Stabilization of Mood From Below Versus Above Baseline in Bipolar Disorder: A New Nomenclature

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Management of bipolar disorder has traditionally emphasized the acute treatment of mania. Although acute treatment of mania is a critical aspect of care, this emphasis has tended to overshadow other important phases of bipolar disorder, such as depression, hypomania, and subsyndromal symptoms. We offer a reconceptualization of bipolar disorder that highlights unmet needs and the importance of differential spectra of efficacy. In this reconceptualization, bipolar disorder can be viewed as an aberration of mood, behavior, and cognition from baseline (euthymia). "Below baseline" is characterized by depression and subsyndromal depression. "Above baseline" is characterized by mania, mixed states, hypomania, and subsyndromal mood elevation. In contrast to the treatment options for mania, the options for depression are limited. This new nomenclature emphasizes the need to develop mood stabilizers that possess the ability to stabilize mood "from below baseline," either alone or in combination with other agents. In this article, the treatment options for bipolar disorder, with a focus on depression and rapid cycling, are discussed according to this new conceptualization of management from below and above baseline.

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The depressive phase of bipolar disorder is associated with considerable morbidity. Indeed, the magnitude of the morbidity associated with the depressed phase of bipolar disorder tends to be underappreciated. Since manic episodes frequently present as medical emergencies requiring hospitalizations, the acute management of this phase consumes significant health care resources and, as a result, tends to receive a great deal of attention. Although these highly acute, and sometimes dramatic, presentations lead to substantial human suffering and cost, the mean duration of the depressive phase of bipolar disorder is longer than that of manic episodes, and runs a chronic course in more than 20% of cases.[1] A recent study[2] evaluating quality-of-life measures documented significantly lower scores for patients with bipolar disorder with depressed or mixed episodes on both the Medical Outcomes Study Short Form-12 (SF-12) mental subscale and the EuroQol when compared with euthymic patients or with patients with a manic or hypomanic episode. In addition, more suicides occur during depressed and mixed episodes.[3] Thus, more effective treatments for bipolar depression are needed and are critical for reducing suffering associated with the disorder and for decreasing the risk of adverse consequences, such as suicide. These observations suggest the need for a mood stabilizer with a broader spectrum of efficacy or combinations of mood stabilizers that collectively result in a bimodal response, managing not only the acute manifestations of mania, but also the morbidity and mortality associated with the depressed and mixed phases of the illness over its natural history.

The "bias" toward the importance of the management of mania over the last 50 years may also have in part been due to the spectrum of efficacy of the available medications. Most of the recently introduced medications (anticonvulsants and atypical antipsychotics) have initially been investigated for use in the management of mania. At present, most of these agents have not been studied compared with placebo in the acute treatment of bipolar depression. Until recently, there has been no systematic effort to develop mood stabilizers for use in the depressed phase of this disorder. Thus, there has been a lack of well-evaluated treatment options for bipolar depression, a clinical dilemma especially problematic for patients with

rapid cycling, whose hallmark has been described as the frequent recurrence of depression.[4]

This review will be organized around a proposed reconceptualization of the treatment of bipolar disorder and a nomenclature for mood stabilizers that emphasizes differences in spectrum of efficacy. We propose a nomenclature that describes these agents as either stabilizing mood "from above baseline" or "from below baseline." We will discuss the currently available treatments accordingly and place special emphasis on how these agents meet unmet needs in the management of depressive symptoms and the rapid-cycling variant of bipolar disorder.

STABILIZING MOOD

A consensus definition of a mood stabilizer remains to be established. Some have defined mood stabilizers as medications that possess direct efficacy, defined as a clinically significant decrease in episode severity, duration, or frequency, in both phases of the illness.[5] Others have proposed that a mood stabilizer be liberally defined as a medication that is effective in decreasing episode severity, duration, or frequency in one phase of bipolar disorder without causing a negative effect on other phases (i.e., without switching or cycle acceleration).[6,7] Treatments that satisfy the first, more conservative definition include lithium and possibly carbamazepine, divalproex sodium, and electroconvulsive therapy (ECT) as well. Treatments satisfying the second definition would include lithium, carbamazepine, divalproex, some of the atypical antipsychotic agents, ECT, and lamotrigine. In this article, the more inclusive definition of mood stabilization is used.

Bipolar rapid cycling, recognized since 1994 as being a distinct course modifier,[8] is a major clinical challenge, and the use of mood stabilizers is especially important because of the potential for antidepressants to destabilize the course of the illness.[9] Not only is this variant of bipolar disorder more difficult to treat, the depressive episodes in bipolar rapid cycling appear to be 2 to 3 times more frequent than hypomanic episodes.[10] The treatment-resistant nature of bipolar rapid cycling was first reported by Dunner and Fieve[11] in 1974 and then later replicated by Kukopulos et al.[12] in 1980. In the 1990s, the studies of divalproex by Calabrese and associates[4,13,14] showed that hypomania and mania in rapid cycling were relatively easy to control, but that depression was more frequently refractory to treatment.

NEW CONCEPTUALIZATION

Bipolar disorder can be viewed as an aberration of mood, behavior, and cognition from baseline (euthymia). "Above baseline" are mania, mixed states, hypomania, and subsyndromal mood elevation. "Below baseline" are depression and subsyndromal depression. We propose that agents stabilizing mood "from above baseline" (Class A) would treat mania or hypomania and would not exacerbate depressive symptoms. In contrast, agents stabilizing mood "from below baseline" (Class B) would effectively treat depressive symptoms without inducing mania or hypomania. Thus, the conceptualization of bipolar disorder proposed provides a novel nomenclature that highlights unmet need and helps to refocus management of the disease by emphasizing the relative efficacy of mood stabilizers to treat different phases of the illness (Table 1).

Table 1. Proposed Nomenclature for Mood Stabilizers

Class A	1. Agents that stabilize mood "from **A**bove baseline"
	2. Agents that possess marked antimanic properties without causing a worsening of depression; ie, lithium, carbamazepine, divalproex, the atypical antipsychotics, and electroconvulsive therapy
Class B	1. Agents that stabilize mood "from **B**elow baseline"
	2. Agents that possess marked antidepressant properties without destabilizing the course of the illness by inducing switches into mania or episode acceleration, ie, lamotrigine, lithium, and electroconvulsive therapy

STABILIZING MOOD FROM ABOVE BASELINE

Stabilizing mood "from above baseline" refers to the management of mania, hypomania, psychotic symptoms associated with manic episodes, and subsyndromal mood elevation. These symptoms can be acutely and prophylactically managed with lithium, divalproex, and carbamazepine, and they are acutely responsive to ECT. Atypical antipsychotics (such as olanzapine, risperidone, and ziprasidone) may also be used, not only for the management of psychotic symptoms in mania, but as specific acute treatments for mania. Many controlled studies have evaluated the antimanic effectiveness of lithium,[15–18] divalproex,[18,19] and carbamazepine,[20–22] and these agents appear to meet specifically our definition of effective mood stabilizers "from above," i.e., they are agents that effectively treat mania and hypomania without inducing depressive episodes. Likewise, there is evidence supporting the classification of ECT and the atypical antipsychotics[23,24] as effective mood stabilizers from above. Conventional antipsychotics do not meet our definition of agents that stabilize mood "from above baseline," as they may worsen the depressive component of the illness.[25]

STABILIZING MOOD FROM BELOW BASELINE

Stabilizing mood "from below baseline" refers to the management of the depressive symptoms of bipolar disorder by agents that have marked antidepressant properties but low risk of switching or cycle acceleration. Currently

available agents that may fit this definition include lithium, lamotrigine, and ECT. Other options that have been explored include carbamazepine and the atypical antipsychotics. Antidepressants do not meet our definition because of their risk of inducing mania or cycle acceleration.

CLASSIFICATION OF THE MEDICATIONS USED IN BIPOLAR DISORDER

Lithium

The effectiveness of lithium in the acute and prophylactic treatment of bipolar depression has been extensively studied. As noted by Goodwin and Jamison,[3] early uncontrolled studies of the use of lithium in bipolar depression did not support its efficacy. However, later controlled studies revealed efficacy in bipolar depression. A review of 7 of these studies found an overall response rate of 79% in bipolar depression.[3] Strakowski et al.[26] noted that studies of lithium in the acute treatment of bipolar depression have reported a wide range of response rates, from 44% to 100%. However, the authors note that many of these responses were not complete. Controlled studies have also confirmed the value of lithium in prophylactic treatment of bipolar disorder.[27,28] These studies suggest that lithium is effective at preventing both depressive and manic episodes. Clinical experience and naturalistic studies, however, suggest that efficacy in controlled studies cannot be duplicated to the same degree in the typical office practice, absent the vigilant follow-up and patient contact that play a large role in controlled trials.

Maj and colleagues,[29] for example, assessed 375 patients with bipolar type I disorder treated with lithium maintenance over a 5-year period, during which lithium levels were checked regularly. Consistent with the naturalistic design, the treating physician could adjust treatment as needed. Of the 337 patients (90%) available for follow-up at 5 years, 228 (68%) were still taking lithium. In these patients, 39% had no affective episode during the study period, and 47% had at least 1 affective episode, although with a considerable reduction in morbidity (50%) as compared with the 2-year period preceding the index episode. However, patients with rapid cycling were underrepresented in the marked responder group and overrepresented in the nonresponder group.

In a recent report by Tondo et al.[30] of lithium maintenance therapy for 360 patients with bipolar type I and bipolar type II disorder, lithium maintenance resulted in statistically significant reductions in (1) annual mean rates of mania, depression, and hospitalization; (2) percentage of time in a mood episode; and (3) episode duration. Specifically, annual mean rates of depression were reduced from 0.84 before lithium to 0.45 during lithium maintenance (46% reduction); percentage of time depressed was reduced from 25% to 12% (52% reduction); and duration of depressive episodes was reduced from 4.84 to 3.27 months (32% reduction). However, the generalizability of this study is complicated by its enrollment, which excluded patients who had comorbid alcohol and drug abuse or those that required extended treatment with concurrent antipsychotics or anticonvulsants.

The studies by Maj and colleagues and Tondo and colleagues thus suggest that lithium maintenance benefits a significant number of patients with bipolar depression, and even if breakthrough episodes are not suppressed, a reduction in morbidity may be achieved. However, dropout rates are high, and a significant number of patients have a suboptimal response, thus emphasizing the need for other options for bipolar depression. These data suggest lithium works well in classic bipolar patients, but less well in those with atypical variants such as rapid cycling. Of all of the mood stabilizers currently available, lithium probably comes closest to meeting our definitions of stabilizing mood from both "above" and "below" baseline.

Divalproex

The effectiveness of divalproex in the acute and prophylactic treatment of bipolar depression has not been extensively studied, and there are no published placebo-controlled acute bipolar depression studies reported to date. However, 2 controlled maintenance studies have shown some evidence of efficacy in preventing depressive episodes.[31,32]

Lamotrigine

Several double-blind, placebo-controlled trials have demonstrated the acute and prophylactic antidepressant activity of lamotrigine in bipolar disorder.[33–37] Its acute antidepressant efficacy has most clearly been demonstrated in patients with bipolar I disorder.[33] Its prophylactic efficacy has been demonstrated in patients with treatment-refractory[37] and rapid-cycling bipolar disorder,[34] as well as a cohort of recently manic patients with bipolar I disorder.[35] In 2 placebo-controlled acute mania studies, lamotrigine failed to show efficacy.[38] In 1 small double-blind comparison with lithium, no difference in acute antimanic efficacy was observed,[39] perhaps due to low statistical power. In 2 of 3 placebo-controlled studies, lamotrigine failed to show acute efficacy in recurrent major depressive episodes[40]; there are, however, anecdotal reports of efficacy in treatment-refractory patients with recurrent major depression.[37]

Carbamazepine

Two controlled trials[41,42] have evaluated the acute antidepressant efficacy of carbamazepine in 78 patients with either unipolar depression or bipolar depression. Carbamazepine appeared to be more effective than placebo, but only one third of patients were moderate-to-marked responders. About half of carbamazepine nonresponders appeared to respond to blinded lithium augmentation. Early

reports suggested that rapid cycling was a predictor of positive response to carbamazepine[43]; more recent data have refuted this observation.[44–46] The only prospective, double-blind, random-assignment study of the efficacy of carbamazepine in the treatment of rapid-cycling bipolar disorder is that of Denicoff and colleagues.[46] In a post hoc analysis,[46] 52 rapid cyclers and outpatients without rapid cycling were evaluated in a 3-year crossover comparison of carbamazepine, lithium, and the combination of the two. More patients with rapid cycling receiving lithium monotherapy (28%) than carbamazepine monotherapy (19%) reported moderate-to-marked improvement; 56% of rapid cyclers receiving the combination reported similar improvement. There is a significant methodological issue that has complicated the interpretation of the data from these 4 reports, however: the reports have all evaluated the efficacy of carbamazepine in mixed cohorts of patients with and without rapid cycling. What remains unclear is whether carbamazepine would be more effective than lithium in a homogeneous rapid-cycling cohort.

Electroconvulsive Therapy

ECT has been shown in open prospective trials and retrospective studies to be an efficacious treatment for bipolar depression, with reported efficacy rates ranging from 50% to 100%.[47–52] Consensus guidelines recommend ECT for patients with severe bipolar depression with psychosis or as second-line therapy for patients with severe depression without psychosis and patients at risk for suicide or with medical complications.[53] However, while ECT has been shown to be safe, its disadvantages include expense, inconvenience, a high relapse rate, and effects on recall and memory, which may limit its use in some patients.[54]

Atypical Antipsychotics

Open-label studies suggest that atypical antipsychotics may treat depressive symptoms associated with the manic phase of bipolar disorder without worsening mania or causing cycle acceleration.[55] However, their efficacy in acute bipolar depression and depression prophylaxis remains to be determined in controlled trials. Open-label studies and case reports have suggested that atypical antipsychotics may be efficacious in the treatment of rapid-cycling disorder,[56–58] but placebo-controlled studies are lacking.

Antidepressants

Traditionally, the depressed phase of bipolar disorder has been treated with antidepressants when lithium and the anticonvulsants have been insufficient. The adjunctive use of antidepressant medications in bipolar depression is common, but this practice can put patients with bipolar disorder at increased risk for the development of hypomania and mania.[59] There is only 1 large, placebo-controlled trial that has been published in bipolar I depression.[60] In that study, paroxetine augmentation of lithium was no more effective than lithium alone or imipramine plus lithium. However, switch rates with paroxetine were significantly lower than those with imipramine plus lithium, confirming prior suggestions that the tricyclic antidepressants (TCAs) present the highest risk of switching. Indeed, Peet[61] pooled data from several published studies and found that manic switch rates were similar for selective serotonin reuptake inhibitors and placebo (3.7% and 4.2%, respectively), which were significantly lower than the rate for TCAs (11.2%).

In a review of 9 clinical studies of switch rates in patients with bipolar I depression, Calabrese and colleagues[62] concluded that low rates of switching were found with lamotrigine, paroxetine, and moclobemide, whereas TCAs and monoamine oxidase inhibitors had the highest rates of switching. Although mixed, the literature on antidepressants suggests a risk of rapid-cycling induction and shows that antidepressants, particularly TCAs, have not been shown to be effective in the treatment of rapid cycling. In addition, in 14 open-label reports since 1956 (N = 71),[63] a 2% to 67% prevalence of episode acceleration has been reported following the use of TCAs and monoamine oxidase inhibitors. Combined, these data suggest that the antidepressants do not fit our definition of agents that stabilize mood "from below baseline."

CONCLUSION

Viewing the management of bipolar disorder from the perspective of stabilization of mood from either above or below baseline helps to refocus management of the disease by emphasizing unmet need and the relative efficacy of mood stabilizers to treat either mania/hypomania or depression. When viewed from this perspective, several pharmacologic options to stabilize "from above baseline" are available, but those that stabilize "from below baseline" are limited. This nomenclature tends to emphasize the importance of achieving a broad spectrum of coverage through the concurrent use of medications that possess complementary differential spectra of efficacy.

Lithium remains the most extensively studied mood stabilizer and has demonstrated the best overall efficacy for the acute and prophylactic management of both phases of bipolar disorder. However, outside the context of controlled clinical trials, patients tend to discontinue lithium due to side effects and inconvenience (the need for monitoring blood levels and renal function, etc.); its effectiveness then becomes highly variable. In several recent double-blind, placebo-controlled trials, lamotrigine has been shown to possess acute and prophylactic antidepressant properties in bipolar I and II depression, including patients with rapid cycling. This new nomenclature emphasizes the need to develop mood stabilizers that possess the ability to stabilize mood "from below baseline," either alone or in combination with other agents. To that end,

prophylactic randomized controlled trials that combine mood stabilizers from both Class A and B (i.e., lithium plus lamotrigine vs. lithium alone, or valproate plus lamotrigine vs. valproate alone) need to be conducted.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), lamotrigine (Lamictal), olanzapine (Zyprexa), paroxetine (Paxil), risperidone (Risperdal), ziprasidone (Geodon).

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