Response, Remission, and Recovery in Bipolar Disorders: What Are the Realistic Treatment Goals?

Gary S. Sachs, M.D., Ph.D., and A. John Rush, M.D.

Bipolar disorder presents particular challenges with regard to assessing response to therapy. Criteria for determining remission and recovery have been suggested for mood disorders, but the clinical usefulness of these terms in bipolar disorder is elusive. Formal psychological rating scales may be impractical in a routine medical practice setting. As an alternative, clinicians might probe for information about particular "signal events," such as sleep disturbances, that may herald mood fluctuations. The ultimate goal of bipolar management should be complete and sustained remission, whenever possible, although most patients will not achieve this status for any significant length of time. Furthermore, overaggressive management might entail pushing medication doses to intolerable levels. Individual treatment goals should always take into account patient acceptance of side effect burden, allowing for trade-offs between treatment effect and quality of life. Noncompliance with therapy, notoriously common among patients suffering from bipolar disorder, can stem from drug side effects, treatment ineffectiveness, or even treatment success if the patient misses the manic symptoms. Despite effective treatment, relapse is common. Realistic treatment goals should strive for sustained symptom abatement while maximizing patient quality of life from visit to visit.

(J Clin Psychiatry 2003;64[suppl 6]:18–22)

The complex nature of bipolar disorder is only partially revealed by its multifaceted etiology and difficult diagnosis. In this chronic, cyclic disease, the clinician is faced with the ongoing challenge of keeping the patient symptom-free and preventing the affective pendulum from swinging too far toward mania or depression. Cure is unattainable and recurrence practically inevitable. It is estimated that more than 90% of individuals who experience a manic episode will have subsequent episodes.[1] How aggressively should the practitioner strive for a complete remission of bipolar symptoms? What are the risks of attempting to manage bipolar disorder aggressively? This article will review the issues surrounding realistic expectations for treatment response in bipolar disorder.

REMISSION AND RECOVERY IN BIPOLAR DISORDER

Although there is no widely agreed upon definition of remission in bipolar disorder, *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria for bipolar episodes define partial remission as the persistence of some signs or symptoms in a patient who previously fulfilled all criteria for bipolar disorder. Full remission is defined as an absence of relevant signs and symptoms for at least 6 months. Criteria have also been outlined for assessing response, remission, and recovery for mood disorders in general. Acute treatment response is generally defined as a clinically significant reduction (e.g., > 50%) in symptom severity, to the point at which the patient no longer meets diagnostic criteria for the condition. Thereafter, the primary goal of continued treatment should be to prevent relapse; that is, to avert the return of symptoms severe enough to meet the criteria for the disorder. The secondary goal is to expand the response into a complete remission, defined as the disappearance of affective symptoms to the degree expected in a mentally healthy person. A sustained

From the Harvard Bipolar Research Program, Massachusetts General Hospital, Boston (Dr. Sachs); and the University of Texas Southwestern Medical Center, Dallas (Dr. Rush).

Presented at the roundtable discussion "Bipolar Disorder: From Clinical Research to Therapeutic Intervention," which was held June 30, 2001, in Berlin, Germany, and supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals, L.P.

Dr. Sachs has been a consultant for Abbott, Glaxo, Janssen, Lilly, BMS, Novartis, Elan, Sanofi, Sigma-Tau, and AstraZeneca; has received grant support from Abbott and Janssen; and has received honoraria from Abbott, Glaxo, Janssen, Lilly, BMS, Solvay, Novartis, Sanofi, AstraZeneca, and Pfizer. Dr. Rush has been a consultant/advisor for Cyberonics, Lilly, Forest, GlaxoSmithKline, and Merck; has received grant/research support from Robert Wood Johnson Foundation, National Institute of Mental Health, and Stanley Foundation; and has served on the speakers bureau for Bristol-Myers, Cyberonics, Forest, GlaxoSmithKline, Merck, and Wyeth-Ayerst.

Corresponding author and reprints: Gary S. Sachs, M.D., Ph.D., Harvard Bipolar Research Program, Massachusetts General Hospital, 50 Staniford St., 5th Fl., Boston, MA 02114 (e-mail: sachsg@aol.com).

period of remission over at least 6 months would be considered a recovery.[2]

These definitions appear to be fairly straightforward, but the evaluation of treatment response in bipolar disease is often difficult. In fact, no consensus currently exists regarding response definitions in this population. Because of the polar nature of the disease, a diminution of symptoms on one end of the spectrum might be viewed as a trend toward improvement or remission, while it may in fact herald a shift in disease expression toward the opposite pole. The frequent co-occurrence of substance abuse in patients with bipolar disorder also complicates an accurate assessment of symptomatic status.

Monitoring disease progression in psychiatric disorders is far more difficult than in many other chronic conditions. No objective measures of disease severity, such as blood pressure or glycosylated hemoglobin, are available. Nor may the patients' subjective assessment of their condition provide uniformly reliable information. Numerous psychological tests have, therefore, been developed to provide some level of objectivity and consistency in assessing mental health status. Clinical studies of bipolar disorder treatment regimens generally use 1 or more of these scaled tools, such as the Young Mania Rating Scale or the Montgomery-Asberg Depression Rating Scale. By tracking test scores over time, the investigator can recognize trends in improvement or relapse.

However, in routine clinical practice it is often more useful to monitor for the presence of particular "signal events" that the patient may associate with relapsing bipolar symptoms. For example, events that might signal the onset of a depressive interval include a decrease in sleep or social behaviors, even simple activities such as calling friends. Through ongoing routine inquiries about lifestyle patterns and activities, the clinician should be able to recognize trends in behavior that could signal worsening mental state.

OPTIMAL TREATMENT GOALS FOR PATIENTS WITH BIPOLAR DISORDER

Treatment goals in bipolar disorder may range from preventing symptom recurrence and suicide[1] to simply decreasing the frequency, severity, and psychosocial consequences of each episode and improving interepisode functional status. Currently among most North American specialty clinics, the goal in bipolar management is complete and sustained remission whenever possible, similar to the recent paradigm shift in depression treatment.[3]

In clinical practice, the criteria for what constitutes "successful" management may depend on a particular patient's needs and willingness to accept certain tradeoffs. For example, if the only way to eliminate the last 20% of depressive symptomatology is to cause frequently recurring manic episodes, a patient may need to accept living with residual depressive symptoms. In some instances, aggressive, remission-driven therapy may involve pushing medication doses to levels that precipitate a huge side effect burden, which may be unacceptable to the patient. Quality of life need not be sacrificed in the name of complete symptom resolution.

Although the continued, overriding goal of treatment may be to achieve remission, it must be understood that complete recovery is not likely and, in some cases, not possible. The cyclic, dynamic nature of bipolar illness demands ongoing assessment. The clinician needs to continually monitor the success of current treatment measures and make additions or adjustments as necessary. Adopting the short-term goal of symptom remission may be more appropriate than striving for a long-term outcome. The endpoint of remission is a feasible, albeit moving, target from visit to visit. At each clinic visit, the clinician should ask, "Could I offer anything else to this patient right now that could improve his/her current symptomatic status or quality of life?"

BARRIERS TO LONG-TERM TREATMENT SUCCESS

Even if the clinician approaches bipolar disease management with the goal of total remission, the patient's role in the treatment process often presents a major obstacle. For example, a patient with bipolar disorder who has been discharged from the hospital with a fair degree of symptom control may require many more months to become fully stabilized and approach a remission phase. Unfortunately, it is quite difficult to maintain consistent contact with these patients for the length of time necessary to achieve full response.

Compliance is notoriously erratic in patients with bipolar disorder for several possible reasons. First, these patients, especially during manic phases, may be quick to discontinue drug treatment when they experience undesirable medication side effects. For example, side effects of lithium, such as weight gain, tremor, and lethargy, often lead to noncompliance.[4] Extrapyramidal side effects (EPS) are especially troublesome and can occur with typical antipsychotics such as haloperidol, fluphenazine, and thiothixene. As a result, clinicians are increasingly prescribing atypical antipsychotic agents such as clozapine, olanzapine, risperidone, and quetiapine. This group of drugs has a much lower risk of EPS and tardive dyskinesia, and evidence of their benefits in bipolar disorder is accumulating.[5,6] In a recent consensus survey of 58 experts in the treatment of bipolar disorder, atypical antipsychotics other than clozapine were rated as first-line agents for the adjunctive treatment of mania and in the combined treatment of psychotic depression.[7]

Differences may exist in side effect tolerance among various ethnic groups. For example, the U.S. white popu-

lation seems willing to pay a higher price in terms of side effects in order to obtain symptom relief. Conversely, Hispanic and African American populations are generally more averse to the side effect burden, even against the backdrop of substantial symptom relief. This issue is undergoing further study. If these trends prove to be robust, this knowledge may help clinicians when making decisions about how hard to push therapy in particular patients.

As in many psychiatric conditions, identifying effective treatment often involves trial and error. If a good response is not obtained with initial therapy, the patient must persist through a series of dosage or medication changes. Each drug and dosage switch presents risks for new or worsened side effects or poor response. If a patient does not respond quickly to a drug regimen or experiences troublesome side effects, he or she may be inclined to give up on the treatment and/or the physician. Alternatively, some patients who start to respond well to therapy actually miss their manic symptoms and discontinue therapy for that reason. Even patients who are initially compliant and achieve long-term symptom relief may become noncompliant later on. For example, a patient who may have been well controlled on lithium or valproate for years may start to think that the illness is no longer active, discontinue the medication, and relapse into a manic state. Patients need to understand that the single worst reason to discontinue treatment is because it is working. Unfortunately, in some instances a health professional allows a patient to stop medication after a decade or two of being symptom-free. In any event, most patients diagnosed with bipolar disorder never get to the point of full response because of treatment noncompliance or lack of physician follow-up.

Another complicating factor relates to the well-supported but still controversial theory that the recurrence of bipolar disease is progressive; that is, the length of the interval between episodes decreases over time.[8] This concept of kindling suggests that vulnerability to bipolar episodes increases with each subsequent episode.[9] Likelihood of recovery may diminish over time in proportion to the number and frequency of relapse episodes. This phenomenon calls for a particular urgency in achieving remission during the first bipolar episode. Unfortunately, the natural progression of bipolar expression and diagnosis often includes a period of years between the onset of symptoms and an accurate diagnosis leading to effective treatment.[10] Therefore, by the time many patients are recognized as having bipolar disorder and enter the care of a qualified clinician, their disease may already be chronic in nature, making them prone to more frequent relapse. As with other aspects of bipolar disorder, the pattern of cycling is difficult to interpret because of the complex nature of the disease and the multiple factors likely responsible for precipitating symptoms. That is, it is unclear if multiple episodes make future treatment more difficult, or if certain patients simply have more intractable, recurrent disease regardless of how aggressively they are managed. Magnetic resonance imaging (MRI) studies in bipolar disorder have found that patients with subcortical white matter lesions may have a poorer outcome than those without these MRI findings, suggesting a possible biological predisposition for poor treatment response.[11] In addition, patients who relapse repeatedly may destroy their social network over time, making it difficult to sort out biological factors from the stress of abandonment. Such patients may never reach a point of recovery.

Table 1. Outcome of Patients With Bipolar Disorder in the Zurich Follow-Up Study[a]

Outcome Status	Patients, % (N = 219)
Recovered (GAS score > 60; no episodes over past 5 years)	16.0
Remitted (GAS score > 60) but still recurrent (< 5 years since last episode)	25.5
Incomplete remission (GAS score 1–60) over more than 5 years	7.8
Incomplete remission, course still recurrent	27.0
Chronic (last episode without remission, minimum length 2 years)	15.9
Suicide	7.8

[a]Reprinted, with permission, from Angst and Sellaro.[8] Median age at follow-up or death = 68 years.
Abbreviation: GAS = Global Assessment Scale.

INCIDENCE OF RELAPSE AND RECURRENCE

In the absence of effective intervention, relapse of bipolar disease is expected in most patients. Based on a 2-year follow-up of patients with bipolar disorder receiving lithium or placebo, 75% of patients receiving placebo were expected to relapse within the first year, compared with 30% to 40% of those receiving lithium.[12] Similarly, Tohen et al.[13] found a recurrence rate of 72% in a study of the natural progression of patients over 4 years following an initial episode of mania.

Despite treatment, relapse in bipolar disease is common. As stated by Angst and Sellaro, "Despite modern treatments the outcome into old age is still poor, full recovery without further episodes rare, recurrence of episodes with incomplete remission the rule, and the development of chronicity and suicide still frequent."[8(p445)] Experience at one of the authors' (G.S.) clinics indicates that slightly more than half of patients with bipolar disorder fail to reach recovery status over the course of a year. Angst and Sellaro reported the lifetime outcome of 219 bipolar patients in their Zurich follow-up study (Table 1). Despite modern treatments, only 16% of patients met the criteria for recovery, while 52% continued to experience recurrent episodes.[8]

Table 2. Maintenance Treatment Recommendations for Bipolar Disorder[a]

Guideline	First-Line Treatment	Next Interventions	Additional Comments
APA[22]	Lithium Valproate	Lamotrigine Carbamazepine Oxcarbazepine	Longevity of treatment based on "individual risks/benefits"
Expert Consensus[7]	Lithium or divalproex sodium	Carbamazepine: second-line treatment	Lifetime prophylaxis after 2 episodes of mania or 1 episode of severe mania; bipolar II after 3 episodes of hypomania or antidepressant-induced mania
TMAP[23]	No specific agent(s) preferred		Prophylaxis after 2 episodes of mania or 1 episode of mania with positive family history; use lowest dose to achieve therapeutic blood levels, taper adjunctive medications
CANMAT[24]	Once asymptomatic, maintain mood stabilizer at optimal serum levels, taper off benzodiazepine ± antipsychotics over 2–3 weeks; taper antidepressants over 6–12 weeks		Indefinite prophylaxis if history of recurrent episodes, severe illness, or with strong family history of bipolar disorder; after a single episode of low severity, or with no family history may taper off pharmacotherapy after 6–12 months over a 1- to 3-month period and monitor annually

[a]Adapted, with permission, from Goldberg.[20]
Abbreviations: APA = American Psychiatric Association Practice Guideline for the Treatment of Patients With Bipolar Disorder, CANMAT = Canadian Network for Mood and Anxiety Treatments, TMAP = Texas Medication Algorithm Project.

SUMMARY OF REALISTIC TREATMENT GOALS

As mentioned previously, realistic management goals may be limited to ongoing, short-term endpoints of obtaining and maintaining acute symptom control and suicide prevention. In most instances, this approach will necessitate some degree of maintenance drug therapy. Table 2 provides a summary of practice guidelines for maintenance treatment of bipolar disorder. The American Psychiatric Association simply asserts that the length of maintenance treatment should be decided on the basis of a case-by-case risk/benefit analysis. Other guidelines consistently recommend ongoing prophylaxis after a second manic episode. Prophylaxis is also recommended after an initial manic episode if the mania is particularly severe or if there is a strong family history of bipolar disorder. The natural course of the illness suggests that once a patient becomes stabilized on a particular mood-stabilizing regimen, therapy should never be discontinued for the sole reason that symptoms have apparently disappeared. In fact, some data suggest that discontinuation of lithium may actually increase the risk of bipolar symptoms, especially of mania.[14]

In the absence of toxicity, long-term lithium administration is appropriate in patients who achieve a good response. Although published case reports have described discontinuation-induced refractoriness or a gradual loss of response to lithium,[4,15] most studies have failed to observe a decline in efficacy.[16,17] Berghöfer and Müller-Oerlinghausen assessed bipolar morbidity in 22 patients treated with lithium for 20 years. Cumulative affective morbidity during the second 10 years was not statistically different from that observed during the first 10 years.[17] Interruption of lithium therapy has been associated with an increased risk for suicide,[18] leading some to suggest that continued lithium administration may be warranted for this reason alone, even if subjective symptom relief is poor.[16]

Continued antidepressant administration is not generally recommended in patients with bipolar disorder because of the risk of precipitating mania or rapid cycling.[19,20] Most guidelines suggest discontinuing the use of antidepressants within 3 to 6 months after depressive symptoms are in remission. However, at least 1 retrospective chart review study found that antidepressant discontinuation increased the risk of depressive relapse approximately 3-fold with no increased risk of mania in patients with bipolar disorder.[21] This issue will no doubt be the subject of further research, hopefully providing further insight into long-term antidepressant use.

Despite effective maintenance treatment, patients may still experience periodic depression or hypomania requiring short-term intervention with appropriate medication. Before assuming treatment refractoriness, it is prudent to rule out secondary causes of re-emergent symptoms, including substance abuse, medication noncompliance, or drug-drug interactions among medications. Patients on long-term lithium treatment who exhibit depressive symptoms should be evaluated for lithium-induced hypothyroidism.

As discussed, individual patients may have specific opinions regarding the acceptability of side effects in the pursuit of mental wellness. It is essential for the clinician to thoroughly explain the expected and potential risks of drug therapy and probe for patient feedback on how aggressively to approach treatment. Patient confidence and trust in the treating physician are critical to foster consistent long-term follow-up. Suicide prevention remains a treatment priority, along with aggressive symptom relief balanced with patient quality of life.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), clozapine (Clozaril and others), divalproex sodium (Depakote), fluphenazine (Prolixin, Permitil, and others) haloperidol (Haldol and others), lamotrigine (Lamictal), olanzapine (Zyprexa), oxcarbazepine

(Trileptal), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Narvane and others).

REFERENCES

1. Muller-Oerlinghausen B, Berghofer A, Bauer M. Bipolar disorder. Lancet 2002;359:241–247
2. US Office of the Surgeon General. Treatment of Mood Disorders. US Office of the Surgeon General, Report on Mental Health 2000. Available at: http://www.lorenbennett.org/osgtreat.htm. Accessed March 6, 2002
3. Ferrier IN. Characterizing the ideal antidepressant therapy to achieve remission. J Clin Psychiatry 2001;62(suppl 26):10–15
4. Hopkins HS, Gelenberg AJ. Treatment of bipolar disorder: how far have we come? Psychopharmacol Bull 1994;30:27–38
5. Ghaemi SN, Katzow JJ. The use of quetiapine for treatment-resistant bipolar disorder: a case series. Ann Clin Psychiatry 1999;11:137–140
6. American Council on Pharmaceutical Education. Understanding bipolar disorder: a treatment update. US Pharmacist Continuing Education, ACPE Program No. 430-000-00-005-H01. Available at: http://www.uspharmacist.com/NewLook/CE/bipolar/lesson.cfm. Accessed March 6, 2002
7. Sachs GS, Printz DJ, Kahn DA, et al. The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. Postgrad Med 2000;Special Issue (April):1–104
8. Angst J, Sellaro R. Historical perspectives and natural history of bipolar disorder. Biol Psychiatry 2000;48:445–457
9. Post RM, Rubinow DR, Ballenger JC. Conditioning and sensitisation in the longitudinal course of affective illness. Br J Psychiatry 1986;149:191–201
10. Lish JD, Dime-Meenan S, Whybrow PC, et al. The National Depressive and Manic-Depressive Association (NDMDA) survey of bipolar members. J Affect Disord 1994;31:281–294
11. Moore PB, Shepherd DJ, Eccleston D, et al. Cerebral white matter lesions in bipolar affective disorder: relationship to outcome. Br J Psychiatry 2001;178:172–176
12. Fleiss JL, Prien RF, Dunner DL, et al. Actuarial studies of the course of manic-depressive illness. Compr Psychiatry 1978;19:355–362
13. Tohen M, Waternaux CM, Tsuang MT. Outcome in mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. Arch Gen Psychiatry 1990;47:1106–1111
14. Suppes T, Baldessarini RJ, Faedda GL, et al. Risk of recurrence following discontinuation of lithium treatment in bipolar disorder. Arch Gen P sychiatry 1991;48:1082–1088
15. Post RM, Leverich GS, Altshuler L, et al. Lithium-discontinuation-induced refractoriness: preliminary observations. Am J Psychiatry 1992;149:1727–1729
16. Berghöfer A, Kossmann B, Müller-Oerlinghausen B. Course of illness and pattern of recurrences in patients with affective disorders during long-term lithium prophylaxis: a retrospective analysis over 15 years. Acta Psychiatr Scand 1996;93:349–354
17. Berghöfer A, Müller-Oerlinghausen B. Is there a loss of efficacy of lithium in patients treated for over 20 years? Neuropsychobiology 2000;42(suppl 1):46–49
18. Tondo L, Jamison KR, Baldessarini RJ. Effect of lithium maintenance on suicidal behavior in major mood disorders. Ann N Y Acad Sci 1997;836:339–351
19. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152:1130–1138
20. Goldberg JF. Treatment guidelines: current and future management of bipolar disorder. J Clin Psychiatry 2000;61(suppl 13):12–18
21. Altshuler L, Kiriakos L, Calcagno J, et al. The impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: a retrospective chart review. J Clin Psychiatry 2001;62:612–616
22. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2002;159:1–50
23. Dennehy EB, Suppes T. Medication algorithms for bipolar disorder. J Pract Psychiatry Behav Health 1999;5:142–152
24. Kusumakar V, Yatham LN, Parikh SV, et al. Bipolar disorder: a summary of clinical issues and treatment options. Halifax, Nova Scotia: CANMAT Monograph; 1997