the optimal outcome for patients with major depression. Unfortunately, antidepressant efficacy is limited to partial response for a significant minority of patients. Incomplete remission of depressive symptoms is associated with increased risk of relapse, decreased functioning in work and social settings, and increased risk of eventual suicide. Factors that increase the likelihood of incomplete remission include chronicity, severe symptomatology, and comorbid illnesses. Strategies to manage incomplete remission include "watchful waiting" (ie, continuing the original medication for another 4 to 8 weeks to see if complete remission will develop), switching antidepressants, or adding a second, adjunctive treatment (ie, either beginning psychotherapy or a second medication to augment the original antidepressant). Augmentation strategies may well prove to be the preferred strategy for improving response if tolerability is not an issue. Although studies on predictive factors have not yielded definitive results, clinicians in practice often select adjunctive agents that target patients' persistent symptoms.

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Most, if not all, contemporary guidelines for the treatment of depression have adopted remission as the optimal outcome of an acute episode of depression.[1,2] This decision is well-justified because patients with incomplete remission have increased risk of relapse,[3] increased chronicity of depressive episodes with shorter durations between episodes,[3] and impairments in workplace performance and social function when compared with those who are fully remitted.[4] They also have increased all-cause mortality[5] and risk of suicide.[6] Essentially, the further a patient is from remission after treatment of an acute episode, the more likely that he or she will have a poorer longer-term outcome.

CLINICAL REMISSION

Clinical remission of a depressive episode represents a nearly complete relief of the signs and symptoms of the presenting episode.[7] Ideally, the patient will have no more symptoms of depression than someone who has never been depressed and, in the most practical terms, the individual will feel back to his or her usual self. A corollary of clinical remission is that, in addition to having virtually complete symptom relief, patients should also be able to return to normal levels of social or functional capacity.

Current definitions of remission are at the clinical level; they are not pathophysiologic. Looking toward the future of psychiatric therapeutics, an optimal treatment might also be hoped for to normalize the pathophysiology of an illness. However, that level of understanding of depression has not yet been reached.

Rates of remission, response without remission, and nonresponse vary from study to study. More than 2,700 patients were treated with citalopram for an average of 10 weeks as part of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study.[8] Only about one-third of the patients achieved remission at the end of the acute phase of treatment. Another approximately 14% improved but still had too many symptoms to be considered remitted; this group could be said to be partially remitted or to be responders without remission. The remainder—approximately one-half of those who received an adequate course of therapy—had either minimal or no improvement as a result of the initial treatment trial and might be classified as resistant to an adequate therapeutic trial of citalopram.

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RISK FACTORS FOR INCOMPLETE REMISSION

In psychometric terms, individuals who are not clinically depressed rarely have more than a few minor symptoms of depression. For example, almost all healthy, normal individuals score below 7 points on the Hamilton Depression Rating Scale (HDRS).[9] For this reason, a score of 7 or less on the HDRS has been a widely used definition of remission. Symptom scores for individuals presenting for treatment of a major depressive episode typically range between 15 and 25 on the HDRS, with an average score of about 20. Thus, a large amount of improvement—about three-quarters reduction of the total symptom burden—is necessary for the average person with major depression to move into a range that is indistinguishable from the never-depressed person. As an even more dramatic amount of change is necessary for individuals with high symptom severity scores to reach remission, high severity is a risk factor for incomplete remission, at least within the first 6 to 8 weeks of therapy.

Other factors that predispose an individual to incomplete remission of depressive symptoms include chronicity and comorbidity.[10] Comorbidity was a strong predictor of nonremission in the STAR*D study,[11] and depressed patients with high levels of anxiety were significantly ($P < .05$) less likely to remit from depressive episodes than were the patients with low anxiety. In fact, high anxiety was a general prognostic indicator of poorer outcomes regardless of which treatment was implemented in STAR*D (Figure 1).[11] In essence, the more complex the presentation, the greater the likelihood that a longer period of treatment will be necessary in order to achieve full remission, and the greater the likelihood at any given time that the patient will still have too high a level of residual symptoms in order to be declared fully remitted, even if he or she has responded to treatment.

CONSEQUENCES OF INCOMPLETE REMISSION

Relapse rates following the citalopram phase of STAR*D showed that, compared with patients in remission, patients who ended the acute phase as responders without remission were about twice as likely to suffer a relapse during the first year after successful treatment, despite ongoing therapy.[10] The prognostic significance of obtaining complete remission can extend beyond the first year of follow-up: outcomes from a long-term, naturalistic study[12] of the course of MDD found that partial response was associated with a persistently increased risk of relapse or recurrence across a decade.

Incomplete remission cannot only impact the likelihood of symptom relapse but may also diminish role functioning. A study[4] of social and work functioning compared outcomes of a large group of patients with chronic forms of major depressive disorder; participants in this study were treated with either imipramine or sertraline. At the end of the 12-week acute phase treatment protocol, incompletely remitted patients were more similar to the nonresponders in functional status than they were to community norms, whereas the fully remitted patients had scores that were comparable to those of the normative population (Figure 2).[4]

GENERAL TREATMENT GUIDELINES

When treating patients with depression, a general rule is to carefully keep track of the patient's symptoms. Patients often are so glad to be feeling better that the global statement, "I'm definitely better" during a clinical visit tends to overpower the importance of recognizing persistent, minor, or residual symptoms. As a result, the clinician who does not systematically survey symptom status may not know that the patient is not yet remitted. Using a standardized symptom assessment measure to track patients' levels of symptom burden is an important first step to optimizing each patient's chances to achieve remission.

Once the depressive symptoms are being tracked, each treatment trial must be given an adequate chance to work for the patient. If the initial treatment is well-tolerated and the patient has made significant improvement but still has residual symptoms, the next step may be as simple as dose optimization or "watchful waiting" (continuing the original medication for an additional 4 to 8 weeks to see if complete remission will develop). Depending on the patient, a slightly higher dose, or, on occasion, a slightly lower dose of the medication, or perhaps only an additional 2 to 4 weeks of continuing that treatment may be all that is needed to reach remission.

If dose and duration optimization do not lead to remission, the diagnosis should be verified. Identifying comorbidities, assessing how comorbid disorders interact with persistent depression, and, if need be, specifically treating
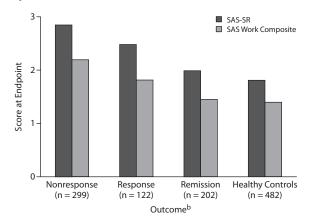
Figure 1. STAR*D Level 2 Remission Rates: Anxious vs Nonanxious Major Depressive Disorder[a]

[a]Data from Fava et al.[11]
*$P < .05$.
Abbreviations: HDRS = Hamilton Depression Rating Scale, STAR*D = Sequenced Treatment Alternatives to Relieve Depression.

Figure 2. Impairment in Work and Relationships Normalizes Only With Remission[a]

[a]Data from Miller et al.[4]
[b]Significant differences ($P \leq .05$) existed in SAS work composite scores between response vs nonresponse, remission vs nonresponse, and remission vs response.
Abbreviation: SAS–SR = Social Adjustment Scale–Self Report.

the comorbid condition(s) is the next step. For example, if an individual experiencing depression also has a substance use disorder, making sure that he or she abstains from substance use may be the necessary intervention in order to ensure a full response to the antidepressant treatment. Likewise, recognizing and correcting a subtle thyroid dysfunction can be all the intervention that is necessary to see an individual with depression move from an incomplete response to a full remission.
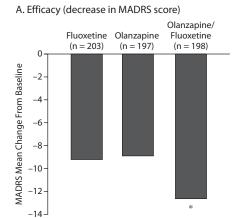
Augmentation Versus Switching

Assuming that a depressed individual's symptoms have been properly tracked and measured, the dosage and duration of the initial antidepressant have been optimized, and all comorbidities have been identified and treated to the extent that is possible, but the patient is still stuck in incomplete treatment response, then a couple of next-step strategies can be considered. One option is to simply switch to a second antidepressant medication. Although it is possible that another antidepressant would produce a complete remission, many clinicians reserve switching antidepressants for patients who have either obtained little symptom relief from the first medication or had trouble tolerating the side effects of an adequate dose of the first antidepressant. Thus, for a patient who has obtained definite symptom relief with the first antidepressant agent and has good tolerability, augmentation strategies probably rank higher than switching to another antidepressant.
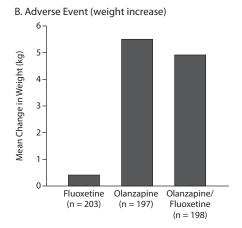
An augmentation approach will build on the partial success of the first treatment, and, by continuing that initial treatment, patients do not have to go through medication withdrawal or cross-titration. The disruptive effects of medication withdrawal and cross-titration should not be minimized. Even if a patient has only improved by as little as 30%, it is remarkable how much the patient may miss that improvement if it is lost during the process of a cross-titration schedule. Thus, one potential advantage of an adjunctive strategy is that, by avoiding discontinuation and cross-titration, a therapeutic benefit may be produced more quickly than would be achieved with switching.

A second potential benefit of adjunctive strategy is that the second medication may be selected to match a patient's specific persistent residual symptoms. For example, an adjunctive medication with sedative/hypnotic properties could be added for a patient with persistent insomnia, or an adjunct medication with alertness/wakefulness-enhancing properties could be added for a patient with persistent fatigue or hypersomnolence.

Figure 3. Benefit-to-Risk Comparison for the Olanzapine-Fluoxetine Combination in Depression

A. Efficacy (decrease in MADRS score)

B. Adverse Event (weight increase)

Data from Thase et al.[19]
*$P < .001$ vs fluoxetine and olanzapine.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

PHARMACOTHERAPEUTIC AUGMENTATION OPTIONS

A meta-analysis[13] of randomized, placebo-controlled lithium augmentation studies confirmed that lithium is an effective adjunctive treatment. Results varied considerably across studies, however, and most of these studies added lithium to tricyclic antidepressant (TCA) therapy. Lithium is one the best studied adjunctive treatments but is not widely used today for the treatment of depression, perhaps because there are easier-to-implement strategies that do not entail a recommendation for blood level monitoring. Lithium should not be overlooked, however, and may be particularly valuable for patients with depressive syndromes that might be viewed as falling within the "softer" end of the bipolar spectrum.

A meta-analysis[14] of studies of the use of thyroid hormone as an adjunct to TCA therapy also found evidence of efficacy. Thyroid augmentation is not as well studied as lithium augmentation and, as with lithium, most of the evidence comes from studies with TCAs. Larger studies are needed, with newer antidepressants. Whether thyroid hormone augmentation has specific antidepressant efficacy for patients taking selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) remains to be seen, but the results of the STAR*D study[15] showed fairly strong, although nonsignificant, trends favoring thyroid hormone augmentation over lithium augmentation in contemporary practice. This result may be because thyroid hormone augmentation is easier to implement. With respect to targeting a particular patient group, thyroid augmentation should be thought of whenever a patient who has not responded to antidepressants is found to have low thyroid function, including those who have elevated thyroid-stimulating hormone levels.

Studies of modafinil have shown modest therapeutic benefit when added to antidepressant therapy, and to date the efficacy appears to be largely limited to the reduction of fatigue and daytime sleepiness.[16] The net result is a small shift in the likelihood that patients receiving modafinil will move from being minimally improved or having responded without remission into remission.

With respect to conventional psychostimulants, the efficacy of methylphenidate augmentation has not yet been established. One small study[17] suggested a beneficial trend, although none of the drug versus placebo differences reached statistical significance. Methylphenidate and other psychostimulants have the potential for abuse and misuse; therefore, these agents should be prescribed very carefully in off-label use as antidepressant therapy.

Atypical Antipsychotic Augmentation

Atypical antipsychotics are increasingly being used as augmenting strategies in the treatment of depression. Many clinicians are convinced that atypical antipsychotics have therapeutic benefit and that their efficacy is not limited to treating subtle psychosis, unrecognized bipolarity, sleep improvement, or anxiety reduction. Aripiprazole, in combination with many antidepressants, and olanzapine, in combination with fluoxetine, have received US Food and Drug Administration (FDA) approval for use in treating depression. A third atypical antipsychotic, quetiapine, has sufficient evidence and is currently under FDA review for this same indication. Perhaps the most important question about these medications is not whether they work but how long they should be maintained. Another important

Figure 4. Benefit-to-Risk Comparison for Aripiprazole in Depression

Data from Berman et al.[20]
*P < .001.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

question is whether these are the most cost-effective strategies to use, particularly for partial responders.

The efficacy of the olanzapine-fluoxetine combination was striking in the first small proof-of-concept study,[18] but even a striking effectiveness profile must be balanced against the fairly high risk of weight gain with this therapy (Figure 3).[19] Weight gain and the associated risk of metabolic side effects, such as dyslipidemia and glucose intolerance, need to be considered when using this antidepressant treatment strategy, and careful monitoring should be provided subsequently to minimize the potential for these adverse outcomes.

Aripiprazole was the first atypical antipsychotic approved for adjunctive use in patients not fully responding to antidepressants and is efficacious compared with placebo (Figure 4).[20] Aripiprazole has a lower risk of metabolic side effects—at least during short-term treatment—than does the olanzapine-fluoxetine combination, but aripiprazole does have one particularly troublesome set of adverse effects, namely, akathisia or less severe restlessness.[20]

Augmentation Options for Comorbid Anxiety

Almost half of patients with major depression have comorbid anxiety,[12] and the presence of anxious symptoms in depression reduces the likelihood that patients will respond fully to antidepressant therapy. In the STAR*D study,[11] augmentation with the antianxiety agent buspirone was compared to augmentation with bupropion, a medication not known to be particularly useful for patients with a lot of anxiety. Curiously, and perhaps counterintuitively, trends—albeit nonsignificant ones—favored bupropion over buspirone among the patients with anxious depression (see Figure 1).

SUMMARY

Incomplete remission is an unfortunate and common outcome during the acute treatment of major depressive disorder and has become broadly recognized as a suboptimal outcome. Patients with complex presentations are at greater risk of incomplete remission. An important change of practice habits in the clinical setting would be to monitor the ongoing level of the symptomatic status of patients to best determine whether their response can be characterized as a full remission or a response without remission. In 2009, the art of practice for patients with depression who are tolerating their initial antidepressant well but have incomplete remission is to augment with psychotherapy and/or pharmacotherapy and select any pharmacotherapeutic adjunct on an individual basis to get the best balance of clinical benefit and minimum risk. A range of adjunctive strategies are now used to treat residual symptoms.

Drug names: aripiprazole (Abilify), bupropion (Aplenzin, Wellbutrin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lithium (Lithobid, Eskalith, and others), methylphenidate (Concerta, Ritalin, and others), modafinil (Provigil), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), quetiapine (Seroquel), sertraline (Zoloft and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, buspirone, lithium, methylphenidate, modafinil, and quetiapine are not approved by the US Food and Drug Administration for the treatment of depression.

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