# Antidepressants for the Acute Treatment of Bipolar Depression: A Systematic Review and Meta-Analysis

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***Objective:*** The role of antidepressants in the acute treatment of bipolar depression remains a contentious issue. A previous meta-analysis of randomized controlled trials (RCTs) concluded that antidepressants were effective and safe for bipolar depression. Several trials published since then suggest that antidepressants may not be as beneficial as previously concluded. The current systematic review and meta-analyses reexamine the efficacy and safety of antidepressant use for the acute treatment of bipolar depression.

***Data Sources:*** EMBASE, MEDLINE, CINAHL, PsycINFO, and the Cochrane Central Register of Controlled Trials databases were searched for double-blind RCTs published from 2003 to 2009 using the following diagnostic medical subject heading (MESH) terms: *bipolar disorder*, *bipolar depression*, *bipolar I disorder*, *bipolar II disorder*, *bipolar III disorder*, *bipolar mania*, *cyclothymia*, *manic depressive psychosis*, *mixed mania* and *depression*, and *rapid cycling* and *bipolar disorder*. Databases of trial registries were also searched for unpublished RCTs. These searches were supplemented by hand searches of relevant articles and review articles.

***Study Selection:*** Trials that compared acute (< 16 wk) antidepressant treatment with either an active drug or a placebo comparator in adult bipolar patients, depressive phase were eligible for inclusion. Main outcome measures were clinical response, remission, and affective switch.

***Data Synthesis:*** Six RCTs (N = 1,034) were identified since publication in 2004 of the first meta-analysis that assessed antidepressant use in the acute treatment of bipolar depression. These studies were combined with earlier studies for a total of 15 studies containing 2,373 patients. Antidepressants were not statistically superior to placebo or other current standard treatment for bipolar depression. Antidepressants were not associated with an increased risk of switch. Studies that employed more sensitive criteria to define *switch* did report elevated switch rates for antidepressants.

***Conclusions:*** Although antidepressants were found to be safe for the acute treatment of bipolar depression, their lack of efficacy may limit their clinical utility. Further high-quality studies are required to address the existing limitations in the literature.

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The management of bipolar disorder has historically centered on treatment of the manic phase of the illness.[1] Depression, however, is the predominant mood experienced[2] and is associated with significantly higher rates of morbidity and mortality relative to mania.[3,4] This has translated into an urgent search for effective treatment strategies for bipolar depression, which has become a salient, albeit much debated, issue. Much of the controversy surrounds the evidence that antidepressant medications, most notably tricyclic antidepressant medications, destabilize mood by inducing an affective switch to mania or hypomania,[5–9] while others have found no such association.[10–12] Although studies have additionally suggested that antidepressant treatment may have the potential to exacerbate disease severity by increasing cycle frequency,[13–15] many of these trials suffer from bias or the lack of adequate control groups to demonstrate causation and effectively address these issues.[16] Given that there are limited treatment options available for bipolar depression, however, clinicians are often left to assess whether the benefits of antidepressant medications might outweigh the potential risks to individual patients. Consistent with the noted risks, most North American guidelines take a conservative treatment approach and recommend antidepressant medications as a second-line treatment option, preferably for short-term use and concurrent with a mood stabilizer.[17,18] There is limited evidence, however, that antidepressant medications are efficacious for the acute treatment of bipolar depression, creating a clear disparity between evidence and clinical practice. Furthermore, recent evidence of the efficacy of medications such as mood stabilizers and atypical antipsychotics means that clinicians have a greater range of options for treating bipolar depression.[19–22] However, approximately 50% of patients with bipolar disorder are prescribed an antidepressant, making them the most widely prescribed class of psychotropic medication for bipolar disorder.[23,24]

In 2004, Gijsman and colleagues[25] published a systematic review and meta-analysis of 12 randomized controlled trials (RCTs) that assessed antidepressant use in the acute treatment of bipolar depression. Antidepressant medications were reported to be efficacious and safe for the treatment of bipolar depression. Randomized controlled trials published since then, however, suggest that antidepressant medications might not be as efficacious as previously concluded. We therefore conducted an updated systematic review and meta-analysis of RCTs addressing the efficacy and safety of acute antidepressant medication use in bipolar depression.

## METHOD

### Search Strategy

A computerized search for randomized controlled trials was conducted using the following databases: EMBASE (2003–July 24, 2008), MEDLINE (2003–July 24, 2008), CINAHL (2003–July 24, 2008), PsycINFO (2003–July 24, 2008), and the Cochrane Central Register of Controlled Trials. Monthly searches up to the time of final acceptance were conducted to ensure the most up-to-date trials were included; the final search was conducted on August 17, 2009. Diagnostic medical subject heading (MESH) terms used were *bipolar disorder*, *bipolar depression*, *bipolar I disorder*, *bipolar II disorder*, *bipolar III disorder*, *bipolar mania*, *cyclothymia*, *manic depressive psychosis*, *mixed mania* and *depression*, and *rapid cycling* and *bipolar disorder*. Each of these terms was combined with the Boolean operator OR, and then combined with the following treatment MESH terms using AND: *antidepressant agent*, *antidepressive agents*, *antidepressive agents second-generation*, *antidepressive agents tricyclic*, *monoamine oxidase inhibitor*, *noradrenaline uptake inhibitor*, *serotonin uptake inhibitor*, *tetracyclic antidepressant agent*, and *tricyclic antidepressant agent*. The search was restricted to randomized controlled trials (RCTs) as publication type and keyword. No language restrictions were implemented. Databases of trial registries were also searched for unpublished RCTs using the search terms *bipolar* AND *antidepressant* (eg, http://www.clinicaltrials.gov and http://controlled-trials.com). The authors were contacted in instances in which completed but unpublished trials were found. The reference lists of select articles and review articles were also hand searched.

### Study Eligibility

In order to be considered for inclusion, studies had to be randomized, double-blind studies comparing acute (< 16 weeks) antidepressant treatment with either an active drug or a placebo comparator in adult men or women with bipolar I or II disorder experiencing a current depressive episode (co-occurring mixed states included). Studies that recruited nonbipolar patients were included only if bipolar patients constituted the majority of patients and if data for these patients were separately analyzed and presented. Both adjunctive and monotherapy antidepressant trials were included. Medication dosages could be fixed or flexible.

Treatments excluded were anticonvulsants, mood stabilizers, anxiolytics, hypericum, ethyl-eicosapentaenoate, inositol and *N*-acetylcysteine, scopolamine, modafinil, and celecoxib. Studies deemed to meet the above inclusion/exclusion criteria after an initial title and abstract screening were retrieved for full-text review. Uncertainty over inclusion at each stage of screening was discussed between authors. Two blinded investigators (M.M.S., research assistant) assessed methodological quality by considering blinding, randomization, allocation concealment, and the reporting of withdrawals as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* by Higgins and Green.[26] Each of these quality parameters were given a score of A (adequate), B (unclear), or C (inadequate). Differences in quality assessment were settled by discussion. An inadequate rating on any 1 of the quality dimensions mentioned above was not means for removal from analyses, but it was taken into account during sensitivity analysis or when significant heterogeneity was apparent. The primary outcome measures of interest were clinical response and remission (defined by the magnitude of symptom reduction on established diagnostic scales) and safety (induction of mania or hypomania). The secondary outcome measure was tolerability of the treatment as indicated by the number of patient dropouts for any reason.

### Data Extraction and Analysis

Data were extracted independently by 2 investigators using a preformed data extraction template that was formulated based on the guidelines and suggestions outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*.[26] The specificity and clarity of the data extraction form was pilot tested using a representative sample of studies to ensure all information required was extracted appropriately and led to consistent extraction between investigators. Upon completion of data extraction, any discrepancies were settled through discussion. When appropriate, authors were contacted to clarify results or provide missing data. In instances in which no reply was received, data were estimated by graphs provided in the article when possible.

Analysis of treatment estimates was performed using a fixed-effects model (Mantel-Haenszel) of binary outcomes with weighted variables. Treatment effect is presented as a pooled risk ratio with 95% confidence intervals reported. For efficacy outcomes, a relative risk greater than 1 indicates that antidepressant medications are beneficial relative to the comparator; for switch data, a relative risk greater than 1 indicates that antidepressant medications are associated with a greater risk of switch than the comparator. The $Z$ statistic was used to determine significance of pooled estimates, with a 2-tailed $P$ value of .05 considered statistically significant. Analyses were performed using an intention-to-treat principle (assumes unfavorable outcome for dropouts), with last-observation-carried-forward data used when provided. For efficacy and safety outcomes, the total number of patients in each treatment arm was defined as those who received at least 1 postbaseline follow-up assessment.

Heterogeneity between studies was assessed using both the $Q$ statistic and the $I^2$ statistic. In instances in which significant heterogeneity was found ($P < .10$), the respective forest plot was visually inspected for outliers. In instances in which outliers were found, sensitivity analyses were performed by excluding these studies to determine their influence on the pooled effect.

A priori sensitivity analyses were performed to determine the effects of bipolar subtype (bipolar I and II disorders), rapid cycling, adjunctive mood stabilizer treatment, and pharmaceutical funding of the trial on the estimated outcomes. This was done by limiting analysis to studies containing patients with bipolar I disorder only, studies including patients with rapid cycling, and studies in which all patients

did or did not receive a mood stabilizer and by excluding studies that were industry funded or, similarly, whose author was affiliated with a pharmaceutical company. Sensitivity analyses were applied only to placebo-controlled studies, given their relatively larger sample size and more homogeneous choice of treatments, which would facilitate detection of meaningful differences.

All analyses were conducted using Review Manager 4.2 Software for Windows provided by the Cochrane Collaboration (Nordic Cochrane Centre, Copenhagen, Denmark, 2003).

## RESULTS

### Study Characteristics

The search strategy yielded a total of 169 trials. Twenty-five trials were retained after an initial title and abstract screening. Of these, 9 were excluded from further evaluation: 4 were duplicate entries from the databases searched; 4 were incomplete, unpublished trials; and 1 was already included in the previous meta-analysis.[27] This left 14 published trials that were retrieved for a more detailed evaluation and 2 unpublished completed trials in which the respective authors were contacted. Of the published trials, 4 were excluded for inappropriate study design based on the inclusion criteria[28–31] and 4 were excluded for having multiple publications.[32–35] With regards to the 2 unpublished completed trials, 1 was not publishable due to insufficient data, and the author could not be contacted for the second trial. This left a total of 6 RCTs (N = 1,034) published between 2004 and 2009. Although Gijsman et al[25] identified 12 RCTs published between 1980 and 2004, 3 of these trials were excluded from our analyses for not meeting the current inclusion criteria.[36–38] This left a total of 15 RCTs (n = 2,373) available for meta-analyses. Descriptive information about these trials is provided in Table 1.

Six studies compared an antidepressant to placebo (n = 1,469), 4 were head-to-head antidepressant comparisons (n = 401), and 5 compared an antidepressant to other pharmacologic treatments (n = 503). Study duration ranged from 4 to 26 weeks (data up to 16 weeks considered only) with the majority of trials ranging from 6 to 8 weeks in length. Eight studies were pharmaceutically funded, of which 5 were in the antidepressant versus placebo comparison group. Seven trials derived their patients from multiple sites. The majority of the sample population were outpatients, with only 3 trials containing a small number of inpatients. Six trials did not report on patient origin. Seven trials contained a mix of bipolar I and II disorder patients, including 1 trial that also included bipolar not otherwise specified. Four trials were inclusive to bipolar I patients only, and the remaining 4 were older studies that diagnosed bipolar disorder based on the *DSM-III-R*, which did not include bipolar II disorder as a separate disorder. Six trials included patients with a history of rapid cycling, 3 excluded such patients, and the remaining 6 trials did not specify rapid cycling in the exclusion/inclusion criteria. Patients were aged 18–71 years, with the majority being women (mean = 61%).

### Methodological Quality

All trials were reported as randomized and double-blind but only 4 explicitly stated the method by which participants were randomly assigned to their respective treatment arms. Poor study quality was associated with inadequate or unclear reporting of blinding protocols, insufficiently described reasons for subject withdrawals, or inadequately described randomization protocols. Eleven studies were unclear as to the use of allocation concealment. Table 1 provides additional details for those studies given a score of "inadequate" along any 1 of these quality dimensions.

### Antidepressant Versus Placebo

Six of 15 studies were eligible for a comparison of the treatment efficacy of antidepressant versus placebo.[27,39–43] Of the 1,469 patients within these 6 trials, 68% received co-treatment with a mood stabilizer. Antidepressants used were paroxetine, fluoxetine, imipramine, and bupropion.

***Clinical response.*** Five of 6 studies comparing an antidepressant (n = 341) to placebo (n = 565) reported on clinical response and were available for meta-analysis. *Response* was defined as a 50% reduction of Hamilton Depression Rating Scale (HDRS) scores in 3 studies,[40,41,43] one of which also required a Clinical Global Impressions-Severity of Illness score of 1 or 2.[41] One study used a 50% reduction in Montgomery-Asberg Depression Rating Scale (MADRS) as a response criterion[27] and another used a 50% reduction in continuous symptom subscales for depression recorded from the Structured Clinical Interview for *DSM-IV* (SUM-D) scores.[39] The pooled treatment effect revealed a small, albeit nonsignificant, benefit of antidepressant over placebo in terms of clinical response (relative risk [RR] = 1.18; 95% CI, 0.99–1.40; $P = .06$; Figure 1A). There was statistically significant heterogeneity present in this analysis, most likely due to the opposing direction of the treatment effect (favors placebo) present in the heaviest weighted study.[39]

***Clinical remission.*** Four studies containing 1,346 participants were available for this comparison of clinical remission.[27,39,41,42] Two studies defined *clinical remission* as an endpoint HDRS of 7 or less,[41,42] with 1 having the additional requirement of a Clinical Global Impressions (CGI) score of 2 or less relative to baseline.[42] *Clinical remission* was also defined as a MADRS score of 12 or less,[27] and Sachs et al[39] used a criterion of 1–7 weeks of euthymia. Patients randomly assigned to antidepressant treatment did not have a significantly better remission rate than those receiving placebo (RR = 1.20; 95% CI, 0.98–1.47; $P = .09$; Figure 1B).

***Affective switch.*** Treatment-emergent *hypomanic* or *manic switch* was defined based on *DSM-IV* criteria or the Young Mania Rating Scale (YMRS). The threshold for detecting switch ranged from a YMRS score of 12 or greater[40,41] to a score of 15 or greater.[27] One study did not specifically state criteria for defining a switch.[43] Pooled treatment estimates from 1,026 patients indicate that antidepressant treatment did not significantly increase or decrease the risk of affective switch relative to placebo (RR = 0.97; 95% CI, 0.62–1.53; $P = .90$; Figure 1C). Overall, the switch rates were


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**Table 1. Study Characteristics**

| RCT | N | Duration, wk | Bipolar Type (n) | Treatment | Concomitant Medication | Outcome Measures | | | Methodological Quality[a] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Response | Remission | Switch | Randomized Procedure | Allocation Concealed | Blinding | Withdrawals Reported |
| Antidepressant vs placebo | | | | | | | | | | | | |
| Sachs et al[39] (2007) | 366 | 26 | *DSM-IV* BDI (240) BDII (114) | Paroxetine vs bupropion | 100% lithium, valproate, carbamazepine, or atypical antipsychotic | 50% reduction on SUM-D with no switch | 1–7 wk of euthymia, without *DSM-IV*–defined switch | *DSM-IV* criteria for hypomania or mania | A | A | A | A |
| Amsterdam et al[40] (2005) | 34 | 8 | *DSM-IV* BDI (32) BDII (2) | Fluoxetine | 26% olanzapine, 12% lithium, 3% valproate | ≥ 50% reduction in HDRS from baseline | N/A | YMRS ≥ 12; YMRS ≥ 8 also considered | B | B | B | A |
| Shelton and Stahl[41] (2004) | 30 | 12 | *DSM-IV* BDI (21) BDII (9) | Paroxetine | 100% risperidone; divalproex, lithium, carbamazepine, or topiramate | ≥ 50% reduction on HDRS and CGI-S = 1 or 2 | HDRS ≤ 7, no longer meeting *DSM-IV* criteria for depression | YMRS ≥ 12; YMRS ≥ 8 also considered | B | B | A | A |
| Tohen et al[27] (2003) | 833 | 8 | *DSM-IV* BDI | Fluoxetine | 100% olanzapine | 50% reduction on MADRS at endpoint + (4wk completed) | ≤ 12 on MADRS | YMRS ≥ 15 | A | A | A | A |
| Nemeroff et al[42] (2001) | 117 | 10 | *DSM-III-R* BDI | Imipramine, paroxetine | 100% lithium | Not reported | ≤ 7 on HDRS and CGI ≤ 2 from baseline | *DSM-III-R* criteria | B | B | B | A |
| Cohn et al[43] (1989) | 89 | 6 | *DSM-III* bipolar disorder | Fluoxetine, imipramine | 25% lithium | 50% reduction in HDRS | N/A | Not reported | C[b] | B | A | A |
| Antidepressant vs other | | | | | | | | | | | | |
| Brown et al[46] (2006) | 410 | 7 | *DSM-IV* BDI | Fluoxetine (olanzapine-fluoxetine combination) vs lamotrigine | 100% olanzapine or lamotrigine | ≥ 50% reduction on MADRS or CGI-S ≤ 3 | MADRS ≤ 12 | YMRS ≥ 15 at any point during study | B | B | A | A |
| Schaffer et al[44] (2006) | 20 | 12 | *DSM-IV* BDI (12) BDII (8) | Citalopram vs lamotrigine | 100% lithium, divalproex, or carbamazepine | ≥ 50% reduction on MADRS from baseline | MADRS ≤ 8 with no switch | YMRS ≥ 12 | B | B | B | A |
| Young et al[48] (2000) | 27 | 6 | *DSM-IV* BDI (11) BDII (16) | Paroxetine vs lithium or divalproex | 100% lithium or divalproex | N/A | N/A | N/A | B | B | A | A |
| Grossman et al[47] (1999) | 16 | 6 | *DSM-IV* BDI | Bupropion vs idazoxan | Lithium (% not reported) | Not reported | N/A | N/A | B | B | A | C[c] |
| Bocchetta et al[45] (1993) | 30 | 4 | *DSM-III-R* bipolar disorder | Amitriptyline vs L-sulpiride | 100% lithium | 50% reduction on HDRS at endpoint | N/A | Not reported | B | B | A | A |

*(continued)*

**Table 1 (continued). Study Characteristics**

| RCT | N | Duration, wk | Bipolar Type (n) | Treatment | Concomitant Medication | Outcome Measures: Response | Outcome Measures: Remission | Outcome Measures: Switch | Methodological Quality[a]: Randomized Procedure | Methodological Quality[a]: Allocation Concealed | Methodological Quality[a]: Blinding | Methodological Quality[a]: Withdrawals Reported |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Antidepressant vs antidepressant | | | | | | | | | | | | |
| Post et al[49] (2006) | 174 | 10 | *DSM-IV* BDI (126) BDII (46) NOS (2) | Sertraline vs venlafaxine vs bupropion | 100% valproate, lithium, atypical antipsychotic, carbamazepine, lamotrigine, or typical antipsychotic | ≥ 50% reduction on IDS or reduction in CGI-S by 2 | IDS ≤ 12 | YMRS > 13; YMRS > 13 or CGI-BP ≥ 3; CGI-BP increase by 2 | A | A | C[d] | A |
| Silverstone et al[51] (2001) | 156 | 8 | *DSM-III-R* bipolar disorder | Moclobemide vs imipramine | 42% lithium 12% carbamazepine 2% valproate 5% lithium + mood stabilizer | 50% reduction on HDRS from baseline or HDRS ≤ 10 | Not reported | YMRS > 10, YMRS ≥ 18 also considered | A | A | A | A |
| Sachs et al[50] (1994) | 15 | 8 | *DSM-III-R* bipolar disorder | Bupropion vs desipramine | 100% lithium, valproate, or carbamazepine | 50% reduction on HDRS from baseline (for ≥ 2 wk) | N/A | Not reported | B | B | A | C[c] |
| Himmelhoch et al[52] (1991) | 56 | 6 | *DSM-III-R*, RDC BDI (24) BDII (32) | Tranylcypromine vs imipramine | None | Moderate or marked improvement on CGI, for at least 2 wk by 6 wk or endpoint | N/A | > 5 Raskin Mania Scale | B | B | C[e] | C[f] |

[a]Studies were assessed for methodological quality by considering quality parameters of blinding, randomization, allocation concealment, and the reporting of withdrawals. Studies were given a score of A (adequate), B (unclear), or C (inadequate) for each of the parameters. [b]Disproportionate amount of patients receiving lithium in the antidepressant treatment arm relative to placebo arm. [c]Withdrawals not reported. [d]Twenty-seven patients were unmasked but included in outcome data. Supplementation data are provided in the original publication showing no significant differences between the masked and unmasked sample groups in terms of patient demographics, clinical response, remission, and switch. [e]Double-blind nature of study may have been compromised—the majority of treating physicians correctly guessed the medication being given based on characteristic side effects. [f]Number of withdrawals reported for each treatment arm but a detailed explanation of reasons for dropouts is missing.

Abbreviations: BDI = bipolar I disorder, BDII = bipolar II disorder, CGI = Clinical Global Impressions scale, CGI-BP = Clinical Global Impressions-Bipolar Version, CGI-S = Clinical Global Impressions-Severity of Illness scale, HDRS = Hamilton Depression Rating Scale, IDS = Inventory for Depressive Symptomatology, MADRS = Montgomery-Asberg Depression Rating Scale, N/A = not applied, NOS = not otherwise specified, RCT = randomized controlled trial, RDC = Research Diagnostic Criteria, SUM-D = Continuous symptom subscales for depression recorded from the Structured Clinical Interview for *DSM-IV*, YMRS = Young Mania Rating Scale.

7.7% for antidepressants and 7.2% for placebo.

Two studies (N = 64) contained additional switch data based on a more liberal criterion for switch, defined as a YMRS score of 8 or greater,[40,41] which allowed for an exploratory analysis of switch defined in this way. Antidepressants used in these studies were fluoxetine and paroxetine. Using a YMRS score of 8 or greater, we found that the switch rate increased to 24% for antidepressants and decreased to 4% for placebo, although the overall effect was not significant (RR = 3.05; 95% CI, 0.62–15.11; $P = .17$). It should be noted, however, that the antidepressant-associated increase in switch is attributed mainly to Amsterdam and colleagues'[40] study comparing fluoxetine, alone or in combination with olanzapine, versus placebo. In this case, those patients receiving fluoxetine alone or in combination with olanzapine experienced a switch rate of 47% compared to 13% for olanzapine monotherapy and 33% for placebo.

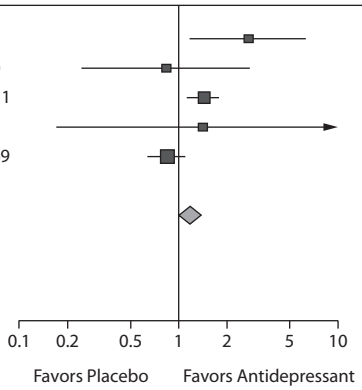
***Tolerability.*** Data from 1,435 patients were available for an assessment of *treatment tolerability*, defined as discontinuation of study treatment. One study,[40] comprising 34 patients, did not report rates of discontinuation for the separate treatment arms and so was not included in this analysis; withdrawal from this study was 59%. Overall, patients randomly assigned to antidepressant treatment were significantly less likely to discontinue treatment relative to those receiving placebo (RR = 0.87; 95% CI, 0.77–0.99; $P = .04$). The discontinuation rate for antidepressants was 51% compared to 55% for placebo.

***Sensitivity analysis.*** A sensitivity analysis to determine the influence of pharmaceutically funded or affiliated studies on the estimated treatment effects as calculated above was not possible given that 5 of the 6 trials comparing antidepressant to placebo were industry funded. Additional sensitivity analyses were conducted to examine the effects of

**Figure 1. Clinical Response (A), Remission (B), and Switch (C) in Randomized Controlled Trials Comparing Antidepressant Versus Placebo for Bipolar Depression**

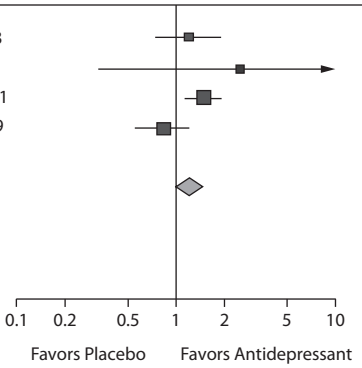
A. Clinical Response

| Study/Subcategory | Antidepressant, n/N | Placebo, n/N | Relative Risk (fixed), 95% CI | Weight, % | Relative Risk (fixed), 95% CI |
|---|---|---|---|---|---|
| Cohn et al[43] (1989) | 30/59 | 5/27 | | 5.13 | 2.75 (1.20–6.30) |
| Shelton and Stahl[41] (2004) | 5/20 | 3/10 | | 2.99 | 0.83 (0.25–2.80) |
| Tohen et al[27] (2003) | 46/82 | 137/351 | | 38.77 | 1.44 (1.14–1.81) |
| Amsterdam et al[40] (2005) | 3/17 | 1/8 | | 1.02 | 1.41 (0.17–11.54) |
| Sachs et al[39] (2007) | 58/163 | 71/169 | | 52.09 | 0.85 (0.65–1.11) |
| Total (95% CI) | 341 | 565 | | 100.00 | 1.18 (0.99–1.40) |
| Total events: 142 (antidepressant), 217 (placebo) | | | | | |
| Test for heterogeneity: $\chi^2_4 = 12.81$ ($P = .01$), $I^2 = 68.8\%$ | | | | | |
| Test for overall effect: $Z = 1.86$ ($P = .06$) | | | | | |



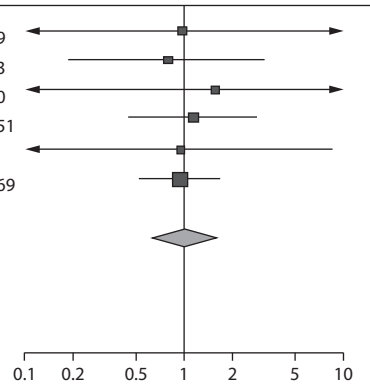

B. Clinical Remission

| Study/Subcategory | Antidepressant, n/N | Placebo, n/N | Relative Risk (fixed), 95% CI | Weight, % | Relative Risk (fixed), 95% CI |
|---|---|---|---|---|---|
| Nemeroff et al[42] (2001) | 29/69 | 15/43 | | 18.01 | 1.20 (0.74–1.97) |
| Shelton and Stahl[41] (2004) | 5/20 | 1/10 | | 1.30 | 2.50 (0.34–18.63) |
| Tohen et al[27] (2003) | 40/82 | 115/351 | | 42.43 | 1.49 (1.14–1.95) |
| Sachs et al[39] (2007) | 32/163 | 40/169 | | 38.26 | 0.83 (0.55–1.25) |
| Total (95% CI) | 334 | 573 | | 100.00 | 1.20 (0.98–1.47) |
| Total events: 106 (antidepressant), 171 (placebo) | | | | | |
| Test for heterogeneity: $\chi^2_3 = 6.10$ ($P = .11$), $I^2 = 50.8\%$ | | | | | |
| Test for overall effect: $Z = 1.72$ ($P = .09$) | | | | | |




C. Affective Switch

| Study/Subcategory | Antidepressant, n/N | Placebo, n/N | Relative Risk (fixed), 95% CI | Weight,h % | Relative Risk (fixed), 95% CI |
|---|---|---|---|---|---|
| Cohn et al[43] (1989) | 2/60 | 1/29 | | 3.97 | 0.97 (0.09–10.23) |
| Nemeroff et al[42] (2001) | 4/74 | 3/43 | | 11.16 | 0.77 (0.18–3.30) |
| Shelton and Stahl[41] (2004) | 1/20 | 0/10 | | 1.93 | 1.57 (0.07–35.46) |
| Tohen et al[27] (2003) | 5/82 | 19/351 | | 21.17 | 1.13 (0.43–2.93) |
| Amsterdam et al[40] (2005) | 2/17 | 1/8 | | 4.00 | 0.94 (0.10–8.92) |
| Sachs et al[39] (2007) | 18/163 | 20/169 | | 57.77 | 0.93 (0.51–1.70) |
| Total (95% CI) | 416 | 610 | | 100.00 | 0.97 (0.62–1.53) |
| Total events: 32 (antidepressant), 44 (placebo) | | | | | |
| Test for heterogeneity: $\chi^2_5 = 0.30$ ($P = 1.00$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $Z = 0.13$ ($P = .90$) | | | | | |




bipolar subtype, presence of rapid cycling, and adjunct mood stabilizer treatment on outcome indices. When these factors were taken into account, there was no change in the overall profile of estimated treatment effects.

## Antidepressant Versus Other Medication

Five studies containing 503 patients were available for comparisons of antidepressant medications to other pharmacologic treatment.[44–48] Seventy percent of these patients received mood stabilizer co-treatment. Citalopram, paroxetine, bupropion, amitriptyline, and fluoxetine were examined. Lamotrigine was used in 2 studies[44,46] and lithium or divalproex in the third.[48]

***Clinical response.*** Four studies (476 patients) reported dichotomous data for clinical response.[44–47] *Response* was defined as a 50% reduction on MADRS score from baseline in 2 studies[44,46] and a 50% reduction in HDRS scores in another.[45] One study did not define the criteria for clinical response.[47] The pooled treatment estimate indicates that antidepressant medications offered nonsignificant benefit


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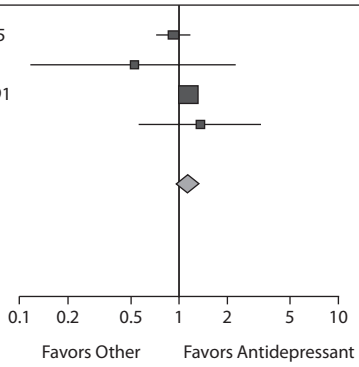
**Figure 2. Clinical Response (A), Remission (B), and Switch (C) in Randomized Controlled Trials Comparing Antidepressant Versus Other Medication for Bipolar Depression**

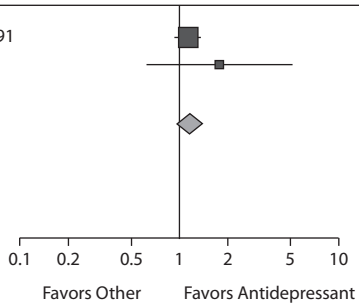
A. Clinical Response

| Study/Subcategory | Antidepressant, n/N | Other, n/N | Relative Risk (fixed), 95% CI | Weight, % | Relative Risk (fixed), 95% CI |
|---|---|---|---|---|---|
| Bocchetta et al[45] (1993) | 12/14 | 14/15 | | 9.77 | 0.92 (0.71–1.18) |
| Grossman et al[47] (1999) | 2/9 | 3/7 | | 2.44 | 0.52 (0.12–2.30) |
| Brown et al[46] (2006) | 139/202 | 114/191 | | 84.74 | 1.15 (0.99–1.34) |
| Schaffer et al[44] (2006) | 6/10 | 4/9 | | 3.04 | 1.35 (0.56–3.28) |
| Total (95% CI) | 235 | 222 | | 100.00 | 1.12 (0.98–1.28) |
| Total events: 159 (antidepressant), 135 (other) | | | | | |
| Test for heterogeneity: $\chi^2_3 = 3.71$ ($P = .29$), $I^2 = 19.1\%$ | | | | | |
| Test for overall effect: $Z = 1.64$ ($P = .10$) | | | | | |



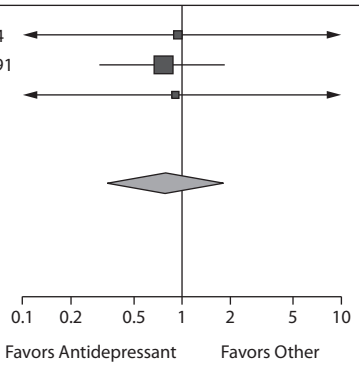

B. Clinical Remission

| Study/Subcategory | Antidepressant, n/N | Other, n/N | Relative Risk (fixed), 95% CI | Weight, % | Relative Risk (fixed), 95% CI |
|---|---|---|---|---|---|
| Brown et al[46] (2006) | 114/202 | 94/191 | | 96.84 | 1.15 (0.95–1.38) |
| Schaffer et al[44] (2006) | 6/10 | 3/9 | | 3.16 | 1.80 (0.63–5.16) |
| Total (95% CI) | 212 | 200 | | 100.00 | 1.17 (0.97–1.41) |
| Total events: 120 (antidepressant), 97 (other) | | | | | |
| Test for heterogeneity: $\chi^2_1 = 0.68$ ($P = .41$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $Z = 1.64$ ($P = .10$) | | | | | |




C. Affective Switch

| Study/Subcategory | Antidepressant, n/N | Other, n/N | Relative Risk (fixed), 95% CI | Weight, % | Relative Risk (fixed), 95% CI |
|---|---|---|---|---|---|
| Bocchetta et al[45] (1993) | 1/15 | 1/14 | | 8.36 | 0.93 (0.06–13.54) |
| Brown et al[46] (2006) | 8/202 | 10/191 | | 83.12 | 0.76 (0.30–1.88) |
| Schaffer et al[44] (2006) | 1/10 | 1/9 | | 8.51 | 0.90 (0.07–12.38) |
| Total (95% CI) | 227 | 214 | | 100.00 | 0.78 (0.35–1.77) |
| Total events: 10 (antidepressant), 12 (other) | | | | | |
| Test for heterogeneity: $\chi^2_2 = 0.03$ ($P = .98$), $I^2 = 0\%$ | | | | | |
| Test for overall effect: $Z = 0.59$ ($P = .56$) | | | | | |




over other pharmacologic treatments in terms of clinical response (RR = 1.12; 95% CI, 0.98–1.28; $P = .10$; Figure 2A).

One study by Young et al[48] reported continuous data comparing the addition of paroxetine or a second mood stabilizer to preexisting mood stabilizer pharmacotherapy (lithium or divalproex). Both groups showed similar improvement on the HDRS over the 6-week trial period.

***Clinical remission.*** Only 2 studies (430 patients) were eligible for a comparison of clinical remission.[44,46] Patients were randomly assigned to adjunct antidepressant treatment, citalopram in 1 study and fluoxetine in the other, with the active comparator being lamotrigine. *Clinical remission* was defined as a final MADRS score of 12 or less in 1 study and 8 or less in the other. Antidepressant medications did not offer statistically significant benefit when compared to lamotrigine (RR = 1.17; 95% CI, 0.97–1.41; $P = .10$; Figure 2B).

***Affective switch.*** Of the 3 studies reporting switch data (460 patients),[44–46] antidepressant treatment was not associated with either an increased or a decreased risk of switch (RR = 0.78; 95% CI, 0.35–1.77; $P = .56$; Figure 2C). This result was based on a switch criterion of a YMRS score of 12 or greater in 1 study[44] and 15 or greater in another.[46] One study did not operationally define switch criteria.[45]

***Tolerability.*** Five studies comprising 503 patients reported discontinuation rates. The rate of withdrawal for the antidepressant group was 31% and 32% for patients receiving other pharmacologic treatments. Overall, antidepressant


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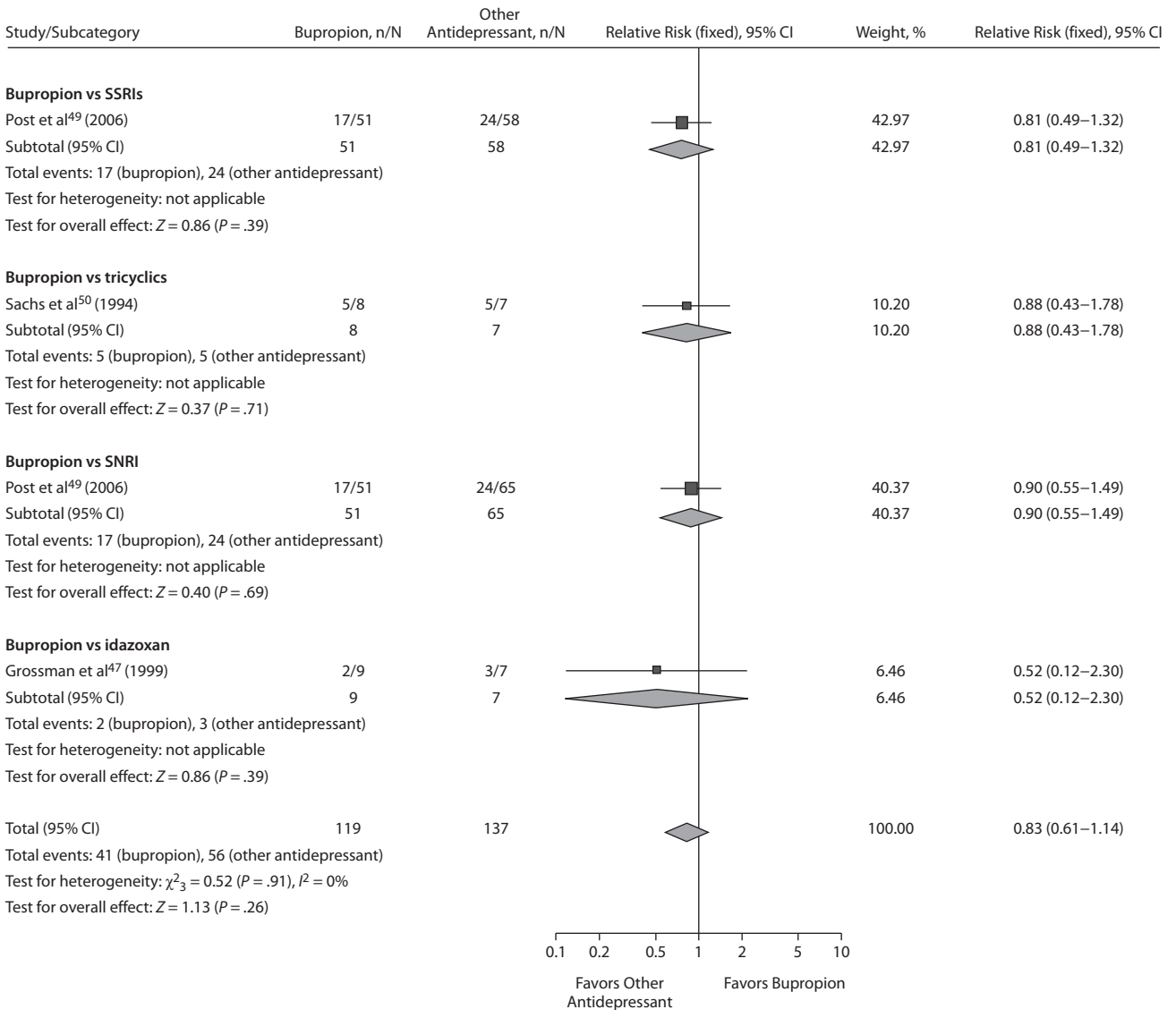
**Figure 3A. Clinical Response in Randomized Controlled Trials Comparing Bupropion to Other Antidepressants for Bipolar Depression**




medications were not associated with an increased or decreased rate of study discontinuation when compared against mood-stabilizing medications.

### Antidepressant Versus Other Antidepressants

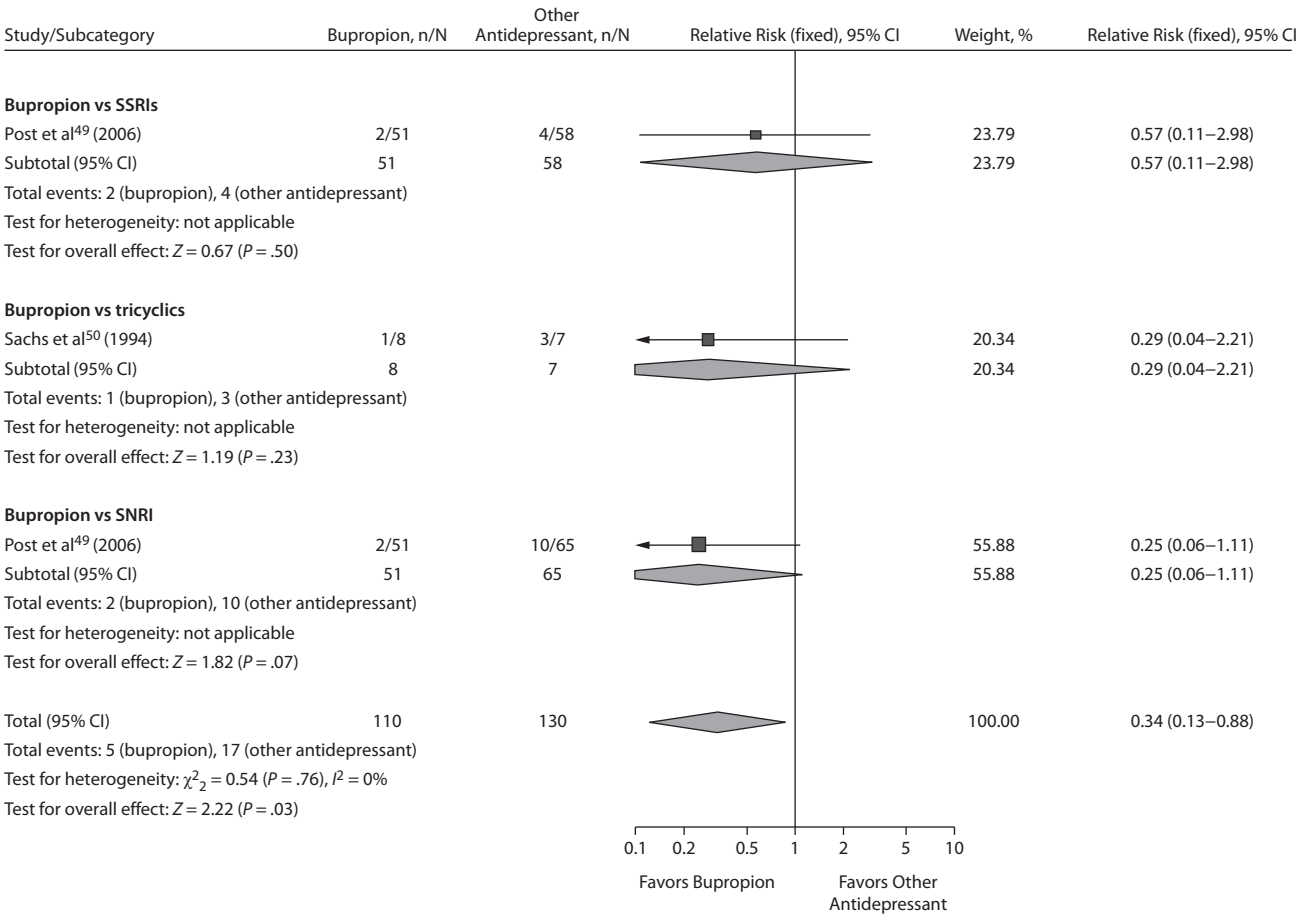
Four studies were retrieved (401 patients) comparing 2 antidepressant treatments.[49–52] Seventy-one percent of these patients received co-treatment with a mood stabilizer. Two studies compared bupropion to other antidepressants[49,50] and were included in that specific meta-analysis (see below). Of the 2 remaining studies in this group, 1 compared moclobemide to imipramine[51] and the other compared tranylcypromine to imipramine.[52]

Silverstone et al[51] defined *clinical response* as a 50% reduction on HDRS or an HDRS score less than 10, and they reported no significant difference on any efficacy measure between either antidepressant treatments. The second study used a definition of a CGI greater than 2 or 3 for clinical response and reported than tranylcypromine was associated with a greater clinical response than imipramine (75% vs 36%).[52] Although the switch rates were comparable between the 2 antidepressants (tranylcypromine, 21%; imipramine, 25%), the authors reported that, regardless of treatment, bipolar I disorder patients had a higher incidence of treatment-emergent mood swings than bipolar II disorder patients (bipolar I, 38%; bipolar II, 13%).

### Bupropion Versus Other Antidepressants

Data for these analyses were derived from 3 trials containing 205 patients.[47,49,50] Ninety-two percent of these patients received mood stabilizer co-treatment. Antidepressant comparators included venlafaxine, sertraline, desipramine, and idazoxan. A fourth trial by Sachs et al[39] compared both bupropion and paroxetine to placebo in bipolar-depressed

**Figure 3B. Affective Switch in Randomized Controlled Trials Comparing Bupropion to Other Antidepressants for Bipolar Depression**




patients but separate outcome data for the bupropion treatment arm could not be obtained.

***Clinical response.*** Three trials (205 patients) were available for this analysis, including 1 study in which bupropion and 2 other antidepressant medications were compared. *Clinical response* was defined as a 50% reduction in Inventory for Depressive Symptomatology (IDS) score in 1 study[49] and a 50% reduction in HDRS scores in the other.[50] The remaining study did not define the criteria used for response.[47] The pooled treatment estimate indicated no difference between bupropion and other antidepressant medications in terms of clinical response (RR = 0.83; 95% CI, 0.61–1.14; *P* = .26; Figure 3A).

***Clinical remission.*** One trial examined bupropion, venlafaxine, and sertraline.[49] *Clinical remission* was defined as an IDS score of 12 or less at study endpoint. Based on these comparisons, remission rates with bupropion were 37% versus 34% with sertraline and 25% with venlafaxine.

***Affective switch.*** Switch criteria were defined by only 1[49] of the 2 studies available for this analysis,[49,50] as a YMRS greater than 13. Based on these studies, bupropion was associated with a significantly reduced risk for affective switch compared to other antidepressants (RR = 0.34; 95% CI, 0.13–0.88; *P* = .03; Figure 3B), most notably tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors (SNRIs). The switch rate was 5% for bupropion compared to 7% for a selective serotonin reuptake inhibitor (SSRI), 15% for the SNRI, and 43% for the tricyclic antidepressant.

Post and colleagues[49] also considered a switch criterion of a Clinical Global Impressions-Bipolar Version score ≥ 3 in addition to a YMRS score greater than 13. In this case, the switch rate for bupropion was 14% compared to 16% for the SSRI and 31% for the SNRI treatment group.

***Tolerability.*** Bupropion was not better tolerated than the other antidepressants, at least as defined by withdrawal rates (RR = 0.77; 95% CI, 0.54–1.09; *P* = .13). One study comparing bupropion to idazoxan did not report withdrawals and was not included in this analysis.[50] The overall discontinuation rate for patients in the bupropion group was 30% compared to 41% in the SSRI group and 45% in the SNRI group.

## DISCUSSION

These analyses examined the efficacy and safety of antidepressant use for the acute (4–16 weeks) treatment of bipolar depression using the best evidence available to date. Fifteen double-blind RCTs were retrieved for systematic review and

meta-analysis. Antidepressant medications were not associated with a statistically significant increase in efficacy compared with placebo or other pharmacologic treatment for the acute treatment of bipolar depression. Although the point estimates in the current analyses indicate a slight benefit of antidepressant use over placebo in terms of response and remission, these did not reach statistical significance. The addition of newer studies reduced the effect size of antidepressant medications against placebo compared to the effect size reported by Gijsman et al.[25] Two earlier trials that Gijsman and colleagues[25] included in their meta-analyses were excluded from the current study for not distinguishing between unipolar and bipolar patients in outcome measures.[36,38] Three new placebo-controlled trials were added, 2 of which reported no benefit of adjunct antidepressant treatment over placebo.[39,41] The largest of these newer trials, the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial,[39] has been both lauded and criticized for a study design that may have included patients more generalizable to the overall population of people with bipolar disorder. Such qualitative differences in study design, however, may have contributed to heterogeneity within the analyses. Although one can argue that this is a limitation of the current findings, this speaks to a larger concern over the methodological consistency across RCTs in psychiatry.

The classes of antidepressant medications studied here, mostly SSRIs and bupropion, did not increase the risk of switch. This finding is consistent with the previous meta-analysis by Gijsman et al[25] and in a recent critical evaluation of the topic.[16] When sensitive diagnostic cut-off scores that detect subthreshold mood states were considered, however, the risk of switch increased in patients receiving antidepressant medications. In 1 study that used a more permissive criterion, the switch rate doubled from 9% to 21%.[49] Although this was not a placebo-controlled study and therefore no conclusions can be drawn as to whether switch was treatment induced or part of the natural course of illness, this does indicate that the specifics of the switch criteria used can influence the reported switch rate. Overall, there were relatively few studies reporting subthreshold mood switching, 2 of which were small and underpowered to detect statistical differences,[40,41] so caution should be taken in the interpretation of these findings. Furthermore, Amsterdam et al[40] reported that no patient who experienced subthreshold mood elevation met *DSM-IV* criteria for manic episode nor did any patient discontinue treatment as a result of a switch. Therefore, whether or not subthreshold mood switching poses a clinically meaningful risk to the patient remains to be determined. There is currently a lack of sufficient data to determine the long-term consequences of any form of mood elevation on clinical features such as acceleration of episode frequency or mood destabilization.[16] Our findings do suggest, however, that differences in the operational definition of switch between studies may account partially for the discrepancies in switch rates encountered across studies.

Bupropion, specifically, has been proposed as an antidepressant of choice because of its relatively low switch rate compared with other antidepressant medications, although a previous study cautioned that bupropion may not be safe in patients with a noted history of antidepressant-associated switch.[53] In the current meta-analysis, bupropion was associated with a significantly reduced risk of switch compared with a tricyclic and the SNRI venlafaxine, but not when compared to the SSRI sertraline. This finding is based on 1 small study and 1 larger study that included patients with rapid cycling forms of bipolar disorder.[49,50] The smaller study by Sachs et al,[50] however, used a modest dose of bupropion compared with a maximally tolerated dose of desipramine, which may have inflated the switch rates in the tricyclic treatment group. Post and colleagues[49] reported that venlafaxine increased the risk of affective switch relative to bupropion in rapid-cycling patients; there was no difference in switch rates among the non–rapid-cycling treatment group. It should be noted that this study was not 100% double-blind, as a small portion of patients were unmasked. Although the authors report that this did not have a major impact on response, remission, or switch rates, their findings should be interpreted with this in mind. A recent retrospective study[54] failed to replicate Post and colleagues' findings,[49] reporting no difference in the incidence of switch between bupropion (36%), SSRIs (30%), and venlafaxine (31%) monotherapy in rapid cycling patients, although monotherapy with second-generation antidepressants as a group was associated with treatment-emergent mania in rapid cyclers.

Bupropion was no more efficacious in terms of clinical response or remission. This is in agreement with the RCT by Sachs et al,[39] which reported no benefit of bupropion over paroxetine for bipolar depression. A similar finding was obtained in a single-blind RCT,[55] which found that bupropion was no more efficacious than the anticonvulsant topiramate in alleviating depressive symptoms.

No direct conclusions can be drawn as to how the inclusion or exclusion of rapid cycling, bipolar I or II disorders, or mood stabilizer co-treatment influence treatment outcomes. Although sensitivity analyses revealed no overall effect, this is most likely due to the relatively few studies available for such analyses and a lack of sufficient data. For instance, only 2 small studies contained groups of patients that received antidepressant monotherapy, and results were combined for both these patients and those who received adjunctive mood stabilizer treatment.[40,43] Therefore, there is no way of determining the specific effects of monotherapy or adjunctive antidepressant therapy on treatment outcomes. Our results do not suggest that there is a greater or less risk associated with antidepressant monotherapy, only that there is a lack of sufficient data to appropriately address this question. It would have been more informative to analyze data for each of the above features separately within the individual trials. Distinct effect sizes, however, could not be reported as separate data for the above groups were not provided in the majority of the original trials. As noted above, Post and colleagues[49] reported increased venlaflaxine-associated switch

rates among the rapid-cycling population, suggesting that inclusion or exclusion of patients with this feature could influence treatment outcomes depending on the antidepressant used. At least 2 studies reported that response and remission rates did not differ between patients with bipolar I and bipolar II disorders.[39,52] In terms of affective switch, Himmelhoch et al[52] reported that bipolar I disorder patients experienced a greater risk of treatment-emergent switch than bipolar II disorder patients. This finding appears consistent with a recent meta-analysis[56] of antidepressant-associated switch comparing the switch rates of patients with bipolar I versus bipolar II disorder within individual trials. Data for the meta-analysis was compiled from RCTs, open-label studies, and naturalistic reports; the switch rate for bipolar I disorder was 14% compared with 7% for bipolar II disorder during acute antidepressant treatment. This result suggests that the ratio of bipolar I to bipolar II disorder patients included in a trial can influence the reported switch rate and should be taken into account in future study designs.

It is interesting that in the analysis of antidepressants compared to other medications, 2 trials[44,46] allowed for a direct comparison to the anticonvulsant lamotrigine, which has been indicated as a first-line option for the acute treatment of bipolar depression.[17,18] Indeed, a recent meta-analysis[19] examining lamotrigine monotherapy to placebo concluded that lamotrigine offered benefit over placebo. In addition, lamotrigine added to lithium was more efficacious than lithium alone.[57] The current analysis indicates that adjunct antidepressant treatment may offer a numerical, although nonsignificant, benefit over lamotrigine in terms of clinical response and remission. No differences were found for affective switch. It should be noted, however, that the 7-week study by Brown et al[46] may not have been a fair comparison given that it took 5 weeks to reach the full titration dose for lamotrigine (200 mg/d) so that patients effectively received only 2 weeks of treatment with lamotrigine at presumed therapeutic levels. Paroxetine was also compared to lithium or divalproex in patients receiving preexisting mood stabilizer treatment.[48] Although both treatments were effective in alleviating depressive symptoms, a significantly greater portion of patients completed paroxetine treatment than those receiving a second mood stabilizer. Young et al[48] concluded that paroxetine may, therefore, have greater clinical utility in the treatment of bipolar depression in terms of tolerability.

Taken together, the present findings suggest that antidepressant medications offer little in the acute treatment of bipolar depression. This information is particularly relevant given the evidence that has emerged to support the efficacy of mood stabilizers and atypical antipsychotics for the treatment of acute bipolar depression[19–22] and for long-term maintenance therapy.[58] It is important to acknowledge, however, that to date there have been relatively few high quality RCTs published examining the role of acute antidepressant treatment in bipolar depression and that methodological limitations often reduce the validity of the extant studies. Such limitations include inadequate reporting of randomization and allocation concealment, small sample sizes, and heterogeneity among diagnostic measures, outcomes, and patient characteristics. On the basis of the constraints imposed by these limitations, the results of this meta-analysis are far from conclusive. There is a paucity of studies examining whether there are some patient characteristics that could identify subgroups for which antidepressants are more likely to have positive benefit; clinicians must therefore continue to make decisions about the risk-benefit ratio of antidepressants on a case-by-case basis. Further studies are required to determine whether there is a role for antidepressant medication in the treatment of some subgroups of patients with bipolar disorder, such as those with bipolar II disorder or those with minimal history of switch into mania or hypomania.

***Drug names:*** bupropion (Aplenzin, Wellbutrin, and others), carbamazepine (Carbatrol, Equetro, and others), celecoxib (Celebrex), citalopram (Celexa and others), desipramine (Norpramin and others), divalproex (Depakote and others), fluoxetine (Prozac and others), fluoxetine/olanzapine (Symbyax), imipramine (Tofranil and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), modafinil (Provigil), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), scopolamine (Transderm), tranylcypromine (Parnate and others), venlafaxine (Effexor and others).

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