The Role of Atypical Antipsychotics in Depression in Primary Care

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Depression is an increasingly prevalent presentation in primary care practice. The use of psychiatric rating scales in primary care can help monitor the severity and course of illness, including the emergence of treatment effects. Unfortunately, treatment effects frequently fall short of optimal patient response. Treatment resistance, in particular, poses an obstacle to the goal of symptom remission and a return to premorbid levels of functioning. Once treatment resistance is established, the clinician must consider increasing the dose of antidepressant, switching to another drug, or augmenting with a second drug as appropriate. There are many augmentation options, some of them limited by cumulative side effects or the potential for drug-drug interactions. Recently, some atypical antipsychotics have proved efficacious, with few side effects, as augmentation therapy for treatment-resistant major depression with and without psychotic features. The serotonergic and noradrenergic properties of these drugs may ameliorate common side effects of selective serotonin reuptake inhibitors as well as the symptoms of anxiety disorders so often comorbid with major depression.

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The last decades have seen us increasingly engaged with treating serious mental illness, mainly depression, in our primary care practices. The psychological and physical symptoms of depression, which affect between 10% and 25% of women and 5% to 12% of men over the course of a lifetime,[1] frequently motivate visits to a primary care physician. Still, outcome often falls short of optimal patient response. Treatment resistance, in particular, poses an obstacle to the goal of depressive symptom remission and a return to premorbid levels of functioning.

Between 29% and 46% of depressed patients achieve no or only partial response to selective serotonin reuptake inhibitor (SSRI) monotherapy.[2] Annually, about 100,000 patients in the United States undergo electroconvulsive therapy due to their lack of response to other treatment approaches; electroconvulsive therapy is not only physically stressful but also expensive, costing approximately $2400 to $6400 per treatment course.[3] Approximately 16% of patients hospitalized with severe depression ultimately commit suicide.[4] Forty-five percent of those patients have seen their primary care physician within the month prior to death.[5] There is ample impetus for primary care physicians to utilize available tools and techniques in treating depressed patients to remission.

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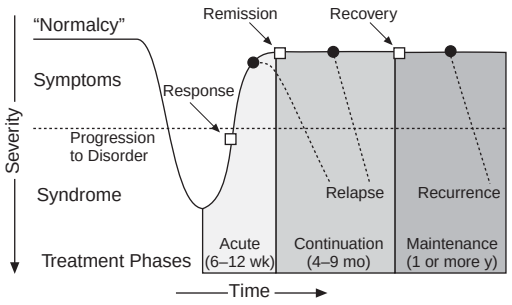
ASSESSING DEPRESSION USING PSYCHIATRIC RATING SCALES

The proper use of psychiatric symptom rating scales can help the clinician measure symptoms and formulate treatment decisions accordingly. Clinician-rated measures are likely to be more accurate than patient-rated measures, for the reason that the cognitive symptoms of depression (e.g., negative outlook) are often the slowest to respond and can therefore skew answers relating to other symptom groups.[6] The Hamilton Rating Scale for Depression (HAM-D), available in 2 versions of either 17 or 21 clinician-rated items, is designed to measure the severity of illness among patients already diagnosed with depression. The 17-item HAM-D is perhaps the most commonly used instrument for clinical assessment of depressive symptoms (Table 1). The HAM-D focuses on the biological neurovegetative symptom complex in depression, including assessments of insight, anxiety, guilt, mood, ability to work, and some physical symptoms. The Montgomery-Åsberg Depression Rating Scale (MADRS) is a 10-item clinician-rated scale that focuses on severity of psychological symptoms and is designed to be sensitive to change over time. Thus, the MADRS is particularly useful in identifying treatment effects. The Clinical Global Impressions-Severity of Illness (CGI-S) and the Clinical Global Impressions-Improvement (CGI-I) scales are clinician-assessed ratings with scores

Table 1. Common Psychiatric Assessment Scales

Scale	Description
Hamilton Rating Scale for Depression	17-item version is most common Clinician-rated scale emphasizes biological neurovegetative symptoms
Montgomery-Åsberg Depression Rating Scale	10-item clinician-rated scale emphasizes psychological symptoms Developed to measure change over time
Clinical Global Impressions-Severity of Illness	Clinician-assessed severity of illness ranges from 1 = normal to 7 = most severely ill
Clinical Global Impressions-Improvement	Clinician-assessed improvement ranges from 1 = very much improved to 7 = much worse

Figure 1. Phases of Treatment for Depression[a]



[a]Adapted from reference 11.

that range from 1 (normal or very much improved) to 7 (most severely ill or very much worse) and are applicable to all categories of psychiatric disorder, including depression. In primary care settings, the depression module of the Patient Health Questionnaire is recognized as a useful brief instrument; based on the DSM-IV criteria for major depression, it can both help establish the diagnosis and measure severity and treatment response over time.[7]

The routine use of clinical rating scales is justified in both psychiatric and primary care settings. They not only provide a firm basis for informed treatment decisions but can also help identify response and remission. Such assessments may have the additional, unintended benefit of reassuring patients that their most problematic symptoms are receiving attention.[6]

Generally speaking, treatment response is defined as at least a 50% decrease from baseline in rating scale score (often the HAM-D), whereas remission is defined as minimal or no symptoms as reflected by a HAM-D score of 7 or less.[8] The patient in remission clearly no longer meets diagnostic criteria of the disorder. An additional aspect of remission, though one that is not universally applied to the definition, is the patient's full return to normal functioning. Functional improvement may lag remission of depressive symptoms significantly.[9,10] Psychosocial treatment must be added to pharmacologic treatment if the depressed patient is to achieve maximal improvement. Pharmacotherapy can evoke remission of symptoms, but engagement in a therapeutic relationship is crucial to enabling patients to mobilize their lives again and to regain normal function following an episode of major depression.

Depression requires long-term treatment (Figure 1).[11] Strides in treatment have allowed us to lower the level of symptoms that we will accept as normal, and more patients are treated to an adequate endpoint. But unfortunately, even those patients with depression who have achieved a strong response tend to discontinue pharmacotherapy prematurely.[12,13] Premature discontinuation of medication reflects an antibiotic model of disease, in which we treat the illness for a short, defined period of time, achieve a good response, and stop the medication. High rates of relapse reveal this treatment model to be inappropriate for patients with depression. Fifty percent of responding patients who discontinue medication after 2 months relapse within the next 9 months to 1 year.[14] In contrast, if patients continue taking the full doses of medication required to attain remission of depression, the rate of relapse and recurrence drops to 15% or less.[14] As with physical diseases and disorders, prolonged and thorough remission improves prognosis.[6] There is a dramatic, data-driven rationale for patients with depression to maintain long-term therapy.[15,16]

INITIAL MANAGEMENT OF APPARENT TREATMENT-RESISTANT DEPRESSION

A major challenge to treatment success is the early appearance of resistance to treatment. The literature on depression argues for a strict and standardized definition of treatment resistance. Consensus defines treatment resistance as failure to respond to 2 adequate trials of different antidepressants. Many experts agree that an adequate antidepressant trial should last at least 4 to 6 weeks. Older age at onset,[17] a history of chronicity,[18] current stressful life events,[19] and poor social support may all be associated with treatment resistance, but no clinical factor is a completely reliable predictor of resistance.[6] When a patient with depression seems to meet the definition of treatment resistance, the clinician must first reassess the diagnosis. Is it possible that a correct diagnosis of physical illness or bipolar disorder, for example, was initially masked by depressive symptoms? The clinician's second step is to search for comorbidities, such as anxiety disorders or substance abuse, that may be impeding response to treatment. Assessing treatment resistance should take into account that patients with multiple psychiatric comorbidities often take longer to respond to treatment. When comorbid disor-

Table 2. Treatment Options for the Confirmed Treatment-Resistant Patient

Switching	Augmentation
Most appropriate for patients with:	Little evidence to guide selection
No response	Symptom characteristics may help guide choice to augmentation agent
Minimal response	
Partial response limited by side effects	Most appropriate for patients with partial response with minimal side effects

ders are present, adding their treatments to the therapeutic regimen can remove obstacles to patient improvement and resolve apparent treatment resistance. The clinician must also confirm that the nonresponding patient is adhering to his or her therapeutic regimen. In primary care especially, we tend to overestimate our patients' adherence.

For the patient whose response to pharmacotherapy has reached a plateau, or for the patient in the first 3 weeks of treatment who has yet to respond, the clinician might simply increase the patient's dose of SSRI as tolerated. For some patients with depression, an increased dose of SSRI is sufficient to stimulate treatment response. For this reason, it is recommended to try 1 or 2 weeks at an increased dose of SSRI for the apparently resistant patient who meets the diagnosis of depression and is adhering to his or her prescription. However, it is not advised to keep the nonresponding patient on an increased dose of SSRI for a longer period of time in the hope that response will emerge. If there is no significant response within 2 weeks, the clinician must try another approach.

MANAGEMENT OF CONFIRMED TREATMENT RESISTANCE

When the depressed patient has completed an adequate trial of an antidepressant medication at an adequate dose without showing treatment response, and none of the above steps have evoked response, then the clinician might consider switching to another SSRI or to another class of antidepressant. Switching is particularly appropriate for 3 groups of patients: those who showed no response to the initial treatment, those who showed only an inadequate response to initial treatment even after a dose increase, and those whose response was limited by side effects (Table 2).

Augmentation, or the use of an adjunctive medication to boost the action of the primary medication, is especially useful to the partial responder whose treatment has not been limited by side effects. For example, adding a second antidepressant from another class is a common approach to treatment resistance, but it also increases both the cumulative side effect profile and the risk of drug-drug interactions. There is little hard evidence to guide clinicians in their selection of augmentation agents, but symptom characteristics serve as guideposts.

Augmentation Agents

Lithium has long been used as augmentation therapy and is most appropriate for the patient who might have unrecognized bipolar disorder. Because lithium works in part through serotonergic effect, there is a scant but present risk of serotonin syndrome when lithium is used to augment serotonergic antidepressants.[20] Another option, especially for patients with subclinical hypothyroidism, is the addition of liothyronine or a similar thyroid medication, which may target the noradrenergic effects of antidepressant medication and stimulate a second mechanism of treatment.[21] Another approach to treatment-resistant depression is to augment with low-dose stimulants such as methylphenidate or dextroamphetamine. If stimulants are beneficial, there is rapid response when they are added, and they might be particularly appropriate for the patient with melancholic depression. However, the medical use of stimulants raises concerns regarding the potential for abuse. Antidepressant augmentation can also be achieved with adjunctive dopamine agonists such as buspirone, which is approved for the treatment of generalized anxiety disorder but should not be combined with antidepressant monoamine oxidase inhibitors.[21,22] The choice of augmentation agent demands close attention to the potential for drug-drug interactions.

Antipsychotics have a long history of use in treating patients with psychotic and delusional depression. Now, the atypical antipsychotics, with their milder side effect profiles, are emerging as beneficial augmentation therapy for patients with treatment-resistant depression without psychotic features. Atypical antipsychotics target both the dopamine and the norepinephrine pathways. Treatment effects via the dopamine pathway may improve symptoms relating to pleasure, motivation, psychomotor activity, insomnia, appetite, and agitation. Effects via the norepinephrine pathway may contribute to pharmacologic activation. The effects of atypical antipsychotics mediated by the serotonin-2A and -2C receptors may in fact resolve side effects caused by concurrent treatment with SSRIs, such as agitation, insomnia, and sexual dysfunction. There is limited but meaningful evidence that using atypical antipsychotics as augmentation therapy for depression may help treat symptoms of comorbid anxiety disorders.

A small number of studies (see "Evidence for Using Atypical Antipsychotics in Mood and Anxiety Disorders"[23] in this supplement), most of them open and uncontrolled, indicate that risperidone or olanzapine added to antidepressant therapy increases patient response to treatment. One study[24] of risperidone as augmentation therapy included 4 patients with difficult-to-treat major depressive disorder (3 with psychotic or paranoid features) who were suffering exacerbations of their illness or who were already taking conventional antipsychotics and wanted to switch. The patients received 1 mg/day to 6 mg/day of risperidone in addition to any existing regimen. Three

patients added risperidone on an "as needed" basis, while 1 received risperidone as a maintenance therapy. Three out of 4 achieved a complete response; posttreatment CGI-S scores were 2.0 and 3.0, compared with pretreatment scores of 4.0 and 5.0.

In a placebo-controlled, double-blind trial[25] of olanzapine for nonpsychotic, treatment-resistant depression, patients were assigned to 1 of 3 medication groups: olanzapine plus the SSRI fluoxetine, olanzapine alone, or fluoxetine alone. The patients taking olanzapine plus fluoxetine achieved greater improvement from baseline on the MADRS than patients taking either monotherapy. Scores on the HAM-D and the CGI-I were better among patients taking the combination than among patients taking olanzapine alone (but not fluoxetine alone). In an open-label extension, patients who had taken olanzapine plus fluoxetine in the double-blind phase maintained their response, but patients who had taken either monotherapy in the first phase did not improve significantly during the second phase.

Ostroff and Nelson[26] added risperidone to the ongoing SSRI treatment of 8 patients with nonpsychotic, treatment-resistant depression. Augmentation with risperidone vastly improved outcome, resulting in reduced scores on HAM-D and remission of symptoms in 1 week or less in all patients.

CONCLUSION

Primary care physicians increasingly treat serious mental illnesses, mainly depression. The use of psychiatric rating scales in primary care can help identify the severity and course of illness, including the emergence of treatment effects. There are many pressing reasons to treat depression to remission; however, a patient's optimal response to treatment can be stymied by apparent or true treatment resistance. When a patient fails to respond to an adequate duration of antidepressant administered at an adequate dosage, the clinician must first verify the diagnosis of depression, screen the patient for comorbid illnesses, and confirm the patient's adherence to the treatment regimen. If these steps do not clear the barriers to treatment response, the clinician must consider increasing the dose of SSRI, switching to another medication, or augmenting with a second medication. There are many augmentation options, though some of them are limited by potential drug-drug interactions or by the cumulative side effect profile. Recently, atypical antipsychotics, usually used at the lower end of their dosage ranges, have proved a safe and useful new augmentation strategy for treatment-resistant major depression with and without psychotic features. The serotonergic and noradrenergic properties of these drugs may ameliorate SSRI side effects and the symptoms of anxiety disorders so often comorbid with major depression. Experience to date has been largely limited to risperidone and olanzapine, and more research is clearly needed.

Drug names: buspirone (BuSpar and others), dextroamphetamine (Adderall and others), fluoxetine (Prozac and others), liothyronine (Cytomel), methylphenidate (Ritalin, Concerta, and others), olanzapine (Zyprexa), risperidone (Risperdal).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, buspirone, dextroamphetamine, liothyronine, lithium, methylphenidate, olanzapine, and risperidone are not approved by the U.S. Food and Drug Administration for the treatment of depression used as augmentation therapy.

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