The Use of Antidepressants in Bipolar Disorder

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Background: Whether or not to use antidepressants in patients with bipolar disorder is a matter of debate. Antidepressant treatment of bipolar depression has been associated with manic switch and cycle acceleration. Furthermore, recent studies have argued against the efficacy of antidepressants in the treatment of bipolar depression. Nevertheless, many clinicians continue to employ antidepressants, especially in the management of severe depression that is unresponsive to mood stabilizers alone.

Objective: Because of the unclear risk-to-benefit ratio of antidepressants in bipolar disorder, we have performed an updated review of the relevant literature. In this article we examine (1) all randomized controlled trials (RCTs) evaluating the use of antidepressants in the treatment of acute bipolar depression and assessing the risk of antidepressant-induced manic switch and (2) non-RCT trials that evaluate the impact of antidepressant discontinuation after acute antidepressant response.

Data Sources: A MEDLINE search of journals, covering the period from January 1966 to July 2007 and supplemented by bibliographic cross-referencing, was performed to identify the relevant studies. The keywords used were *antidepressant, bipolar depression, bipolar disorder, switch, manic switch, antidepressant-induced mania, predictors,* and *antidepressant discontinuation*. Criteria used to select studies included (1) English language and (2) studies published in peer-reviewed journals.

Data Synthesis: Randomized, double-blind, placebo-controlled studies have demonstrated that antidepressants exert some efficacy in the treatment of bipolar depression in some populations of patients. Moreover, the risk of manic switch, although not totally countered, appears to be strongly reduced when antidepressants are given in combination with a mood stabilizer and when new-generation antidepressants are preferred over old tricyclic antidepressants. Finally, some studies have proven that the continuous use of antidepressants after the remission of a major depressive episode helps to prevent further depressive relapses without causing a significant increase in manic relapses.

Conclusions: Clearly, there is a place for antidepressants in bipolar disorder; however, it is important to be cautious and evaluate their use on a case-by-case basis. Looking at specific depressive symptoms might help physicians in making the choice of whether to prescribe or not prescribe antidepressants.

(J Clin Psychiatry 2008;69:1307–1318)

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We acknowledge Taryn Belmonte, B.A., of the University of Pittsburgh, for her thorough editing of the manuscript. Ms. Belmonte reports no relevant financial disclosure.

Dr. Fagiolini is a consultant for Bristol-Myers Squibb, Novartis, and Pfizer and is a member of the speakers/advisory boards for Bristol-Myers Squibb and Pfizer. Dr. Swartz has received grant/research support from and is a member of the speakers/advisory board for Bristol-Myers Squibb and has received honoraria from Bristol-Myers Squibb and AstraZeneca. Drs. Salvi, Maina, and Frank report no financial affiliations or other relationships relevant to the subject of this article.

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Antidepressant use in bipolar disorder is controversial. Recently published American Psychiatric Association guidelines suggest that antidepressant use in the context of bipolar disorder should be limited to severe depression.[1] Consensus conference guidelines similarly recommend antidepressant discontinuation shortly after remission of a major depressive episode.[2–4] Recent data demonstrate that antidepressant medications are at once ineffective and harmful in individuals with bipolar disorder.[5–7] Despite these concerns, however, antidepressants are frequently used to treat patients with bipolar disorder,[8,9] typically as adjuncts to mood stabilizing agents that have failed or partially failed to resolve depressive episodes. Thus, practicing psychiatrists who manage the vast majority of patients who suffer from bipolar disorder—many of whom would most likely refuse to participate in or would not meet the inclusion/exclusion criteria for the randomized placebo-controlled trials that primarily inform the psychiatric evidence base—continue to believe in the clinical utility of antidepressants, especially for patients who do not respond to mood stabilizer or antipsychotic monotherapy.

Because of the unclear risk-to-benefit ratio of antidepressants in bipolar disorder and the appearance of recent publications readdressing this topic, we have performed an updated review of the relevant literature. In this article we examine (1) all randomized controlled trials (RCTs) evaluating the use of antidepressants in the treatment of acute bipolar depression and assessing the risk of antidepressant-induced manic switch and (2) non-RCT trials that evaluate the impact of antidepressant discontinuation after acute antidepressant response. A

MEDLINE search of journals, covering the period from January 1966 to July 2007 and supplemented by bibliographic cross-referencing, was performed to identify the relevant studies. The keywords used were *antidepressant*, *bipolar depression*, *bipolar disorder*, *switch*, *manic switch*, *antidepressant-induced mania*, *predictors*, and *antidepressant discontinuation*. Criteria used to select studies included (1) English language and (2) studies published in peer-reviewed journals.

ACUTE ANTIDEPRESSANT EFFICACY AND SAFETY

Regarding the use of antidepressants in bipolar disorder, it has been written that "the risk-to-benefit ratio can be understood as the risk being greater than 0 with a yet unproven benefit for the medications."[10(p19)] Nevertheless, there is evidence that, at least in some subgroups of patients, antidepressants work. A systematic review of 12 RCTs (N = 1088) has indeed demonstrated by means of meta-analytic statistical methods that "antidepressants are effective in the short-term treatment of bipolar depression."[11(p1537)] Moreover, the authors, using the same methodology, evaluated the likelihood of switching to mania. They reported that there was no evidence of an increased risk of switch in the trials.[11]

However, the publication of 6 new RCTs[7,12–16] that were not included among the 12 trials mentioned above underscores the need for an updated review of antidepressant efficacy and safety in bipolar depression. Table 1 summarizes the RCTs that report efficacy and switch rates of antidepressants in bipolar depression. Eighteen studies were conducted including a total of 2515 bipolar disorder patients, with more subjects meeting criteria for bipolar I disorder (N = 1798) than for bipolar II disorder (N = 262). The best-studied antidepressant drugs in bipolar depression, in terms of number of RCTs, are paroxetine (6 RCTs)[7,12,22–24,26] and bupropion (5 RCTs),[7,15,20,21,27] followed by fluoxetine (4 RCTs)[13,14,17,28] and the tricyclic antidepressant imipramine (4 RCTs).[17,18,24,25] Other antidepressants, such as tranylcypromine and venlafaxine, have been less consistently evaluated in bipolar depression.

Paroxetine

Paroxetine is the most widely evaluated antidepressant in the treatment of bipolar depression, having been compared to placebo and active comparator in 2 RCTs[7,24] and to other agents in 4 RCTs.[12,22,23,26] In the earlier placebo-controlled trial,[24] subjects meeting criteria for acute bipolar depression (N = 117) were treated with lithium and randomly assigned to 10 weeks of add-on treatment with paroxetine, imipramine, or placebo. The authors found no overall difference between treatment groups, although in patients with low baseline lithium levels (≤ 0.8 mEq/L), both paroxetine and imipramine were superior to placebo. Furthermore, rates of completion were highest in the paroxetine-treated patients, demonstrating overall good tolerability.[24]

As part of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), Sachs and colleagues[7] recently published the results of a large RCT comparing antidepressants to placebo as an add-on treatment for individuals experiencing an episode of bipolar depression despite optimized treatment with a mood stabilizer. Subjects were randomly assigned to either an antidepressant (paroxetine or bupropion, N = 179) or placebo (N = 187). There were few exclusion criteria in this trial; thus, the sample included relatively large percentages of individuals meeting criteria for rapid cycling (27% and 30% for antidepressants and placebo, respectively) and comorbid substance abuse (17% and 16%, respectively). After 26 weeks, the rate of sustained response was not different for antidepressants and placebo (23.5% vs. 27.3%).[7] The authors concluded that antidepressants are of limited effectiveness in bipolar disorder.

The generalizability of these findings is partially weakened by the fact that only 13% of all eligible depressed bipolar patients in STEP-BD were enrolled in this study,[7] raising the concern that the final sample may have consisted primarily of depressed patients whose risk-to-benefit ratio for the use of an antidepressant was judged (by the patient, a family member, or the referring physician) to be relatively neutral. For example, a patient with a history of an antidepressant-induced manic switch or a patient whose current depressive episode is complicated by agitation or by the presence of other comorbid manic symptoms may have felt uncomfortable with the possibility of receiving an antidepressant. Likewise, a patient with anergic depression and a history of response to the combination of a mood stabilizer and an antidepressant may have refused to participate in a trial that had a 50% likelihood of receiving placebo. Switch rates to mania were comparable (10%) in both groups, despite the fact that 30% of the sample met criteria for rapid cycling.[7]

Paroxetine has been compared to other antidepressants, such as imipramine,[24] amitriptyline,[22] venlafaxine,[26] and bupropion.[7] Overall, rates of response range from 32% to over 60%, without any difference between paroxetine and the active comparator in efficacy and completion rates at endpoints. Response rates with paroxetine were faster than with amitriptyline, with overall better response rates at week 4.[22] In all studies, except the recent STEP-BD trial,[7] paroxetine use was associated with slightly higher completion rates than the comparator.

In a study by Young et al.,[23] the addition of paroxetine to an initial mood stabilizer was compared to the addition of a second mood stabilizer for treatment of patients with bipolar depression. Both groups showed significant improvement in depressive symptoms during the 6-week trial. However, there were significantly more noncompleters in the group that received the 2 mood stabilizers

Table 1. Efficacy Trials of Antidepressants in Bipolar Disorder

Study	N	Drugs (N)	Type of Bipolar Disorder	Length of Study, wk	Completion Rates by Drug Treatment Group	Outcome	Concurrent Mood Stabilizer	Rate of Switch Into Hypomania or Mania by Drug Treatment Group
Cohn et al (1989)[17]	89	Fluoxetine (30) Imipramine (30) Placebo (29)	DSM-III-R bipolar disorder	6	Fluoxetine, 57% Imipramine, 47% Placebo, 34%	Response[a]: fluoxetine > imipramine > placebo (86% vs 57% vs 38%)	Lithium, 20%	Imipramine, 6.7% Fluoxetine, 0% Placebo, 3.4%
Himmelhoch et al (1991)[18]	56	Tranylcypromine (28) Imipramine (28)	Bipolar I, 43% Bipolar II, 57%	6	Tranylcypromine, 71% Imipramine, 20%	Response[a]: tranylcypromine > imipramine (81% vs 48%)	None	Tranylcypromine, 21% Imipramine, 25%
Bocchetta et al (1993)[19]	30	Amitriptyline (15) L-sulpiride (15)	DSM-III-R bipolar disorder	4	Amitriptyline, 87% L-sulpiride, 100%	Response[a]: amitriptyline = L-sulpiride (86% vs 93%)	Lithium, 100% (serum lithium levels: 0.5–1.0 mEq/L)	Amitriptyline, 6.7% L-sulpiride, 6.7%
Sachs et al (1994)[20]	19	Bupropion (9) Desipramine (10)	DSM-III-R bipolar disorder	8	Bupropion, 100% Desipramine, 100%	Response[a]: bupropion = desipramine (55% vs 50%)	Lithium, 67% Valproate, 27% Carbamazepine, 7%	Bupropion, 11% Desipramine, 30%
Grossman et al (1999)[21]	16	Bupropion (9) Idazoxan (7)	Bipolar I	6	Bupropion, 78% Idazoxan, 100%	Mean decrease in HAM-D score: bupropion, 6.9; idazoxan, 10.7	Lithium (% not defined)	Not reported
Bauer et al (1999)[22]	42	Paroxetine (19) Amitriptyline (23)	DSM-III-R bipolar disorder	6	Not reported	Mean CGI score reduction > 1 in both groups. Rate of response at week 6 not reported (> 60% for both groups without statistical differences)	Lithium, 100% (serum lithium levels: 0.62–0.70 mEq/L)	Paroxetine, 5.3% Amitriptyline, 0%
Young et al (2000)[23]	27	Lithium/divalproex (16) Paroxetine (11)	Bipolar I, 41% Bipolar II, 59%	6	Lithium/divalproex, 62.5% Paroxetine, 100% (Paroxetine > lithium; $p < .01$)	Significant reduction in HAM-D and GAF scores for both groups (values not reported)	Lithium/divalproex, 100% (serum lithium level: 0.8 mEq/L)	Lithium/divalproex, 6.3% Paroxetine, 0%
Nemeroff et al (2001)[24]	117	Paroxetine (35) Imipramine (39) Placebo (43)	DSM-III-R bipolar disorder	10	Paroxetine, 71% Imipramine, 59% Placebo, 63%	HAM-D and CGI mean score reduction: paroxetine and imipramine > placebo for lithium serum levels ≤ 0.8 mEq/L	Lithium, 100% (serum lithium levels: 0.5–1.2 mEq/L)	Paroxetine, 0% Imipramine, 7.7% Placebo, 2.3%
Silverstone (2001)[25]	156	Moclobemide (81) Imipramine (75)	DSM-III-R bipolar disorder	8	Moclobemide, 67% Imipramine, 71%	Response[a]: moclobemide = imipramine (46% vs 53%)	Lithium, 47% Carbamazepine, 17% Divalproex, 3%	Moclobemide, 3.7% Imipramine, 11.1%
Vieta et al (2002)[26,b]	60	Paroxetine (30) Venlafaxine (30)	Bipolar I, 73% Bipolar II, 27%	6	Paroxetine, 80% Venlafaxine, 73%	Response[a]: paroxetine = venlafaxine (43% vs 48%). Remission[c]: paroxetine = venlafaxine (32% vs 33%)	Lithium, 70% Valproate, 25% Carbamazepine, 27% Other, 15%	Paroxetine, 3% (100% hypomania) Venlafaxine, 13% (50% mania, 50% hypomania)
McIntyre et al (2002)[27,b]	36	Bupropion (18) Topiramate (18)	Bipolar I, 53% Bipolar II, 47%	8	Bupropion, 72% Topiramate, 56%	Response[a]: bupropion = topiramate (59% vs 56%)	Lithium, 36% Divalproex, 64% AAP, 17% (serum lithium level: 1.16 mEq/L)	Not reported

(continued)

Table 1 (continued). Efficacy Trials of Antidepressants in Bipolar Disorder

Study	N	Drugs (N)	Type of Bipolar Disorder	Length of Study, wk	Completion Rates by Drug Treatment Group	Outcome	Concurrent Mood Stabilizer	Rate of Switch Into Hypomania or Mania by Drug Treatment Group
Tohen et al (2003)[28]	833	Olanzapine/fluoxetine (86) Olanzapine (370) Placebo (377)	Bipolar I	8	Olanzapine/fluoxetine, 64% Olanzapine, 48% Placebo, 38%	Response[d]: olanzapine/fluoxetine > olanzapine > placebo (56% vs 39% vs 30%)	None	Olanzapine/fluoxetine, 6.4% Olanzapine, 5.7% Placebo, 6.7%
Shelton and Stahl (2004)[12]	30	Risperidone/paroxetine (10) Risperidone (10) Paroxetine (10)	Bipolar I, 70% Bipolar II, 30%	12	Risperidone/paroxetine, 60% Risperidone, 50% Paroxetine, 80%	Response[a]: risperidone/paroxetine = risperidone = paroxetine (30% vs 30% vs 20%)	Lithium, 27% Divalproex, 43% Carbamazepine, 17% Topiramate, 13%	Risperidone/paroxetine, 0% Risperidone, 0% Paroxetine, 10%
Amsterdam and Schults (2005)[13]	34	Olanzapine/fluoxetine (9) Olanzapine (8) Fluoxetine (8) Placebo (9)	Bipolar I, 94% Bipolar II, 6%	8	Rate not reported by treatment group. Whole sample, 59%	All groups experienced a significant overall reduction in mean HAM-D and MADRS scores over time (p = .006)	Lithium, 12.5% Divalproex, 2.5%	Olanzapine/fluoxetine, 44% Olanzapine, 12.5% Fluoxetine, 50% Placebo, 33%
Brown et al (2006)[14]	410	Olanzapine/fluoxetine (205) Lamotrigine (205)	Bipolar I	7	Olanzapine/fluoxetine, 67% Lamotrigine, 65%	CGI-S mean score reduction: olanzapine/fluoxetine > lamotrigine (–1.43 vs –1.18; p = .042). Response[d]: olanzapine/fluoxetine = lamotrigine (69% vs 60%)	None	Olanzapine/fluoxetine, 4% Lamotrigine, 5.2%
Schaffer et al (2006)[16]	20	Citalopram (10) Lamotrigine (10)	Bipolar I, 60% Bipolar II, 40%	12	Citalopram, 50% Lamotrigine, 70%	MADRS mean score reduction: citalopram = lamotrigine (–14.2 vs –13.3)	Lithium, 50% Divalproex, 45% Carbamazepine, 10% (serum lithium level: 0.76 mEq/L)	Citalopram, 10% Lamotrigine, 10%
Post et al (2006)[15]	174	Bupropion (51) Sertraline (58) Venlafaxine (65)	Bipolar I, 73% Bipolar II, 26% Bipolar NOS, 1%	10	Bupropion, 71% Sertraline, 72% Venlafaxine, 62%	Response[e]: bupropion = sertraline = venlafaxine (49% vs 53% vs 51%)	Lithium, 37% Valproate, 53% Carbamazepine, 9% Lamotrigine, 5% AAP, 17%	Bupropion, 9% Sertraline, 10% Venlafaxine, 29% (venlafaxine > bupropion and sertraline; p = .002)
Sachs et al (2007)[7]	366	Bupropion or paroxetine (179) Placebo (187)	Bipolar I, 68% Bipolar II, 32%	26	Bupropion or paroxetine, 66% Placebo, 66%	Durable recovery[f]: bupropion or paroxetine = placebo (23% vs 27%)	Adequate mood stabilizer, 84%	Bupropion or paroxetine, 10% Placebo, 10%

[a]Decrease in HAM-D score of ≥ 50%.
[b]Single-blind study.
[c]HAM-D score ≤ 10, CGI score = 1.
[d]Decrease in MADRS score of ≥ 50%.
[e]Decrease in IDS score of ≥ 50% or a CGI-BP score ≤ 2.
[f]At least 8 consecutive weeks of euthymia.
Abbreviations: AAP = atypical antipsychotics, CGI = Clinical Global Impressions scale, CGI-BP = Clinical Global Impressions scale for Bipolar Illness, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression, IDS = Inventory for Depressive Symptomatology, MADRS = Montgomery-Asberg Depression Rating Scale, NOS = not otherwise specified.

than in the group that received a mood stabilizer and paroxetine.[23]

Shelton and Stahl[12] studied 30 depressed patients with bipolar disorder who were receiving a steady dose of a mood stabilizer and were randomly assigned to 12 weeks of double-blind treatment with risperidone (plus placebo), paroxetine (plus placebo), or the combination of risperidone and paroxetine. The authors concluded that risperidone, paroxetine, and the combination of the 2 are equally but modestly effective when added to a mood stabilizer for the treatment of bipolar depression. Interestingly, the switch rate into mania or hypomania was very low, with only 1 patient in the paroxetine plus placebo condition experiencing mild hypomania.[12]

In conclusion, these studies demonstrate that paroxetine may be effective for a subset of patients meeting criteria for bipolar depression. It is impossible to ascertain from extant data, however, which specific clinical characteristics predict a favorable response to paroxetine. In addition, it appears that switch rates are low when paroxetine is administered in conjunction with a mood stabilizer.

Fluoxetine

Fluoxetine has been studied in 4 RCTs, yielding a total of 338 fluoxetine-treated subjects. In 1989, Cohn and colleagues[17] performed the first randomized placebo-controlled trial evaluating the acute efficacy of an antidepressant in a sample of depressed patients that was limited to individuals meeting criteria for bipolar disorder. Eighty-nine patients were randomly assigned to fluoxetine, imipramine, or placebo and were followed for 6 weeks. Fluoxetine showed the highest response rate (≥ 50% reduction in Hamilton Rating Scale for Depression total score): 86% with fluoxetine versus 57% with imipramine and 38% with placebo.[17]

The preponderance of evidence supporting the utility of fluoxetine in bipolar depression comes from its use in combination with olanzapine. Three studies evaluating the efficacy of olanzapine/fluoxetine combination in bipolar depression have been published in recent years,[13,14,28] leading to inclusion of this combination as a recommended agent for the treatment of bipolar depression in bipolar disorder guidelines.[29]

Tohen and colleagues[28] compared olanzapine/fluoxetine combination to olanzapine alone and to placebo as an acute treatment for depression in individuals meeting criteria for bipolar I disorder. Olanzapine/fluoxetine combination was found to be superior to placebo beginning at week 1, and this statistical separation of drug and placebo continued throughout the 8-week trial. In addition, olanzapine/fluoxetine combination was superior to olanzapine monotherapy from weeks 4 to 8 in this study. At the end of the 8 weeks, olanzapine/fluoxetine combination was associated with the highest response rate (56%) compared to both olanzapine alone (39%) and placebo (30%).[28] A reanalysis[30] on the same sample showed that patients treated with olanzapine/fluoxetine combination experienced better health-related quality of life than those treated with olanzapine alone or with placebo on both mental and physical components of self-perceived health.[30]

An independent, subsequent study[13] replicating the prior methodology in a sample of mostly bipolar I patients failed to find any difference between olanzapine/fluoxetine combination, olanzapine alone, fluoxetine alone, and placebo over 8 weeks. The total sample size (N = 34), however, was probably underpowered to detect group differences.[13]

Finally, fluoxetine in combination with olanzapine has been compared to lamotrigine.[14] Four hundred ten patients were randomly assigned to either olanzapine/fluoxetine combination or lamotrigine for 7 weeks. At the end of the trial, mean reductions in Montgomery-Asberg Depression Rating Scale and Clinical Global Impressions scale scores were significantly greater for patients treated with olanzapine/fluoxetine combination than for those treated with lamotrigine. The difference between the 2 groups was evident at week 1, although response rates did not significantly differ at endpoint (olanzapine/fluoxetine combination, 69% vs. lamotrigine, 60%; p = .073).[14] In conclusion, data regarding fluoxetine alone in the treatment of acute bipolar depression are scarce. Despite this fact, the superiority of olanzapine/fluoxetine combination over olanzapine alone implies a synergistic efficacy that is most likely driven by the antidepressant.

Fluoxetine is not associated with greater levels of manic switching. Rates of switch to mania with fluoxetine are similar to those seen with paroxetine. The only exception to this is seen in the small study by Amsterdam and Schults.[13] In this study, the significantly higher switch rates in patients treated with fluoxetine compared to patients treated with olanzapine alone were most probably a function of the low rates of concomitant use of a mood stabilizer.

Bupropion

Bupropion has been compared to several antidepressants, such as desipramine,[20] sertraline and venlafaxine,[15] and paroxetine,[7] with response rates for bupropion ranging from 32% to 55%. Bupropion was as efficacious as the comparators, with a benign profile of side effects.

Bupropion has also been compared in a double-blind study to idazoxan[21] and in a single-blind study to topiramate[27]: both trials showed equality of bupropion to the comparator in terms of response and completion rates. Although these trials were well designed, the sample size for each was notably small. The total number of bupropion-treated bipolar patients in the earlier 3 studies[20,21,27] was 36. Recent studies have employed larger samples. Post and colleagues[15] randomly assigned 174 bipolar depressed patients to bupropion, sertraline, or venlafaxine

for 10 weeks of acute treatment as an adjunct to 1 or more mood stabilizers. Response rates for bupropion, sertraline, and venlafaxine were equivalent (49%, 53%, and 51%, respectively).[15]

Previous uncontrolled studies had considered bupropion as a particularly safe antidepressant drug in terms of the risk of manic induction,[31,32] while other authors more recently reported a substantially equivalent risk of switch with bupropion or selective serotonin reuptake inhibitors (SSRIs).[33,34] Double-blind clinical trials have confirmed the latter observations, reporting similar switch rates with bupropion and paroxetine[7] or sertraline.[15]

Tricyclic Antidepressants

The use of tricyclic antidepressants in bipolar depression has been studied in 7 RCTs: 4 with imipramine, 2 with amitriptyline, and 1 with desipramine. Although all these tricyclic antidepressants have demonstrated superiority over placebo in bipolar depression, they generally showed lower response rates when compared to the newer antidepressants.

Imipramine has been well studied, with established superior efficacy over placebo in 2 studies.[17,24] It has, however, been found to be less effective than fluoxetine[17] and tranylcypromine.[18] Himmelhoch and colleagues[18] found very high rates of manic switch, which can be largely explained by the lack of concomitant mood stabilizer therapy. Although imipramine showed similar response and completion rates when compared to the reversible monoamine oxidase A inhibitor moclobemide in an 8-week study of 156 bipolar depressed patients,[25] it caused more side effects, such as dry mouth, constipation, tremors, palpitations, and higher switch rates (11.1% for imipramine vs. 3.7% for moclobemide).[25]

Other tricyclic antidepressants have far less evidence supporting their efficacy than does imipramine. Amitriptyline has been subjected to 2 very small studies in which it was compared to paroxetine[22] and L-sulpiride.[19] In the 6-week comparison with paroxetine,[22] amitriptyline-treated patients reported a slower response, with significantly lower rates of response at week 4. Furthermore, severe tremor and dry mouth were more prevalent in the tricyclic group.[22] Desipramine has been compared to bupropion in a very small study[20] employing 19 trials in 15 patients, again with similar response rates between the 2 drugs but with far higher switch rates in desipramine-treated patients.[20]

In conclusion, tricyclic antidepressants have relatively little evidence supporting their efficacy for the acute treatment of bipolar depression. Furthermore, their use is burdened by a higher prevalence of side effects and lower completion rates, as well as elevated rates of antidepressant-induced mania, as reported in almost all double-blind studies. Thus, compounds other than tricyclic antidepressants should be selected when treating bipolar depression.

Monoamine Oxidase Inhibitors

In a double-blind placebo-controlled study, Himmelhoch et al.[35] showed that after 6 weeks of treatment, tranylcypromine successfully treated depressive symptoms in a mixed unipolar and bipolar sample. Ten years later, the same group compared tranylcypromine and imipramine as monotherapy in patients with bipolar depression.[18] Tranylcypromine was superior to imipramine after 6 weeks, with a greater proportion of patients treated with the monoamine oxidase inhibitor both responding and completing the trial, probably because of the more favorable side effect profile of tranylcypromine. Moreover, response was sustained across 10 weeks of continuation treatment in 71% of the tranylcypromine responders.[18]

Tranylcypromine was recently compared to lamotrigine for the acute treatment of bipolar depression in a 10-week, randomized, open-label trial.[36] In this trial, patients taking mood stabilizers at therapeutic levels experienced a breakthrough episode and were randomly assigned to the monoamine oxidase inhibitor or lamotrigine. Although the small sample size of 20 patients did not allow the investigators to detect any significant differences, the rate of response with tranylcypromine was 70% versus 30% with lamotrigine. The authors pointed out the need for studies with bigger sample sizes in order to further evaluate this provocative finding. Albeit not an RCT—and not adequately powered, this study[36] highlights the apparently minimal effect of lamotrigine when it is added to ongoing mood stabilizers in the acute treatment of bipolar depression.

In conclusion, a single RCT and 2 other studies with methodological flaws do not allow us to draw definitive conclusions about the efficacy of tranylcypromine; however, despite the prejudice against tranylcypromine because of the dietary restrictions, the extant data are promising and warrant further investigation.

Other Antidepressants

Venlafaxine efficacy in bipolar depression has been evaluated in both a single-blind[26] and a double-blind study.[15] Vieta and colleagues[26] randomly assigned 60 patients experiencing a breakthrough episode of depression while on mood stabilizers to 6 weeks of treatment with venlafaxine or paroxetine. Response and remission rates were equal in both of the groups at endpoint.[26] In the second study,[15] subjects were randomly assigned to venlafaxine, sertraline, or bupropion, and venlafaxine efficacy was equal to the other 2 antidepressants.[15] However, both studies reported significantly higher rates of switch to mania or hypomania with venlafaxine than with the comparators; thus, venlafaxine, as well as tricyclic antidepressants, should be used with caution in bipolar disorder.

Citalopram was compared to lamotrigine in a small RCT for bipolar patients experiencing a breakthrough depressive episode while on mood stabilizers.[16] In this

study, citalopram was titrated at a much slower rate than usual and reached a low mean final dose (21 mg/d). Despite this fact, citalopram-treated patients responded better numerically than patients on lamotrigine. The small sample size once again prevented any possibility of finding significant differences between the groups.[16]

In conclusion, several well-designed clinical trials show efficacy for antidepressants as acute treatments for bipolar depression, thereby supporting their limited use in the management of this illness. Fluoxetine, in association with olanzapine, has the greatest amount of data supporting its role as a treatment for bipolar depression. Paroxetine exhibits partial proof of efficacy, while evidence for bupropion is less conclusive. The unfavorable side effect profile and the liability for manic switch should discourage practitioners from the use of tricyclic antidepressants in bipolar disorder. Data regarding other antidepressants are still inconclusive.

RISK OF MANIC SWITCH

The biggest issue a clinician must consider when prescribing antidepressants for patients with bipolar disorder is the risk of manic switch. Early descriptions by Goodwin and Jamison estimated the risk of mania in patients with bipolar disorder treated with antidepressants as ranging from 30% to 70%.[37] More recently, this range has been reported to be closer to 20% to 40%.[5]

While there is substantial evidence that antidepressants, when administered alone, are associated with a higher incidence of manic episodes, concurrent therapy with mood stabilizers exerts a protective effect. An early retrospective report[38] found that observed manic switches during treatment with tricyclic antidepressants were all associated with low levels of lithium. Prien and colleagues[39] found that the incidence of mania over a 2-year study of treatments for bipolar depression was 53% for bipolar patients taking imipramine alone, 28% for those taking lithium and imipramine, and 26% for those taking lithium alone. Lithium appeared to counter the risk of manic switch associated with the antidepressant.[39] Rouillon et al.[40] reached similar conclusions in a pooled analysis of data from 15 placebo-controlled studies of mixed unipolar-bipolar samples, finding that 158 bipolar patients had an incidence of manic switch of 51% with imipramine treatment, 28% when lithium was added, and 21% when lithium was administered alone.[40]

In recent years, Boerlin and colleagues[41] conducted a 2-year naturalistic study of 29 patients with bipolar disorder who were treated with mood stabilizers alone or in combination with antidepressants. Rates of manic episodes were equal regardless of the presence of the antidepressants: 26% with mood stabilizers alone versus 29% with the added antidepressant. Interestingly, switch rates were higher with tricyclic antidepressants and monoamine oxidase inhibitors than with fluoxetine.[41] Another naturalistic study[42,43] of 158 patients treated with different antidepressants reported that treatment with a mood stabilizer decreased the risk of manic switch, with a 0.30 odds ratio. Conversely, the use of tricyclic antidepressants was associated with the highest likelihood of switch, with a 3.76 odds ratio. Nevertheless, 59% of those patients who switched were taking mood stabilizers at that time, demonstrating that the protective effect of mood stabilizers is not complete.[42,43] This finding was recently replicated by Ghaemi and colleagues,[6] who reviewed the clinical records of 41 patients with bipolar depression treated with antidepressants and found a rate of manic switch of 81% without mood stabilizers and 19% with mood stabilizers. In contrast, Bauer et al.[44] conducted a naturalistic study of 182 patients with bipolar I and II disorders, finding that those who took antidepressants were as likely to experience manic symptomatology on daily mood assessments as those who did not. In this study, over 90% of patients were treated with mood stabilizers, and almost all antidepressants were SSRIs. According to the investigators, this constricted variability in their sample may in part explain their findings.[44]

These naturalistic studies have several limitations. First, they often rely on clinical charts and retrospective reviews that may be inaccurate. Second, in naturalistic studies it is not possible to eliminate the bias of clinical judgment: were those patients who were given antidepressant medications perceived, for some reason, to be less vulnerable to the emergence of mania? Finally, given the highly unpredictable course of bipolar disorder, these naturalistic studies commonly fail to differentiate with absolute certainty between antidepressant-induced episodes of mania or hypomania and episodes emerging from the natural course of bipolar disorder. This failure may lead to an overestimate of antidepressant-induced episodes.

These methodological issues underscore the importance of evaluating the specific definition of antidepressant-induced manic switch used by investigators. Altshuler and colleagues[45] employed the criteria of proximity to the episode, change in severity, and change in cycling pattern in order to improve the diagnostic accuracy of antidepressant-induced episodes. In their study, 51 lithium-refractory bipolar patients treated with heterocyclic antidepressants were evaluated for the occurrence of hypomanic or manic episodes. Employing this method, the majority of switches were judged as unlikely to be directly attributable to the use of antidepressants. Within the "real" antidepressant-induced manic episodes, 25% of patients who were taking no antimanic medication had a manic switch versus 10% for those who continued to receive lithium.[45] All of these results, although coming from uncontrolled, naturalistic studies, support the protective function of mood stabilizers with respect to the

emergence of mania, whether antidepressant-induced or a function of the natural course of the illness.

Some studies have shown that the risk of manic switch varies with the class of antidepressants. In a review of clinical data from patients with bipolar depression, tricyclic antidepressants were shown to be associated with switching to a manic state in 11% of cases, compared with 3.7% for SSRIs, whose rate of switch was equal to placebo (4.2%).[46] In a more recent systematic review of antidepressant use in bipolar depression, tricyclic antidepressants were associated with switching to a manic state in 10% of cases, compared with 3.2% for all other antidepressants.[11]

In our review, all the RCTs except two[21,27] have reported on the rate of switch during acute treatment with antidepressants. From the analysis of the 16 acute-treatment RCTs that provided information on manic switches, we conclude the following:

1. Studies that did not employ concurrent, adequate, mood stabilizer treatment reported considerably higher rates of switch.[13,18]
2. SSRIs (fluoxetine and paroxetine) and bupropion are associated with switch rates comparable to those for placebo over 6 to 26 weeks of treatment.[7,17,24,28]
3. Tricyclic antidepressants (most data on imipramine) are associated with a higher likelihood of manic switch than are SSRIs and bupropion.[17,20,24]
4. Venlafaxine is associated with a higher likelihood of manic switch than are SSRIs (paroxetine and sertraline) and bupropion.[15,26]

In toto, the extant literature suggests that the newer antidepressants (with the exception of venlafaxine), when added to ongoing, appropriate treatment with mood stabilizers, are relatively safe, although it is clear that the rate of switch to mania cannot be reduced to zero. The higher rate of manic switches observed with the use of tricyclic antidepressants and venlafaxine might be tentatively explained by their additional noradrenergic activity: antidepressants with a broader spectrum of action or that potently block norepinephrine uptake are more likely to be associated with manic switches than those with narrower modes of action or less potent noradrenergic effects.[15]

Several studies[47–53] have looked at clinical predictors of antidepressant-induced hypomanic and manic episodes (Table 2). Data emerging from these studies might help the clinician to understand which subgroups are at highest risk for manic switch, which, in turn, may drive clinical decision-making. Seven studies have compared groups of bipolar patients with and without hypomanic or manic episodes while on antidepressant treatment. A history of substance abuse, a previous high number of depressive episodes, and previous antidepressant trials all predict a manic switch during antidepressant treatment.[47–53]

Two studies have found that individuals with bipolar II disorder are more vulnerable to hypomanic or manic switch while receiving antidepressant treatment than are those with bipolar I disorder.[50,52] However, these results are in contrast to an earlier observation that found a similarly low risk of switch for imipramine-treated individuals with bipolar II depression and with unipolar depression.[54] Furthermore, data from 2 RCTs[18,55] have shown a higher rate of switch in patients with bipolar I depression than in those with bipolar II depression, regardless of the antidepressant used, while the majority of the other RCTs reported no difference between antidepressant-treated patients with bipolar I disorder and those with bipolar II disorder. Therefore, the current evidence does not clearly establish whether there is a difference in the risk of manic episode during antidepressant treatment between those with bipolar I disorder and those with bipolar II disorder.

ANTIDEPRESSANT DISCONTINUATION

Most of the acute RCTs do not provide information on the efficacy and safety of antidepressants over the long term. In fact, the great majority of these studies have been short-term trials (6 to 12 weeks), with only 1 study prolonging the double-blind observation to 26 weeks. Given the frequent emergence of breakthrough depressive episodes despite continued treatment with a mood stabilizer such as lithium,[56] clinicians have questioned whether it is in fact advisable to discontinue the antidepressant after remission of a major depressive episode in individuals with bipolar disorder.

Several double-blind studies[39,57–60] have assessed the impact of antidepressant treatment over the long term. Some found that antidepressants (most notably imipramine) did not result in better outcomes in preventing depressive relapses when given alone or in combination with lithium and compared to lithium alone. These studies also reported that imipramine heightened the risk of manic episodes over 2 years.[39,57–60] In 1 of these studies,[57] patients were given imipramine without any concurrent mood stabilizer, while in 2 other studies,[58,59] only stable patients on lithium therapy were included, showing that the addition of an antidepressant in patients doing well on lithium therapy is very likely to worsen the course of illness. Only 1 study[39] evaluated patients recently remitted from an acute episode, thus directly addressing the question of whether or not it is advisable to continue antidepressants after remission from a major depressive episode. In this study, 117 patients who remitted from an acute episode of mania or depression were randomly assigned to a 2-year follow-up with lithium and imipramine versus lithium and placebo. Twenty-two percent of imipramine-treated patients and 29% of placebo-treated

Table 2. Studies on Predictors of Antidepressant-Induced Manic Switch in Bipolar Patients

Study	Type of Study	N	Type of Bipolar Disorder	Definition of Antidepressant-Induced Mania or Hypomania	Predictors of Antidepressant-Induced Mania or Hypomania
Stoll et al (1994)[47]	Retrospective; blind assessments	49 with AIM 49 with spontaneous mania	DSM-III-R bipolar disorder	At least 3 days of antidepressant treatment during the 2 weeks prior to episode	Prior antidepressant treatment
Henry et al (2001)[48]	Prospective; patients with major depressive episode	12 with AIM 32 without AIM	Bipolar I, 70% Bipolar II, 30%	Switch from major depressive episode into mania	No mood stabilizer treatment vs lithium treatment Hyperthymic temperament
Goldberg and Whiteside (2002)[49]	Retrospective	21 with AIM 32 without AIM	Bipolar I, 62% Bipolar II, 38%	Onset within 12 weeks after initiation of antidepressant treatment	High number of previous antidepressant trials History of substance use disorder
Serretti et al (2003)[50]	Retrospective; cross-sectional	169 with AIM 247 without AIM	Bipolar I, 70% Bipolar II, 30%	Switch from major depressive episode into mania during antidepressant treatment	More bipolar II Higher number of previous major depressive episodes More delusions at index episode Less exposure to mood stabilizers
Bottlender et al (2004)[51]	Retrospective	39 with AIM 119 without AIM	Bipolar I, 100%	Switch from major depressive episode into mania during antidepressant treatment	Higher number of symptoms of mixed depression No mood stabilizer treatment Tricyclic antidepressant treatment
Manwani et al (2006)[52,a]	Retrospective	70 with AIM 265 without AIM	Bipolar I, 76% Bipolar II, 15% Bipolar NOS, 9%	Onset within 12 weeks after initiation of antidepressant treatment	More bipolar II More females History of substance use disorder Tricyclic antidepressant vs bupropion treatment
Mundo et al (2006)[53]	Retrospective	30 with AIM 106 without AIM	Bipolar I, 40% Bipolar II, 56% Schizoaffective disorder, bipolar type, 4%	Hypomanic or manic episode during antidepressant treatment	No mood stabilizer treatment Tricyclic antidepressant treatment

[a]Numbers refer to antidepressant trials.
Abbreviations: AIM = antidepressant-induced mania or hypomania, NOS = not otherwise specified.

patients relapsed during the 2 years, with no difference between the groups.[39] Nevertheless, when the effect of index episode was taken into account, it appeared that patients who had remitted from a depressive episode were less likely to relapse if lithium was combined with the antidepressant than if lithium was taken alone.[60]

In more recent years, 4 studies[61–64] with different designs have tried to address this question. Altshuler and colleagues[61] reviewed the charts of 44 subjects with bipolar disorder who were followed for 1 year after the remission of a major depressive episode. Patients were clustered in 2 groups. In the first group, antidepressants were discontinued within 6 months (mean, 42 days) after remission. In the second group, antidepressants were continued for up to 1 year. Patients who were taken off antidepressants were at higher risk for depressive relapse, with a 68% relapse rate at the end of follow-up versus 32% for those who continued antidepressant treatment. Stratification according to length of antidepressant treatment demonstrated a significant advantage for those patients who continued the antidepressant treatment for at least 8 months.[61]

The same research group followed 84 patients with bipolar disorder prospectively for 1 year.[62] These patients achieved remission from a depressive episode with the addition of an antidepressant to an ongoing mood stabilizer regimen. The risk of depressive relapse among the 43 subjects who stopped antidepressant treatment within 6 months after remission (discontinuation group) was compared with the risk among the 41 subjects who continued taking antidepressants beyond 6 months (continuation group). Discontinuing antidepressants soon after

remission was associated with a higher risk of depressive relapse. The risk of manic relapse was not significantly associated with continuing use of the antidepressant. The authors concluded that maintenance of antidepressant treatment in combination with a mood stabilizer might be warranted in some patients with bipolar disorder.[62]

In a third study,[63] patients with bipolar II depression who responded to open-label fluoxetine were randomly assigned to 6 months of double-blind fluoxetine or placebo continuation. Although the outcome appeared more favorable for patients in the continuation antidepressant arm (43% depressive relapse vs. 100% in the placebo arm), the fact that only 12 patients entered the continuation treatment phase most likely prevented findings of any significant difference between the groups.[63]

Another study[64] evaluated a large sample of 589 patients with bipolar disorder treated with antidepressants in a naturalistic setting after the remission of a depressive episode. Time to relapse was compared for patients who discontinued effective antidepressants within 6 months versus beyond 6 months of treatment. Survival analyses showed differences between the groups, with the lowest relapse rates seen in patients treated with antidepressants beyond 6 months. Patients whose antidepressant treatment lasted for 9 to 12 months after acute depressive remission achieved the best outcome. As a result, the authors suggested that antidepressant treatment should be continued for 9 to 12 months after remission of a depressive episode.[64]

It is interesting to note that in all these studies, patients in the continuation antidepressant groups had the same rate of manic relapse as patients whose antidepressant was discontinued within 6 months. This finding suggests that in some patients, emergence of mania during long-term antidepressant treatment may not be a concern.

Most of these studies have substantial limitations including small sample size[63] and retrospective design.[61,64] In the single prospective study,[62] patients were not randomly assigned and raters were not blind to treatment. Nevertheless, in the absence of studies suggesting the opposite, these studies show that patients who have a favorable acute response to antidepressants might benefit from at least 1 year of continued treatment with the same agents.

CONCLUSIONS

Given the failure to find an advantage for the addition of antidepressant medication to an ongoing mood stabilizer in the large STEP-BD effectiveness trial, caution is clearly necessary before advocating for liberal use of antidepressants in patients with bipolar disorder. However, our review of published RCTs, although not quantitative, provides evidence for the utility of antidepressants in the treatment of bipolar disorder and particularly for the continuation of antidepressants in those who have a positive response to acute antidepressant treatment.

A careful review of the literature indicates that some antidepressants—specifically fluoxetine and paroxetine—are effective agents for a substantial proportion of depressed bipolar patients. In contrast, other medications, such as the tricyclic antidepressants, show limited evidence of efficacy and are associated with higher rates of manic switch and, therefore, should be avoided. Finally, there is uncontrolled yet nevertheless compelling evidence suggesting that, for patients whose major depressive episodes have responded to adjunctive antidepressant treatment, antidepressants should be continued for over 6 months and possibly up to 1 year. These findings should encourage researchers to conduct additional studies to clarify the role of antidepressants in the long-term management of bipolar disorder.

Confusion about whether or not antidepressants are appropriate treatments for bipolar disorder is most likely driven by the fact that even DSM-IV–defined bipolar I and II disorders are probably heterogeneous groups of disorders with different underlying biology. Seemingly conflicting reports about efficacy and safety may reflect differential effects in different subpopulations. Indeed, our literature review suggests that when making decisions about antidepressant use in individuals with bipolar disorder, it may be important to consider specific clinical characteristics.

For instance, because of an increased risk of manic switch in patients with a history of substance abuse and a high number of previous episodes, it is important to be cautious with antidepressants in this group. Similarly, clinicians may wish to avoid prescribing antidepressants to individuals with co-occurring manic and hypomanic symptoms during depressive episodes. Indeed, a recently published trial[65] involving over 335 depressed patients with bipolar disorder concluded that, in patients whose depressive episode was accompanied by manic symptoms, "antidepressants do not hasten time to recovery relative to treatment with mood stabilizers alone, and treatment with antidepressants may lead to greater manic symptom severity."[65(p1348)] On the other hand, patients whose symptoms are primarily characterized by anergia, psychomotor retardation, and reversed vegetative symptoms may respond well to classical antidepressants.[18,66]

The evidence of a subpopulation of patients who lack response to antidepressants and/or are more prone to develop mixed features and of another subpopulation of patients who show a satisfactory and prolonged response without manic/mixed switches suggests, yet again, that patients with bipolar disorder are a heterogeneous population about whom we should not make generalized statements concerning the efficacy and safety (or lack thereof) of antidepressants. As recently suggested by McElroy and colleagues,[67] it may be useful to subtype patients on the

basis of their response to antidepressant treatment. This additional information would permit researchers to study the correlates of response/nonresponse and thus appropriately inform the treatment choice.

Clearly, there is a need for methodologically rigorous trials designed to identify clinical indicators for the use (or the nonuse) of antidepressant medications in patients with bipolar depression.

Drug names: bupropion (Wellbutrin and others), carbamazepine (Carbatrol, Equetro, and others), citalopram (Celexa and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), risperidone (Risperdal), sertraline (Zoloft and others), topiramate (Topamax), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

REFERENCES

1. American Psychiatric Association. Practice Guideline for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2002 Apr;159(suppl 4):1–50
2. Frances AJ, Kahn DA, Carpenter D, et al. The Expert Consensus Guidelines for treating depression in bipolar disorder. J Clin Psychiatry 1998; 59(suppl 4):73–79
3. Sachs GS, Printz DJ, Kahn DA, et al. The Expert Consensus Guideline Series: Medication Treatment of Bipolar Disorder 2000. Postgrad Med 2000 Apr;spec no:1–104
4. Marangell LB, Bauer MS, Dennehy EB, et al. Prospective predictors of suicide and suicide attempts in 1,556 patients with bipolar disorders followed for up to 2 years. Bipolar Disord 2006 Oct;8(5 pt 2):566–575
5. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord 2003;5:407–420
6. Ghaemi SN, Rosenquist KJ, Ko JY, et al. Antidepressant treatment in bipolar versus unipolar depression. Am J Psychiatry 2004;161(1): 163–165
7. Sachs GS, Nierenberg AA, Calabrese JR, et al. Effectiveness of adjunctive antidepressant treatment for bipolar depression. N Engl J Med 2007; 356(17):1711–1722
8. Ghaemi SN, Hsu DJ, Thase ME, et al. Pharmacological treatment patterns at study entry for the first 500 STEP-BD participants. Psychiatr Serv 2006;57(5):660–665
9. Lim PZ, Tunis SL, Edell WS, et al. Medication prescribing patterns for patients with bipolar I disorder in hospital settings: adherence to published practice guidelines. Bipolar Disord 2001;3(4):165–173
10. Ostacher MJ. The evidence for antidepressant use in bipolar depression. J Clin Psychiatry 2006;67(suppl 11):18–21
11. Gijsman HJ, Geddes JR, Rendell JM, et al. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004;161(9):1537–1547
12. Shelton RC, Stahl SM. Risperidone and paroxetine given singly and in combination for bipolar depression. J Clin Psychiatry 2004 Dec; 65(12):1715–1719
13. Amsterdam JD, Shults J. Comparison of fluoxetine, olanzapine, and combined fluoxetine plus olanzapine initial therapy of bipolar type I and type II major depression—lack of manic induction. J Affect Disord 2005;87(1):121–130
14. 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 Jul;67(7):1025–1033
15. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 2006;189:124–131
16. Schaffer A, Zuker P, Levitt A. Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression. J Affect Disord 2006 Nov;96(1–2):95–99
17. 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(4):313–322
18. Himmelhoch JM, Thase ME, Mallinger AG, et al. Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry 1991;148(7):910–916
19. Bocchetta A, Bernardi F, Burrai C, et al. A double-blind study of L-sulpiride versus amitriptyline in lithium-maintained bipolar depressives. Acta Psychiatr Scand 1993;88(6):434–439
20. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994 Sep;55(9):391–393
21. Grossman F, Potter WZ, Brown EA, et al. A double-blind study comparing idazoxan and bupropion in bipolar depressed patients. J Affect Disord 1999 Dec;56(2–3):237–243
22. Bauer M, Zaninelli R, Müller-Oerlinghausen B, et al. Paroxetine and amitriptyline augmentation of lithium in the treatment of major depression: a double-blind study. J Clin Psychopharmacol 1999;19(2):164–171
23. Young LT, Joffe RT, Robb JC, et al. Double-blind comparison of addition of a second mood stabilizer versus an antidepressant to an initial mood stabilizer for treatment of patients with bipolar depression. Am J Psychiatry 2000;157(1):124–126
24. 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(6):906–912
25. Silverstone T, on behalf of the Moclobemide Bipolar Study Group. Moclobemide vs imipramine in bipolar depression: a multicentre double-blind clinical trial. Acta Psychiatr Scand 2001 Aug;104(2):104–109
26. Vieta E, Martínez-Arán A, Goikolea JM, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry 2002 Jun;63(6): 508–512
27. McIntyre RS, Mancini DA, McCann S, et al. Topiramate versus bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study. Bipolar Disord 2002;4(3):207–213
28. 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(11):1079–1088
29. Suppes T, Dennehy EB, Hirschfeld RM, et al, for the Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder. The Texas Implementation of Medication Algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry 2005 Jul;66(7):870–886
30. Shi L, Namjoshi MA, Swindle R, et al. Effects of olanzapine alone and olanzapine/fluoxetine combination on health-related quality of life in patients with bipolar depression: secondary analyses of a double-blind, placebo-controlled, randomized clinical trial. Clin Ther 2004;26(1): 125–134
31. Wright G, Galloway L, Kim J, et al. Bupropion in the long-term treatment of cyclic mood disorders: mood stabilizing effects. J Clin Psychiatry 1985 Jan;46(1):22–25
32. Haykal RF, Akiskal HS. Bupropion as a promising approach to rapid cycling bipolar II patients. J Clin Psychiatry 1990 Nov;51(11):450–455
33. Fogelson DL, Bystritsky A, Pasnau R. Bupropion in the treatment of bipolar disorders: the same old story? J Clin Psychiatry 1992 Dec; 53(12):443–446
34. Joffe RT, MacQueen GM, Marriott M, et al. Induction of mania and cycle acceleration in bipolar disorder: effect of different classes of antidepressant. Acta Psychiatr Scand 2002 Jun;105(6):427–430
35. Himmelhoch JM, Fuchs CZ, Symons BJ. A double-blind study of tranylcypromine treatment of major anergic depression. J Nerv Ment Dis 1982;170(10):628–634
36. Nolen WA, Kupka RW, Hellemann G, et al. Tranylcypromine vs. lamotrigine in the treatment of refractory bipolar depression: a failed but clinically useful study. Acta Psychiatr Scand 2007 May;115(5):360–365
37. Goodwin FK, Jamison KR. Manic Depressive Illness. New York, NY: Oxford University Press; 1990
38. Jann MW, Bitar AH, Rao A. Lithium prophylaxis of tricyclic-antidepressant–induced mania in bipolar patients. Am J Psychiatry 1982;139(5):683–684
39. Prien RF, Kupfer DJ, Mansky PA, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: report of the NIMH Collaborative Study Group comparing lithium carbonate,

imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 1984;41(11):1096–1104
40. Rouillon F, LeJoyeux M, Filteau MJ. Unwanted effects of long-term treatment. In: Montgomery SA, Rouillon F, eds. Long-Term Treatment of Depression. Chichester, United Kingdom: Wiley; 1992:81–111
41. Boerlin HL, Gitlin MJ, Zoellner LA, et al. Bipolar depression and antidepressant-induced mania: a naturalistic study. J Clin Psychiatry 1998 Jul;59(7):374–379
42. Bottlender R, Rudolf D, Strauss A, et al. Antidepressant-associated maniform states in acute treatment of patients with bipolar-I depression. Eur Arch Psychiatry Clin Neurosci 1998;248(6):296–300
43. Bottlender R, Rudolf D, Strauss A, et al. Mood-stabilisers reduce the risk of developing antidepressant-induced maniform states in acute treatment of bipolar I depressed patients. J Affect Disord 2001 Mar;63(1–3):79–83
44. Bauer M, Rasgon N, Grof P, et al. Do antidepressants influence mood patterns? a naturalistic study in bipolar disorder. Eur Psychiatry 2006 Jun;21(4):262–269
45. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152(8):1130–1138
46. Peet M. Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994;164(4):549–550
47. Stoll AL, Mayer PV, Kolbrener M, et al. Antidepressant-associated mania: a controlled comparison with spontaneous mania. Am J Psychiatry 1994;151(11):1642–1645
48. Henry C, Sorbara F, Lacoste J, et al. Antidepressant-induced mania in bipolar patients: identification of risk factors. J Clin Psychiatry 2001 Apr;62(4):249–255
49. Goldberg JF, Whiteside JE. The association between substance abuse and antidepressant-induced mania in bipolar disorder: a preliminary study. J Clin Psychiatry 2002 Sep;63(9):791–795
50. Serretti A, Artioli P, Zanardi R, et al. Clinical features of antidepressant associated manic and hypomanic switches in bipolar disorder. Prog Neuropsychopharmacol Biol Psychiatry 2003 Aug;27(5):751–757
51. Bottlender R, Sato T, Kleindienst N, et al. Mixed depressive features predict maniform switch during treatment of depression in bipolar I disorder. J Affect Disord 2004;78(2):149–152
52. Manwani SG, Pardo TB, Albanese MJ, et al. Substance use disorder and other predictors of antidepressant-induced mania: a retrospective chart review. J Clin Psychiatry 2006 Sep;67(9):1341–1345
53. Mundo E, Cattaneo E, Russo M, et al. Clinical variables related to antidepressant-induced mania in bipolar disorder. J Affect Disord 2006; 92(2–3):227–230
54. Kupfer DJ, Carpenter LL, Frank E. Possible role of antidepressants in precipitating mania and hypomania in recurrent depression. Am J Psychiatry 1988;145(7):804–808
55. Altshuler LL, Suppes T, Black DO, et al. Lower switch rate in depressed patients with bipolar II than bipolar I disorder treated adjunctively with second-generation antidepressants. Am J Psychiatry 2006;163(2):313–315
56. Geddes JR, Burgess S, Hawton K, et al. Long-term lithium therapy for bipolar disorder: systematic review and meta-analysis of randomized controlled trials. Am J Psychiatry 2004;161(2):217–222
57. Prien RF, Klett CJ, Caffey EM Jr. Lithium carbonate and imipramine in prevention of affective episodes: a comparison in recurrent affective illness. Arch Gen Psychiatry 1973;29(3):420–425
58. Quitkin FM, Kane J, Rifkin A, et al. Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients: a double-blind study. Arch Gen Psychiatry 1981;38(8):902–907
59. Kane JM, Quitkin FM, Rifkin A, et al. Lithium carbonate and imipramine in the prophylaxis of unipolar and bipolar II illness: a prospective, placebo-controlled comparison. Arch Gen Psychiatry 1982;39(9): 1065–1069
60. Shapiro DR, Quitkin FM, Fleiss JL. Response to maintenance therapy in bipolar illness: effect of index episode. Arch Gen Psychiatry 1989;46(5): 401–405
61. Altshuler L, Kiriakos L, Calcagno J, et al. The impact of antidepressant discontinuation versus antidepressant continuation on 1-year risk for relapse of bipolar depression: a retrospective chart review. J Clin Psychiatry 2001 Aug;62(8):612–616
62. Altshuler L, Suppes T, Black D, et al. Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up. Am J Psychiatry 2003;160:1252–1262
63. Amsterdam JD, Shults J. Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study. Int Clin Psychopharmacol 2005;20(5):257–264
64. Fu AZ, Christensen DB, Hansen RA, et al. Second-generation antidepressant discontinuation and depressive relapse in adult patients with bipolar depression: results of a retrospective database analysis. Clin Ther 2006; 28(6):979–989
65. Goldberg JF, Perlis RH, Ghaemi SN, et al. Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: findings from the STEP-BD. Am J Psychiatry 2007;164(9):1348–1355
66. Fagiolini A, Frank E, Cherry CR, et al. Clinical indicators for the use of antidepressants in the treatment of bipolar I depression. Bipolar Disord 2002;4(5):277–282
67. McElroy SL, Kotwal R, Kaneria R, et al. Antidepressants and suicidal behavior in bipolar disorder. Bipolar Disord 2006 Oct;8(5 pt 2):596–617

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