Bipolar Depression: Molecular Neurobiology, Clinical Diagnosis and Pharmacotherapy
Edited by C.A. Zarate and H.K. Manji

Pharmacological treatment of acute bipolar depression

Gary S. Sachs, Louisa G. Sylvia and Hannah G. Lund

Bipolar Clinic and Research Program, Massachusetts General Hospital, 50 Staniford St, Suite 580, Boston, MA 02114, USA

Abstract

Acute depression is the condition for which bipolar patients most often seek treatment. The foundation of evidence-based practice is the practitioner's obligation to inform the patient of proven therapies that may exist to treat their condition. The best guidance for meeting this obligation in clinical practice comes from double-blind, placebo-controlled trials with adequate sample size, referred to in this chapter as Category A evidence. This level of evidence is currently available for only four pharmacological treatments, lamotrigine, olanzapine plus fluoxetine, olanzapine monotherapy, and quetiapine. Interestingly, the most common treatment for bipolar depression – the adjunctive use of standard antidepressants along with lithium or valproate – has not been shown to be effective in any Category A study. Additional treatments for bipolar depression are needed for the many depressed bipolar patients who do not respond adequately to currently available treatments. Several classes of medications show promise for these patients. Exploring the variety of mechanisms by which these medications work may shed light on the pathophysiology of bipolar disorder.

Introduction

The debate over litigation arising from the care of a patient with bipolar disorder suffering from depression played an important role in the ascension of evidence-based practice. Lessons illustrated by this case remain relevant to care nearly two decades later. As articulated by Klerman [1] in testimony and publications, American psychiatrists began referring to the right of patients to be informed about evidence-based treatments. The resulting perspective helped move psychiatric practice from a position where any school of thought could be cited as sufficient basis for justifying care given to patients to a position that granted primacy to clinical trial data. Today, proven treatments are preferred over unproven treatments, even while we acknowledge that unproven does not mean that a treatment is necessarily ineffective.

Bipolar depression remains a clinical challenge, and debate over its treatment continues into the 21st century. Although abnormal mood elevation is the cardinal diagnostic feature of bipolar disorder, depression is more than three

times as common as episodes of mood elevation and represents the doorway through which bipolar patients most often enter treatment [2].

This chapter will review the state of evidence supporting pharmacological treatments for bipolar depression. Management of the acute phase of bipolar depression remains controversial. While this largely reflects a continued scarcity of high quality studies, the past decade has seen the publication of the first fully-powered, placebo-controlled trials for bipolar depression as well as a number of new therapeutic agents.

State of the evidence

All published evidence is not created equal. The best guidance for clinical decision-making comes from double-blind, randomized, placebo-controlled trials with adequate samples. Studies meeting these criteria are referred to here as category A studies [3]. Table 1 offers a simple grading system intended to help the reader draw distinctions between these studies. Over the past 5 years, clinicians treating bipolar disorder have seen a healthy increase in the number of agents with Category A evidence. Comparison between these agents, however, is not as simple as comparing outcomes across studies or calculating an

Table 1. Categories of clinical evidence

A:	Double-blind, placebo-controlled trials with adequate sample size
B:	Double-blind, controlled trials without placebo or without adequate sample size; controlled studies without randomization
C:	Naturalistic or open-label trials/non-experimental descriptive studies or case control studies
D:	Uncontrolled observations, case series, and single case reports
E:	Absence of published studies. However, Category A evidence supports a class effect

effect size. Direct head-to-head studies are required to confidently compare medications.

Approach to clinical management

Recognition of bipolar depression

Patients with bipolar depression, by definition, meet criteria for a current major depressive episode and a lifetime history of bipolar disorder. To make the diagnosis, a clinician must determine whether the patient has experienced clinically significant abnormal mood elevation in the past. Confident diagno-

sis of bipolar depression requires the identification of at least one specific episode meeting criteria for mania or hypomania. Thus, the pathway to appropriate treatment requires recognition of a clinical state other than that observed at the time the patient presents for treatment. Guidelines and quality standards are beginning to recognize the importance of inquiring about a past personal or family history of mania in the assessment of every patient with acute depression [4]. While data from DSM field trials show high rates of agreement for acute mania and reasonably good rates for acute depression [5], these studies do not guide clinical practice on the reliability of eliciting a past history of mania or hypomania from a currently depressed patient. Bipolar disorder cannot be ruled out in the absence of input from collateral sources, particularly in the face of severe acute depression [6]. Care of bipolar depression can be greatly facilitated by clear documentation in the medical record of an index episode of hypomania or mania.

Initiation of sequential measurement-based treatment

The patient's right to evidence-based treatment necessitates that clinicians be aware of treatments supported by adequate clinical trial data (Category A evidence) and that these be offered to patients. Where multiple treatment options are supported by high quality evidence, it is appropriate to present these options to patients as a menu of reasonable choices [3]. Revicki [7] has shown that bipolar patients are generally able to weigh the risk benefit tradeoffs presented by clinicians, which is requisite for patient participation as collaborators in formulating their treatment plan. Thus, patients who are non-responsive to a treatment can be offered each of the reasonable options sequentially based on the patient's preference.

Integrating routine outcome measurement

After patients have agreed to use a medication, it is useful for patients and their doctors to agree on how progress will be measured [8, 9]. While formal depression severity scales such as the Hamilton Depression Rating Scale (HAM-D) or self report scales like the Inventory of Depressive Symptoms (IDS) have the virtue of generating numbers, even raw symptom counts provide serviceable aides to navigating a complex and changing clinical course. The clinical monitoring form and waiting room self-report form, used at the Massachusetts General Hospital Bipolar Clinic are available at *www.manicdepressive.org*. Using these measures facilitates individualized management in which beneficial treatments are continued, and ineffective or intolerable treatments are withdrawn. The pitfalls of repetitious indecisive trials can be avoided by carrying out each intervention with sufficient dose and duration to declare a definitive outcome (beneficial, ineffective, or intolerable).

Options supported by Category A Evidence (at least one positive adequately powered double-blind, placebo-controlled, clinical trial)

Lamotrigine

Calabrese and colleagues [10] first demonstrated the efficacy of lamotrigine for treating bipolar depression. In this 7-week, multicenter, double-blind, fixed-dose study, 195 patients were treated with lamotrigine (50 or 200 mg/day) or placebo. The trend favoring lamotrigine on the primary outcome measure (mean change in HAM-D score) fell just short of statistical significance; however, significant improvements over placebo were found for key secondary endpoints, such as change in Montgomery-Asberg Depression Rating Scale (MADRS) and CGI-BP (Clinical Global Impression for Bipolar Disorder Scale) mean scores. Lamotrigine was not associated with an increased risk of Treatment Emergent Affective Switch (TEAS) compared to placebo. Although subsequent Glaxo-sponsored studies of lamotrigine for bipolar depression resulted in failed trials, trends in these results have consistently favored lamotrigine. In a recent meta-analysis of monotherapy studies lamotrigine did demonstrate efficacy in the acute treatment of bipolar depression, despite results not reaching statistical significance in four out of five placebo-controlled studies [11].

Nierenberg and colleagues [12] randomized Bipolar I and II patients with depression who were unresponsive to at least two trials of standard antidepressants combined with mood stabilizers to receive open treatment with lamotrigine (150–250 mg), risperidone (up to 1–6 mg), or inositol (10–25 g). This Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) randomized, open-label study reported positive results for lamotrigine (24% 'recovered') compared with risperidone (5% 'recovered'). Outcomes for inositol (17% recovered) did not significantly differ from either risperidone or lamotrigine.

Van der Loos and colleagues showed a statistically significant benefit for lamotrigine over placebo as an adjunct to lithium for bipolar depression [13]. In addition, Brown and colleagues randomized bipolar depressed patients to receive either lamotrigine or combined treatment with olanzapine and fluoxetine (OFC) [14]; although response rates were generally comparable between the groups, lamotrigine was associated with significantly less weight gain, sedation, dry mouth, and tremor than combined treatment with OFC.

Olanzapine and OFC

The only fully-powered, placebo-controlled trial examining these agents is particularly valuable because it involves a direct comparison between two active arms and a placebo control. Tohen and colleagues [15] randomized Bipolar I depressed subjects to receive placebo (n = 355), olanzapine (n = 352), or OFC (n = 82) and reported a statistically significant advantage

for olanzapine over placebo. OFC was found to have superior efficacy to olanzapine monotherapy as well as placebo. The groups did not differ in treatment-emergent antidepressant switch (TEAS) rates. The study by Brown and colleagues [14] mentioned above was a double-blind, 7-week, controlled trial that randomized Bipolar I depressed patients (n = 205) to OFC or lamotrigine. Although response rates did not differ significantly between treatment groups, time to 50% reduction in their MADRS score was significantly shorter with OFC. There was no significant difference in rates of TEAS between groups, although OFC was associated with significantly more weight gain, somnolence, dry mouth, and tremor.

Quetiapine

There are five adequately-powered, double-blind, placebo-controlled trials demonstrating the efficacy of quetiapine for bipolar depression. The first of these [16] was a double-blind trial (BOLDER I) that randomized 542 patients with bipolar depression to placebo, quetiapine 300 mg, or quetiapine 600 mg [9]. Both dosages of quetiapine resulted in significantly higher response rates (58%) compared to placebo (36%) at 8 weeks, as well as a significant advantage over placebo on mean change from baseline in MADRS score. No differences between the groups were found in TEAS rates. These results have recently been replicated by two subsequent trials with similar design (one of which used the extended release form of quetiapine). Two additional studies used variations on the same design with the addition of an active control; one study used lithium and the other used paroxetine. These yielded results for placebo and quetiapine that were similar to the prior study outcomes, but neither of the active control groups differed from placebo.

Importantly, the overall study results include outcomes for patients with Bipolar I and Bipolar II disorder [16, 17]. Because most other studies excluded patients with Bipolar II disorder, it is worth noting that quetiapine is the only agent that has shown a statistically significant benefit in the treatment of Bipolar II depression [16, 17] and has the largest effect size (.91 and 1.09, for 300 and 600 mg/day of quetiapine in the BOLDER I study, respectively) observed in any trial for Bipolar I disorder. Slightly lower effect sizes were observed in subsequent studies, likely reflecting the impact of expectancy following BOLDER I and the tendency of trials with more arms to have higher placebo response rates.

Standard antidepressant medications

Until recently, clinical management of bipolar depression was extrapolated from accumulated experience and research in treating unipolar depression due to the dearth of evidence for bipolar patients. More than two dozen agents have

been approved by the US Food and Drug Administration, or other regulatory authorities, for treating unipolar depression. The appropriateness of these agents for bipolar patients cannot be determined based on studies of unipolar depression, because the mechanisms by which these drugs act remain poorly understood and because the trials establishing the efficacy of these agents typically excluded bipolar patients.

In this century, a total of five Category A studies have been reported involving imipramine (one study), paroxetine (three studies) and bupropion (one study) with bipolar patients (see Fig. 1).

The first Category A study for bipolar depression was reported by Nemeroff and colleagues [18]. This study randomized depressed Bipolar I subjects treated with lithium (0.5–1.2 mmol per liter) to double-blind adjunctive treatment with placebo, paroxetine, or imipramine. Overall, this study found no benefit for paroxetine or imipramine over placebo on any of the efficacy measures. Among the subgroup with lithium levels between 0.5 and 0.8 mmol/L, however, there was a significant advantage for patients receiving paroxetine. No differences were found between the groups in the rate of TEAS. Unfortunately, confidence in this finding is limited, because the study had no formal rating scale to assess mood elevation and was likely insensitive to TEAS.

The largest placebo-controlled study of standard antidepressants was carried out by STEP-BD. This National Institute of Mental Health sponsored double-blind study randomized 366 patients to receive treatment with a mood stabilizer (lithium, carbamazepine, valproate) and placebo or a mood stabilizer

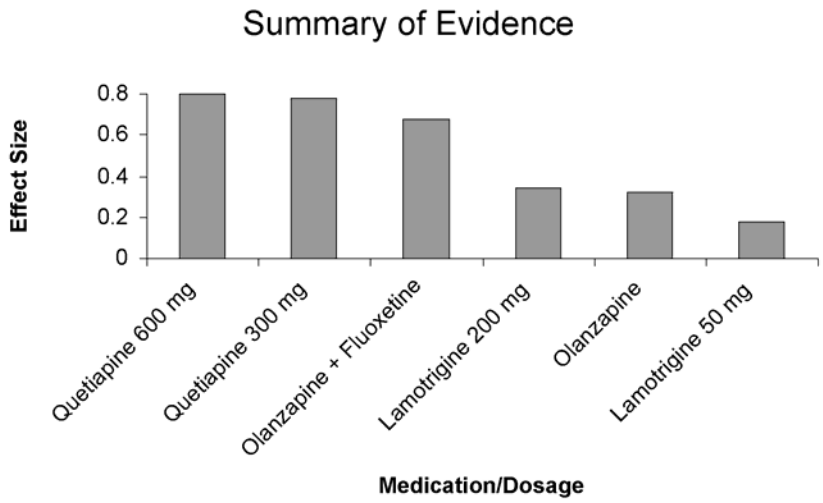

Figure 1. In a pooled analysis of patients with Bipolar I disorder from two randomized controlled trials (BOLDER I and II), effect sizes were 0.78 and 0.80 for quetiapine 300 and 600 mg/daily dosages, respectively [39]. In a study of olanzapine *versus* olanzapine + fluoxetine (OFC) in combination, effect sizes were .32 and .68, respectively [15]. When lamotrigine 200 mg and 50 mg were compared *versus* placebo, effect sizes were .18 and .34, respectively [10].

and an antidepressant (bupropion or paroxetine) [19]. There were no group differences in regards to subjects' likelihood of achieving a durable recovery (eight consecutive weeks euthymic) (27% in placebo group and 24% in antidepressant groups), their TEAS scores (10–11%, both groups), or other outcome measures. Thus, there was evidence of neither benefit nor harm in adjunctive use of bupropion or paroxetine.

In summary, no Category A study has found a statistically significant benefit to adding a standard antidepressant to lithium, carbamazepine, or valproic acid. OFC was superior to treatment with placebo and superior to treatment with olanzapine monotherapy, but this single study represents the only available high-quality evidence supporting the practice of administering a standard antidepressant medication to depressed patients with bipolar disorder [15]. The degree to which this finding generalizes to combining fluoxetine with other agents, or the possibility that olanzapine might potentiate other agents, is unclear.

Studies without placebo control

The Stanley Foundation Bipolar Network (SFBN) conducted a randomized, double-blind comparison of adjunct bupropion, sertraline, or venlafaxine to ongoing mood stabilizer treatment in 159 patients with bipolar disorder [20, 21]. Overall TEAS into hypomania and mania occurred in 11.4% and 7.9%, respectively, of acute treatment trials (10 weeks), and in 21.8% and 14.9% of the continuation trials (1-year duration). The rate of TEAS was higher in patients with Bipolar I disorder (30.8%) than in those with Bipolar II disorder (18.6%). The risk of switch into hypomania or mania was significantly increased in subjects treated with venlafaxine (15%) compared to bupropion (4%) or sertraline (7%).

In a 6-week, randomized, single-blind trial, Vieta and colleagues [22] compared the efficacy of mood stabilizers with adjunctive paroxetine (n = 30) to mood stabilizers with adjunctive venlafaxine (n = 30), and found no significant differences in terms of treatment response rates between the groups (paroxetine 43%, venlafaxine 47%). Rates of TEAS were 3% in the paroxetine group and 13% in the venlafaxine group. Silverstone and colleagues [23] compared the antidepressant efficacy of moclobemide (n = 81), and imipramine (n = 75) in patients with bipolar disorder, 64% of whom were prescribed concomitant mood stabilizers. No statistically significant differences between the two groups were found on any of the efficacy measures. The trend for higher rates of study withdrawal due to TEAS did not reach statistical significance (moclobemide = 3.7%, imipramine = 11%).

Amsterdam and colleagues [24] evaluated the efficacy of fluoxetine in a randomized, double-blind, placebo-controlled study (n = 34). Significant reductions in mean HAM-D and MADRS ratings, without an increase in YMRS scores, were reported in the active and placebo groups. These investigators also

reported that in patients with bipolar depression who received 8 weeks of open-label fluoxetine treatment, 48% showed a HAM-D reduction of greater than 50%, while 7.3% developed TEAS (YMRS ≥8) [25]. Other small double-blind studies of standard antidepressant use in bipolar depression include those of add-on tranylcypromine [26, 27] and desipramine *versus* bupropion [28].

Studies without randomization

Altshuler and colleagues [29] reported quasi-experimental results from the SFBN. Among the 1,078 patients with bipolar disorder, about 50% became depressed and had a standard antidepressant added to their treatment regimen. 15% of these patients, for whom there was a clinical intent-to-treat with a standard antidepressant, achieved remission. A comparison of remitted patients (depending on whether antidepressants were continued for more than 6 months or discontinued before 6 months) revealed that 20–25% experienced a relapse into depression over the first 4 months regardless of whether or not antidepressants were continued. Significantly lower rates of relapse into depression over 1 year were observed for those who remained on antidepressants (36%) compared with those who discontinued (70%). However, when interpreting this finding one must consider that the reasons for antidepressant discontinuation are not apparent; for example, treatments may have been discontinued due to lack of efficacy. A similarly designed study [30] reported 1-year outcome rates of antidepressant treatment in 59 patients with bipolar depression and found comparable results, which are also subject to the same limitations.

A STEP-BD study reported a quasi-experimental comparison of outcomes for 1,000 patients with bipolar disorder treated openly and followed prospectively for 1 year. In this sample, 18% of patients experienced the onset of a new depressive episode, including 5% who had multiple depressive episodes [31]. Outcome analysis for the first depressive episode revealed no statistically significant advantage to adding standard antidepressant medications compared to subjects managed without a standard antidepressant. Rates of TEAS were 14.6% irrespective of the use of standard antidepressants.

Meta-analyses and systematic reviews

Gijsman and colleagues [32] reported a meta-analysis of 12 randomized, controlled trials on the efficacy and safety of antidepressants for the short-term treatment of bipolar depression, and found antidepressants to be significantly more effective than placebo. A similar analysis for the TEAS data from these studies indicated that, overall, antidepressants did not cause higher rates of TEAS than placebo, but an association was found for the subgroup treated with tricyclic antidepressants. Several caveats pertain to translating these meta-analysis findings into clinical use. Chief among these is that the results do not

support the use of any one antidepressant. The 'response rates' used in the meta-analysis were overestimates of drug effectiveness because the studies based response solely on depression outcomes; thus the count includes successful responses cases in which a switch to mania had occurred. For instance, about 25% of the responders in the tranylcypromine and imipramine studies became manic [26]. The TEAS findings are also limited by the lack of any formal assessment for TEAS in most studies. Meta-analyses are most appropriate as a means of pooling underpowered homogeneous studies and are less desirable when high-quality, fully-powered studies are available.

Lithium

The American Psychiatric Association (APA) Guidelines recommend lithium as an initial treatment for bipolar depression of mild to moderate severity. There is, however, little statistical evidence comparing the antidepressant efficacy of lithium to placebo. Prior to 2008, relevant studies were limited to small placebo-controlled studies, crossover studies, or non-randomized samples. The recently completed AstraZeneca-sponsored comparison of lithium, quetiapine, and placebo showed no benefit for lithium compared to placebo. While the assay sensitivity of this trial was ostensibly established based on its success in detecting a substantial benefit for the groups treated with quetiapine (300 mg and 600 mg), the trial design may have inadvertently disadvantaged lithium relative to quetiapine; lithium is widely used by the eligible population and lithium-responsive subjects would have been unlikely to enroll. In addition, lithium and placebo would be disadvantaged to the extent that quetiapine's sedative qualities and other adverse effects may have unblinded raters.

Studies intended to test other adjunctive treatments in which subjects in all treatment groups received lithium cannot prove lithium's efficacy, but may nonetheless be instructive for clinical practice. The efficacy of lithium can be estimated to some extent based on the aforementioned double-blind trial by Nemeroff and colleagues [18], in which no overall benefit was found for the addition of standard antidepressants to lithium compared with lithium monotherapy at lithium levels ≥0.8 mEq/l. Where lithium was dosed at levels ≤0.8 mEq/L, add-on antidepressant treatment was more beneficial than lithium monotherapy [18]. This finding suggests that subtherapeutic lithium levels are less effective than therapeutic lithium levels, but does not allow any conclusions to be drawn about the relative efficacy of lithium compared with antidepressants or placebo.

Valproate

Evidence supporting the antidepressant properties of valproate is limited. Three small placebo-controlled trials suggest valproate may have beneficial

effects for bipolar depression [33–35]. As with lithium, enthusiasm for use of valproate in bipolar depression is often muted by historical perspectives that may not apply to contemporary clinical nomenclature. When analyzing treatment effect in a large, open case-series, Lambert (1966) found moderate improvement in only 22% of 103 'manic-depressive' patients treated with valpromide; this likely discouraged use of valproate in a manner similar to Cade's reported impression that lithium was ineffective for depression [36]. Because Lambert's series also largely comprised subjects who would be classified as having unipolar depression according to DSM-IV criteria, the question of valproate's antidepressant efficacy for bipolar patients remains open.

Carbamazepine

Controlled studies supporting the efficacy of carbamazepine in bipolar depression are scarce. Post and colleagues [37] published a randomized, double-blind study of 35 patients with bipolar depression. They found at least mild improvement in symptoms (CGI ratings) in 57%, and a more substantial improvement in 34.3% of patients treated with carbamazepine. This group also conducted a meta-analysis of carbamazepine treatment in unipolar and bipolar depression (including several small, open-label, and controlled studies), reporting that response rates to carbamazepine treatment were observed in 56% of open-label trials and 44% of controlled studies [38].

Conclusion

The right of patients to be made aware of evidence-based treatment options carries with it a need for practicing clinicians to be aware of the treatment options supported by Category A evidence. Currently, only four medications meet Category A criteria for use in bipolar depression: lamotrigine, olanzapine, OFC, and quetiapine. Regardless of whether patients accept these treatments, a measurement-based approach provides a systematic means of working towards individualized treatment.

Finally, this chapter has focused on the acute treatment of bipolar depression with currently available therapeutics. Chapter 12 of this volume, by Zarate and Manji, explores the utility of novel therapeutics currently under investigation for the treatment of bipolar depression.

References

1 Klerman GL (1990) The psychiatric patient's right to effective treatment: implications of Osheroff v. Chestnut Lodge. *Am J Psychiatry* 147: 409–418

2 Judd LL, Schettler PJ, Akiskal HS, Maser J, Coryell W, Solomon D, Endicott J, Keller M (2003)

Long-term symptomatic status of bipolar I *versus* bipolar II disorders. *Int J Neuropsychopharmacol* 6: 127–137
3 Sachs GS (2007) Bipolar disorder clinical synthesis: where does the evidence lead? *Focus* V: 1–11
4 Johnson SL, Brickman AL (2006) Diagnostic inconsistency: a marker of service utilization in bipolar disorder. *Manag Care Interface* 19: 41–45
5 Keller MB, Hanks DL, Klein DN (1996) Summary of the DSM-IV mood disorders field trial and issue overview. *Psychiatr Clin North Am* 19: 1–28
6 Bowden CL (2001) Strategies to reduce misdiagnosis of bipolar depression. *Psychiatr Serv* 52: 51–55
7 Revicki DA, Hanlon J, Martin S, Gyulai L, Nassir Ghaemi S, Lynch F, Mannix S, Kleinman L (2005) Patient-based utilities for bipolar disorder-related health states. *J Affect Disord* 87: 203–210
8 Rush AJ, Kraemer HC, Sackeim HA, Fava M, Trivedi MH, Frank E, Ninan PT, Thase ME, Gelenberg AJ, Kupfer DJ et al (2006) Report by the ACNP Task Force on response and remission in major depressive disorder. *Neuropsychopharmacology* 31: 1841–1853
9 Rush AJ, Trivedi MH, Ibrahim HM, Carmody TJ, Arnow B, Klein DN, Markowitz JC, Ninan PT, Kornstein S, Manber R et al (2003) The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biol Psychiatry* 54: 573–583
10 Calabrese JR, Bowden CL, Sachs GS, Ascher JA, Monaghan E, Rudd GD (1999) A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. Lamictal 602 Study Group. *J Clin Psychiatry* 60: 79–88
11 Calabrese J, Huffman RF, White R, Edwards S, Thompson T, Ascher J, Monaghan E, Leadbetter R (2008) Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. *Bipolar Disord* 10: 323–333
12 Nierenberg AA, Ostacher MJ, Calabrese JR, Ketter TA, Marangell LB, Miklowitz DJ, Miyahara S, Bauer MS, Thase ME, Wisniewski SR et al (2006) Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry* 163: 210–216
13 van der Loos ML, Kolling P, Knoppert-van der Klein EA, Nolen W (2007) Lamotrigine in the treatment of bipolar disorder. A review. *Tijdschr Psychiatr* 49: 95–103
14 Brown EB, McElroy SL, Keck PE, Jr, Deldar A, Adams DH, Tohen M, Williamson DJ (2006) A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination *versus* lamotrigine in the treatment of bipolar I depression. *J Clin Psychiatry* 67: 1025–1033
15 Tohen M, Vieta E, Calabrese J, Ketter TA, Sachs G, Bowden C, Mitchell PB, Centorrino F, Risser R, Baker RW et al (2003) Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. *Arch Gen Psychiatry* 60: 1079–1088
16 Calabrese JR, Keck PE Jr, Macfadden W, Minkwitz M, Ketter TA, Weisler RH, Cutler AJ, McCoy R, Wilson E, Mullen J (2005) A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 162: 1351–1360
17 Thase ME, Macfadden W, Weisler RH, Chang W, Paulsson B, Khan A, Calabrese JR (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: 600–609
18 Nemeroff CB, Evans DL, Gyulai L, Sachs GS, Bowden CL, Gergel IP, Oakes R, Pitts CD (2001) Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. *Am J Psychiatry* 158: 906–912
19 Sachs GS, Nierenberg AA, Calabrese JR, Marangell LB, Wisniewski SR, Gyulai L, Friedman ES, Bowden CL, Fossey MD, Ostacher MJ et al (2007) Effectiveness of adjunctive antidepressant treatment for bipolar depression. *N Engl J Med* 356: 1711–1722
20 Leverich GS, Altshuler LL, Frye MA, Suppes T, McElroy SL, Keck PE Jr, Kupka RW, Denicoff KD, Nolen WA, Grunze H et al (2006) Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. *Am J Psychiatry* 163: 232–239
21 Post RM, Altshuler LL, Leverich GS, Frye MA, Nolen WA, Kupka RW, Suppes T, McElroy S, Keck PE, Denicoff KD et al (2006) Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. *Br J Psychiatry* 189: 124–131
22 Vieta E, Martinez-Aran A, Goikolea JM, 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: 508–512
23 Silverstone T (2001) Moclobemide *versus* imipramine in bipolar depression: a multicentre double-blind clinical trial. *Acta Psychiatr Scand* 104: 104–109
24 Amsterdam JD, Shults J, Brunswick DJ, Hundert M (2004) Short-term fluoxetine monotherapy for bipolar type II or bipolar NOS major depression – low manic switch rate. *Bipolar Disord* 6: 75–81
25 Amsterdam JD, Garcia-Espana F, Fawcett J, Quitkin FM, Reimherr FW, Rosenbaum JF, Schweizer E, Beasley C (1998) Efficacy and safety of fluoxetine in treating bipolar II major depressive episode. *J Clin Psychopharmacol* 18: 435–440
26 Himmelhoch JM, Thase ME, Mallinger AG, Houck P (1991) Tranylcypromine *versus* imipramine in anergic bipolar depression. *Am J Psychiatry* 148: 910–916
27 Nolen WA, Kupka RW, Hellemann G, Frye MA, Altshuler LL, Leverich GS, Suppes T, Keck PE Jr, McElroy S, Grunze H et al (2007) Tranylcypromine *versus* lamotrigine in the treatment of refractory bipolar depression: a failed but clinically useful study. *Acta Psychiatr Scand* 115: 360–365
28 Sachs GS, Lafer B, Stoll AL, Banov M, Thibault AB, Tohen M, Rosenbaum JF (1994) A double-blind trial of bupropion *versus* desipramine for bipolar depression. *J Clin Psychiatry* 55: 391–393
29 Altshuler L, Suppes T, Black D, Nolen WA, Keck PE Jr, Frye MA, McElroy S, Kupka R, Grunze H, Walden J et al (2003) Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. *Am J Psychiatry* 160: 1252–1262
30 Joffe RT, MacQueen GM, Marriott M, Trevor Young L (2004) A prospective, longitudinal study of percentage of time spent ill in patients with bipolar I or bipolar II disorders. *Bipolar Disord* 6: 62–66
31 Goldberg JF, Perlis RH, Ghaemi SN, Calabrese JR, Bowden CL, Wisniewski S, Miklowitz DJ, Sachs GS, Thase ME (2007) Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. *Am J Psychiatry* 164: 1348–1355
32 Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM (2004) Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. *Am J Psychiatry* 161: 1537–1547
33 Davis LL, Bartolucci A, Petty F (2005) Divalproex in the treatment of bipolar depression: a placebo-controlled study. *J Affect Disord* 85: 259–266
34 Sachs G, Altshuler L, Ketter T, Suppes T, Rasgon N, Frey M, Collins M (2001) Divalproex *versus* placebo for treatment of Bipolar depression. 40th American College of Neuropsychopharmacology (ACNP), Waikoloa, Hawaii; December 9–13, 2001
35 Ghaemi SN, Gilmer WS, Goldberg JF, Zablotsky B, Kemp DE, Kelley ME, Bauer AD, Fleck J, Filkowski MM, Stan VA et al (2007) Divalproex in the treatment of acute bipolar depression: a preliminary double-blind, randomized, placebo-controlled pilot study. *J Clin Psychiatry* 68: 1840–1844
36 Lambert PA, Carraz G, Borselli S, Carbel S (1966) Action neuro-psychotrope d'un nouvel antiépileptique: le Dépamide [Neuropsychotropic action of a new antiepileptic: valpromide]. *Ann Med Psychol Paris* 124: 707–710
37 Post RM, Uhde TW, Roy-Byrne PP, Joffe RT (1986) Antidepressant effects of carbamazepine. *Am J Psychiatry* 143: 29–34
38 Post R, Ketter T, Uhde T, Ballenger JC (2007) Thirty years of clinical experience with carbamazepine in the treatment of bipolar illness: principles and practice. *CNS Drugs* 21: 47–71
39 Weisler RH, Hirschfeld R, Cutler AJ, Gazda T, Ketter TA, Keck PE, Swann A, Kalali A (2006) Extended-release carbamazepine capsules as monotherapy in bipolar disorder: pooled results from two randomised, double-blind, placebo-controlled trials. *CNS Drugs* 20: 219–231