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Treatment Resistant Depression—Going Beyond Traditional Antidepressant Therapy

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In the treatment of depression, symptom remission is the desired goal given its implications for better daily functioning and better longer-term prognosis.[1] Although an increasing number of antidepressant agents are available for treating depression, about half of patients do not respond and as many as 2/3 of patients do not achieve remission after the first-line treatment trial. Patients who do not respond to adequate trials of antidepressant monotherapy may be considered treatment resistant. This article will explore treatment alternatives in treatment-refractory depression.

To determine whether a patient truly has treatment-resistant depression, the clinician must consider several variables including:

- Correct diagnosis
- Comorbid medical conditions
- Comorbid psychiatric conditions
- Psychosocial stressors
- Appropriate drug therapy
- Appropriate dose
- Appropriate duration
- Medication adherence
- Psychotherapeutic and social interventions tried

During initial treatment, clinicians should allow for an adequate dose and duration because some patients experience delayed response and remission. Trivedi and colleagues discovered that many patients required treatment for 8 weeks or longer before responding or remitting.[2] Factors that increase the likelihood of delayed remission include older age, illness chronicity, co-occurring psychiatric or medical disorders, and severe symptomatology.[3]

Information from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found that after an adequate trial of a selective serotonin reuptake inhibitor (Level 1), 70% of patients did not experience a complete remission of symptoms. Higher rates of remission were associated with patients who were: female, Caucasian, higher education level, marriage or cohabitation, employed, insured, shorter current episode, and fewer concurrent general medical or psychiatric disorders. Of the 30% of patients who did experience remission, 33.5% had a relapse of depressive symptoms within the 12-month follow-up period.

During the second level (Level 2) of the STAR*D trial, patients with an unsatisfactory response to the SSRI were given the opportunity to augment therapy or switch to a new antidepressant. Only 25% of patients who switched therapy (to either another SSRI, bupropion SR, or venlafaxine XR) achieved remission. There were no significant differences in remission rates, tolerability, or side-effect burden among the antidepressants. Also of importance, this study found that intolerance to or lack of efficacy with the first SSRI did not portend intolerance or lack of efficacy with the second SSRI. In the augmentation phase, approximately 30% of patients treated with either bupropion-SR or buspirone in addition to their initial SSRI achieved remission. The study authors concluded that augmentation with bupropion-SR was preferred over buspirone because of greater reduction in measured depression symptoms from baseline and fewer overall side effects. Of those who achieved remission in this second level of treatment, 47.4% ended up having a relapse.

During Level 3, patients who did not achieve remission in level 2 could agree to augment their current antidepressant (with lithium or thyroid supplementation) or switch to a different antidepressant (mirtazapine or nortriptyline). Remission rates did not differ significantly between mirtazapine and nortriptyline (12.3% and 19.8% respectively). The study authors suggest there may be only limited utility to three sequential trials of antidepressant monotherapy. Similarly, the rates of remission for both lithium and thyroid supplementation appeared to be similar (15.9% and 24.7% respectively). The study authors did slightly favor thyroid supplementation, however, primarily because of slight advantages in effectiveness and tolerability, and the lack of need for blood level monitoring. Overall, a total of 13.7% of level 3 patients achieved remission. Total relapse rate for all successful level 3 treatments was 42.9%.

Level 4 patients could either participate in monoamine oxidase inhibitor therapy (MAOI) (tranylcypromine) or combination therapy with venlafaxine XR and mirtazapine. Remission rates for both groups were low with only 6.9% of the tranylcypromine group and 13.7% of the combination treatment group achieving remission (overall remission rate between the two groups equaled 13%). Due to a more favorable side effect profile and the lack of dietary interactions, the authors favored the combination of venlafaxine XR and mirtazapine over the MAOI. Low remission rates for both groups suggested that switching antidepressant medication after failure to achieve remission with three previous medication trials provides only limited chance for success. The findings from the STAR*D study are summarized in Tables 1 and 2.

Table 1. STAR*D Treatment Level Progression

Level 1	SSRI Monotherapy
Level 2 *Switch Antidepressants* **or** *Augment Level 1*	Switch to: SSRI, bupropion SR, or venlafaxine XR Augment with: bupropion SR
Level 3 *Switch Antidepressants* **or** *Augment Level 2*	Switch to: mirtazapine or nortriptyline Augment with: lithium or thyroid
Level 4 *Switch Antidepressant*	Switch to: monoamine oxidase inhibitor –or- combination of venlafaxine XR and mirtazapine

Table 2. STAR*D remission, relapse & intolerance rates

Level	Remission Rate	Relapse Rate	Intolerance Experienced
Level 1 (n=3671)	36.8%	33.5%	16.3%
Level 2 (n=1439)	30.6%	47.4%	19.5%
Level 3 (n=390)	13.7%	42.9%	25.6%
Level 4 (n=123)	13.0%	50.0%	30.1%

Beyond the findings from the STAR*D trial, other alternatives for the treatment of refractory depression exist. The algorithm for the treatment of major depressive disorder developed by the Texas Medication Algorithm Project recommend the following treatments for patients who do not respond to monoamine oxidase inhibitors or combination antidepressant therapy (step 4 of the algorithm): SSRI or SNRI augmentation with an atypical antipsychotic, SSRI augmentation with lamotrigine or electroconvulsive therapy (ECT).[4] Evidence regarding the effectiveness of psychotherapy for treatment-resistant depression is limited. A recent high-quality trial found that patients who did not respond to citalopram and who received cognitive behavior therapy (with or without continued citalopram) had similar response and remission rates to those who received other medication regimens.[5]

The prevalence of antidepressant augmentation with atypical antipsychotics is increasing. While some studies have demonstrated an effect superior to placebo, others have failed to do so. In a meta-analysis reviewing placebo-controlled trials of atypical antipsychotic augmentation in major depressive disorder, none of the atypicals demonstrated superiority over the others (mean odds ratios did not differ among the atypical agents). Atypical antipsychotics were associated with a significantly increased risk of discontinuation due to adverse events (odds ratio=3.91).[6] Prior to the initiation of an atypical antipsychotic, clinicians are advised to consider the following:

- Clearly defined goals of antipsychotic treatment should be established at the start of therapy and reassessed throughout its course
- Augmentation with atypical antipsychotics is not recommended as first-line treatment
- The side effect burden associated with the atypical antipsychotic class (significant movement disorders, metabolic abnormalities, and other potentially long-term adverse effects even at lower doses) often outweigh their benefit
- Routine monitoring for metabolic abnormalities (glucose, lipids, weight) is recommended
- Atypical antipsychotics are a more expensive alternative to other augmentation strategies (Table 3)

Table 3. Comparative Cost of Antidepressant Augmentation

Augmentation Agent	Cost/30 days*
lithium	$17
Synthroid (levothyroxine)	$7
lamotrigine	$215
Abilify (aripiprazole)	$550
Symbyax (olanzapine/fluoxetine)	$375
risperidone	$90
Zyprexa (olanzapine)	$590

*Average retail cost for 30-days to OHP; August 2009. Excludes rebate

Successful treatment of refractory depression often requires a series of medication trials. The findings from the STAR*D trial suggests the following key clinical insights:

- Longer courses of treatment (12 to 14 weeks) may be necessary for patients who initially fail to respond to the prescribed therapy
- Remission, rather than response, should be the goal of antidepressant therapy
- When more treatment steps are required, lower acute remission rates (especially in the third and fourth treatment steps) and higher relapse rates during the follow-up phase are to be expected

Failure of adequate antidepressant trials (including therapeutic doses for a minimum of 6 weeks) often leads to the need for antidepressant augmentation. Augmentation with lithium or thyroid supplementation is generally considered earlier in the treatment course than atypical antipsychotics.

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