Defining and Improving Response to Treatment in Patients With Bipolar Disorder

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Functional outcomes are more meaningful measures of response to treatment for bipolar disorder than are scores on various psychiatric rating scales (all of which have limitations) used to gauge improvement in symptoms. With the former approach, patients are considered to be in remission if they achieve normal or near-normal levels of functioning in occupational, family, and social settings. Sleep patterns are reliable indicators of whether a patient with bipolar disorder is likely to relapse or sustain remission in the near term. Regularly scheduled nightly sleep periods may help prevent rapid cycling in patients with mania, while perturbations in circadian rhythms may be early markers of impending relapse. Medications used to attain response and/or remission in maintenance therapy include lithium and valproate. The choice of mood stabilizer depends on the patient's symptoms, prior response to a mood stabilizer, and tolerance of the drug. For patients requiring additional therapy, combination regimens with mood stabilizers and atypical antipsychotics appear effective. Psychoeducation for patients and families and interpersonal psychotherapy also can help prolong remission.

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Defining response to therapy for bipolar disorder can be a difficult and intricate process. Response to therapy for psychiatric disorders cannot be measured objectively with plasma levels or bacterial cultures, as is the case with treatments for somatic illnesses. Instead, clinical definitions of remission and numeric rating scales have been developed to evaluate a patient's course during treatment. For example, the 2002 American Psychiatric Association (APA) Practice Guideline for treating patients with bipolar disorder defines remission as "a complete return to baseline level of functioning and a virtual lack of symptoms."[1(p6)] The Young Mania Rating Scale (YMRS) classifies remission as a score of 12 or less. On the YMRS, a score of 13 to 19 indicates minimal severity mania, 20 to 25 is mild, 26 to 37 is moderate, and 38 or higher is severe. Patients are considered responders to therapy if their YMRS score decreases by more than 50% from its pretreatment level. With the Hamilton Rating Scale for Depression (HAM-D), a patient is classified as "normal" if he or she has a score of 7 or less; in comparison, 23 is the score for very severe depression, and 8 to 13 is the range for mild depression.

Other scales attempt to measure a patient's overall psychosocial functioning by assessing psychiatric symptoms and social and occupational functioning during a specified period. The 100-point Global Assessment Scale (GAS) provides a summary score of a patient's ability to function, with ratings of 80 or higher indicative of remission. Ratings from 71 to 79 indicate some degree of psychiatric disability, and most people receiving psychiatric treatment have ratings of 70 or less. Another overall evaluation scale is the Clinical Global Impressions scale (CGI), which is used extensively in clinical trials of drugs for psychiatric disorders. The CGI can be used to evaluate the overall effectiveness of a medication by assessing its therapeutic efficacy and the impact of its adverse events on a patient's functioning.[2]

Both the rating scales administered by clinicians and the self-rating scales completed by patients have benefits and limitations. The scales provide valid data about patient status, reliably reflecting symptom change. Their assessments are reproducible: clinicians in geographically diverse regions who interview different patients usually produce the same measures of degree of improvement. With self-rating scales, clinical studies have concluded that patients' self-assessments are as accurate as physician-administered rating scales during and at the conclusion of treatment, but not at the beginning of therapy.[2]

The accuracy of clinician-administered scales, however, depends on the rater's knowledge and skill, and the results can vary with a patient's mood and willingness to

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Table 1. Benefits and Limitations of Psychiatric, Clinician, and Self-Rating Scales

Benefits
Psychiatric rating scales
Reliably reflect symptom change, are reproducible
Clinician and self-rating scales
Are reliable, reproducible
Limitations
All scales
Do not adequately address remission or functioning
Self-rating scales
Are vulnerable to limitations in insight

assess his or her condition honestly. In addition, self-rating scales do not adequately address how well people function at the end of studies. The presence or absence of symptoms may not reflect functionality, because some patients function quite well despite experiencing severe symptoms, while others exhibit few overt symptoms but are nearly dysfunctional. Therefore, a direct correlation does not always exist between the outcome measures of assessment scales and patients' functionality. Benefits and limitations of these scales are presented in Table 1.

Considering the serious morbidity of bipolar disorder, an assessment of remission should extend beyond symptom reduction to focus on improvement in functioning. Therefore, the North Central Regional Working Group of the Bipolar Care OPTIONS program proposed a new definition of remission: "an improvement in symptoms to the extent that the patient can achieve a normal or near-normal level of functioning in occupational, family, and social settings."[3]

SLEEP: AN IMPORTANT OBJECTIVE MEASURE OF PROGRESS IN BIPOLAR DISORDER

Although changes in sleep patterns are not the most important symptom of bipolar disorder, sleep quality is one of the most objective measures of improvement or deterioration. Individuals with bipolar disorder have a predisposition or vulnerability to perturbations in circadian rhythms and sleep-wake cycles. Therefore, sleep is a key marker of impending relapse and an indication of treatment response. Disrupted sleep, and especially shortened length of sleep, can trigger or at least signal the onset of manic or hypomanic episodes.[4,5] Lack of sleep can cause a switch from depression to mania in 5% to 6% of patients.[6] Uniform sleep duration and regularly scheduled nighttime sleep periods may help prevent rapid cycling in patients with mania. Nowlin-Finch and colleagues reported that mania resolved quickly in patients who slept for prolonged periods during their first night of hospitalization.[7]

Because sleep is an area that people can understand and control, patient and family education on the importance of regular sleeping patterns might help minimize or delay relapse. Improvements in sleep patterns have been a goal of interpersonal psychotherapy, which focuses on behavioral interventions to ensure that patients have a relatively regular and predictable schedule. Interpersonal psychotherapy and behavioral techniques can improve patients' circadian rhythms, reduce sleep-wake cycle vulnerabilities, and improve overall functioning and a patient's ability to control symptoms.[8]

PHARMACOTHERAPY FOR LONG-TERM REMISSION OF BIPOLAR DISORDER

The APA Practice Guideline[1] recommends treatment with a maintenance medication following recovery from a single manic episode to prevent relapse and reduce subthreshold symptoms and suicide risk. The goals of maintenance therapy are reduction of cycling frequency and mood instability, as well as improvement in overall functioning. The APA guideline suggests using pharmacotherapy in ways that "yield good tolerability and do not predispose the patient to nonadherence."[1(p10)]

The mood stabilizers lithium and valproate (or divalproex) often are the initial therapy for acute episodes of bipolar disorder. Clinical trials have demonstrated that the 2 agents have similar efficacy in acute treatment. To determine the efficacy of these agents in long-term therapy, Bowden and colleagues compared lithium with divalproex in a randomized, double-blind, parallel-group multicenter trial (N = 372) conducted over 52 weeks.[9] Treatment results did not differ significantly for the primary outcome measure, time to recurrence of any mood episode during maintenance therapy. Secondary measures included time to a manic or depressive episode, mean change from baseline scores on the Schedule for Affective Disorders Schizophrenia-Change Version, and GAS scores during maintenance therapy. Divalproex-treated patients had a longer duration of successful prophylaxis than lithium-treated patients as well as less deterioration in depressive symptoms and GAS scores.

Individualizing care to optimal effect requires considering a patient's prior response to a mood-stabilizing agent, tolerability of an agent's side effect profile, and specific symptoms. Patients who respond favorably to lithium tend to be those with purely manic episodes; few lifetime episodes; absence of rapid cycling, psychotic features, comorbid symptomatology, and substance abuse; and previous positive response to lithium. Patients with mixed symptoms and rapid cycling are likely to respond better to divalproex.

Atypical Antipsychotics in the Treatment of Bipolar Disorder

Combination therapy with a mood stabilizer and another agent often is necessary in managing bipolar disorder. Antipsychotics have been used concurrently with a mood stabilizer at initiation of treatment and as add-on

agents after initiating mood stabilizer therapy. The main concern with using conventional antipsychotics is their side effect profile; for example, many of these agents have been associated with movement disorders such as tardive dyskinesia. The introduction of atypical antipsychotics, which offer a more acceptable side effect profile, has allowed for more extensive use of mood stabilizer/antipsychotic combination therapy for bipolar disorder. The atypical antipsychotics that have been studied most extensively are olanzapine and risperidone.[1]

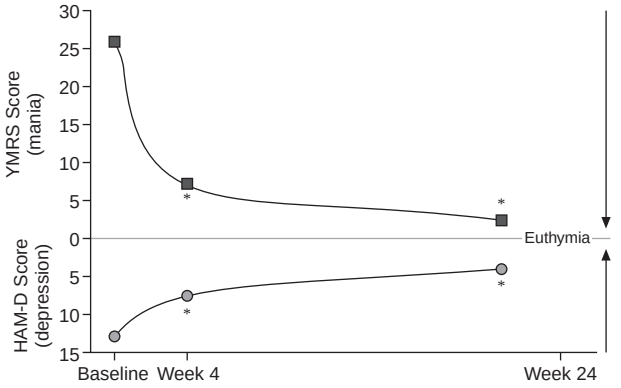
Olanzapine has shown promise in combination maintenance therapy. In a 6-week study[10] of 344 patients who had a poor response to monotherapy with a mood stabilizer (as indicated by a YMRS score ≥ 16), those patients who received olanzapine in addition to a mood stabilizer had a mean decrease in their YMRS scores of 13.11, compared with a mean decrease of 9.10 in those patients who received mood stabilizer monotherapy (p = .003). A total of 78.6% of patients receiving olanzapine plus a mood stabilizer achieved remission (defined as a YMRS score ≤ 12), compared with 65.8% of patients who received mood stabilizer monotherapy (p = .01).[10]

In an assessment of time to reduction of acute manic symptoms, risperidone plus a mood stabilizer for 3 weeks was as efficacious as a mood stabilizer with the conventional antipsychotic haloperidol, and both were superior to a mood stabilizer alone.[11] In this double-blind study, 156 patients were randomly assigned to receive risperidone, the conventional antipsychotic haloperidol, or placebo in combination with a mood stabilizer (valproate or lithium). Using reduction in YMRS scores as the primary outcome measure, the risperidone/mood stabilizer combination therapy was more effective than a mood stabilizer alone in treating acute mania and was found to be as effective as haloperidol plus a mood stabilizer. The risperidone/mood stabilizer combination also was more effective than a mood stabilizer alone in patients with and without psychosis and in those with pure manic episodes. The severity of extrapyramidal symptoms (EPS) was significantly greater (p < .001) in the haloperidol group than in the placebo group; the severity of EPS was similar in the risperidone plus mood stabilizer and placebo plus mood stabilizer groups.

In an open-label 10-week extension[12] of that trial, patients receiving risperidone plus a mood stabilizer experienced continued improvement by 3 criteria of remission. Among all patients receiving risperidone plus a mood stabilizer, 73% had YMRS scores ≤ 12, 59% had YMRS scores of ≤ 8, and 31% had both YMRS scores of ≤ 8 and HAM-D scores of ≤ 7 at the conclusion of the study. The researchers concluded that this increase in remission rates supported continuing combination treatment during a maintenance phase.[12]

In a 24-week maintenance study, adjunctive risperidone reduced both bipolar mania and depression. Risperidone was added to any mood stabilizer that patients already were receiving in this open-label, multicenter trial (N = 541). The addition of risperidone resulted in highly significant improvements (p < .0001) on YMRS and HAM-D scores at 6 weeks and 6 months (Figure 1) and on the CGI and the Positive and Negative Syndrome Scale at 4 weeks and 6 months. Two percent of the patients had exacerbation of mania during the first 6 weeks of the study.[13]

Figure 1. Risperidone as Adjunctive Medication in Maintenance Therapy in Bipolar Disorder (N = 541)[a]



[a]Data from Vieta et al.[13]
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.
*p < .001 vs. baseline.

Whether antipsychotic drugs should be discontinued once a patient has achieved therapeutic plasma levels of a mood stabilizer is open to debate. In the olanzapine study cited previously, patients participated partially because they had experienced limited responses to mood stabilizer monotherapy. Patients who improved while on combination treatment tended to avoid relapse if they stayed on the combination, whereas patients on monotherapy tended to relapse.[10] These results may suggest that if patients improve on combination therapy while in the hospital, they should continue to take the combination after discharge.

Antiepileptic Agents in the Treatment of Bipolar Disorder

The observation that some antiepileptic medications can improve mood, alertness, and social interactions in some patients stimulated an interest in employing these drugs for their mood-stabilizing properties. Outcome measures for antiepileptic drugs include reducing the risk for mania and rapid cycling, especially in patients with depressive symptoms, and improving patient mood without inducing mania.

Third-generation antiepileptic drugs appear to be more effective than mood stabilizers in treating bipolar depression. In one study, 155 outpatients with bipolar I disorder and a major depressive disorder received the antiepileptic

lamotrigine at 50-mg/day or 200-mg/day dosages or placebo as monotherapy for 7 weeks. Lamotrigine, 200 mg/day, demonstrated significant antidepressant efficacy relative to placebo as measured by several depression rating scales. Lamotrigine, 50 mg/day, showed significant efficacy compared with placebo on fewer measures and had a lower proportion of responders than the 200-mg/day dosage.[14] In the first prospective, placebo-controlled study on the subject, Calabrese and coworkers evaluated lamotrigine as maintenance therapy in rapid-cycling bipolar disorder. Forty-one percent of lamotrigine patients versus 26% of those taking placebo were stable without relapse for 6 months on monotherapy.[15]

Clinical investigations of other third-generation antiepileptic drugs have had mixed results. Preliminary data suggested that carbamazepine has some acute antidepressant and antimanic effects. In further clinical studies, carbamazepine* demonstrated moderate efficacy in treating acute depression and greater effectiveness than lithium in preventing acute mania.[16,17] Studies of another antiepileptic, gabapentin,* have shown that the drug is not effective in adjunctive therapy for bipolar disorder and less effective than lamotrigine in monotherapy.[18,19]

ENCOURAGING THERAPEUTIC ADHERENCE

Key steps in improving remission rates and preventing relapse include giving patients the following:

- A clear understanding of the predictors of relapse
- Effective preventive measures
- Definitions of remission that are agreed on by both physician and patient and that extend beyond rating scales to consideration of patients' level of functioning
- Better strategies to reduce nonadherence to treatment

The last point—providing strategies to reduce nonadherence with therapeutic regimens—is particularly important. Patients who are discharged from the hospital should be given a structured, ideally verifiable schedule for taking medications. In selecting drug regimens, psychiatrists should be mindful of factors, such as a medication's side effects or cost, that affect adherence. Tolerability of a mood stabilizer is a key to effective maintenance therapy. The use of lithium at high doses (producing a blood drug level of 0.8–1 mEq/L) is more effective in maintenance therapy than low doses (those that result in a blood drug level of 0.4–0.6 mEq/L), but the associated side effects often are more severe. After 10 years of lithium therapy, 10% to 20% of patients display kidney changes, including interstitial fibrosis, tubular atrophy, and glomerular sclerosis.[1] The use of divalproex for 1 year is associated with increased appetite, which can lead to weight gain, as well as, uncommonly, reduced white blood cell and platelet counts.[1]

Tolerability is an issue in maintenance therapy with atypical antipsychotics as well. In a study of weight gain in 573 schizophrenic patients receiving olanzapine for 3 years, the median weight gain was 13 lb after 39 weeks. Serum glucose and cholesterol levels and diastolic blood pressure rose with weight gain, but the increase was not clinically significant.[20] In the Vieta et al. 6-month study of risperidone in bipolar II disorder, the most frequent side effects were mild weight gain and mild EPS, which diminished halfway through the study. No cases of newly emergent tardive dyskinesia were reported. Previous concerns about exacerbation of manic symptoms were not confirmed.[13]

As noted previously, combination therapy also can decrease the probability of patients adhering to their treatment regimens by inducing additional adverse effects and increasing the cost of therapy.

Psychoeducation Improves Adherence

Adherence to drug regimens is enhanced when patients and their families or significant others receive psychoeducation, which is most simply defined as patient education about a psychiatric disorder and its treatment. Twenty-one weeks of psychoeducation in addition to standard pharmacologic treatment prevented relapses and extended the time to recurrence in patients with bipolar disorder who were euthymic at study entry, according to a recent report by Colom and colleagues.[21] After 2 years' follow-up, patients who had received weekly psychoeducation in structured small group settings had higher lithium levels than a control group receiving standard care without the structured psychoeducation. The higher lithium levels indicate better compliance with therapy.

Patients and their family members or significant others can act cooperatively to help prevent relapse. User-friendly assessment scales such as the National Institute of Mental Health's Life Chart, the STEP-mood chart, or the Internal State Scale can be used in tandem to help identify mood fluctuations and serve as an adjunct to clinician monitoring. A consistent, continuing relationship between a psychiatrist, a patient, and the patient's family can help identify initial symptoms of mood episodes by differentiating pure from dysphoric mania and identifying subthreshold depression in mixed mania.[1,22,23] Akiskal and colleagues found that self-assessment by manic patients is potentially useful, although patients' lack of insight, poor judgment, and distractibility require professional assessment.[22] Hantouche et al. determined that self-assessment could be an accurate method for identifying the subthreshold depressive symptomatology of mixed mania, which can be missed in clinical evaluation.[23]

Patients and their families and significant others can be taught to recognize preliminary symptoms of manic or

depressive episodes, which can lead to the initiation of treatment early in the course of an episode. Education also can enable patients and their family members or close friends to recognize preliminary indications of a good response to therapy, and so draw encouragement to continue with their treatment.

*These agents have not been approved by the U.S. Food and Drug Administration for the treatment of bipolar disorder.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril and others), divalproex (Depakote), gabapentin (Neurontin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), olanzapine (Zyprexa), risperidone (Risperdal).

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