An Evidence-Based Medicine Strategy for Achieving Remission in Bipolar Disorder

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Controlled trials have demonstrated the efficacy of several classes of drugs for achieving acute response in bipolar mania and depression. For many years, clinical response has been the primary outcome in the majority of short-term efficacy studies. However, there is a growing consensus that the optimal goal in the long-term management of bipolar disorder is remission. The purpose of this article is to briefly summarize the clinical importance of remission in bipolar disorder and to review data on the effectiveness of available treatments for achieving and sustaining remission.

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WHY IS REMISSION IMPORTANT?

In the acute treatment of bipolar disorder, response is typically defined as a ≥ 50% reduction from baseline in symptoms. Yet, one can easily see the challenge presented by using this metric as an end point. For example, the typical score at baseline for entry into acute mania clinical trials is a total score of 26 to 36 on the Young Mania Rating Scale (YMRS),[1] while the typical minimum score for admission into the study is ≥ 18. Thus, a 50% reduction in symptom severity (response) would place many patients with a score of 13 to 18 at study end point, a score that still indicates significant residual manic symptomatology in patients. In fact, a few of the "responders" could still be considered eligible for entry into the study. Similarly, in the treatment of bipolar depression, a patient who achieves a ≥ 50% reduction in scores on the Hamilton Rating Scale for Depression[2] (HAM-D) or Montgomery-Asberg Depression Rating Scale[3] (MADRS) continues to experience significant subsyndromic depressive symptoms.

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Why is the presence of residual symptomatology clinically significant? There are at least 3 empirical answers to this question. First, subsyndromic affective symptoms are highly persistent and cause significant subjective distress. Long-term naturalistic follow-up studies have found that patients experience clinically significant affective symptoms approximately 50% of the days in a year, with subsyndromal or minor depressive symptoms being the most frequent, followed by major depression and hypomania.[4,5] Second, subsyndromic levels of affective symptomatology are associated with significant impairment in functioning and quality of life, even among patients meeting criteria for remission.[6–8] Finally, residual affective symptomatology is associated with a 1.5- to 4-fold increased risk of relapse.[9,10] There appears to be a "dose-response" relationship between subsyndromic affective symptoms and risk of relapse. The risk of depressive relapse increases by 14% for every persistent DSM-IV depressive symptom and by 20% for every persistent manic/hypomanic symptom.[10]

Thus, "response" may be an adequate measure to assess how treatment is progressing early in the disease process, but it is an inadequate measure for clinicians and patients when the full disease course is considered. In layman's terms, response is "getting better" rather than "getting well." For a measure of wellness, clinicians rely on the term *remission*.

REMISSION AND RECOVERY: DEFINITIONS

According to the DSM-IV, remission is achieved when "during the past 2 months, no significant signs or symptoms of the disturbance were present."[11(p415)] The American Psychiatric Association Practice Guideline for the Treatment of Patients With Bipolar Disorder similarly emphasizes the need to achieve "a virtual lack of symptoms."[12]

Table 1. Severity Ratings of Commonly Used Mania and Depression Rating Scales

Rating	YMRS	MRS	HAM-D	MADRS
Severe	≥ 38	≥ 33	≥ 24	≥ 31
Moderate	26–37	21–32	18–23	25–30
Mild	20–25	15–20	13–17	15–24
Minimal	13–19	10–14	8–12	11–14
Remission	≤ 12	≤ 9	≤ 7	≤ 10

Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, MRS = Mania Rating Scale, YMRS = Young Mania Rating Scale.

Cut scores have been proposed on various clinical scales to operationally quantify threshold levels of manic and depressive symptomatology, below which a patient may be considered to be in remission. In clinical trials of bipolar disorder, the most frequently used mania rating scales are the YMRS[13] and Mania Rating Scale (MRS).[14] The most frequently used depression rating scales are the MADRS and HAM-D.

The YMRS and MRS are both 11-item clinician-rated scales that rate the severity of common symptoms of mania on a 5-point Likert scale (some subscale questions may be differentially weighted in scoring). Cut scores for each scale for mania and depression are shown in Table 1.

Other scales may also be used that are not specific to mood assessments. The Clinical Global Impressions-Severity of Illness[15] (CGI-S) and -Improvement[15] (CGI-I) scales are widely used, single-item measures of overall illness-related severity and improvement. A CGI-S score of 1 (not ill at all) or a CGI-I score of 1 (very much improved) are occasionally used as stand-alone remission criteria. However, it is preferable to use scales (e.g., MADRS, HAM-D) that directly assess key clinical dimensions of bipolar disorder. The CGI scales have also been used as 1 of several measures in composite criteria of remission.

The face validity of the proposed remission criteria appears to be good. However, few studies have evaluated the validity of these symptom-related remission criteria in bipolar patient samples against patient-centered outcomes such as quality of life, functional status, and other more subjective assessments that are very pertinent to patients.

When considering patient-centered outcomes, there is less consensus about which scales are the most valid and useful for measuring function and quality of life in bipolar disorder. One of the simplest and most widely used is the Global Assessment of Functioning (GAF) scale, which is a single-item measure that asks the clinician to provide a combined rating of an individual's psychological, social, and occupational functioning on a continuum that ranges from superior mental health to severe illness.[16] Individuals with a GAF score ≥ 81 have absent or minimal evidence of functional impairment, a GAF score of 71 to 80 indicates transient impairment, a GAF score of 61 to 70 indicates mild impairment, a GAF score of 51 to 60 indicates moderate impairment, and a score of ≤ 50 indicates severe impairment.[16] Some research suggests that the GAF is a reliable and valid measure of functioning in patients with a wide range of mental illness.[17]

Various criteria have also been proposed for full or sustained remission, or what some call "recovery." The DSM-IV defines full remission as being without significant symptoms, but does not operationally define symptom severity criteria on depression or mania rating scales. It is useful to distinguish between remission and recovery. Patients in remission may be considered "recovered" if their remission has continued for a criterion duration of time (from 2 months to 2 years) and if their remission is associated with a full return to normal functioning.[18] The return to normal functioning is the crucial criterion that distinguishes remission, which is largely a symptom-based outcome, from recovery. The importance of this distinction is underscored by a series of studies that have demonstrated continued functional impairment in patients who have achieved remission but still have residual or "subsyndromal" symptoms that have limited their return to functioning.[8,19]

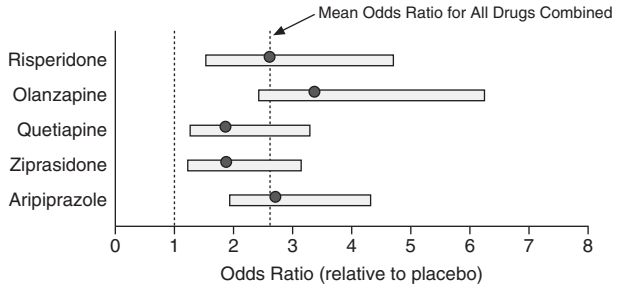
REMISSION IN BIPOLAR MANIA: DATA FROM CONTROLLED CLINICAL TRIALS

For patients meeting DSM-IV criteria for bipolar mania, response rates after 3 weeks of acute treatment with atypical antipsychotic medications average between 45% and 60%.[20] Response rates for mood stabilizers (lithium, valproate, carbamazepine) are in the same range, compared to placebo response rates of approximately 30%. A recent meta-analysis of the efficacy of monotherapy with atypical antipsychotics (Figure 1) reported an odds ratio of approximately 2.5 relative to placebo.[1]

Fewer double-blind, placebo- or comparator-controlled trials have been published that report remission rates after acute treatment. Pooled data are available demonstrating that 3 weeks of monotherapy with risperidone,[21] olanzapine,[20] and quetiapine[22] each results in remission rates that are significantly higher than placebo using a YMRS score ≤ 12 as the remission criterion. The magnitude of remission after acute treatment is in the range of 40% to 50%, with an odds ratio relative to placebo similar to what is observed when response is used as the outcome. Results of controlled comparator trials have not found significant differences between atypical and conventional antipsychotics in the ability to achieve remission after short-term treatment.[23–25] As in clinical trials of schizophrenia, the between-class differences are more attributable to tolerability than efficacy.

Three studies are available that provide remission data for acute treatment comparisons of mood stabilizers versus quetiapine[26] and olanzapine.[27,28] Treatment with

Figure 1. Efficacy of Atypical Antipsychotic Drugs as Acute Monotherapy for Bipolar Mania: Odds Ratios [95% CI] Relative to Placebo for 50% Improvement (random effects model)[a,b,c,d]



[a]Adapted with permission from Perlis et al.[1]
[b]Bars represent 95% confidence intervals.
[c]All atypicals were significant vs. placebo.
[d]There were no significant between-drug differences.

quetiapine and lithium as acute monotherapy interventions appears to have comparable efficacy in achieving remission within the 12-week study treatment period.[26] In contrast, treatment with olanzapine was reported to produce higher remission levels compared with divalproex over the 47-week study.[28]

Two double-blind, placebo-controlled trials have evaluated the efficacy of combination pharmacotherapy in achieving remission, defined as a YMRS score ≤ 12. In 1 study,[29] treatment with quetiapine, in combination with the mood stabilizers lithium or divalproex, resulted in significantly higher week 3 remission rates than monotherapy with the mood stabilizer. Clinically significant depression, defined as a 4-point or greater increase in the MADRS score to a total score of at least 18, occurred in 10% of each treatment group by week 3. In a second study,[30] treatment with combination therapy with quetiapine and a mood stabilizer produced significant remission rates compared to monotherapy with a mood stabilizer. Treatment-emergent depression occurred in 17% of patients receiving adjunctive quetiapine and in 14% of patients taking mood stabilizers alone.[30]

When assessing remission data, it is important to realize that most clinical trials were not designed to measure remission. Remission rates, when available, are usually a secondary measure.[26] The clinical trial's primary measure is the response to the active drug compared with placebo or an active comparator. This important distinction impacts the clinician's interpretation of the literature in 2 ways.

First, the clinician must be aware that the definition of remission varies across studies. Though a YMRS score ≤ 12 is commonly used, it may not be the best indication for remission, as it still permits significant residual symptoms. Thus, when studies use a more stringent YMRS score, remission rates naturally decline.[23] Further, limiting the definition of remission to manic symptomatology ignores the possibility that depressive symptoms may develop during the course of acute treatment. For example, in one 3-week mania treatment study,[24] clinically significant depression (HAM-D score ≥ 15) developed in 16.8% of patients treated with haloperidol and 9.4% of patients taking olanzapine. Studies that report remission based on lower YMRS scores and dual mania/depression remission criteria are available for several of the atypical antidepressants.[31,32] As might be expected, remission rates are somewhat lower when more stringent composite criteria are applied.

Second, the duration of the clinical trial is highly correlated with the levels of remission achieved in the trial. For example, in one 3-week trial,[29] remission rates were higher for quetiapine (47%) and lithium (49%) compared to placebo (22%). When the study was extended to include an additional 9 weeks (12 weeks total) of treatment, remission rates (last-observation-carried-forward analysis) were 69% for quetiapine and 72% for lithium (72%) compared to 34% for placebo. In a study of similar design,[25] remission rates for quetiapine versus placebo were not significantly different at 3 weeks; however, an additional 9 weeks of treatment increased remission rates to 61% for quetiapine and 63% for haloperidol compared to 38% for placebo ($p < .001$ for both comparisons).

REMISSION IN BIPOLAR DEPRESSION: DATA FROM CONTROLLED CLINICAL TRIALS

Compared to bipolar mania, there are relatively few clinical trials available that evaluate the treatment of bipolar depression, and many of these studies have small sample sizes. From an evidence-based medicine standpoint, this is both unfortunate and paradoxical, since depressive episodes in bipolar disorder are much (> 2-fold) more frequent and persistent than manic or hypomanic episodes.[4,5]

Current practice guidelines recommend lithium or lamotrigine as the initial treatments for bipolar depression.[12] But the evidence to support this recommendation is weak: for lithium, it is based on consistently favorable results from multiple small and/or poorly designed trials[33,34]; for lamotrigine, it is based on the results of 1 large study[35] that found efficacy to be most consistently significant for the 200-mg dose. Almost no data on remission rates are available from early trials of lithium or lamotrigine in bipolar depression.

In the past 5 years, a series of articles have reported remission data from double-blind bipolar depression trials of antidepressants combined with mood stabilizers[36–41] and atypical antipsychotics (without concurrent mood stabilizers; Table 2 includes a summary).[42–44] Published remission data are not available for aripiprazole and ziprasidone in bipolar depression. Among available studies, monotherapy

Table 2. Recent Double-Blind Studies Reporting Remission Data of Patients Diagnosed With Bipolar Depression

Study	Drug, Sample Size	Treatment Duration, wk	Mood Stabilizer	Remission Criteria	Remission Rate, %
Nemeroff et al 2001[36]	Imipramine, N = 35 Paroxetine, N = 35 Placebo, N = 43	10	Lithium	HAM-D score ≤ 7	46 39 35
McIntyre et al 2002[37]	Bupropion–sustained release, N = 18 Topiramate, N = 18	8	Divalproex, lithium	HAM-D score ≤ 7	25 40
Vieta et al 2002[38]	Paroxetine, N = 28 Venlafaxine, N = 27	6	Lithium, valproate, carbamazepine	HAM-D score ≤ 10 and CGI-I score ≤ 1	32 33
Tohen et al 2003[42]	Olanzapine, N = 351 Olanzapine/fluoxetine, N = 82 Placebo, N = 355	8	None	MADRS score ≤ 12	33* 49* 25
Brown et al 2006[44]	Olanzapine/fluoxetine, N = 205 Lamotrigine, N = 205	7	None	MADRS score ≤ 12 (≤ 7)	56 (37)[b] 49 (31)[b]
Shelton and Stahl 2004[41]	Risperidone, N = 10 Paroxetine, N = 10 Risperidone + paroxetine, N = 10	12	Divalproex, lithium, carbamazepine, topiramate	HAM-D score ≤ 7	10 20 30
Calabrese et al 2005[43]	Quetiapine-300 mg, N = 172 Quetiapine-600 mg, N = 170 Placebo, N = 169	8	None	MADRS score ≤ 12	53* 53* 28
Schaffer et al 2006[39]	Citalopram, N = 10 Lamotrigine, N = 10	12	None	MADRS score ≤ 8	60 33
Post et al 2006[40]	Bupropion, N = 51 Sertraline, N = 58 Venlafaxine, N = 65	10	Lithium, valproate, carbamazepine, lamotrigine[a]	IDS score ≤ 12	37 34 25

[a]Twenty-two percent of patients were also taking a concomitant antipsychotic.
[b]The first number relates to patients with a MADRS score ≤ 12, and the number in parentheses relates to patients with a MADRS score ≤ 7.
*p < .05 vs. placebo.
Abbreviations: CGI-I = Clinical Global Impressions-Improvement, HAM-D = Hamilton Rating Scale for Depression, IDS = Inventory of Depression Symptomatology, MADRS = Montgomery-Asberg Depression Rating Scale.

with quetiapine appeared to be the most effective treatment among the atypical antipsychotic drugs studied, followed closely by the olanzapine-fluoxetine combination therapy.[42–44] The results of many of the bipolar depression studies must be viewed with caution due to small sample sizes.

In the Post et al. study,[40] switch to mania or hypomania by 10 weeks was significantly more frequent among patients treated with venlafaxine (21%) than either bupropion (14%) or sertraline (16%, p = .03). Higher switch rates were also reported in the Vieta et al. study[38] for venlafaxine (13%) versus paroxetine (3%) and in the Nemeroff et al. study[36] for imipramine (8%) versus paroxetine (2%). The rate of premature discontinuation from the Post et al.[40] study was also higher for venlafaxine (45%) compared to sertraline (41%) and bupropion (31%).

Several tentative clinical conclusions may be drawn from these results. First, venlafaxine appears to be a poor choice in bipolar depression due to a lower remission rate, a higher switch rate, and a higher overall attrition rate.[38,40] Treatment of bipolar depression with tricyclic antidepressants is associated with a significantly increased risk of switching compared to selective serotonin reuptake inhibitor antidepressants.[45] The shared risk may be attributable to the dual serotonin/norepinephrine reuptake–inhibiting mechanism of action shared by tricyclic antidepressants and venlafaxine. The risk of switching for venlafaxine is correlated with high bipolar episode frequency (≥ 4 per year). A second conclusion is that antidepressants appear to have lower efficacy overall in bipolar depression compared to what is observed in the extensive literature on unipolar depression.

SUSTAINED REMISSION AND RECOVERY

A small number of controlled trials have examined the ability to sustain remission during maintenance therapy of bipolar mania. In a double-blind, 47-week treatment study, remission of manic symptoms increased from week 3 to week 47 in patients who took olanzapine (47% up to 57%) and divalproex (34% up to 46%).[28] It should be noted that use of dual remission criteria (both mania and depression) resulted in a substantial reduction in remission rates for both olanzapine (30%) and divalproex (28%).[28] This is not surprising given the higher percent of days per year spent experiencing depression. It does, however, underscore the challenge in devising effective long-term treatment strategies that will ensure sustained remission of all affective symptoms.

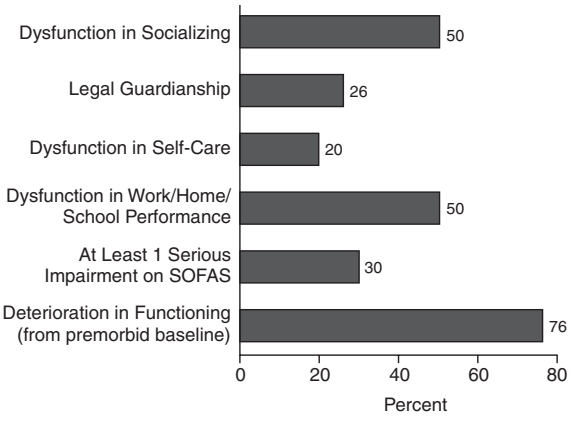
The difficulty in achieving (and maintaining) sustained remission is illustrated by a prospective study of patients (N = 113) diagnosed with bipolar mania who received 28 weeks of open-label treatment with olanzapine after completing a 3-week, double-blind, placebo-controlled trial.[46]

Seventy percent of patients achieved symptomatic remission at some time during the trial, while 30% did not. Of the 70% who achieved remission, half of them achieved sustained remission (defined as ≥ 8 weeks in remission), while the other half failed to do so. Among the subgroup of sustained remitters, 23% became symptomatic again, while only 12% (of the total sample) maintained their remission through to the end of open-label treatment.[46] As expected, the subgroup reporting sustained remission had significantly higher scores on the Medical Outcomes Study 36-Item Short-Form Health Survey, but unemployment rates were similar for both the sustained and nonsustained remission groups (32% vs. 30%).[46]

The gap between symptomatic remission and sustained remission with functional recovery is illustrated by a 2-year naturalistic follow-up study of patients hospitalized with a first-episode manic (or mixed) episode.[47] At 2 years, 72% of patients met stringent remission criteria (YMRS score ≤ 5, HAM-D score ≤ 8). In contrast, rates of functional recovery (defined as a return to an occupational level and residential status that equaled or exceeded the patient's highest level in the year before hospitalization) were much lower at 6 months (40%) and at 2 years (43%).[47]

Returning the patient with bipolar disorder to full functional recovery remains an elusive goal. One concern is that the measures of functioning and quality of life employed in standard clinical trials do not fully capture the scope of bipolar-related impairment, as illustrated by results from a community sample of patients with bipolar disorder[48] in which 76% of patients reported significant deterioration in functioning from their premorbid baseline screen (Figure 2). Future treatment research using remission and recovery as gold standard end points will benefit from an increased use of patient-centered outcomes, currently reported in a minority of treatment studies.

Figure 2. Functional Impairment in the Past Year: Social and Occupational Functioning Assessment Scale (SOFAS) Data in Bipolar I Patients in the Community (N = 112)[a]



[a]Based on Morgan et al.[48]

TREATMENT STRATEGIES FOR MANAGING PATIENTS WHO DO NOT ACHIEVE REMISSION

An important clinical question is what constitutes an adequate trial in both bipolar mania and bipolar depression. At present, there are insufficient empirical data to determine the maximal duration of acute treatment beyond which further clinical improvement (to remission) is unlikely to occur. It is at this asymptotic point that other treatment strategies should be considered.

Large effectiveness trials are needed to evaluate whether (and when) switching or augmentation is the optimal strategy for converting clinical response to remission and recovery. It is hoped that the anticipated results of the Systematic Treatment Enhancement Program for Bipolar Disorder[49] study will help elucidate these clinical conundrums. Studies of bipolar depression are probably more urgent, because less information is available, and the overall burden of illness is higher.

Research to enhance remission cannot be counted as successful unless progress can be made in understanding and solving the problems of attrition and treatment nonadherence. Nonadherence in bipolar patients has been estimated to occur in > 40% of patients.[50] Attrition rates are the same or higher in long-term bipolar treatment studies.[49] Little prospective research has been conducted to test various strategies for increasing treatment adherence and reducing discontinuation.[50]

PREDICTORS OF REMISSION

Multiple studies have attempted to identify predictors of clinical outcome in bipolar disorder.[51–54] Variables identified by these studies as predicting a favorable clinical outcome include (1) treatment adherence, (2) absence of psychotic symptoms, (3) absence of alcohol or substance abuse, (4) lower depression scores, (5) absence of history of rapid cycling or high number of previous episodes, (6) absence of Axis I psychiatric comorbidity, (7) later age at first onset, and (8) higher levels of premorbid functioning.

Several points may be made about predictive models. First, no published data are available that specifically predict remission and that also meet the following minimal methodological criteria: (1) are based on multivariate models to identify independent predictors, (2) have an adequate sample size and correction for multiple comparisons, (3) use a representative sample of bipolar patients that is not limited to a convenience sample of manic patients entering a treatment study, and (4) use a multidimensional (manic and depressive) remission criterion. Second, published studies that report predictors of clinical outcome often have contradictory results. Finally, the amount of variance accounted for by the model tends to be relatively low.

CONCLUSIONS

An evidence-based review finds that remission rates for current treatments of bipolar disorder are significant compared to placebo, but the magnitude of this gold standard outcome continues to be low. Treatment response in mania is relatively high and occurs in the first few weeks of treatment, while response in bipolar depression is somewhat lower and slower to occur. However, residual symptoms after acute treatment occur in the majority of patients, are highly persistent, and are very resistant to continued therapy. Even when sustained remission is achieved, it is not typically maintained for long periods of time. As a result, only a minority of patients achieve a full functional recovery.

Given that the prevalence of bipolar disorder is more than 3-fold higher than schizophrenia and the chronicity and burden imposed by the illness, the relative dearth of adequately powered treatment studies is striking. A future research agenda must include remission and recovery as standard outcomes and must systematically examine augmentation and other treatment strategies that will optimize the likelihood of achieving these outcomes.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), divalproex (Depakote), haloperidol (Haldol and others), imipramine (Tofranil, Surmontil, and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine/fluoxetine (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), topiramate (Topamax), venlafaxine (Effexor and others), ziprasidone (Geodon).

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

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