Treatment of Bipolar Depression

Evolving Recommendations

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KEYWORDS

• Lithium • Anticonvulsants • Atypical antipsychotics • Anxiety • Substance abuse • Rapid cycling • Neurotrophic factors • Psychoeducation

KEY POINTS

- Depression is the most common and most difficult-to-treat phase of bipolar disorder, and it is associated with multiple psychiatric and medical comorbidities.
- Antidepressant augmentation of a mood stabilizer is no longer a first-line treatment recommendation and is replaced by selected atypical antipsychotics.
- The comorbidities of bipolar depression and goal of achieving and maintaining remission almost invariably require complex combination therapy.
- After the atypical antipsychotics, most of the potential treatments and augmentation strategies are off-label, so careful monitoring and evaluation of individual patients is essential.
- A greater number of depressive episodes is associated with more cognitive dysfunction, brain abnormalities, and treatment refractoriness, such that early and sustained pharmacoprophylaxis is the key to treatment success.

INTRODUCTION

Treatment of bipolar depression is a critical problem in psychiatry, as bipolar depression is responsible for enormous personal and occupational losses, psychiatric and medical comorbidities, cognitive dysfunction, and many years of lost life expectancy. Bipolar depression is the more difficult phase of bipolar disorder to treat, and patients undergoing naturalistic treatment are depressed 3 times more than they are manic.[1] Despite the high prevalence of bipolar depression and its severe consequences, there has been a many decades-long deficit in clinical treatment research and studies of the syndrome. Conventional treatment of bipolar depression toward the end of the twentieth century typically included antidepressant augmentation of mood stabilizers. However, the past decade has seen increasing evidence that this is not only a generally ineffective treatment approach,[2–4] but one that may be counterproductive. Given

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this evidence and new information about the efficacy of several atypical antipsychotics in monotherapy or adjunctive therapy of bipolar depression, recommended treatment paradigms have evolved toward the use of mood stabilizers with atypical antipsychotics and away from the unimodal antidepressants for the treatment of bipolar depression.[5]

However, treatment choices and sequences are confounded by a variety of factors. None of the mood stabilizers (lithium carbamazepine, lamotrigine, and valproate) are well documented for their acute antidepressant effects and none of them are approved by the Food and Drug Administration (FDA) for this indication. However, they are typically involved in the long-term prophylaxis of bipolar disorder, and bipolar depression breaking through these agents alone and in combination during preventive treatment is quite common.

Given the occurrence of a breakthrough depression, the addition of an atypical antipsychotic has become a primary recommendation in most treatment guidelines. Nonetheless, the treatment options for an emergent bipolar depression in the absence of mood stabilizer treatment are poorly delineated by the literature, although monotherapy with atypical antipsychotics is the only FDA-approved approach. Despite the emerging evidence of the inadequacy of antidepressant augmentation of mood stabilizers for bipolar depression, the unimodal antidepressants are still one of the most widely used treatment strategies.[6]

We briefly review the evidence of the inadequacy of antidepressants and the potential liabilities of their first-line use in the treatment of bipolar depression. The usefulness of the mood stabilizers in the treatment of acute bipolar depression also is reviewed, as well the data of the atypical antipsychotics. A major focus of this article is on the prevention of recurrences of bipolar depression, which is a primary objective of long-term treatment. This discussion again raises clinical treatment dilemmas about decision making because of a paucity of treatment research.

Another confounding variable is the high incidence of psychiatric and medical comorbidities in bipolar disorder, and these, too, have been inadequately studied. In particular, anxiety disorder comorbidity and rapid cycling are predictors of a poor outcome in the treatment of bipolar disorder, as is childhood-onset disorder. The treatment algorithms for these common variations have not been determined. Likewise, alcohol and substance abuse are extraordinarily common in the context of bipolar disorder and treatment of these comorbidities specifically in patients with bipolar disorder has rarely been studied. Therefore, one must make indirect inferences from the literature on studies of treatments for the primary disorders of alcohol and substance abuse as they might best apply to those with bipolar disorders who have these comorbidities. Given the paucity of treatment information about the acute and preventive treatment of bipolar depression, the clinician is at an extreme disadvantage in arriving at appropriate treatment algorithms for achieving and maintaining remission.

There is wide agreement that remission is the goal of clinical therapeutics, as partial treatment with resulting residual depressive symptoms appears to be a predictor and precursor to relapse into a more full-blown episode. Here again the literature is substantial about achieving improvement and clinical response, but virtually absent as to what maneuvers might be most applicable for achieving and/or maintaining remission in bipolar depression. Although there are a multitude of secondary treatment options available to augment the mood stabilizers (MS) or atypical antipsychotics (AA), evidence for their efficacy in bipolar depression is scanty and indirect. Nonetheless, in an effort to achieve the goal of remission, it becomes necessary to use a variety of approaches that are not yet supported by randomized controlled clinical trials and other accepted classes of evidence-based medicine. Therefore, in this article, we attempt