Optimizing Treatment Outcomes in Bipolar Disorder Under Ordinary Conditions

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The gold standard for establishing the efficacy of a drug is the randomized controlled trial (RCT). In the past decade, there has been an increasing recognition of the important difference between RCTs designed to demonstrate efficacy and treatment studies designed to evaluate the effectiveness of various therapies in actual clinical practice. This distinction is especially true for bipolar disorder, a complex illness whose treatment response is significantly influenced by various moderating baseline factors (e.g., comorbidity, severity, treatment resistance) and mediating factors (e.g., adequacy of dose and treatment duration, use of concomitant medications, treatment adherence). To reduce sources of variance in treatment outcome, RCTs rely on restrictive entry criteria in an attempt to control moderating factors and on highly standardized study procedures in an attempt to control mediating factors. The goal is to reduce the heterogeneity in the patient sample and in treatments administered and thereby to increase the internal validity of the study. Unfortunately, the results of rigorously controlled RCTs with strong internal validity are often not highly generalizable to the real-world setting of actual clinical practice. The aim of this paper is to briefly review key variables that influence treatment outcome of bipolar disorder in real-world clinical settings and to discuss strategies for optimizing treatment outcomes under ordinary conditions. *(J Clin Psychiatry 2008;69[suppl 3]:11–19)*

THE IMPORTANCE OF CORRECT DIAGNOSIS

The optimal management of bipolar disorder begins with its accurate diagnosis. Individuals misidentified as having unipolar illness may respond less well to antidepressants than to mood-stabilizing agents, while treatments for bipolar disorder may be less effective in mood disorder patients who do *not* have bipolar illness. The misdiagnosis rate for bipolar disorder (BPD) remains high, with 69% of survey respondents (411/600) from the National Depressive and Manic-Depressive Association reporting that their BPD had previously been misdiagnosed.[1] The most common incorrect diagnoses were unipolar depression (60%), an anxiety disorder (26%), schizophrenia (18%), and borderline or antisocial personality disorder (17%). Women were more likely than men to be misdiagnosed with unipolar depression (68% vs. 43%), while men were more likely to be misdiagnosed with schizophrenia (28% vs. 14%). Misdiagnosed patients saw an average of 4 physicians before they were diagnosed as having BPD, and fully 35% went 10 years or longer before receiving specific treatment.

The presence of comorbidity contributes to the misdiagnosis of BPD. The odds of being misdiagnosed were 2 times greater in patients with panic disorder or generalized anxiety disorder, while misdiagnosis was 20% less likely if psychosis was present.[2] Compared to patients with correctly diagnosed BPD, patients who were misdiagnosed were significantly more likely to receive antidepressants (odds ratio [OR] = 2.1) and anxiolytics/hypnotics (OR = 1.5) and were significantly less likely to receive anticonvulsants (OR = 0.4), lithium (OR = 0.3), and antipsychotics (OR = 0.5).[2] Misdiagnosis and subsequent use of potentially inappropriate pharmacotherapies are associated with a significant increase in social impairment, hospitalization rates, and overall treatment costs.[2–5] In addition, there is at least some evidence to suggest that delayed treatment initiation may reduce the subsequent efficacy of some mood stabilizers, such as lithium.[6]

A largely unexamined issue is the diagnostic validity of the "bipolar spectrum" in patients who manifest *some* features of BPD but do not meet strict DSM-IV criteria for BPD. There exists no consensus agreement about the con-

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cept of a "bipolar spectrum," in cases in which DSM-IV criteria for symptoms or duration are not met or in which confounding factors (such as substance abuse or severe personality disorders) make the diagnosis unclear; little is known about the best nosologic formulation, treatment strategy, or outcomes for patients who would be classified by DSM-IV as having bipolar disorder not otherwise specified (NOS).

The heterogeneity of its clinical presentation and the likelihood of comorbidity make the correct diagnosis of BPD a challenge. This difficulty is especially pronounced in the primary care setting, which is frequently the first point of medical contact. Several brief, patient-rated instruments have been validated as screening tools. The Mood Disorder Questionnaire (MDQ),[7] consisting of 13 items with yes-no responses, has very good sensitivity (0.73) and specificity (0.90) in outpatient psychiatric settings. In the general community, its specificity remains high (0.97), but its sensitivity falls substantially (0.28).[8] Thus, use of the MDQ in the community is associated with a high false negative rate (i.e., it misses approximately 72% of patients with undiagnosed bipolar disorder); in contrast, patients with a positive score on the MDQ have a relatively high probability of a BPD diagnosis (i.e., the false positive rate is only 3%). The MDQ also is considered to be a more useful screen for bipolar I disorder than bipolar II disorder or bipolar disorder NOS. However, as a screening tool, positive MDQ scores should not be clinically interpreted as a proxy for a careful, systematic diagnostic interview.

A second instrument, the Bipolar Spectrum Diagnostic Scale (BSDS), [9] has been developed to screen for patients with bipolar II disorder or bipolar disorder NOS. The BSDS has undergone preliminary testing in a subgroup of affectively ill patients in a tertiary care clinic, but it has not yet been validated in psychiatric, medical, or community settings; therefore, its performance characteristics are uncertain.

In a recent study by Perlis, et al.,[10] a stepwise logistic regression analysis of bipolar depression patients (N = 477) vs. unipolar MDD patients (N = 1074) identified 2 variables as being the most significantly associated with a greater likelihood of having a bipolar diagnosis: (1) family history of BPD (OR = 6.0); and (2) higher episode frequency—1 to 5 previous episodes (OR = 16.2); more than 5 episodes (OR = 40.8). Age at onset occurred significantly earlier in patients with bipolar depression on the initial univariate analysis but was only weakly significant on the multivariate analysis. Various clinical symptoms were also significant and contributed modestly to the overall model, with the most significant items being MADRS item 1 (apparent sadness; OR = 0.70); HAM-A item 3 (fears; OR = 1.4), and HAM-A item 4 (insomnia; OR = 0.63). (Note that an OR < 1.0 indicates a greater likelihood of unipolar MDD.) The full model correctly classified 87% of patients as unipolar or bipolar, with a sensitivity of 69% and a specificity of 95%. A second, smaller study by Solomon et al.[11] (bipolar depression, N = 45; unipolar depression, N = 167) reported similar findings with significantly higher episode frequency in bipolar disorder vs. unipolar depression (84% vs. 39%, with ≥ 2 previous episodes; $p < .001$), positive family history of bipolar disorder (82% vs. 58%; $p < .01$), and earlier age at onset (23 vs. 33 years; $p < .001$). Delusions were significantly more frequent in the bipolar sample (22% vs. 8%; $p < .01$). The same study found similar differences for patients with bipolar II disorder for earlier age at onset, higher episode frequency, and delusions but not for family history. The authors[11] tested a simple 3-item Screening Assessment of Depression-Polarity, with binary responses to questions about episode frequency, family history, and presence of delusions. In this pilot sample, the assessment sensitivity was 82%, and the specificity was 61%. Both assessments need more testing in more representative outpatient psychiatric and/or primary care settings.

UNIPOLAR TO BIPOLAR POLARITY CONVERSION

An uncommon but nonetheless critical longitudinal event among patients presenting with unipolar major depression is the occurrence of a manic or hypomanic episode, particularly among younger depressed patients. At 10-year follow-up in the National Institute of Mental Health (NIMH) Collaborative Study on the Psychobiology of Depression,[12] 5.2% of patients with an index diagnosis of unipolar depression had developed a manic episode, and 5.0% had developed hypomania, although since most entrants to this study were over age 35, it afforded little opportunity to identify patients whose polarity conversions very likely would have occurred earlier during their peak years of risk for developing mania or hypomania (i.e., late teens and early 20s). The percentage of patients initially identified with "unipolar" depression who experience manic episodes varies greatly across studies but may be as high as 50%.[13,14] The peak risk window for unipolar to bipolar polarity conversion, during adolescence and young adulthood, is consistent with findings summarized in the previous section that show bipolar depression to have an earlier onset than unipolar depression.[14,15] Studies suggesting that "hyperthymic temperament" is a risk factor may also be tapping into the same early onset risk factor.[16] Other significant risk factors for conversion to bipolar include a family history of bipolar disorder and history of depression with psychotic features—both consistent with the findings from the study by Perlis and colleagues.[10]

One unresolved issue is whether mania or hypomania that occurs during treatment of unipolar depression is iatrogenic or, more accurately, the precipitation of an un-

derlying bipolar diathesis. By current DSM-IV nosology, the appearance of manic/hypomanic states during treatment is diagnosed as an "antidepressant-induced" mood disorder.[17] Manic switches during unipolar MDD treatment call into question the long-term accuracy of an initial affective illness diagnosis, particularly since patients who develop antidepressant-induced manias are thought to be at increased risk for spontaneous manic episodes or hypomanic episodes. Therefore, some authors have suggested that few—if any—treatment-related switches are iatrogenic.[18] On the other hand, evidence favoring at least a partial iatrogenic contribution to antidepressant-induced mania comes from the fact that treatment with venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is associated with a significantly increased switch rate relative to treatment with a selective serotonin reuptake inhibitor (sertraline, paroxetine) or treatment with bupropion.[14,19] The iatrogenic effect is thought to owe, in part, to the noradrenergic activity of the SNRI, akin to that seen with tricyclic antidepressants.[14,20]

RISK OF MANIC/HYPOMANIC SWITCHING AMONG PREVIOUSLY DIAGNOSED BIPOLAR PATIENTS

Among patients with established BPD, an important treatment concern is the risk of mood destabilization associated with antidepressant treatment. As noted above, use of SNRIs or antidepressants that potently inhibit noradrenergic reuptake appears to increase the risk of affective polarity switch. Risk of switching is also significantly higher in patients with bipolar I disorder compared to those with bipolar II disorder and in patients with BPD whose immediately previous episode was mania/hypomania, and not depression.[14,21] Switching may occur during either the acute or continuation phases of treatment.[14] In one study, the risk of switching during antidepressant augmentation of mood stabilizers in patients with bipolar depression was approximately 50% by 1 year.[14] Recent findings from the NIMH Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)[22] suggest that, overall, antidepressants added to traditional mood stabilizers neither improve recovery from bipolar depression nor heighten the risk for mood destabilization; however, in the presence of baseline mania symptoms[23] or the setting of prior antidepressant-induced manic episodes,[24] the risk for induction or worsening of mania symptoms with antidepressants may be significantly elevated with any antidepressant. The magnitude of this risk underscores the importance of conducting double-blind, head-to-head studies that compare mood stabilizer/antidepressant combinations to drugs that have shown promising antidepressant effects (e.g., lamotrigine[25,26] or certain atypical antipsychotics such as quetiapine or olanzapine/fluoxetine combination).[27,28]

PSYCHIATRIC COMORBIDITY AND TREATMENT OUTCOME

No adequately powered, prospective randomized controlled trials (RCTs) have been published that systematically examine the effect of psychiatric comorbidity on treatment response. This is a major gap in the treatment research field, since BPD is associated with an unusually high rate of Axis I and Axis II comorbidity. Lifetime rates of Axis I comorbidity are approximately 65%, while current Axis I comorbidity occurs in approximately 33% of patients.[29,30] Approximately 40% of patients with bipolar I and bipolar II disorders have 2 or more comorbid Axis I diagnoses.[30]

Among the most common Axis I comorbidities with bipolar disorder are substance use disorders (SUDs), with lifetime prevalence rates generally ranging from 40% to 60%.[29–31] Alcohol is the most frequently abused substance, although polysubstance abuse or dependence also appears to be common.[32] The presence of a comorbid SUD is associated with significantly lower rates of treatment adherence, higher anxiety disorder comorbidity, more suicide attempts, and poorer outcome, especially in terms of functioning and quality of life.[31–34] An analysis of the first 1000 patients in the STEP-BD program suggests that patients with BPD who have been able to achieve a sustained remission of their SUD have an improved outcome, but the degree of improvement continues to be less than that observed in the group of patients with no substance use history.[35] At this point, sufficient longitudinal data are not available to determine whether BPD primarily influences SUD outcome or whether SUD is the primary influence on the course of BPD. Preliminary data from a bipolar II sample suggest that the major determinant of outcome when both disorders are present is the status of the BPD.[36] There are few large, prospective RCTs that test the efficacy of short- and long-term treatments of bipolar disorder in the presence of comorbid SUD, although a recent 24-week, placebo-controlled study of divalproex in alcoholic bipolar patients found significant improvement in alcohol-related symptoms regardless of the effects of divalproex on mood.[37]

The lifetime prevalence of a comorbid anxiety disorder is approximately 50%, with generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder each occurring in approximately 25% of patients with BPD.[29,30] The STEP-BD study reported 1-year follow-up data for its first 1000 subjects, comparing clinical outcomes in the subgroup (32%) with a current anxiety disorder diagnosis versus patients with no anxiety diagnosis.[38] Among patients (N = 151) who were experiencing a depressive episode at the beginning of the observation period, the presence of a comorbid anxiety disorder was associated with a 34% lower likelihood of recovery by 1 year (hazard ratio [HR] = 0.66; p = .020). Among patients (N = 165) who

were not currently in an affective episode, the presence of a comorbid anxiety disorder was associated with a significantly increased risk of relapse (HR = 1.76; p = .001).

Axis II personality disorders are also a very common form of bipolar comorbidity, with a lifetime prevalence of any one disorder estimated to occur in approximately two thirds of patients.[29,39] In a study of bipolar patients from the Cornell Bipolar Research Program (N = 100; 95% outpatients; 73% BP-I), 30% had a current Cluster B diagnosis consisting of borderline (17%), narcissistic (8%), antisocial (6%), or histrionic (5%) personality disorder.[40] The presence of a Cluster B diagnosis was associated with a higher rate of suicide attempts, lifetime substance abuse, and a history of physical or emotional abuse.

MEDICAL COMORBIDITY AND TREATMENT OUTCOME

Bipolar disorder appears to be associated with a wide range of medical comorbidities, although there is much less research available evaluating the risk of medical illness specifically in bipolar disorder compared to unipolar depression.

Bipolar patients have significantly increased rates of obesity and diabetes and are at increased risk for metabolic syndrome.[41] The extent to which obesity and related metabolic problems are characteristics of bipolar disorder itself or are iatrogenic byproducts of pharmacologic treatment is still unclear. Overall, a depression diagnosis is associated with a significantly increased risk of cardiac disease and cardiac mortality.[42,43] Again, it is not known whether the risk is higher or lower in patients whose depressions are bipolar rather than unipolar.

Studies in outpatient[44,45] and community settings[46] have found that a diagnosis of BPD is associated with an approximately 2-fold increase in the diagnosis of migraine. There are some data[45] to suggest that migraine comorbidity may be higher in bipolar II than bipolar I disorder, but further research is needed to confirm this finding. Any long-term bipolar treatment strategy must take into account the potential effect on existing medical comorbidities.

WHAT CONSTITUTES AN ADEQUATE TRIAL IN ACUTE MANIA?

Expert consensus treatment guidelines, supported by evidence-based medicine reviews, suggest that the treatment of choice for acute mania is monotherapy with a mood stabilizing agent—lithium, carbamazepine, or valproate sodium (62% of survey respondents)—followed by combined therapy with a mood stabilizer plus an atypical antipsychotic (30% of survey respondents); however, a small minority does recommend monotherapy with an atypical antipsychotic.[47,48] The American Psychiatric Association Practice Guideline for the Treatment of Patients with Bipolar Disorder[49] advises the initiation of combination therapy with a standard mood stabilizer (e.g., lithium, carbamazepine, or valproate sodium) plus an antipsychotic at the outset of treatment for severe, hospitalized mania, particularly in the presence of psychosis.

In the modern health care climate, practitioners sometimes feel compelled to titrate medications faster than is recommended either by the manufacturer or by clinical trial data, based on hopes that the medication(s) will reach therapeutic efficacy faster. The safety and efficacy of rapid or oral loading strategies have been established for some antimanic agents (such as divalproex[50] or olanzapine[51]), but such strategies may be impractical or difficult to tolerate with others, such as lithium.[52] Still others may pose greater safety hazards if rapidly titrated but with no known likelihood for faster onset or better efficacy (as when titrating lamotrigine faster than recommended for acute bipolar depression). Busy practitioners and hospitalists also sometimes feel compelled to abort a trial of a specific medication prematurely, before pharmacodynamic efficacy can realistically be determined.

What constitutes an adequate trial in acute mania is an empirical question that can only be answered by studies specifically designed to evaluate the dose-response and time-response (and remission) relationships among the various treatments. Such studies would be able to provide data on the probability of eventual response (or remission) at various levels of improvement and at various time points (e.g., day 3, day 7, day 10). Such study designs, using signal detection or conditional probability-analytic strategies, have been reported for unipolar major depression but currently are not available for acute mania or bipolar depression.[53] In the absence of such data, treatment guidelines have been promulgated based on evidence-based reviews of the literature, supplemented by input from expert panels.[54]

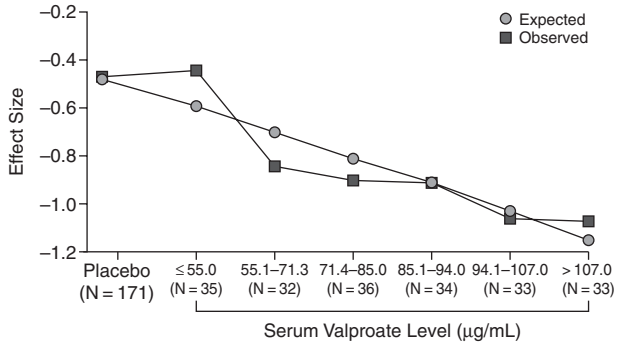
In the 2004 Expert Consensus Guidelines for the Treatment of Bipolar Disorder, 72% of survey respondents felt that 1 week of acute treatment constituted an adequate trial if *no signs of response* had occurred by then, although expert opinion on adequate trial duration ranged from 4 days to 3 weeks.[47] There was much less consensus as to what constituted an adequate trial duration in patients showing a partial response, with experts suggesting 1 week (9%), 2 weeks (46%), 3 weeks (24%), or 4 or more weeks (21%).[47] Furthermore, the recommended next-step treatment in the face of partial response is to add an atypical antipsychotic if the patient has partially responded to monotherapy with a mood stabilizer, to add a mood stabilizer in the face of partial response to an atypical antipsychotic, and to switch to an alternative atypical antipsychotic if partial response has occurred after combination therapy.[47] Again, expert panel recommendations are a useful interim step, but it is

Table 1. Optimal Dosing Targets in Acute Mania: Recommendations of the Michigan Implementation of Medication Algorithms[a]

Agent	Target Dose or Blood Level	Maximum Recommended Dose or Blood Level
Lithium	0.8–1.0 mEq/L	1.2 mEq/L
Divalproex	80 µg/mL	125 µg/mL
Oxcarbazepine	600–1200 mg/day	2400 mg/day
Olanzapine	10–15 mg/day	20 mg/day
Risperidone	2 mg/day	6 mg/day
Quetiapine	200–600 mg/day	800 mg/day
Ziprasidone	40–160 mg/day	160 mg/day
Aripiprazole	15 mg/day	30 mg/day

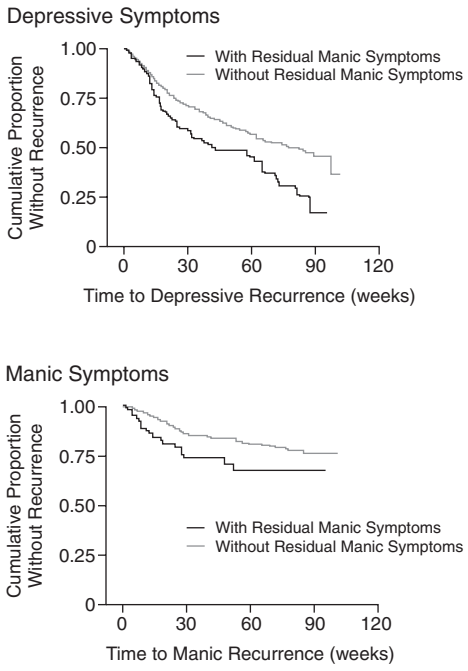
[a]Data from *Closing the Quality Gap in Michigan*.[54]

Figure 1. The Relationship Between Serum Valproate Levels and Treatment Response: Pooled Effect Size Data[a]



[a]Reprinted with permission from Allen et al.[55]

Figure 2. Differential Recurrence Rates Over 2 Years of Follow-Up Based on the Presence or Absence of Residual Manic Symptoms: Results From the STEP-BD Program[a,b]



[a]Reprinted with permission from Perlis et al.[48]
[b]~50% of patients maintained remission during the 2-year study.
Abbreviation: STEP-BD = Systematic Treatment Enhancement Program for Bipolar Disorder.

always preferable to base treatment decisions on a foundation of randomized, double-blind clinical trials.

Recommendations for optimal dosing in acute mania also have been made based on evidence-based medicine reviews (Table 1).[54] Controlled trials point to a high correlation between serum drug level and antimanic response to divalproex (Figure 1),[55] although clinical trials have not so clearly demonstrated any relationship between serum drug levels and psychotropic response with other mood-stabilizing anticonvulsants such as carbamazepine or lamotrigine. Recent data also demonstrate a link between receptor occupancy (determined in vivo by positron emission tomography radioligand imaging) and response to atypical antipsychotics.[56,57] Optimal use of atypical antipsychotics and those anticonvulsants that possess mood stabilizing properties will be aided by future illness-specific research that examines plasma levels or receptor occupancy relative to treatment response.

There are insufficient data as to how the presence of various comorbid psychiatric disorders might alter choice of drug (monotherapy vs. combination therapy) or might result in different dosing or treatment recommendations.

RESIDUAL SYMPTOMS AND RISK OF RECURRENCE: THE IMPORTANCE OF REMISSION

Despite the use of evidence-based pharmacotherapies, affective relapse has been observed to occur in at least half of individuals with BPD followed for up to 2 years.[48] In addition to full syndromic recurrence, patients diagnosed with BPD often experience subsyndromic levels of affective symptoms. For example, in long-term naturalistic outcome data from the NIMH Collaborative Depression Study,[58,59] patients diagnosed with bipolar II disorder were found to spend a proportion of days experiencing affective symptoms that was comparable, or greater, to that reported by those with bipolar I disorder, as manifested by (1) subsyndromic levels of depressive or hypomanic symptoms (16.2% vs. 14.1% of days), (2) minor depression/dysthymic/hypomanic levels of symptoms (27% vs. 20.1% of days), and (3) depressive or manic symptoms at the syndromal level (12.6% vs. 12.3% of days). Consequently, patients with bipolar II disorder reported a somewhat lower percentage of asymptomatic

days than did those with bipolar I disorder (44.2% vs. 53.4%).

Recent findings from the STEP-BD trial identified residual manic symptoms as significant predictors of time to depressive or manic recurrence (Figure 2).[48] Residual manic symptoms at recovery and proportion of days of elevated mood in the preceding year were significantly associated with shorter time to manic, hypomanic, or mixed episode recurrence. For every additional hypomanic/manic symptom, the risk of recurrence increased by 20%.

These data, together with similar results from other treatment studies of bipolar disorder,[48,59] illustrate the importance of aggressively treating bipolar symptoms. The goal of treatment is full remission, since residual or subsyndromal symptoms after an incomplete remission can in themselves impair psychosocial functioning,[60] and subsyndromal symptoms after a "response" (i.e., ≥ 50% reduction from baseline symptom severity) often lead to an eventual full recurrence.[61] Once again, few clinical trials have taken remission as a primary end point, and effectiveness trials that systematically test various augmentation strategies are not available.

CHOICE OF AGENT FOR PROPHYLACTIC TREATMENT

Ideally, information to support rational decision-making as to the choice of prophylactic treatment would come from large, randomized effectiveness trials with sufficient statistical power to control in multivariate analyses for baseline clinical and demographic features (such as rapid cycling, or early age at onset) that may confound effects on treatment outcome. Such efforts are presently underway through follow-up studies such as the NIMH STEP-BD,[22] the NIMH Collaborative Depression Study,[58,59] and the Stanley Bipolar Network.[62,63] At present, the aggregate of available data suggests that lithium may be most effective in patients with classical manias, discrete euthymic intervals, and a positive family history of lithium response.[64,65] Other clinical variables identified as predicting a more favorable prophylactic response to lithium include absence of psychiatric comorbidity, introduction of lithium early in the course of illness, and a cyclic pattern in which the index episode was mania, followed by depression (rather than vice versa).[64,65]

A recent meta-analysis by Geddes and colleagues[64] observed that lithium exerts a more robust prophylactic effect against mania (~40% risk reduction) than depression (~22% risk reduction). Despite the somewhat lower depression prophylaxis, treatment with lithium significantly reduces risk of suicide (OR = 0.26).[66] Conversely, discontinuation of lithium was associated with a significant increase in suicidality in the 6 to 9 months postdiscontinuation.[67] Some authors have suggested that lithium warrants consideration in the pharmacotherapy regimen of any patient with BPD in whom risk for suicidal behaviors is of high concern.

RISK ASSOCIATED WITH RAPID DISCONTINUATION OF LITHIUM THERAPY

Despite the weight of the evidence supporting the long-term protective effects of maintenance therapy with lithium, treatment discontinuation is a frequent occurrence. As may be expected, the risk of relapse (both into mania and depression) is significantly increased postdiscontinuation. A pooled analysis of available studies indicates that, when compared to gradual lithium discontinuation, rapid cessation (i.e., fewer than 14 days) is associated with a significant increase in time until relapse into mania (5.0-fold) or depression (2.8-fold), as well as fatal suicide attempts (2-fold).[68] The risk of relapse after rapid discontinuation was higher in patients with bipolar II disorder compared to those with bipolar I disorder.[68] It is not certain whether similar rebound effects are observed after rapid discontinuation of anticonvulsants or atypical antipsychotics.

CLINICAL INDICATIONS FOR USE OF ANTICONVULSANTS AND ATYPICAL ANTIPSYCHOTICS

Since the advent and widened use of carbamazepine and divalproex for the treatment of BPD, numerous other anticonvulsant agents have received attention as possible mood stabilizers. From a mechanistic standpoint, agents that diminish brain excitatory amino acid (e.g., glutamate, aspartate) transmission are thought to exert an antidepressant effect, while those that elevate inhibitory neurotransmission (particularly γ-aminobutyric acid) are thought to exert an antimanic effect.[69] However, with the exception of lamotrigine,[70,71] there are no positive randomized, placebo-controlled trials to support the use of anticonvulsant agents other than carbamazepine and divalproex in the treatment of acute mania.

Evidence from double-blind trials suggests that 2 atypical antipsychotics, olanzapine[72,73] and aripiprazole,[74] have significant prophylactic efficacy in patients with bipolar I who present with manic or mixed states. In the case of olanzapine, robust prophylactic efficacy has been observed with respect to both mania and depression.[73] In a 6-month study of the maintenance of effect of aripiprazole, a lower rate of relapses into mania was observed with aripiprazole than placebo, although separation from placebo was not evident for the prevention of depression.[74] In addition, the 6-month duration of that study provided information more directly on risk for relapse (i.e., a return of symptoms from an index episode) rather

than recurrence (i.e., the occurrence of a new episode) during maintenance pharmacotherapy.

OPTIMIZING OUTCOMES THROUGH TREATMENT ADHERENCE

Treatment nonadherence, whether partial or full, is high in patients diagnosed with bipolar disorder, typically estimated in the range of 40% to 60%.[75,76] The consequences of nonadherence include lower response and remission rates during acute episodes, higher relapse rates during euthymic periods, worse quality of life and functioning, and increased hospitalizations and suicide attempts.

Predictors of nonadherence can be usefully grouped into demographic, clinical/illness, therapeutic, and attitudinal/personality categories.[77] The presence of demographic and illness variables alerts clinicians that a patient may be at high risk for nonadherence. The therapeutic and attitudinal variables should be evaluated and addressed in treatment sessions with the patient. Preliminary research suggests that the best method for managing negative predictors of adherence is to apply a collaborative care model in which patients become active partners in their own treatment, with a focus on increasing each patient's illness management skills.[78]

An important feature of the collaborative care model is a psychoeducational approach in which patients are provided with good information on their illness and the drugs used to treat it. Given the chronicity of BPD and the high risk of relapse, it is especially important to identify in each patient the characteristic prodromal signs and symptoms that warn of an impending acute depressive or manic episode. Studies suggest that patients can detect prodromes and that recognition can reduce the likelihood of recurrence.[79]

A parallel adherence issue, which has been less intensively studied, is clinician adherence to treatment guideline recommendations. Adherence to guidelines has been shown to significantly improve clinical outcomes.[80,81] In naturalistic practice settings, adherence to guideline recommendations tends to be very low (one third),[82] despite the fact that physicians generally have very positive attitudes toward treatment guidelines in terms of their usefulness, educational value, and favorable impact on quality of care.[83] There is some evidence that deviation from guideline recommendations may be greater among more experienced clinicians[84] or when recommendations are perceived as a threat to physician autonomy. But no consistent and significant predictors of physician adherence to treatment guideline recommendations have been identified.[83,85]

CONCLUSION

The optimal treatment of BPD is complicated by (1) difficulties and delay in diagnosis (and reasoning through an accurate differential diagnosis), (2) high levels of comorbidity that both directly and indirectly complicate the course of illness, (3) frequent treatment nonadherence, and (4) high risk of relapse and recurrence, especially in the presence of residual symptoms.

Over the past few years, significant progress has been made in identifying characteristics of the clinical presentation of bipolar disorder that have high discriminative validity versus unipolar depression. Dissemination of this information and the development of screening tests based on this research should reduce the average delay in diagnosis, which may be as high as 10 years in one third of patients.

Given the high lifetime prevalence of comorbid psychiatric (about 65%)[29,30] and substance use disorders (about 40%–60%)[29–31] in patients with a bipolar diagnosis, clinicians must regularly be alert to the emergence of comorbid conditions and treat them accordingly. Further effectiveness research is needed to provide a broader database about optimal management strategies for bipolar disorder with comorbid psychiatric or substance use disorders.

Similar effectiveness studies are needed to address 2 other important treatment issues. First, what are the most effective augmentation strategies in treatment responders with persistent residual affective symptoms? Residual affective symptoms hasten relapse, but there is insufficient information on the best next-step treatments to achieve full remission. Second, the decision on choice of drug for both acute and maintenance therapy now largely rests on the clinical expertise of individual physicians, often supplemented by extrapolation from efficacy-based studies in populations that may not be generalizable to most "real-world" patients. The number of clinical variables that may constitute prescriptive predictors of differential acute and maintenance treatment response is daunting, but the prevalence, chronicity, and burden associated with BPD argue that the return on investment is highly favorable.

Perhaps more than the treatment of any other psychiatric illness, long-term pharmacologic treatment of BPD is a therapeutic challenge that does not take place in a vacuum. Nonadherence, which occurs in approximately half of all patients, should be viewed as the result, not the cause, of treatment failure. Active partnerships between clinicians and patients are essential to optimize treatment outcomes. Appropriate pharmacotherapies are most effective when coupled with structured psychosocial interventions that incorporate psychoeducation about the illness, restructure cognitive distortions, improve coping strategies for family-based or other interpersonal stresses, and foster regular patterns of sleep hygiene and social rhythms.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), divalproex

(Depakote), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), norepinephrine (Levophed and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal and others), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), sertraline (Zoloft and others), valproate (Depacon and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, fluoxetine, lamotrigine, paroxetine, sertraline, and venlafaxine are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression; divalproex is not approved for the treatment of alcohol dependence; and oxcarbazepine is not approved for the treatment of bipolar disorder.

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