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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

a significantly greater decrease in MADRS score and increased rate of response (52.5% vs. 43.3%; p=0.0498) and remission (38.5% vs. 29.2%; p=0.038), but not recovery (13.7% vs. 9.4%; p=0.156). Concern has been raised as to whether the positive evidence base for olanzapine or quetiapine in bipolar depression represents a therapeutic benefit (i.e., addressing core symptoms of depression) versus a side effect benefit of a sedating, weight-liable compound promoting sleep and appetite that, as such, addresses key non-core symptoms of insomnia and poor appetite/weight loss. In addition to a quetiapine core symptom analysis (Suppes et al., 2010), a recent pooled analysis of olanzapine monotherapy studies in acute bipolar depression reported that core symptoms of depression (6 items from the MADRS) showed greater improvement with olanzapine compared with placebo (Tohen et al., 2013).

Although the atypical antipsychotics, as a class, have antimanic properties (e.g., 6 agents are approved for acute mania), this does not appear to be the case for bipolar depression, as the current evidence base for both aripiprazole and ziprasidone has negative studies (Sachs et al., 2011; Thase et al., 2008). The six-week ziprasidone study that failed to show separation from placebo for bipolar depression (Sachs et al., 2011) and a recent post hoc analysis of the subject rating data (Lombardo et al., 2012) both emphasize the importance of data monitoring in the course of a clinical trial. Furthermore, the analysis of two 8-week trials of aripiprazole did show statistically significant separation from placebo through week six, but did not, at the final 8-week end point, show a statistically significant difference between drug and placebo (Thase et al., 2008). Major concerns for quetiapine, lurasidone, olanzapine, and OFC focus on risks of weight gain with associated risk of diabetes, cardiometabolic factors, and tardive dyskinesia. Tardive dyskinesia cannot be estimated from short-term trials, though data suggest that the tardive dyskinesia risk is lower with second-generation atypical versus first-generation typical antipsychotic agents, which have estimates of ~3–5% per year of exposure (Kane, 2006). In this issue, Dr. David Kemp reviews the clinical management of side effects associated with commonly used treatments for bipolar depression.

3.2. Mood stabilizers in the treatment of acute bipolar depression

There is merit to initially treating an episode of bipolar depression with monotherapy from the standpoint of minimizing pharmacokinetic interactions and maximizing treatment adherence. As such, evaluating antimanic and maintenance mood stabilizers for their efficacy in bipolar depression may obviate the need for augmentation or adjunctive therapy.

Despite lithium's gold standard status as an active comparator in acute mania, it is not FDA-approved for bipolar depression. There has been little contemporary systematic research on the acute antidepressant response to lithium, and the limited recent data available are negative (Bhagwagar and Goodwin, 2002; Fountoulakis and Vieta, 2008). One exploratory post hoc analysis has suggested a differential antidepressant response based on serum lithium levels. In a 10-week, placebo-controlled comparison study evaluating adjunctive antidepressant therapy, lithium-maintained bipolar I depressed participants were randomized to paroxetine (n=35, mean daily dose 32.6 mg), imipramine (n=39, mean daily dose 166.7 mg), or placebo (n=43) stratified by naturalistic maintenance therapeutic (>0.8 mmol/L) versus nontherapeutic (≤0.8 mmol/L) lithium level (Nemeroff et al., 2001). The primary outcome measures, baseline to endpoint change in the Hamilton Rating Scale for Depression (HAM-D) and treatment response (HAM-D ≤7 or Clinical Global Impression [CGI] global improvement ≤2), were not significantly different among the 3 groups, nor was there a difference found among the groups in a post hoc analysis of participants with a therapeutic lithium level. However, in the group with nontherapeutic lithium level, adjunctive selective serotonin reuptake inhibitor (SSRI) and tricyclic antidepressant (TCA) treatments were both associated with a significant reduction in depressive symptoms compared with placebo, indirectly suggesting that for patients who can achieve and tolerate a higher serum level of lithium, adjunctive treatment may not be necessary, although this needs to be confirmed prospectively. Similar findings have been observed in depression prophylaxis. In a non-enriched, post hoc analysis of bipolar I patients stabilized from a manic/mixed or depressive episode, time to recurrence of any mood, manic, or depressive event was significantly longer in patients who achieved a median lithium level between 0.6 and 1.2 mEq/L (n=201) versus patients randomized to placebo (n=404) and versus patients who achieved a median lithium level <0.6 mEq/L (n=137) (Nolen and Weisler, 2013). Although the groups were not stratified on the basis of therapeutic level of lithium (>0.8 mmol/L), these data emphasize that when tolerable, higher dosing of mood stabilization treatment may be associated with better mood outcomes, although this also needs to be confirmed prospectively.

There is increasing recognition that subtle changes in thyroid economy related to lithium may reduce therapeutic effectiveness, particularly for depression. Support for this premise comes from studies demonstrating that lower mean serum free T4 or increased adjusted mean thyroid-stimulating hormone (TSH) levels during lithium maintenance treatment were associated with more affective episodes (p<0.01), increased depression severity (p<0.01), and a higher percentage of participants requiring intervention for depression (Frye et al., 1999a; Frye et al., 2009b). This, in turn, may relate to thyroid-induced changes on brain function, as neuroimaging of medication-free participants with treatment-resistant mood disorders, primarily rapid-cycling bipolar disorder, has demonstrated a significant inverse correlation between peripheral TSH levels and cerebral blood flow and cerebral glucose metabolism (Marangell et al., 1997b).

Lamotrigine, a drug approved by the FDA for the maintenance phase (i.e., delaying manic and depressive recurrence) of bipolar I disorder, is not FDA-approved for acute bipolar depression, but a meta-analysis (5 studies, 1 positive, 4 negative) and 1 controlled LamLit study suggest possible efficacy in acute bipolar depression (Geddes et al., 2009; Goodwin et al., 2004; van der Loos et al., 2009).

The meta-analysis of 5 placebo-controlled trials (n=1072 bipolar I and II patients) with variable study duration (7–10 weeks) and dosing regimens (fixed dose, 50 mg vs. 200 mg; flexible dosing 100–400 mg), reported a modest benefit of lamotrigine monotherapy as assessed by a ≥50% decrease in MADRS (relative risk [RR]=1.22; 95% CI, 1.06–1.41) or HAM-D (RR=1.27; 95% CI, 1.09–1.47) scores; a planned subgroup analysis revealed a greater treatment effect in patients with severe depression (Geddes et al., 2009). Remission rates were not significantly different with lamotrigine relative to placebo.

These monotherapy data have been further supported by the LamLit study, an 8-week, randomized, placebo-controlled trial of 124 lithium-maintained bipolar I/II depressed outpatients, in which adjunctive therapy with 200 mg lamotrigine resulted in greater improvement in the MADRS score and a higher response rate than did adjunctive placebo (51.6% vs. 31.7%) (van der Loos et al., 2009).

Finally, divalproex sodium, approved for acute mania, has also been studied as monotherapy for bipolar depression. In a meta-analysis of 4 small, short-term (6–8 week) placebo-controlled trials with a total of 142 bipolar I or II patients, divalproex

monotherapy resulted in a significant difference in both depression symptom scale score reduction (Smith et al., 2010) and rates of clinical response (RR=2.1; 95% CI, 1.1–2.43; p=0.02) and remission (RR=1.61; 95% CI, 1.12–2.53; p=0.04) (Bond et al., 2010; Smith et al., 2010). Although divalproex is not FDA-approved for maintenance treatment, secondary analyses of maintenance studies suggest reduced depressive recurrence with divalproex and less need for adjunctive antidepressant therapy (Bowden et al., 2000; Gyulai et al., 2003).

3.3. Antidepressants in the treatment of bipolar depression

One of the most controversial topics in mood disorder management is the disconnect between the evidence base and the clinical use of antidepressants in bipolar disorder (Pacchiarotti et al., 2013). Although naturalistic and prescription data suggest that the use of antidepressants in bipolar disorder is highly prevalent (Baldessarini et al., 2007), the evidence base to suggest efficacy is far from robust. Paroxetine is the SSRI most rigorously studied in bipolar depression. The cumulative data to date for paroxetine suggest less effectiveness in improving depression versus quetiapine monotherapy, with a higher switch rate to mania/hypomania (McElroy et al., 2010); no better results than placebo in reducing depressive symptoms in lithium-maintained patients (Nemeroff et al., 2001); and no added benefit as adjunct treatment to mood stabilizers compared with placebo in measures of durable recovery, defined as 8 consecutive weeks of euthymia without switch to mania/hypomania (Sachs et al., 2007). Moreover, a meta-analysis of randomized double-blind trials comparing acute antidepressant treatment with either placebo or active comparator likewise demonstrated no significant benefit of antidepressant therapy in rates of response (n=1145; RR=1.17; 95% CI, 0.88–1.57; p=0.28) or remission (n=1146; RR=1.14; 95% CI, 0.90–1.45; p=0.28) (Sidor and MacQueen, 2012; Sidor and MacQueen, 2011). Antidepressants may result in better outcomes for patients with bipolar II depression, as evidenced by the significant benefit of depression prophylaxis with fluoxetine in these patients compared with lithium or placebo maintenance (Amsterdam and Shults, 2010). These data highlight the important need for further steps in identifying clinical patterns associated with antidepressant treatment response.

A second concern regarding antidepressant use in bipolar disorder is safety. Pooled treatment estimates do not suggest an increased acute risk of switch from depression to mania/hypomania (Sidor and MacQueen, 2012; Sidor and MacQueen, 2011). However, smaller analyses have suggested that venlafaxine (Post et al., 2006; Vieta et al., 2002) and TCAs (Peet, 1994) have been associated with higher acute switch rates than other antidepressant compounds. Furthermore, there is increasing recognition that additional clinical and genomic correlates may be associated with antidepressant-induced mania (AIM) (Frye et al., 2009a; Frye et al., 2014; in press). Five studies reported in an earlier meta-analysis (Biernacka et al., 2012), plus additional work from Frye et al. (2014), have evaluated genomic variation of the SLC6A4 promoter and AIM in adults (total, N=453 AIM+ cases; N=725 AIM– controls) (Frye et al., 2014; Ferreira Ade et al., 2009; Masoliver et al., 2006; Mundo et al., 2001; Rousseva et al., 2003; Serretti et al., 2004). The meta-analysis demonstrated a weak, not statistically significant association of the S allele with AIM+ (OR, 1.87; 95% CI 0.99–1.85; p=0.059). In order to optimize the potential clinical impact of pharmacogenomic research of AIM, future studies should include adequate sample size and rigorously assessed patient characteristics (e.g., family history, rapid cycling, concurrent mood stabilization, and length of antidepressant exposure).

4. Discussion

4.1. Future directions

There is an urgent need to develop new trial designs and novel treatments for bipolar depression. The delays have been multifactorial, and an optimal trial design (i.e, duration, symptom scale measurement, outcome and adverse event measurement, biomarkers of response) has yet to be determined. This is in contrast with the now conventional 3-week, placebo-controlled design for acute mania studies, with a 50% reduction in symptom severity, as measured by the Young Mania Rating Scale (YMRS), as a key outcome measure; this was the template for most of the more than 60 studies in a recent meta-analysis (Cipriani et al., 2011). The trial design for the OFC and quetiapine pivotal trials in bipolar depression was an 8-week placebo-controlled study with at least a 50% reduction in the MADRS score as the primary response outcome measure (Calabrese et al., 2005; McElroy et al., 2010; Thase et al., 2006; Tohen et al., 2003; Young et al., 2010). However, some studies of bipolar depression have used a 6-week outcome with positive results (Frye et al., 2007a; Loebel et al., 2014a; Loebel et al., 2014b), or had the primary outcome measure met at 6 weeks but not at the 8-week a priori defined outcome endpoint (Thase et al., 2008).

Secondly, there is increasing interest in alternative rating scales, such as the Inventory for Depressive Symptoms, which includes quantification of atypical (non-melancholic) symptoms (Calabrese et al., 2010; Frye et al., 2007a; Post et al., 2006; Rush et al., 1986; Rush et al., 1996).

Thirdly, while treatment-emergent or antidepressant-induced mania would meet criteria for conventional response and remission, there has been debate on how best to quantify this event (i.e., adverse event or safety issue vs. lack of overall mood response) (Frye et al., 2014; in press). There has been progress to more reliably capture this event with instruments such as the CGI for Bipolar Disorder–change from preceding phase (Spearing et al., 1997), or outcomes such as durable recovery or treatment effectiveness response (Sachs et al., 2007).

Finally, there has been little symptom scale development for the assessment of mixed symptoms in depression. As "mixed features" are recognized as a specifier for bipolar disorder in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, and are known to be a risk factor for poor outcome (Judd et al., 2012), developing a symptom severity measure has obvious clinical research appeal. The YMRS scale was originally developed for manic inpatients, and its sensitivity to detect subtle hypomanic/manic symptoms may be limited. Self-report pilot scales such as the modified version of the Hypomania Checklist-32 may have merit and warrant further study (Altinbas et al., 2014; Prieto et al., 2014; in press).

New trial designs should not only standardize trial duration and primary outcome measurement scales, but also utilize outcome measures that focus not only on response and remission but also on cognition, quality of life, functional improvement, recovery, and targeted comorbidity patterns (i.e., suicidality, addiction, anxiety disorders, obesity, cardiovascular disease), which may have long-term prognostic implications. Additionally, effective community translation and dissemination of the data that provide the clinician with a greater ability to understand the practical impact of the study (i.e., effect size, number needed to treat [NNT], number needed to harm [NNH], ratio of NNT to NNH) would foster substantial progress. In this issue, Dr. Terence Ketter and colleagues use NNT and NNH approaches to evaluate the safety and efficacy of treatments for bipolar depression.

In addition to the evolution of trial design, novel compounds beyond atypical antipsychotics and novel treatment interventions

need to be studied. For example, early controlled evaluations or biomarker development studies of the glutamatergic compounds ketamine (Zarate, Jr. et al., 2012) and riluzole (Brennan et al., 2010; Zarate, Jr. et al., 2005), the dopamine D_2/D_3 receptor partial agonist pramipexole (Goldberg et al., 2004; Zarate, Jr. et al., 2004), and the dopamine transport inhibitors modafinil (Frye et al., 2007a) and armodafinil (Calabrese et al., 2010), clearly warrant further evaluation; however, positive results were observed in only one (Calabrese et al., 2014) of three (Adler et al., 2014; Frye et al., 2013) subsequent clinical trials of armodafinil. Early interest in inflammatory models of illness progression (Leboyer et al., 2012) and feasibility and early controlled studies of N-acetylcysteine (Berk et al., 2012) and celecoxib (Nery et al., 2008) warrant further study as well. Treatments focused on circadian rhythms such as sleep deprivation (Smeraldi et al., 1999; Szuba et al., 1994) and thyrotropin-releasing hormone (Frye et al., 1999b; Marangell et al., 1997a) may be effective by themselves, but may also be used as accelerating paradigms in reducing bipolar depressive symptoms faster to, in turn, reduce morbidity and symptom severity (Altshuler et al., 2003).

Characterization of illness staging may also help to inform treatment options and stratify responses to improve both clinical trial design and data interpretation. For example, illness progression is associated with structural brain changes, functional decline, and an increasing vulnerability to relapse of depressive episode and treatment resistance (Dodd et al., 2013). Multiple neurobiological mechanisms mediate this neuroprogression, including alteration of neurotransmitters, neurotrophic factors, inflammatory mediators, insulin dysfunction, oxidative stress, mitochondrial dysfunction, and hypothalamic-pituitary-adrenal axis dysregulation (Brietzke et al., 2011; Dodd et al., 2013). As the field moves forward and appreciation of the effect of integrative biological systems on disease progression and corresponding treatment response increases, we will be far better placed to develop more targeted and individualized treatments for bipolar depression (Tye, 2013). Ideally, if multiple measures across these intertwined biological systems can be incorporated into study design, we will be much better placed to correlate treatment response profiles with pathophysiological disease processes. This, in turn, will facilitate identification of novel treatments or treatment combinations for bipolar depression that can be individualized for each patient in accordance with their unique biosignature (Phillips and Kupfer, 2013). Last, but not least, this type of research must aim to keep pace with recent calls to address diagnostic issues from a different, more strictly neurobiological (genetic, neural circuit–, and systems-based), approach (Cuthbert and Insel, 2013). Clinical research samples can have different configurations to assess dimensions such as severity and causation.

4.2. 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. However, both topics are beyond the scope of this review.

5. Conclusions

While the number of treatment options for bipolar depression has increased over the last decade, there is a substantial unmet need for new interventions that are efficacious and effective, and that have a low side effect burden. Future registrational trials will need to establish initial efficacy, together with well-characterized treatment-response profiles. This strategy will provide the necessary foundation on which a personalized medicine approach can be established within the field of psychiatry, and encourages eventual diagnostic improvements in addition to further pursuit and development of individual predictors or biomarkers of response.

Conflict of interest

Dr. Frye has served on advisory boards for Janssen and Teva and as a consultant to Allergan, Merck, Mitsubishi Tanabe Pharma Co, Myriad, Sunovion, Takeda Global Research, and United BioSource. He has received grant support from Pfizer, Myriad, the National Institute of Mental Health (NIMH), the National Institute of Alcohol Abuse and Alcoholism (NIAAA), the National Alliance for Research on Schizophrenia and Depression (NARSAD), and the Mayo Foundation. He has developed CME presentations for Sanofi-Aventis and has received travel support from AstraZeneca, Bristol-Myers Squibb, CME Outfitter, GlaxoSmithKline, and Otsuka. Dr. Prieto has served on the speakers' bureau and developed CME presentations for GlaxoSmithKline and has received travel support from GlaxoSmithKline, Lilly, Lundbeck, Pharmavita, and the government of Chile. Dr. Bobo has no potential conflicts of interest to disclose. Dr. Kung has received grant support from AssureRx Health. Dr. Veldic has no potential conflicts of interest to disclose. Dr. Alarcon receives royalties from Manual Moderno (MX) and has developed CME presentations for Sociedad Uruguaya de Psiquiatria Biologica and Fundacion Santa Fe (Colombia). Dr. Moore has no potential conflicts of interest to disclose. Dr. Choi has no potential conflicts of interest to disclose. Dr. Biernacka has no potential conflicts of interest to disclose. Dr. Tye has no potential conflicts of interest to disclose.

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Contributors' statement

Mark Frye wrote the first draft of the manuscript. Each of the coauthors (Drs. Prieto, Bobo, Kung, Veldic, Alarcon, Moore, Choi, Biernacka, and Tye) contributed critical revisions and suggestions to the manuscript and approved the final manuscript.

References

Adler, C., Ketter, T., Frye, M.A., Yang, R., Bauer, M., 2014. Randomized, double-blind, placebo-controlled trial of adjunctive armodafinil (150 mg/day) in adults with bipolar I depression: Safety and primary efficacy findings. Presented at: 167th Annual Meeting of the American Psychiatric Association; May 3–7, 2014; New York, NY. Poster NR6-038.

Altinbas, K., Ozerdem, A., Prieto, M.L., Fuentes, M.E., Yalin, N., Ersoy, Z., Aydemir, O., Quiroz, D., Oztekin, S., Geske, J.R., Feeder, S.E., Angst, J., Frye, M.A., 2014. A multinational study to pilot the modified Hypomania Checklist (mHCL) in the assessment of mixed depression. J. Affect. Disord. 152–154, 478–482.

Altshuler, L.L., Frye, M.A., Gitlin, M.J., 2003. Acceleration and augmentation strategies for treating bipolar depression. Biol. Psychiatry 53 (8), 691–700.

Altshuler, L.L., Gitlin, M.J., Mintz, J., Leight, K.L., Frye, M.A., 2002. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. J. Clin. Psychiatry 63 (9), 807–811.

Amsterdam, J.D., Shults, J., 2010. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. Am. J. Psychiatry 167 (7), 792–800.

Baldessarini, R.J., Leahy, L., Arcona, S., Gause, D., Zhang, W., Hennen, J., 2007. Patterns of psychotropic drug prescription for U.S. patients with diagnoses of bipolar disorders. Psychiatr. Serv. 58 (1), 85–91.

Baldessarini, R.J., Undurraga, J., Vazquez, G.H., Tondo, L., Salvatore, P., Ha, K., Khalsa, H.M., Lepri, B., Ha, T.H., Chang, J.S., Tohen, M., Vieta, E., 2012. Predominant recurrence polarity among 928 adult international bipolar I disorder patients. Acta Psychiatr. Scand. 125 (4), 293–302.

Berk, M., Dean, O.M., Cotton, S.M., Gama, C.S., Kapczinski, F., Fernandes, B., Kohlmann, K., Jeavons, S., Hewitt, K., Moss, K., Allwang, C., Schapkaitz, I., Cobb, H., Bush, A.I., Dodd, S., Malhi, G.S., 2012. Maintenance N-acetyl cysteine treatment for bipolar disorder: a double-blind randomized placebo controlled trial. BMC. Med. 10, 91.

Bhagwagar, Z., Goodwin, G.M., 2002. The role of lithium in the treatment of bipolar depression. Clin. Neurosci. Res. 2 (3), 222–227.

Biernacka, J.M., McElroy, S.L., Crow, S., Sharp, A., Benitez, J., Veldic, M., Kung, S., Cunningham, J.M., Post, R.M., Mrazek, D., Frye, M.A., 2012. Pharmacogenomics of antidepressant induced mania: a review and meta-analysis of the serotonin transporter gene (5HTTLPR) association. J. Affect. Disord. 136 (1–2), e21–e29.

Bond, D.J., Lam, R.W., Yatham, L.N., 2010. Divalproex sodium versus placebo in the treatment of acute bipolar depression: a systematic review and meta-analysis. J. Affect. Disord. 124 (3), 228–234.

Bowden, C.L., Calabrese, J.R., McElroy, S.L., Gyulai, L., Wassef, A., Petty, F., Pope, H.G., Jr., Chou, J.C., Keck, P.E., Jr., Rhodes, L.J., Swann, A.C., Hirschfeld, R.M., Wozniak, P.J.; Divalproex Maintenance Study Group, 2000. A randomized, placebo-controlled 12-month trial of divalproex and lithium in treatment of outpatients with bipolar I disorder. Arch. Gen. Psychiatry 57 (5), 481–489.

Brennan, B.P., Hudson, J.I., Jensen, J.E., McCarthy, J., Roberts, J.L., Prescot,

A.P., Cohen, B.M., Pope, H.G., Jr., Renshaw, P.F., Ongur, D., 2010. Rapid enhancement of glutamatergic neurotransmission in bipolar depression following treatment with riluzole. Neuropsychopharmacology 35 (3), 834–846.
Brietzke, E., Kapczinski, F., Grassi-Oliveira, R., Grande, I., Vieta, E., McIntyre, R.S., 2011. Insulin dysfunction and allostatic load in bipolar disorder. Expert. Rev. Neurother. 11 (7), 1017–1028.
Calabrese JR, Frye MA, Yang R, Ketter TA; Armodafinil Treatment Trial Study Network, 2014. Efficacy and safety of adjunctive armodafinil in adults with major depressive episodes associated with bipolar I disorder: a randomized, double-blind, placebo-controlled, multicenter trial. J. Clin. Psychiatry, published online ahead of print July 22, 2014.
Calabrese, J.R., Hirschfeld, R.M., Frye, M.A., Reed, M.L., 2004. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a U.S. community-based sample. J. Clin. Psychiatry 65 (11), 1499–1504.
Calabrese, J.R., Keck, P.E., Jr., Macfadden, W., Minkwitz, M., Ketter, T.A., Weisler, R.H., Cutler, A.J., McCoy, R., Wilson, E., Mullen, J.; the BOLDER Study Group, 2005. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am. J. Psychiatry 162 (7), 1351–1360.
Calabrese, J.R., Ketter, T.A., Youakim, J.M., Tiller, J.M., Yang, R., Frye, M.A., 2010. Adjunctive armodafinil for major depressive episodes associated with bipolar I disorder: a randomized, multicenter, double-blind, placebo-controlled, proof-of-concept study. J. Clin. Psychiatry 71 (10), 1363–1370.
Chiesa, A., Chierzi, F., De, R.D., Serretti, A., 2012. Quetiapine for bipolar depression: a systematic review and meta-analysis. Int. Clin. Psychopharmacol. 27 (2), 76–90.
Cipriani, A., Barbui, C., Salanti, G., Rendell, J., Brown, R., Stockton, S., Purgato, M., Spineli, L.M., Goodwin, G.M., Geddes, J.R., 2011. Comparative efficacy and acceptability of antimanic drugs in acute mania: a multiple-treatments meta-analysis. Lancet 378 (9799), 1306–1315.
Cuthbert, B.N., Insel, T.R., 2013. Toward the future of psychiatric diagnosis: the seven pillars of RDoC. BMC. Med. 11, 126.
Dodd, S., Maes, M., Anderson, G., Dean, O.M., Moylan, S., Berk, M., 2013. Putative neuroprotective agents in neuropsychiatric disorders. Prog. Neuropsychopharmacol. Biol. Psychiatry 42, 135–145.
Ferreira Ade, A., Neves, F.S., da Rocha, F.F., Silva, G.S., Romano-Silva, M.A., Miranda, D.M., De, M.L., Correa, H., 2009. The role of 5-HTTLPR polymorphism in antidepressant-associated mania in bipolar disorder. J. Affect. Disord. 112 (1–3), 267–272.
Fountoulakis, K.N., Vieta, E., 2008. Treatment of bipolar disorder: a systematic review of available data and clinical perspectives. Int. J. Neuropsychopharmacol. 11 (7), 999–1029.
Frye, M.A., 2011. Bipolar disorder – a focus on depression. N. Engl. J. Med. 364 (1), 51-59.
Frye, M.A., Denicoff, K.D., Bryan, A.L., Smith-Jackson, E.E., Ali, S.O., Luckenbaugh, D., Leverich, G.S., Post, R.M., 1999a. Association between lower serum free T4 and greater mood instability and depression in lithium-maintained bipolar patients. Am. J. Psychiatry 156 (12), 1909–1914.
Frye, M.A., Gary, K.A., Marangell, L.B., George, M.S., Callahan, A.M., Little, J.T., Huggins, T., Cora-Locatelli, G., Osuch, E.A., Winokur, A., Post, R.M., 1999b. CSF thyrotropin-releasing hormone gender difference: implications for neurobiology and treatment of depression. J. Neuropsychiatry Clin. Neurosci. 11 (3), 349–353.
Frye, M.A., Grunze, H., Suppes, T., McElroy, S.L., Keck, P.E., Jr., Walden, J., Leverich, G.S., Altshuler, L.L., Nakelsky, S., Hwang, S., Mintz, J., Post, R.M., 2007a. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. Am. J. Psychiatry 164 (8), 1242–1249.
Frye, M.A., Helleman, G., McElroy, S.L., Altshuler, L.L., Black, D.O., Keck, P.E., Jr., Nolen, W.A., Kupka, R., Leverich, G.S., Grunze, H., Mintz, J., Post, R.M., Suppes, T., 2009a. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. Am. J. Psychiatry 166 (2), 164–172.
Frye, M.A., Ketter, T.A., Yang, R., 2013. Efficacy and safety of armodafinil as an adjunctive therapy for the treatment of a major depressive episode associated with bipolar I disorder. Bipolar Disord. 15 (s1), 126–127.
Frye, M.A., McElroy, S.L., Prieto, M.L., Harper, K.L., Kung, S., Chauhan, M., Crow, S., Sutor, B., Galardy, C.W., Veldic, M., Palmer, B.A., Geske, J.R., Fuentes, M., Cuellar-Barboza, A.B., Seymour, L.R., Mori, N., Biernacka, J.M., 2014. Clinical risk factors and serotonin transporter gene variants associated with antidepressant-induced mania. J. Clin. Psychiatry in press.
Frye, M.A., Thomas, M.A., Yue, K., Binesh, N., Davanzo, P., Ventura, J., O'Neill, J., Guze, B., Curran, J.G., Mintz, J., 2007b. Reduced concentrations of N-acetylaspartate (NAA) and the NAA-creatine ratio in the basal ganglia in bipolar disorder: a study using 3-Tesla proton magnetic resonance spectroscopy. Psychiatry Res. 154 (3), 259–265.
Frye, M.A., Yatham, L., Ketter, T.A., Goldberg, J., Suppes, T., Calabrese, J.R., Bowden, C.L., Bourne, E., Bahn, R.S., Adams, B., 2009b. Depressive relapse during lithium treatment associated with increased serum thyroid-stimulating hormone: results from two placebo-controlled bipolar I maintenance studies. Acta Psychiatr. Scand. 120 (1), 10–13.
Geddes, J.R., Calabrese, J.R., Goodwin, G.M., 2009. Lamotrigine for treatment of bipolar depression: independent meta-analysis and meta-regression of individual patient data from five randomised trials. Br. J. Psychiatry 194 (1), 4–9.
Goldberg, J.F., Burdick, K.E., Endick, C.J., 2004. Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression. Am. J. Psychiatry 161 (3), 564–566.
Goodwin, F.K., Jamison, K.R., 2007. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. 2nd ed. Oxford University Press, New York, NY.
Goodwin, G.M., Bowden, C.L., Calabrese, J.R., Grunze, H., Kasper, S., White, R., Greene, P., Leadbetter, R., 2004. A pooled analysis of 2 placebo-controlled 18-month trials of lamotrigine and lithium maintenance in bipolar I disorder. J. Clin. Psychiatry 65 (3), 432–441.
Gyulai, L., Bowden, C.L., McElroy, S.L., Calabrese, J.R., Petty, F., Swann, A.C., Chou, J.C., Wassef, A., Risch, C.S., Hirschfeld, R.M., Nemeroff, C.B., Keck, P.E., Jr., Evans, D.L., Wozniak, P.J., 2003. Maintenance efficacy of divalproex in the prevention of bipolar depression. Neuropsychopharmacology 28 (7), 1374–1382.
Judd, L.L., Akiskal, H.S., Schettler, P.J., Endicott, J., Maser, J., Solomon, D.A., Leon, A.C., Rice, J.A., Keller, M.B., 2002. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch. Gen. Psychiatry 59 (6), 530–537.
Judd, L.L., Schettler, P.J., Akiskal, H., Coryell, W., Fawcett, J., Fiedorowicz, J.G., Solomon, D.A., Keller, M.B., 2012. Prevalence and clinical significance of subsyndromal manic symptoms, including irritability and psychomotor agitation, during bipolar major depressive episodes. J. Affect. Disord. 138 (3), 440–448.
Kane, J.M., 2006. Tardive dyskinesia circa 2006. Am. J. Psychiatry 163 (8), 1316–1318.
Kessler, R.C., Akiskal, H.S., Ames, M., Birnbaum, H., Greenberg, P., Hirschfeld, R.M., Jin, R., Merikangas, K.R., Simon, G.E., Wang, P.S., 2006. Prevalence and effects of mood disorders on work performance in a nationally representative sample of U.S. workers. Am. J. Psychiatry 163 (9), 1561–1568.
Leboyer, M., Soreca, I., Scott, J., Frye, M., Henry, C., Tamouza, R., Kupfer, D.J., 2012. Can bipolar disorder be viewed as a multi-system inflammatory disease? J. Affect. Disord. 141 (1), 1–10.
Loebel, A., Cucchiaro, J., Silva, R., Kroger, H., Hsu, J., Sarma, K., Sachs, G., 2014a. Lurasidone monotherapy in the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am. J. Psychiatry 171 (2), 160–168.
Loebel, A., Cucchiaro, J., Silva, R., Kroger, H., Sarma, K., Xu, J., Calabrese, J.R., 2014b. Lurasidone as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression: a randomized, double-blind, placebo-controlled study. Am. J. Psychiatry 171 (2), 169–177.
Lombardo, I., Sachs, G., Kolluri, S., Kremer, C., Yang, R., 2012. Two 6-week, randomized, double-blind, placebo-controlled studies of ziprasidone in outpatients with bipolar I depression: did baseline characteristics impact trial outcome? J. Clin. Psychopharmacol. 32 (4), 470–478.
Marangell, L.B., George, M.S., Callahan, A.M., Ketter, T.A., Pazzaglia, P.J., L'Herrou, T.A., Leverich, G.S., Post, R.M., 1997a. Effects of intrathecal thyrotropin-releasing hormone (protirelin) in refractory depressed patients. Arch. Gen. Psychiatry 54 (3), 214–222.
Marangell, L.B., Ketter, T.A., George, M.S., Pazzaglia, P.J., Callahan, A.M., Parekh, P., Andreason, P.J., Horwitz, B., Herscovitch, P., Post, R.M., 1997b. Inverse relationship of peripheral thyrotropin-stimulating hormone levels to brain activity in mood disorders. Am. J. Psychiatry 154 (2), 224–230.
Masoliver, E., Menoyo, A., Perez, V., Volpini, V., Rio, E.D., Perez, J., Alvarez, E., Baiget, M., 2006. Serotonin transporter linked promoter (polymorphism) in the serotonin transporter gene may be associated with antidepressant-induced mania in bipolar disorder. Psychiatr. Genet. 16 (1), 25–29.
McElroy, S.L., Weisler, R.H., Chang, W., Olausson, B., Paulsson, B., Brecher, M., Agambaram, V., Merideth, C., Nordenhem, A., Young, A.H.; EMBOLDEN II (Trial D1447C00134) Investigators, 2010. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J. Clin. Psychiatry 71 (2), 163–174.
Mundo, E., Walker, M., Cate, T., Macciardi, F., Kennedy, J.L., 2001. The role of serotonin transporter protein gene in antidepressant-induced mania in bipolar disorder: preliminary findings. Arch. Gen. Psychiatry 58 (6), 539–544.
Nemeroff, C.B., Evans, D.L., Gyulai, L., Sachs, G.S., Bowden, C.L., Gergel, I.P., Oakes, R., Pitts, C.D., 2001. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am. J. Psychiatry 158 (6), 906–912.
Nery, F.G., Monkul, E.S., Hatch, J.P., Fonseca, M., Zunta-Soares, G.B., Frey, B.N., Bowden, C.L., Soares, J.C., 2008. Celecoxib as an adjunct in the treatment of depressive or mixed episodes of bipolar disorder: a double-blind, randomized, placebo-controlled study. Hum. Psychopharmacol. 23 (2), 87–94.
Nolen, W.A., Weisler, R.H., 2013. The association of the effect of lithium in the maintenance treatment of bipolar disorder with lithium plasma levels: a post hoc analysis of a double-blind study comparing switching to lithium or placebo in patients who responded to quetiapine (Trial 144). Bipolar Disord.

15 (1), 100–109.
Pacchiarotti, I., Bond, D.J., Baldessarini, R.J., Nolen, W.A., Grunze, H., Licht, R.W., Post, R.M., Berk, M., Goodwin, G.M., Sachs, G.S., Tondo, L., Findling, R.L., Youngstrom, E.A., Tohen, M., Undurraga, J., Gonzalez-Pinto, A., Goldberg, J.F., Yildiz, A., Altshuler, L.L., Calabrese, J.R., Mitchell, P.B., Thase, M.E., Koukopoulos, A., Colom, F., Frye, M.A., Malhi, G.S., Fountoulakis, K.N., Vazquez, G., Perlis, R.H., Ketter, T.A., Cassidy, F., Akiskal, H., Azorin, J.M., Valenti, M., Mazzei, D.H., Lafer, B., Kato, T., Mazzarini, L., Martinez-Aran, A., Parker, G., Souery, D., Ozerdem, A., McElroy, S.L., Girardi, P., Bauer, M., Yatham, L.N., Zarate, C.A., Nierenberg, A.A., Birmaher, B., Kanba, S., El-Mallakh, R.S., Serretti, A., Rihmer, Z., Young, A.H., Kotzalidis, G.D., MacQueen, G.M., Bowden, C.L., Ghaemi, S.N., Lopez-Jaramillo, C., Rybakowski, J., Ha, K., Perugi, G., Kasper, S., Amsterdam, J.D., Hirschfeld, R.M., Kapczinski, F., Vieta, E., 2013. The International Society for Bipolar Disorders (ISBD) Task Force Report on Antidepressant Use in Bipolar Disorders. Am. J. Psychiatry 170 (11), 1249–1262.
Peet, M., 1994. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br. J. Psychiatry 164 (4), 549–550.
Phillips, M.L., Kupfer, D.J., 2013. Bipolar disorder diagnosis: challenges and future directions. Lancet 381 (9878), 1663–1671.
Post, R.M., Altshuler, L.L., Leverich, G.S., Frye, M.A., Nolen, W.A., Kupka, R.W., Suppes, T., McElroy, S., Keck, P.E., Denicoff, K.D., Grunze, H., Walden, J., Kitchen, C.M., Mintz, J., 2006. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br. J. Psychiatry 189, 124–131.
Prieto, M.L., Youngstrom, E.A., Ozerdem, A., Altinbas, K., Quiroz, D., Aydemir, O., Yalin, N., Geske, J.R., Feedeer, S.E., Angst, J., Frye, M.A., 2014. Different patterns of manic / hypomanic symptoms in depression: a pilot modification of the Hypomania Checklist - 32 to assess mixed depression. J. Affect. Disord. In press.
Rousseva, A., Henry, C., van den Bulke, D., Fournier, G., Laplanche, J.L., Leboyer, M., Bellivier, F., Aubry, J.M., Baud, P., Boucherie, M., Buresi, C., Ferrero, F., Malafosse, A., 2003. Antidepressant-induced mania, rapid cycling and the serotonin transporter gene polymorphism. Pharmacogenomics J. 3 (2), 101–104.
Rush, A.J., Giles, D.E., Schlesser, M.A., Fulton, C.L., Weissenburger, J., Burns, C., 1986. The Inventory for Depressive Symptomatology (IDS): preliminary findings. Psychiatry Res. 18 (1), 65–87.
Rush, A.J., Gullion, C.M., Basco, M.R., Jarrett, R.B., Trivedi, M.H., 1996. The Inventory of Depressive Symptomatology (IDS): psychometric properties. Psychol. Med. 26 (3), 477–486.
Sachs, G.S., Ice, K.S., Chappell, P.B., Schwartz, J.H., Gurtovaya, O., Vanderburg, D.G., Kasuba, B., 2011. Efficacy and safety of adjunctive oral ziprasidone for acute treatment of depression in patients with bipolar I disorder: a randomized, double-blind, placebo-controlled trial. J. Clin. Psychiatry 72 (10), 1413–1422.
Sachs, G.S., Nierenberg, A.A., Calabrese, J.R., Marangell, L.B., Wisniewski, S.R., Gyulai, L., Friedman, E.S., Bowden, C.L., Fossey, M.D., Ostacher, M.J., Ketter, T.A., Patel, J., Hauser, P., Rapport, D., Martinez, J.M., Allen, M.H., Miklowitz, D.J., Otto, M.W., Dennehy, E.B., Thase, M.E., 2007. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N. Engl. J. Med. 356 (17), 1711–1722.
Serretti, A., Artioli, P., Zanardi, R., Lorenzi, C., Rossini, D., Cusin, C., Arnoldi, A., Catalano, M., 2004. Genetic features of antidepressant induced mania and hypo-mania in bipolar disorder. Psychopharmacology (Berl.) 174 (4), 504–511.
Sidor, M.M., MacQueen, G.M., 2012. An update on antidepressant use in bipolar depression. Curr. Psychiatry Rep. 14 (6), 696–704.
Sidor, M.M., MacQueen, G.M., 2011. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J. Clin. Psychiatry 72 (2), 156–167.
Smeraldi, E., Benedetti, F., Barbini, B., Campori, E., Colombo, C., 1999. Sustained antidepressant effect of sleep deprivation combined with pindolol in bipolar depression. A placebo-controlled trial. Neuropsychopharmacology 20 (4), 380–385.
Smith, L.A., Cornelius, V.R., Azorin, J.M., Perugi, G., Vieta, E., Young, A.H., Bowden, C.L., 2010. Valproate for the treatment of acute bipolar depression: systematic review and meta-analysis. J. Affect. Disord. 122 (1–2), 1–9.
Solomon, D.A., Leon, A.C., Coryell, W.H., Endicott, J., Li, C., Fiedorowicz, J.G., Boyken, L., Keller, M.B., 2010. Longitudinal course of bipolar I disorder: duration of mood episodes. Arch. Gen. Psychiatry 67 (4), 339–347.
Spearing, M.K., Post, R.M., Leverich, G.S., Brandt, D., Nolen, W., 1997. Modification of the Clinical Global Impressions (CGI) Scale for use in bipolar illness (BP): the CGI-BP. Psychiatry Res. 73 (3), 159–171.
Strakowski, S.M., Adler, C.M., Almeida, J., Altshuler, L.L., Blumberg, H.P., Chang, K.D., DelBello, M.P., Frangou, S., McIntosh, A., Phillips, M.L., Sussman, J.E., Townsend, J.D., 2012. The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disord. 14 (4), 313–325.
Suppes, T., Datto, C., Minkwitz, M., Nordenhem, A., Walker, C., Darko, D., 2010. Effectiveness of the extended release formulation of quetiapine as monotherapy for the treatment of acute bipolar depression. J. Affect. Disord. 121 (1-2), 106–115.
Szuba, M.P., Baxter, L.R., Jr., Altshuler, L.L., Allen, E.M., Guze, B.H., Schwartz, J.M., Liston, E.H., 1994. Lithium sustains the acute antidepressant effects of sleep deprivation: preliminary findings from a controlled study. Psychiatry Res. 51 (3), 283–295.
Thase, M.E., Jonas, A., Khan, A., Bowden, C.L., Wu, X., McQuade, R.D., Carson, W.H., Marcus, R.N., Owen, R., 2008. Aripiprazole monotherapy in nonpsychotic bipolar I depression: results of 2 randomized, placebo-controlled studies. J. Clin. Psychopharmacol. 28 (1), 13–20.
Thase, M.E., Macfadden, W., Weisler, R.H., Chang, W., Paulsson, B., Khan, A., Calabrese, J.R.; BOLDER II Study Group, 2006. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J. Clin. Psychopharmacol. 26 (6), 600–609.
Tohen, M., Katagiri, H., Fujikoshi, S., Kanba, S., 2013. Efficacy of olanzapine monotherapy in acute bipolar depression: a pooled analysis of controlled studies. J. Affect. Disord. 149 (1–3), 196–201.
Tohen, M., McDonnell, D.P., Case, M., Kanba, S., Ha, K., Fang, Y.R., Katagiri, H., Gomez, J.C., 2012. Randomised, double-blind, placebo-controlled study of olanzapine in patients with bipolar I depression. Br. J. Psychiatry 201 (5), 376–382.
Tohen, M., Vieta, E., Calabrese, J., Ketter, T.A., Sachs, G., Bowden, C., Mitchell, P.B., Centorrino, F., Risser, R., Baker, R.W., Evans, A.R., Beymer, K., Dubé, S., Tollefson, G.D., Breier, A., 2003. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch. Gen. Psychiatry 60 (11), 1079–1088.
Tye, S.J., 2013. Allostatic overload: transcriptomic insights into the molecular basis of antidepressant resistance. Bipolar Disord. 15(Suppl 1), 41.
van der Loos, M.L., Mulder, P.G., Hartong, E.G., Blom, M.B., Vergouwen, A.C., de Keyzer, H.J., Notten, P.J., Luteijn, M.L., Timmermans, M.A., Vieta, E., Nolen, W.A., 2009. Efficacy and safety of lamotrigine as add-on treatment to lithium in bipolar depression: a multicenter, double-blind, placebo-controlled trial. J. Clin. Psychiatry 70 (2), 223–231.
Vieta, E., Martinez-Aran, A., Goikolea, J.M., Torrent, C., Colom, F., Benabarre, A., Reinares, M., 2002. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J. Clin. Psychiatry 63 (6), 508–512.
World Health Organization, 2008. The global burden of disease: 2004 update. Geneva, Switzerland, World Health Organization, http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed October 17, 2014.
Young, A.H., McElroy, S.L., Bauer, M., Philips, N., Chang, W., Olausson, B., Paulsson, B., Brecher, M.; for the EMBOLDEN I (Trial 001) Investigators, 2010. A double-blind, placebo-controlled study of quetiapine and lithium monotherapy in adults in the acute phase of bipolar depression (EMBOLDEN I). J. Clin. Psychiatry 71 (2), 150–162.
Zarate, C.A., Jr., Brutsche, N.E., Ibrahim, L., Franco-Chaves, J., Diazgranados, N., Cravchik, A., Selter, J., Marquardt, C.A., Liberty, V., Luckenbaugh, D.A., 2012. Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial. Biol. Psychiatry 71 (11), 939–946.
Zarate, C.A., Jr., Payne, J.L., Singh, J., Quiroz, J.A., Luckenbaugh, D.A., Denicoff, K.D., Charney, D.S., Manji, H.K., 2004. Pramipexole for bipolar II depression: a placebo-controlled proof of concept study. Biol. Psychiatry 56 (1), 54–60.
Zarate, C.A., Jr., Quiroz, J.A., Singh, J.B., Denicoff, K.D., De, J.G., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2005. An open-label trial of the glutamate-modulating agent riluzole in combination with lithium for the treatment of bipolar depression. Biol. Psychiatry 57 (4), 430–432.