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Review

Current landscape, unmet needs, and future directions for treatment of bipolar depression

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ABSTRACT

Background: Depression is the predominant pole of illness disability in bipolar disorder and, compared with acute mania, has less systematic research guiding treatment development. The aim of this review is to present the therapeutic options currently available for managing bipolar depression and to highlight areas of unmet need and future research.
Methods: Literature search of PubMed, PsycINFO, and Cochrane databases and bibliographies from 2000 to August 2013 for treatments that have regulatory approval for bipolar depression or early controlled preliminary data on efficacy.
Results: Treatment options for bipolar depression have increased over the last decade, most notably with regulatory approval for olanzapine/fluoxetine combination, quetiapine, and lurasidone. Conventional mood stabilizers lamotrigine and divalproex have meta-analyses suggesting acute antidepressant response. Manual-based psychotherapies also appear to be effective in treating bipolar depression. The therapeutic utility of unimodal antidepressants, as a class, for the treatment of patients with bipolar depression, as a group, remains to be confirmed. There is a substantially unmet need to develop new interventions that are efficacious, effective, and have low side effect burden.
Limitations: Additional compounds are currently being developed that may ultimately be applicable to the treatment of bipolar depression and early open-trial data encourage further studies, but both of these topics are beyond the scope of this review.
Conclusion: Future registrational trials will need to establish initial efficacy, but increasing interest for personalized or individualized medicine will encourage further studies on individual predictors or biomarkers of response.

Contents

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1. Introduction

The World Health Organization has ranked bipolar disorder or manic-depressive illness among the leading causes of disability globally, irrespective of gross national income (World Health Organization, 2008). The morbidity associated with bipolar disorder is increasingly recognized as not the result of mania, about which arguably there has been substantial progress in identifying the underlying neurobiology of the disease state (Frye et al., 2007b; Strakowski et al., 2012), but of depression, treatment-resistant depression, suicidality, and a wide range of medical comorbid disorders (Goodwin and Jamison, 2007). Episodes of bipolar depression, compared with acute mania, are longer, more frequent, and more likely associated with suicidality and work-related disability (Altshuler et al., 2002; Baldessarini et al., 2012; Calabrese et al., 2004; Judd et al., 2002; Kessler et al., 2006; Solomon et al., 2010). Despite these high social and public healthcare costs demarcating depression as the predominant pole of illness burden, depression treatment development has lagged substantially compared with both antimanic and maintenance pharmacotherapies.

There are 10 drugs approved by the US Food and Drug Administration (FDA) for acute mania (lithium, anticonvulsants divalproex sodium [delayed and extended release] and carbamazepine extended release, typical antipsychotic chlorpromazine, and atypical antipsychotics aripiprazole, asenapine, olanzapine, quetiapine [immediate and extended release], risperidone, and ziprasidone) and 7 drugs approved for maintenance treatment (lithium, lamotrigine, aripiprazole, olanzapine, quetiapine [immediate and extended release] adjunctive therapy, risperidone long-acting intramuscular injection, and ziprasidone adjunctive therapy) (Frye, 2011). Over the past decade, however, there have been only 3 treatments approved by the FDA for bipolar depression: olanzapine-fluoxetine (2003), quetiapine [immediate and extended release] monotherapy (2006 and 2008), and lurasidone monotherapy and adjunctive therapy (2013). Some of the delay in treatment development for the depressive phase of bipolar disorder may be related to extensive use of unimodal antidepressants and psychotherapies in the absence of systematic evaluation of bipolar depression. With the exception of fluoxetine, all current regulatory-approved antidepressants have received their indication in major depressive disorder following trials that directly excluded patients with a history of mania (bipolar I) or hypomania (bipolar II). This approach has minimized the available evidence base that could otherwise inform the clinician on how best to utilize these treatments in bipolar disorder. In fact, based on the meta-analysis by Sidor and MacQueen (2011; 2012), the therapeutic utility of antidepressants for the depressed phase of the illness remains to be confirmed. This article reviews the current landscape of treatment options for bipolar depression, emphasizing points of unmet need and strategic areas for subsequent research and treatment development.

2. Methods

We searched PubMed, PsycINFO, and Cochrane databases and bibliographies from 2000 to August 2013 for English-language articles using the following terms: bipolar disorder, manic-depressive illness, depression, and treatment. Clinical trials registered on ClinicalTrials.gov or trials with a randomized placebo-controlled design were considered in this review. The search results were reviewed for studies related to currently approved treatments or compounds under clinical investigation for the treatment of bipolar depression.

3. Results

3.1. Approved treatments

Of the 3 approved treatments for bipolar depression, quetiapine has the largest evidence base, encompassing more than 2500 bipolar I and II depressed subjects who participated in four 8-week, placebo-controlled trials (Calabrese et al., 2005; McElroy et al., 2010; Thase et al., 2006; Young et al., 2010). Quetiapine, both 300- and 600-mg doses, resulted in a greater baseline-to-endpoint decrease in the Montgomery–Åsberg Depression Rating Scale (MADRS) score, higher rate of response (≥50% symptom reduction), and higher rate of remission (MADRS score ≤12) compared with placebo. Two of the trials included lithium (Young et al., 2010) or paroxetine (McElroy et al., 2010) as active comparators and quetiapine (300 and 600 mg daily) again resulted in a greater baseline-to-endpoint decrease in MADRS score and higher rates of response. In the paroxetine study, there was more than a 3-fold increase in treatment-emergent switch to mania with paroxetine (10.7%) compared with quetiapine (3%). A meta-analysis summarizing all of these clinical trials reported significantly higher rates of response (odds ratio [OR], 2.00; 95% confidence interval [CI], 1.27–2.32) and remission (OR, 1.98; 95% CI, 1.70–2.30) with quetiapine compared with placebo (Chiesa et al., 2012), with additional data supporting core symptoms of bipolar depression as having significantly improved with quetiapine versus placebo (Suppes et al., 2010).

The Program to Evaluate the Antidepressant Impact of Lurasidone (PREVAIL) registrational trials assessed the efficacy of lurasidone in bipolar depression. PREVAIL 1 enrolled 348 bipolar I depressed lithium- or valproate-treated participants who were randomized to adjunctive lurasidone 20 to 120 mg daily versus placebo for 6 weeks (Loebel et al., 2014b). Compared with placebo, lurasidone was associated with a significant reduction in MADRS scores from baseline to endpoint with a corresponding increased rate of response (57% vs. 42%) and remission (50% vs. 35%). The PREVAIL 2 trial enrolled 505 bipolar I depressed participants randomized to 6 weeks of lurasidone monotherapy (20–60 mg daily or 80–120 mg daily) or placebo (Loebel et al., 2014a). Again, compared with placebo, lurasidone was associated with a significant baseline-to-endpoint reduction in the MADRS score, with a corresponding increased rate of response (52% vs. 30%) and remission (41% vs. 25%).

The first approved treatment for bipolar depression was olanzapine/fluoxetine combination (OFC). Its approval was based on an exploratory addition of OFC to an 8-week, placebo-controlled randomized trial comparing olanzapine monotherapy (n=370) with placebo (n=377) in participants with bipolar I depression (Tohen et al., 2003). Although a different analytic approach (i.e., mixed-effect model repeated measure versus last observation carried forward) and a very small sample size (n=86, or approximately 10% of the study sample), the combination of olanzapine (mean daily dose 7.4 mg) plus fluoxetine (mean daily dose 39.3 mg) was superior to placebo in baseline to 8-week endpoint changes in MADRS score and response (56.1% vs. 30.4%) and remission (48.8% vs. 24.5%) rates. Most likely related to the antimanic properties of olanzapine, the manic switch rate was not significantly different between the combination (6.4%) and placebo (6.7%) groups. Although olanzapine monotherapy (mean dose 9.7 mg daily) was superior to placebo in improving depression, the overall decrease in MADRS score was significantly greater with OFC.

The evidence base for olanzapine has increased with a 6-week, placebo-controlled study evaluating olanzapine monotherapy (n=343) for bipolar I depression (Tohen et al., 2012). Compared with placebo (n=171), olanzapine was associated with