An Analysis of the Efficacy of Treatments for Bipolar Depression

Andrew A. Nierenberg, M.D.

Individuals with bipolar disorder are euthymic approximately half of the time, but recurring mood episodes are common, and time spent ill is predominated by depressive symptoms. Despite the prevalence of depression in bipolar disorder, evidence suggests that antidepressants are not likely to benefit most patients. Lithium, long considered a first-line treatment for bipolar disorder, is not the most effective agent for preventing bipolar depression. This article reviews multiple pharmacologic options that should be considered by clinicians treating bipolar disorder in both acute and maintenance phases.
(J Clin Psychiatry 2008;69[suppl 5]:4–8)

Bipolar disorder had an estimated annual economic burden of $45 billion in 1991 in the United States.[1] A study[2] of patients in an insured population found that patients with bipolar disorder incurred greater total costs than general medical outpatients, patients with unipolar depression, and patients with diabetes. Although bipolar disorder is less prevalent than major depressive disorder—with a lifetime prevalence of about 1% and lifetime subthreshold prevalence of 2.4% to 4.7%[3,4]—it is more disabling and chronic than depression.[5] People with bipolar disorder take more sick leave and have higher rates of short-term disability than those without,[6] are at risk for suicide attempts and completed suicide,[7] and have an increasingly worsened prognosis with each additional mood episode.[8]

Diagnosis is difficult because bipolar disorder is often comorbid with, and shares symptoms with, a variety of psychiatric disorders, including unipolar depression,[9] borderline personality disorder,[10] schizophrenia,[11] anxiety, and substance use disorder.[12] Additionally, medical conditions such as migraine, respiratory disorders, circulatory disorders, epilepsy, and multiple sclerosis may exhibit similar symptoms or be more prevalent in patients with bipolar disorder.[13] Hirschfeld and colleagues[14] found that 69% of patients with bipolar disorder were initially misdiagnosed, with as many as 35% of these patients being symptomatic for 10 years or longer before receiving the correct diagnosis. The median lag time between the onset of bipolar symptoms and first treatment is 6 years.[15] Misdiagnosis and delayed treatment can have serious consequences, including decreased treatment efficacy and a 2-fold increase in the risk of suicide.[16] After their first bipolar episode, 72% of patients may recover symptomatically, but only 43% experience functional recovery after 2 years,[17] which demonstrates a significant lag between symptomatic and functional recovery.

People with bipolar disorder spend approximately half of their time euthymic, but when they are ill, depressive symptoms predominate. Judd and colleagues[18,19] followed 146 patients with bipolar I disorder for almost 13 years and found that patients spent 31.9% of the time with depressive symptoms, 5.9% of the time with cycling or mixed symptoms, and 9.3% of the time with mania.[18] A group of 86 patients with bipolar II disorder who were also followed for about 13 years spent 50.3% of their time with depressive symptoms, 2.3% with cycling or mixed symptoms, and 1.3% with hypomania.[19] So, for both bipolar I and II disorders, patients spend more time depressed than manic or hypomanic (Figure 1). Depressive symptoms include not only major depressive episodes that occur during the course of bipolar disorder but also substantial subsyndromal symptoms.

PHARMACOTHERAPY FOR ACUTE TREATMENT OF BIPOLAR DEPRESSION

Approved and off-label pharmacotherapeutic treatments for bipolar depression in both the acute phase and the maintenance phase include agents such as anticonvulsants, mood stabilizers, atypical antipsychotics, and

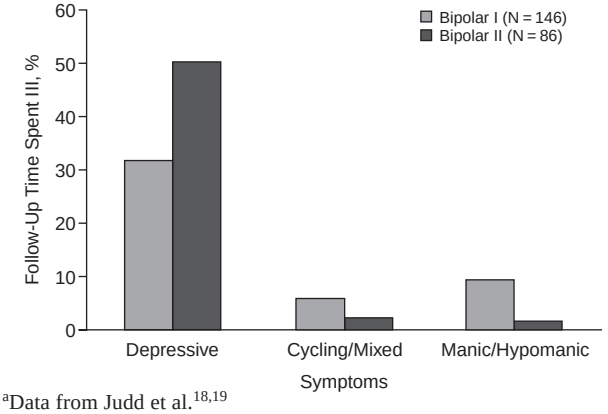
From the Department of Psychiatry, Harvard Medical School and the Depression Clinical and Research Program and the Bipolar Research Program, Massachusetts General Hospital, Boston.

This article is derived from the planning teleconference series "Easing the Burden of Bipolar Disorder: From Urgent Situations to Remission," which was held in February and March 2008 and supported by an educational grant from Eli Lilly and Company.

Dr. Nierenberg has received research support from Bristol-Myers Squibb, Cederroth, Cyberonics, Forest, Eli Lilly, GlaxoSmithKline, Janssen, Lichtwer, the National Alliance for Research on Schizophrenia and Depression, the National Institute of Mental Health, Pfizer, the Stanley Foundation, and Wyeth-Ayerst; is a member of the speakers bureaus for Bristol-Myers Squibb, Cyberonics, Forest, Eli Lilly, GlaxoSmithKline, and Wyeth-Ayerst; and is a consultant or a member of the advisory board for Abbott, BrainCells, Bristol-Myers Squibb, Cederroth, Eli Lilly, GlaxoSmithKline, Genaissance, Innapharma, Janssen, Novartis, Pfizer, Sepracor, Shire, and Somerset.

Corresponding author and reprints: Andrew A. Nierenberg, M.D., Massachusetts General Hospital, 15 Parkman St., WACC 812, Boston, MA 02114 (e-mail: anierenberg@partners.org).

Figure 1. Symptomatology of Patients With Bipolar I and II Disorder During Long-Term Follow-Up[a]



[a]Data from Judd et al.[18,19]

antidepressants, although the usefulness of antidepressants in bipolar treatment is a subject of continued debate in the field. Agents approved by the U.S. Food and Drug Administration (FDA) to treat bipolar depression or bipolar mood episodes are the olanzapine-fluoxetine combination and quetiapine monotherapy for acute treatment and lamotrigine for maintenance and preventive treatment.

Antidepressant Treatment in Acute Bipolar Depression

A fundamental question is whether or not antidepressants are effective and safe in bipolar depression. Because of concerns about efficacy and the possibility of antidepressant-induced mood switching, it is generally not recommended that antidepressants be used without a concurrent mood stabilizer when treating patients with bipolar disorder. More research is needed on this question, especially concerning long-term treatment.

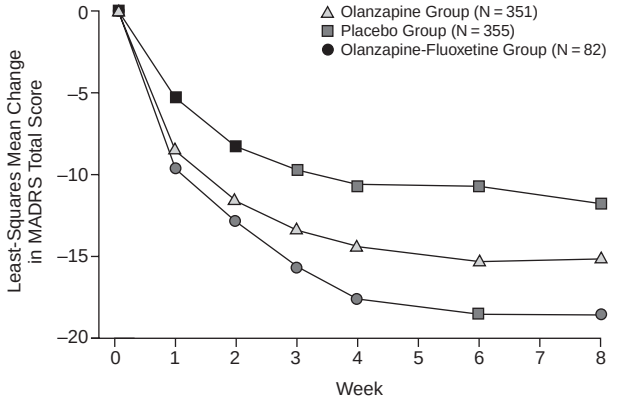
A large 8-week study[20] showed favorable results for an antidepressant versus placebo in bipolar depression, but the antidepressant was used in conjunction with an atypical antipsychotic; specifically, the olanzapine-fluoxetine combination was used. In a meta-analysis, Gijsman and colleagues[21] examined the results of that study[20] and 4 others[22–25] that compared response and/or remission rates of an antidepressant against those of placebo for up to 10 weeks. The antidepressants used by the other studies were fluoxetine, paroxetine, imipramine, tranylcypromine, and deprenyl, but only the patients taking tranylcypromine and deprenyl were not taking concurrent medications. These studies favored antidepressants over placebo for treating bipolar depression. However, most of these trials had small sample sizes, and some had methodological problems including insufficiently defined response measurements and failure to distinguish subjects who were or were not receiving concurrent medication when reporting response rates. Thus, not enough evidence exists to support antidepressant efficacy for patients with bipolar depression.

Clinicians should keep in mind that antidepressant monotherapy treatment of bipolar disorder may increase the risk for some patients of switching to mania, hypomania, or mixed states.[26] The meta-analysis[21] found that the rate of switching was higher with tricyclic antidepressants (10.0%) than with the other antidepressants combined (3.2%).[27] One study[23] compared lithium plus paroxetine, lithium plus imipramine, and lithium plus placebo. Overall, paroxetine and imipramine were no different than placebo in alleviating the depressive symptoms of bipolar disorder in patients taking lithium. However, the study was underpowered, with only 117 patients. Interestingly, superiority was noted between the 2 active drugs and placebo among patients who had low serum lithium levels, but this does not indicate any efficacy for the antidepressants so much as it demonstrates that the placebo does not work if the lithium level is too low. And again, if the lithium level is too low, patients may switch to mania or hypomania due to the presence of an antidepressant.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD),[28] a more recent, large, semi-naturalistic series of studies, was reasonably powered and contained an embedded randomized trial that added an antidepressant (bupropion or paroxetine) or placebo to ongoing treatment with a mood stabilizer among patients with bipolar disorder who were experiencing a major depressive episode. Outcome measurements were rigorously defined and consistent with *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria. The primary outcome, called *durable recovery*, was defined as at least 8 consecutive weeks of euthymia with no more than 2 depressive symptoms or 2 manic symptoms. A second outcome measurement, *transient remission*, which was defined as 1 to 7 consecutive weeks of euthymia, was added because the trial was only 16 weeks long, and if a subject recovered at week 12, he or she might sustain the remission for the remaining 4 weeks but could not be called *recovered*. The third important outcome measurement was *treatment-affective switch*, which applied to subjects who switched into mania or hypomania from depression.

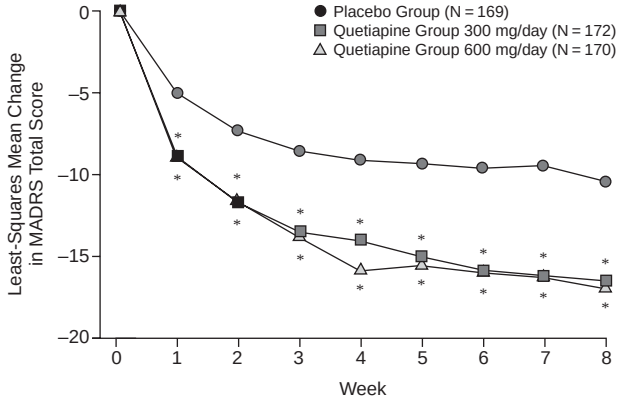
Of the patients who had an antidepressant added to mood stabilizer treatment, 23.5% achieved durable recovery, and 27.3% of those who had placebo added achieved durable recovery.[29] So, no statistically significant difference in durable recovery was found between the antidepressant and placebo groups, and in fact, the group that received placebo had slightly more improvement. In addition, no difference was noted between the groups in regard to treatment-emergent switching into mania.[29] Of the patients taking an antidepressant and a mood stabilizer, 10.1% experienced a treatment-emergent affective switch, compared with 10.7% of patients being treated with placebo plus a mood stabilizer. Thus, no harm or benefit occurred in this study by adding an antidepressant.

Figure 2. Improvement in Acute Bipolar Depression Using Olanzapine With or Without Fluoxetine[a]



[a]Reprinted with permission from Tohen et al.[20] Improvement in MADRS scores with use of olanzapine and the olanzapine-fluoxetine combination was significantly greater than with use of placebo throughout the study ($p < .001$). Improvement in MADRS scores with use of olanzapine-fluoxetine combination was significantly greater than with use of olanzapine at weeks 4 to 8 ($p < .02$).
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 3. Improvement in Acute Bipolar Depression With Quetiapine[a]



[a]Reprinted with permission from Calabrese et al.[33]
*Intent-to-treat, last-observation-carried-forward analysis. Improvement in MADRS total score with both doses of quetiapine (600 mg/day and 300 mg/day) was significantly greater than with placebo at every assessment ($p < .001$).
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Other Pharmacologic Treatments for Acute Bipolar Depression

A controlled, multicenter study[30] of lamotrigine, an anticonvulsant that also acts as a mood stabilizer, evaluated the agent's efficacy compared with that of placebo in 195 subjects with bipolar I disorder who were experiencing a major depressive episode. For 7 weeks, subjects received lamotrigine monotherapy dosed at 50 mg/day or 200 mg/day or placebo. Subjects taking the higher dose of lamotrigine had significantly improved scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17), the Hamilton Rating Scale for Depression (HAM-D) Item 1 (depressed mood), the Montgomery-Asberg Depression Rating Scale (MADRS), the Clinical Global Impressions-Severity of Illness scale (CGI-S), and the Clinical Global Impressions-Improvement scale (CGI-I) compared with the placebo group, and some of these improvements were significant by the third week of treatment. Efficacy superior to that of placebo was also demonstrated on some measures in the group receiving the lower dose of lamotrigine. The results of this trial have not been replicated in 4 additional studies.[31] While lamotrigine is not approved by the FDA for the acute treatment of bipolar depression, lamotrigine is approved for the prevention of mood episodes in bipolar disorder.

Tohen et al.[20] compared the combination of the atypical antipsychotic olanzapine and the antidepressant fluoxetine with olanzapine monotherapy and placebo in patients with bipolar I depression. Improvement in MADRS scores with olanzapine and the olanzapine-fluoxetine combination was significantly greater ($p < .001$) than with placebo for all 8 weeks of the study (Figure 2).

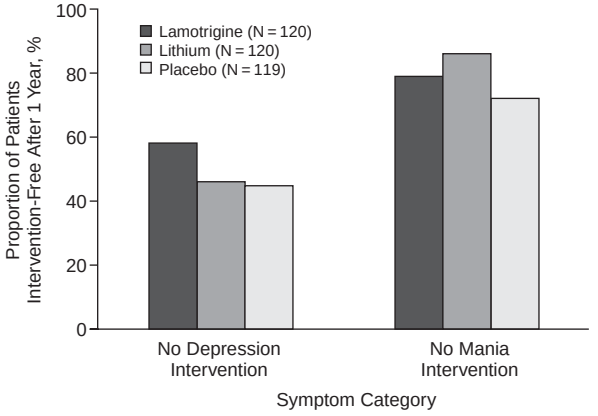
A 7-week study[32] comparing the olanzapine-fluoxetine combination with lamotrigine found that subjects receiving the combination treatment had significantly greater changes from baseline on the CGI-S, MADRS, and the Young Mania Rating Scale (YMRS), and patients receiving the combination treatment responded sooner than those taking lamotrigine. However, differences between treatment groups were insignificant when response was defined as a MADRS score reduced by 50% or more or as a CGI-S score of 3 or less. Patients receiving lamotrigine experienced a significantly higher incidence of suicidality and self-injurious behavior ($p = .037$), whereas increases in weight, triglycerides, and total cholesterol were greater with olanzapine-fluoxetine than with lamotrigine ($p \leq .001$).

Like olanzapine-fluoxetine, quetiapine monotherapy is approved by the FDA for the treatment of acute bipolar depression. In 1 study[33] of quetiapine monotherapy in patients with bipolar I or II depression, significant improvement was found in MADRS scores for quetiapine at a dose of either 600 mg/day or 300 mg/day compared with placebo (Figure 3). A second study confirmed these results.[34] The higher dose was slightly more effective but was associated with more treatment discontinuation owing to adverse events than the lower dose. Another study[35] found that quetiapine-treated patients with bipolar depression were more likely to experience antipsychotic-induced movement disorders than patients with schizophrenia.

PHARMACOTHERAPY FOR MAINTENANCE TREATMENT OF BIPOLAR DEPRESSION

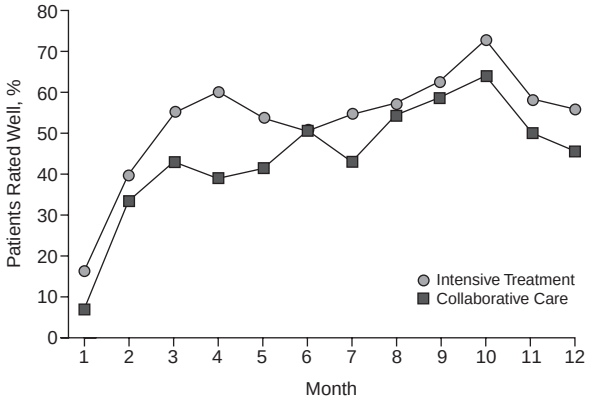
Once a successful acute treatment medication has been found and the depressive episode is in remission, treatment must then be geared toward relapse prevention. When

Figure 4. Survival Comparison for Recently Depressed Patients With Bipolar Disorder Treated With Lamotrigine or Lithium[a]



[a]Data from Calabrese et al.[38]

Figure 5. Adjunctive Intensive Psychosocial Intervention Versus Collaborative Care in Patients With Bipolar Disorder[a]



[a]Reprinted with permission from Miklowitz et al.[41]

interpreting maintenance study results, the polarity of patients' index episode should be considered. For example, if the sample included patients who were recently manic, then the results may not necessarily be indicative of the agent's success in treating patients with bipolar disorder who had depressive symptoms in their index episode.

A meta-analysis[36] examined randomized, double-blind, placebo-controlled maintenance trials of lithium, lamotrigine, divalproex, olanzapine, and carbamazepine. While the authors called lithium the gold standard for relapse prevention, they stated that lithium may be more effective in mania prevention than depression prevention. They concluded that, for many patients, no monotherapy is sufficient for long-term maintenance therapy of bipolar disorder.

Maintenance treatment for bipolar disorder with olanzapine or lithium was studied in 431 patients who had achieved symptomatic remission with the combination of these agents.[37] Patients had manic or mixed bipolar disorder before remission and had a history of 2 or more manic or mixed episodes within 6 years. Significantly fewer patients taking olanzapine experienced any symptomatic (30.0%) or syndromal (26.2%) recurrence (according to HAM-D or YMRS scores and DSM-IV criteria) than those taking lithium (38.8% and 35.8%, respectively). No significant difference was found between groups for the development of a depressive episode ($p = .15$), but significantly fewer patients taking olanzapine experienced a manic ($p = .02$) or mixed ($p = .005$) episode than those taking lithium in the 12-month trial.

Lamotrigine has also been found to be efficacious in preventing mood episodes in patients with bipolar I disorder. In an 18-month placebo-controlled study[38] of 463 stabilized patients who were recently depressed, lamotrigine outperformed lithium in preventing bipolar depression, whereas lithium was more effective in the prevention of mania (Figure 4). However, the incidence of depressive relapse was almost 3 times greater than that of manic relapse. Both agents had a significantly longer time to intervention for any mood episode than placebo ($p = .029$). Research on the combination of lamotrigine and lithium is needed.

In an 18-month study[39] of 175 patients with bipolar I disorder who were recently manic or hypomanic, both lamotrigine and lithium prolonged the time to intervention for any mood episode significantly more than placebo ($p = .006$). In preventing bipolar depression, lamotrigine was superior to placebo ($p = .02$), whereas lithium was more effective than placebo ($p = .006$) in the prevention of mania, hypomania, or a mixed episode.

Although lithium appears to be insufficient for preventing bipolar depression, a meta-analysis[40] suggested that lithium is effective in preventing suicide, self-harm, and death from other causes. Thus, combining lithium with other effective medications may be clinically useful.

ADJUNCTIVE NONPHARMACOLOGIC TREATMENTS FOR BIPOLAR DISORDER

In addition to pharmaceutical treatment options, adjunctive psychosocial interventions for patients with bipolar disorder include cognitive-behavioral therapy, family-focused therapy, interpersonal and social rhythm therapy, and group psychoeducation. In the STEP-BD study, Miklowitz et al.[41] found that patients receiving intensive psychosocial interventions in addition to pharmacotherapy over 1 year not only had better recovery rates than those who received collaborative care (brief psychoeducation) but also recovered up to 110 days sooner (Figure 5).

CONCLUSION

In summary, the olanzapine-fluoxetine combination and quetiapine monotherapy have FDA approval for the treatment of acute bipolar major depressive episodes, and

lamotrigine is approved for the prevention of mood episodes, although it has more of an effect on bipolar depression than on mania or hypomania. Other agents have also been found to be efficacious for acute or maintenance treatment of bipolar depression. Many patients will require polypharmacy for acute and long-term treatment, and, while many clinicians use judicious polypharmacy strategies, most combinations have not been studied. Future research should focus on evaluating real-world combinations in naturalistic settings. Also, structured psychosocial interventions are an important component of the effective management of bipolar disorder and should be used in conjunction with pharmacotherapy as a part of everyday practice.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), carbamazepine (Carbatrol, Equetrol, and others), divalproex (Depakote), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine combination (Symbyax), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), tranylcypromine (Parnate).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, bupropion, carbamazepine, divalproex, fluoxetine, imipramine, lithium, olanzapine, paroxetine, tranylcypromine, and deprenyl are not approved by the U.S. Food and Drug Administration for the treatment of bipolar depression.

REFERENCES

1. Wyatt RJ, Henter I. An economic evaluation of manic-depressive illness–1991. Soc Psychiatry Psychiatr Epidemiol 1995;30:213–219
2. Simon GE, Unutzer J. Health care utilization and costs among patients treated for bipolar disorder in an insured population. Psychiatr Serv 1999;50:1303–1308
3. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry 2007;64:543–552
4. Faravelli C, Rosi S, Alessandra Scarpato M, et al. Threshold and subthreshold bipolar disorders in the Sesto Fiorentino Study. J Affect Disord 2006;94:111–119
5. Kessler RC, Merikangas KR, Wang PS. Prevalence, comorbidity, and service utilization for mood disorders in the United States at the beginning of the twenty-first century. Annu Rev Clin Psychol 2007;3:137–158
6. Kleinman NL, Brook RA, Rajagopalan K, et al. Lost time, absence costs, and reduced productivity output for employees with bipolar disorder. J Occup Environ Med 2005;47:1117–1124
7. McIntyre RS, Muzina DJ, Kemp DE, et al. Bipolar disorder and suicide: research synthesis and clinical translation. Curr Psychiatry 2008;10:66–72
8. Cusin C, Serretti A, Lattuada E, et al. Impact of clinical variables on illness time course in mood disorders. Psychiatry Res 2000;97:217–227
9. Akiskal HS. Searching for behavioral indicators of bipolar II in patients presenting with major depressive episodes: the "red sign," the "rule of three" and other biographic signs of temperamental extravagance, activation and hypomania. J Affect Disord 2005;84:279–290
10. Perugi G, Akiskal HS. The soft bipolar spectrum redefined: focus on the cyclothymic, anxious-sensitive, impulse-dyscontrol, and binge-eating connection in bipolar II and related conditions. Psychiatr Clin North Am 2002;25:713–737
11. Taylor MA, Abrams R. Manic-depressive illness and good prognosis schizophrenia. Am J Psychiatry 1975;132:741–742
12. Mitchell JD, Brown ES, Rush AJ. Comorbid disorders in patients with bipolar disorder and concomitant substance dependence. J Affect Disord 2007;102:281–287
13. McIntyre RS, Soczynska JK, Beyer JL, et al. Medical comorbidity in bipolar disorder: re-prioritizing unmet needs. Curr Opin Psychiatry 2007;20:406–416
14. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? results of the National Depressive and Manic-Depressive Association 2000 survey of individuals with bipolar disorder. J Clin Psychiatry 2003;64:161–174
15. Wang PS, Berglund P, Olfson M, et al. Failure and delay in initial treatment contact after first onset of mental disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:603–613
16. Ben Abla T, Ellouze F, Amri H, et al. Unipolar versus bipolar depression: clues toward predicting bipolarity disorder [in French]. Encephale 2006;32(6 pt 1):962–965
17. Tohen M, Zarate CA Jr, Hennen J, et al. The McLean-Harvard First-Episode Mania Study: prediction of recovery and first recurrence. Am J Psychiatry 2003;160:2099–2107
18. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
19. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269
20. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079–1088. Correction 2004;61:176
21. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004;161:1537–1547
22. Himmelhoch JM, Fuchs CZ, Symons BJ. A double-blind study of tranylcypromine treatment of major anergic depression. J Nerv Ment Dis 1982;170:628–634
23. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158:906–912
24. Cohn JB, Collins G, Ashbrook E, et al. A comparison of fluoxetine, imipramine, and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol 1989;4:313–322
25. Mendlewicz J, Youdim MB. Antidepressant potentiation of 5-hydroxytryptophan by L-deprenil in affective illness. J Affect Disord 1980;2:137–146
26. Cousins DA, Young AH. The armamentarium of treatments for bipolar disorder: a review of the literature. Int J Neuropsychopharmacol 2007;10:411–431
27. Fountoulakis KN, Grunze H, Panagiotidis P, et al. Treatment of bipolar depression: an update. J Affect Disord 2008 Jul;109(1–2):21–34
28. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2003;53:1028–1042
29. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007;356:1711–1722
30. Calabrese JR, Bowden CL, Sachs GS, et al, for the Lamictal 602 Study Group. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
31. Calabrese JR, Huffman RF, White RL, et al. Lamotrigine in the acute treatment of bipolar depression: results of five double-blind, placebo-controlled clinical trials. Bipolar Disord 2008;10:323–333
32. Brown EB, McElroy SL, Keck PE Jr, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry 2006;67:1025–1033
33. Calabrese JR, Keck PE Jr, Macfadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry 2005;162:1351–1360
34. Thase ME, Macfadden W, Weisler RH, et al. Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study). J Clin Psychopharmacol 2006;26:600–609. Correction 2007;27:51
35. Gao K, Kemp DE, Ganocy SJ, et al. Antipsychotic-induced extrapyramidal side effects in bipolar disorder and schizophrenia: a systematic review. J Clin Psychopharmacol 2008;28:203–209
36. Muzina DJ, Calabrese JR. Maintenance therapies in bipolar disorder: focus on randomized controlled trials. Aust N Z J Psychiatry 2005;39:652–661
37. Tohen M, Greil W, Calabrese JR, et al. Olanzapine versus lithium in the maintenance treatment of bipolar disorder: a 12-month, randomized, double-blind, controlled clinical trial. Am J Psychiatry 2005;162:1281–1290
38. Calabrese JR, Bowden CL, Sachs G, et al, for the Lamictal 605 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder. J Clin Psychiatry 2003;64:1013–1024
39. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003;60:392–400. Correction 2004;61:680
40. Cipriani A, Pretty H, Hawton K, et al. Lithium in the prevention of suicidal behavior and all-cause mortality in patients with mood disorders: a systematic review of randomized trials. Am J Psychiatry 2005;162:1805–1819
41. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. Arch Gen Psychiatry 2007;64:419–426