NEURAL REGENERATION RESEARCH
Volume 8, Issue 31, November 2013

www.nrronline.org

doi:10.3969/j.issn.1673-5374.2013.31.009 [http://www.nrronline.org; http://www.sjzsyj.org]
Zhang YL, Yang H, Liang W, Dai P, Wang CH, Yang SC, Zhang YL. Antidepressants for bipolar disorder: a meta-analysis of randomized, double-blind, controlled trials. Neural Regen Res. 2013;8(31):2962-2974.

Antidepressants for bipolar disorder

A meta-analysis of randomized, double-blind, controlled trials

Yingli Zhang[1, 2], Huan Yang[1], Shichang Yang[3], Wei Liang[4], Ping Dai[5], Changhong Wang[2], Yalin Zhang[1]

1 *Mental Health Institute, Second Xiangya Hospital, Central South University, Changsha 410011, Hunan Province, China*
2 *Psychological Counseling Center, Second Affiliated Hospital of Xinxiang Medical University, Xinxiang 453002, Henan Province, China*
3 *Department of Psychology, Xinxiang Medical University, Xinxiang 453000, Henan Province, China*
4 *Department of Clinical Psychology, Second Affiliated Hospital of Xinxiang Medical University, Xinxiang 453002, Henan Province, China*
5 *Sichuan University Library, Chengdu 610041, Sichuan Province, China*

Research Highlights

(1) The use of antidepressants in the treatment of bipolar disorder remains controversial. To the best of our knowledge, there have been no meta-analysis papers of randomized, double-blind, controlled trials and the therapeutic effects and safety of long-term antidepressants in the treatment of bipolar disorder were not evaluated.
(2) The study involved new large-sample double-blind randomized controlled trials, excluded open-label design studies, and supplemented studies involving homogeneous patients. Strict inclusion criteria included limitation to double-blind randomized controlled studies and interventional treatment without use of antipsychotics to make the study results more objective and convincing.
(3) The present results do not support that antidepressants are more effective in the treatment of bipolar disorder. Antidepressants are not superior to placebo and other medication in short-term, and long-term use of antidepressants cannot achieve higher response and remission rates of bipolar disorder. These findings guide future clinical studies and provide evidence for preparing treatment strategy for bipolar disorder.

Abstract

OBJECTIVE: To examine the efficacy and safety of short-term and long-term use of antidepressants in the treatment of bipolar disorder.

DATA SOURCES: A literature search of randomized, double-blind, controlled trials published until December 2012 was performed using the PubMed, ISI Web of Science, Medline and Cochrane Central Register of Controlled Trials databases. The keywords “bipolar disorder, bipolar I disorder, bipolar II disorder, bipolar mania, bipolar depression, cyclothymia, mixed mania and depression, rapid cycling and bipolar disorder”, AND “antidepressant agent, antidepressive agents second-generation, antidepressive agents tricyclic, monoamine oxidase inhibitor, noradrenaline uptake inhibitor, serotonin uptake inhibitor, and tricyclic antidepressant agent” were used. The studies that were listed in the reference list of the published papers but were not retrieved in the above-mentioned databases were supplemented.

STUDY SELECTION: Studies selected were double-blind randomized controlled trials assessing the efficacy and safety of antidepressants in patients with bipolar disorder. All participants were aged 18 years or older, and were diagnosed as having primary bipolar disorder. Antidepressants or antidepressants combined with mood stabilizers were used in experimental interventions. Placebos, mood stabilizers, antipsychotics and other antide pressants were used in the control interventions. Studies that were quasi-randomized studies, or used antidepressants in combination with antipsychotics in the experimental group were excluded. All analyses were conducted using Review Manager 5.1 provided by the Cochrane Collaboration.

Yingli Zhang, Studying for doctorate, Chief physician.

Corresponding author: Yalin Zhang, M.D., Professor, Mental Health Institute, Second Xiangya Hospital, Central South University, Changsha 410011, Hunan Province, China, zhangyl69@vip.sina.com.

Received: 2013-06-24
Accepted: 2013-08-25
(N201302023)

Funding: This study was supported in part by the Key Projects of Science and Technology Research of the Department of Education in Henan Province, China, No.13A320869 and a special fund from Henan Health Science and Technology Innovation Talent Project, No. 4173 (2010-2015).

Author contributions: Zhang YL and Yang H designed this study, wrote the protocol and performed the statistical analysis. Liang W and Dai P designed the literature retrieval protocol and searched the database. Zhang YL managed the literature retrieval and analysis, and wrote the first draft of the manuscript. Yang SC and Wang CH advised and checked the manuscript. Zhang YL designed the study. All authors approved the final manuscript.

Conflicts of interest: None declared.

MAIN OUTCOME MEASURES: The primary outcome was the response and switching to mania. The secondary outcomes included remission, discontinuation rate, and suicidality.

RESULTS: Among 5 001 treatment studies published, 14 double-blind randomized controlled trials involving 1 244 patients were included in the meta-analysis. Eleven short-term studies and three maintenance studies were included. Studies suggested that patients treated with antidepressants were not significantly more likely to achieve higher response and remission rates in the short-term or long-term treatment than patients treated with placebo and other medications. Antidepressants were not associated with an increased risk of discontinuation, relapse or suicidality. When one antidepressant was compared with another, no significant difference in efficacy and tolerability was found.

CONCLUSION: Existing evidence of efficacy does not support the short-term or long-term application of antidepressant therapy in patients with bipolar disorder, although the tolerability and safety of antidepressants have been generally acknowledged. There is a need for large-sample, double-blind, randomized controlled trials to elucidate the role of antidepressants in patients with different subcategories of bipolar disorder.

Key Words

neural regeneration; evidence-based medicine; bipolar disorder; bipolar depression; antidepressant; response; switching to mania; suicidality; meta-analysis; grants-supported paper; neuroregeneration

INTRODUCTION

Bipolar disorder is a major psychotic disorder characterized by a chronic and highly recurrent course. Bipolar disorder is associated with a high rate of morbidity, disability[1], and comorbid anxiety and drug abuse[2], and has a major effect on social and occupational development[3-4]. The average onset age of bipolar disorder is between 20 and 40 years, while the lifetime prevalence ranges from 0.5% to 1.5%, with equal occurrence in women and men[5-6]. Because of its early onset and chronicity, bipolar disorder is one of the top thirty causes of worldwide disability[7-8].

Bipolar disorder is characterized by periods of mania, depression and mixed episodes. Most patients experience multiple episodes, with each lasting 3–6 months[9]. In the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)[10], bipolar disorder has been subcategorized into bipolar I and bipolar II disorders. Current data indicate that bipolar II disorder is more prevalent than bipolar I[11]. Despite mania being the hallmark of bipolar disorder, depression is the most important quantitative aspect of the illness and the one associated with higher levels of impaired social functioning and suicidality[3].

Over the last half-century, the management of bipolar disorder has been centered on manic phase treatment, and a great deal of research attention has been received regarding bipolar disorder treatment during this period[12-13]. While mood stabilizers, especially lithium, are the first the potential to increase the manic switch, while others recommend short-term antidepressant treatment and choice in the treatment of bipolar disorder, their efficacy in treating depression is suboptimal[14]. Studies have suggested that lithium reduces the rates of manic relapse and depressive relapse by about 40% and 25%, respectively[15]. Although there is some evidence that atypical antipsychotics are effective in the treatment of bipolar depression[16-17], the resulting adverse effects, such as weight gain, prolactin elevation, hyperglycemia, hyperlipidemia, and extrapyramidal symptoms, have become troublesome issues[18-19]. Meanwhile, little progress has been made on reducing the length of depressive episodes in bipolar disorder for the last 20 years[20]. It has been shown that pharmacological management of bipolar depression is an exceptionally difficult task[21]. Appropriate treatments for bipolar depression remain controversial. Avoiding antide pressant use has usually been proposed by clinical guide lines, considering the potential risk for switching to mania or rapid cycling during the treatment, while mood stabilizers (*e.g.*, lithium, divalproex, and lamotrigine) as first line treatment drugs for bipolar disorder have been recommended[22-23]. However, recent reports have shown that short-term second-generation antidepressant treatment is effective for the treatment of bipolar disorder, and that second-generation antidepressant monotherapy might be associated with a relatively low manic switch rate[24-25]. Meanwhile, the use of mood stabilizers for acute episodes of depression, either alone or in combination with an antidepressant, has generally been recommended by treatment guidelines published over the past 5 to 10 years[26-28].

Some studies and treatment guidelines suggest that antidepressant treatment for bipolar disorder may have early discontinuation[18, 29]. However, many of these are based on a single or several randomized controlled

groups, rather than all high-quality randomized controlled trials presently. When most guidelines extrapolate from studies of patients taking tricyclic antidepressants (TCAs)[30], the guidelines of bipolar depression with antidepressants are not informed by a rich evidence base and remain controversial. Meanwhile, little attention has been received for long-term antidepressant therapy of bipolar disorder.

To the best of our knowledge, there are two review studies describing the efficacy and safety of antidepressants used in patients with bipolar disorder[31-32]. Unfortunately, their conclusions are inconsistent with each other. Specifically, the evidence for the effectiveness of antidepressants in the treatment of bipolar disorder is mostly based on an open-label trial, with potential high risk of bias, which is not powered or blinded to properly address clinical outcomes. Moreover, since that time, a number of double-blind, randomized controlled trials have been conducted.

Given the high rates of suicidality and the negative effect on psychosocial function of bipolar disorder, the uncertain efficacy of antidepressants for the treatment of bipolar depression in the acute and maintenance phases, and controversies regarding benefits and potential risks, it is important to reevaluate and provide a quantitative review of antidepressant medication use in bipolar disorder. In this systematic review, double-blind randomized controlled trials were included to assess the efficacy and safety of short-term and long-term antidepressant use in the treatment of bipolar disorder and reduce the risks of study bias.

MATERIALS AND METHODS

Data retrieval

Studies were found by performing literature retrieval in the PubMed, ISI Web of Science, Medline and Cochrane Central Register of Controlled Trials databases until December 2012, and by conducting a cross-reference search of the eligible articles to identify additional studies not found in the electronic search.

The English terms used for retrieval of literature regarding diagnosis included bipolar disorder, bipolar I disorder, bipolar II disorder, bipolar III disorder, bipolar mania, bipolar depression, cyclothymia, manic depressive psychosis, mixed mania and depression, rapid cycling, manic depressive and bipolar affective disorder. The English terms used for literature regarding intervention and antidepressive agents were 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.

Inclusion and exclusion criteria

Inclusion criteria

(1) Double-blind randomized controlled trials comparing antidepressants alone or in combination with mood stabilizers against placebos, mood stabilizers, antipsychotics or other antidepressants. (2) Participants aged 18 years or older, and with a primary diagnosis of bipolar disorder according to DSM third edition, revised (DSM-III-R)[33] or DSM-IV[10]. (3) Experimental interventions involving antidepressant mono-therapy or antidepressants in combination with mood stabilizers. No restrictions on category and dosages of antidepressant were applied. (4) Comparator intervention involving placebos, mood stabilizers, antipsychotics and other antidepressants. (5) Use of a valid and reliable scale [*e.g.*, Hamilton Depression Rating Scale (HAMD)[34], Young Mania Rating Scale (YMRS)[35], Montgomery Asberg Depression Rating Scale (MADRS)[36]] or a standardized psychiatric interview [*e.g.*, Structured Diagnostic Interview for DSM-IV(SCID)[37]] to assess changes in illness severity.

Exclusion criteria

(1) Studies that were quasi-randomized studies, such as those allocating use during alternate days of the week. (2) Repeatedly published literature. (3) Letters, reviews, editorials and other non-original research. (4) Treatments that included antidepressants in combination with antipsychotics. (5) Experimental treatments in which mood stabilizers, anxiolytics, alpha antagonists, inositol and N-acetylcysteine, scopolamine, and modafinil were used. (6) Studies without intact data or that did not provide data in adequate form. (7) Animal studies.

Quality evaluation and data extraction

Two independent reviewers extracted data and assessed the quality of methodological reports of selected studies using data extraction forms. The following data were recorded: authors and year of publication, sample size, gender, inpatient or outpatient status, dosage of the intervention agent, treatment duration, response, remission, switch mania, all cause discontinuation. The criteria for quality assessment were based on recommendations in the Cochrane Handbook for Systematic Reviews of Intervention[38]. For crossover studies, only data from the first crossover sequence were used. If multiple measures were used, HAMD and YMRS were used as first choice for data extraction. Disagreements were resolved

through discussion.

Outcome measurements

The primary outcomes were the clinical response and the rate of switching to mania. Clinical response was defined by the study authors and included the proportion of participants experiencing a greater than 50% improvement on scale. The secondary outcomes included remission defined by the study authors, discontinuation for any reason, relapse, and suicidality (suicidal thinking or behavior).

Statistical analysis

All analyses were conducted using Review Manager 5.1 provided by the Cochrane Collaboration (http://ims. cochrane.org/revman/download). For binary outcomes, the relative risks were calculated using a Mantel-Haenszel fixed-effect model, and 95% confidence intervals (*CI*) were calculated. Analyses were performed using an intent-to-treat principle, with last observation carried forward data used when provided. For efficacy and safety outcomes, the total number of patients was defined as those who received at least one post baseline follow-up assessment. Heterogeneity was assessed using χ^2 and I^2 tests by fixed-effect model ($I^2 \geq 50\%$ was initially identified as heterogeneity). The Z statistic was used to determine significance of pooled estimates, with a two- tailed *P* value of 0.05 considered statistically significant. Sensitivity analyses were performed to determine the effects of adjunctive mood stabilizer treatment and pharmaceutical funding of the trial on the estimated outcomes.

RESULTS

Data retrieval results

Five thousand and one studies were initially identified through the electronic search. First pass screening eliminated 4 951 studies, leaving 50 studies that were considered potentially relevant for further inspection. After screening the full text, 14 randomized controlled trials[39-52] (*n* = 1 244) were available for meta-analyses. Figure 1 shows the selection process for the articles.

Baseline analysis and quality estimation

Seven studies (*n* = 895)[39-41, 43, 45-46, 48] compared one or more antidepressants with placebo, of which three studies (*n* = 433)[39, 41, 48] assessed long-term outcome. Four studies (*n* = 97)[42, 49-50, 52] compared an antidepressant with other pharmacologic treatments. Three studies (*n* = 252)[44, 47, 51] compared two different antidepressants. The majority of the studies included patients between the ages of 18 and 65 years.

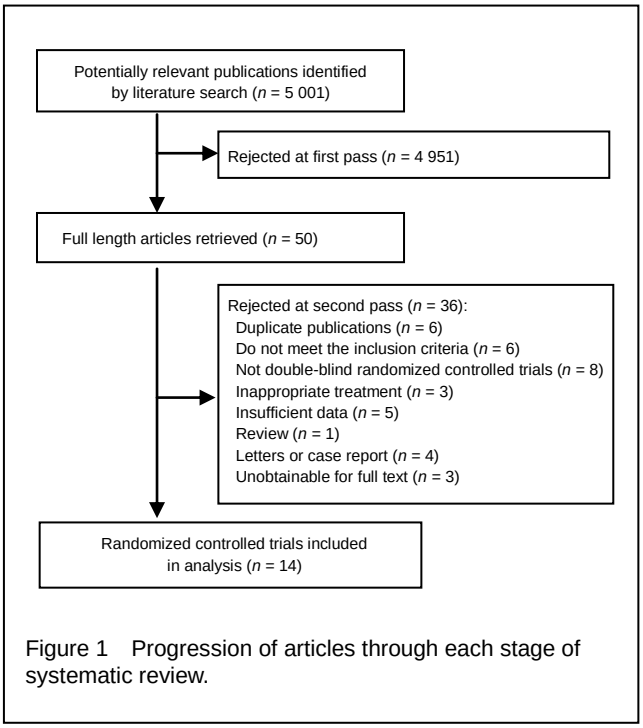


Figure 1 Progression of articles through each stage of systematic review.

The duration of short-term treatments was 4 to 12 weeks, and that of long-term treatments was 26 to 50 weeks. Two studies were pharmaceutically funded. Seven trials contained a mix of bipolar I and II disorder patients. Two studies only included bipolar II patients, and five studies did not include bipolar II disorder as a separate disorder (Table 1 provides additional details for those studies). All included studies were reported as double-blind randomized controlled trials, but only two of them explicitly stated the method of random sequence generation. Poor study quality was associated with inadequate or unclear reporting of blinding, randomization protocols, selective reporting, incomplete outcome data, or grants from a pharmaceutical company (Figure 2).

Meta-analysis results

Antidepressant versus placebo

Clinical response: In three studies[39, 41, 43], response was defined as at least a 50% reduction of HAMD score from baseline. In two studies[40, 45], response was defined as at least a 50% reduction of MADRS. In one study[48], response was defined as at least a 50% decrease on Subscales for Depression of Clinical Monitoring Form (SUM-D). Three short-term studies[43, 45-46] were included and found that the overall effect revealed a small, but not significant, benefit of antidepressant use over placebo [three randomized controlled trials, *n* = 445, *RR* = 1.23, 95%*CI*: 0.94, 1.62, *P* = 0.14], but the I^2 value of 63% and the significant heterogeneity test indicated a substantial heterogeneity (*P* = 0.07).

Table 1 Characteristics of double-blind, randomized controlled trials included in the meta-analysis

Study	Sample size (*n*)	Sex (F/M, *n*)	Bipolar type (*n*)	Treatment	Duration (week)	Concomitant medication	Response	Remission	Switch mania	Assessment scale
Antidepressant *vs.* placebo										
Amsterdam and Shults, [39] 2005	12	9/3	*DSM-IV* BD II and BD NOS MD	Fluoxetine 20 mg/d *vs.* placebo	24	Olanzapine, lithium, valproate	≥ 50% reduction in baseline HAMD-17 score	HAMD-17 ≤ 9, or a final 17-item 'atypical symptom' HAMD ≤ 9	HAMD-17 ≥ 14 plus DSM-IV criteria, YMR scores ≥ 8	HAMD-17, YMRS
Amsterdam and Shults, [40] 2005	17	5/12	*DSM-IV* BD I, BD II depression	Fluoxetine 10–30 mg/d *vs.* olanzapine 5–20 mg/d *vs.* fluoxetine 10–40 mg/d plus olanzapine 5–15 mg/d *vs.* placebo	8	Olanzapine, lithium, valproate	≥ 50% reduction in baseline HAMD and MADRS score	HAMD-17 ≤ 9 or final HAMD-17 ≤ 9	DSM-IV, YMRS scores ≥ 8	HAMD-28, MADRS, YMRS
Amsterdam and Shults, [41] 2010	55	28/27	*DSM-IV* BD II	Fluoxetine 10–40 mg/d *vs.* lithium 300–1 200 mg/d *vs.* placebo	50	Short-term zolpidem (≤ 10 mg), lorazepam (≤ 2.0 mg), or trazodone (≤ 75 mg)	≥ 50% reduction in baseline HAMD score	HAMD ≤ 8	HAMD ≥ 14 plus DSM-IV criteria	HAMD, YMRS
Cohn *et al*, [43] 1989	89	51/38	BD depression	Fluoxetine 20–80 mg/d *vs.* imipramine, placebo	6	Lithium, chloral hydrate (0.5–1 mg) for insomnia	≥ 50% reduction in baseline HAMD score	Not defined	Not defined	HAMD, Raskin Depression Scale, CGI
McElroy *et al*, [45] 2010	239	156/83	*DSM-IV* BDI, BD II	Quetiapine 300 mg/d *vs.* quetiapine 600 mg/d *vs.* paroxetine 20 mg/d *vs.* placebo	8	Lorazepam (1–3 mg/d), zolpidem tartrate (≤ 10 mg/d), zaleplon (≤ 20 mg/d), zopiclone (≤ 7.5 mg/d), and chloral hydrate	≥ 50% decrease from baseline in MADRS total score	MADRS total score ≤ 12 at week 8	Not defined	MADRS, CGI, SDS
Nemeroff *et al*, [46] 2001	117	65/52	*DSM-III-R* BD depressive phase	Paroxetine 20–50 mg/d *vs.* imipramine 50–300 mg/d *vs.* placebo	10	Lithium	Not defined	HAMD-21 ≤ 7 or CGI global improvement score ≤ 2	Not defined	HAMD-21, GCI
Sachs *et al*, [48] 2007	366	209/157	*DSM-IV* BDI, BD II	Paroxetine *vs.* bupropion *vs.* mood stabilizer plus placebo	26	Mood stabilizer	≥ 50% decrease from baseline in SUM-D	DSM IV, 50% improvement from baseline SUM-D score	DSM IV	MADRS, YMRS, SUM-D
Antidepressant *vs.* other medication										
Bocchetta *et al*, [42] 1993	30	20/10	*DSM-III-R* BD	Amitriptyline 50–75 mg/d *vs.* L-sulpiride 50–75 mg/d	4	Lithium; lorazepam as a hypnotic at entry	≥ 50% reduction in HRSD-17 score	Not defined	DSM-III-R	HAMD, BDI, SAS, GAF
Schaffer and colleagues, [49] 2006	20	17/3	*DSM-IV* BD I, BD II, major depression	Citalopram 10–50 mg/d *vs.* lamotrigine 50–200 mg/d	12	Mood stabilizer	≥ 50% decline in the MADRS	MADRS score ≤ 8	Not defined	HAMD, MADRS, YMRS, CGI
Shelton and Syahl, [50] 2004	20	10/10	*DSM-IV* BD I, BD II	Risperidone 4 mg/d plus placebo *vs.* Paroxetine 20 mg/d plus placebo	12	Mood stabilizer, lorazepam 3 mg/d	≥ 50% reduction in HAMD and CGI-S = 1 or 2	HDRS score ≤ 7, DSM-IV	YMRS ≥ 12; YMRS ≥ 8 also considered	HAMD, BDI
Young *et al*, [52] 2000	27	18/9	*DSM-IV* BD I, BD II	Paroxetine 36 mg/d *vs.* mood stabilizer (lithium, divalproex)	6	Mood stabilizers	Not defined	Not defined	Not defined	HAMD-17, YMRS
Antidepressant *vs.* antidepressant										
Himmelhoch *et al*, [44]1991	56	34/22	*DSM-III-R* BD I , BD II	Imipramine 100–150 mg/d *vs.* tranylcypromine 20–30 mg/d	6	Not reported	≥ 50% reduction in baseline HAMD score	HAMD ≤ 7 and CGI ≤ 2 from baseline	DSM-III-R	HAMD-17, BDI, CGI
Pilhatsch *et al*, [47] 2010	40	22/18	*DSM-III-R* BD	Paroxetine 20–40 mg/d *vs.* amitriptyline, 75–150 mg/d	6	Lithium	≥ 50% reduction in HAMD-21 score	HAMD21 score of ≤ 8	Not defined	HAMD-21, CGI
Silverstone. [51] 2001	156	65/91	*DSM-III-R* BD	Moclobemide 450 ± 750 mg/d *vs.* imipramine 150 ± 250 mg/d	8	Mood stabilizers	≥ 50% decline in HAMD	HAMD ≤ 10	YMRS ≥ 10	HAMD-17, MADRS, CGI, YMRS

F: Female; M: male; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised; BD: bipolar disorder; BD I: bipolar I disorder, BD II: bipolar II disorder; NOS MD: not otherwise specified, major depression; HAMD: Hamilton Depression Rating Scale; YMRS: Young Mania Rating Scale; MADRS: Montgomery-Asberg Depression Rating Scale; CGI: Clinical Global Impressions scale; SUM-D: Continuous symptom subscales for depression; SAS: Zung's Self-Rating Anxiety Scale; GAF: Global Assessment of Functioning scale.

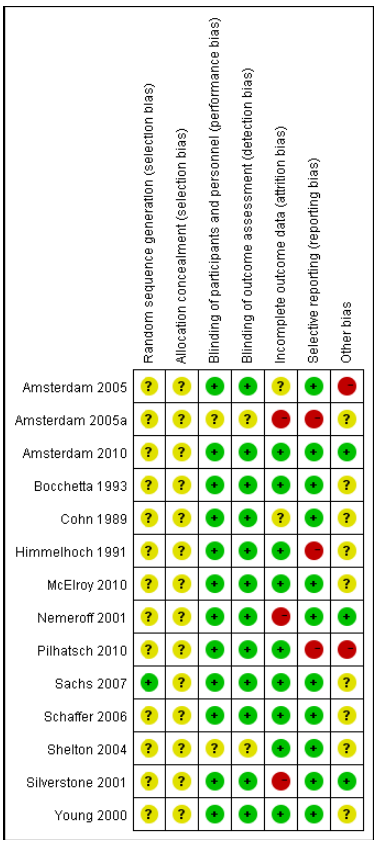


Figure 2 Risk of bias: low risk of bias (+), high risk of bias (–), unclear risk of bias.

Cohn *et al* [43] [*n* = 89, *RR* = 2.90, 95%*CI*: 1.26, 6.69] indicated a benefit for antidepressants, but McElroy *et al* [45] [*n* = 239, *RR* = 1.00; 95%*CI*: 0.70, 1.43] and Nemeroff *et al* [46] [*n* = 117, *RR* = 1.12, 95%*CI*: 0.68, 1.85] did not. The mean dose of antidepressant in the Cohn *et al*'s study[43] (fluoxetine 62 mg/d) was higher than those in the McElroy *et al* [45] (paroxetine 20 mg/d) and Nemeroff *et al*'s studies[46] (paroxetine 32 mg/d), which may contribute to the heterogeneity of the data.

Excluding Cohn's study, the results were no longer heterogeneous, but the effect was equivocal [two randomized controlled trials, *n* = 356, *RR* = 1.04; 95%*CI*: 0.78, 1.39, *P* = 0.79]. Additionally, long-term data was equivocal between antidepressant and placebo [one randomized control trial, *n* = 366, *RR*= 0.85; 95%*CI*: 0.65, 1.13, *P* = 0.27][48] (Figure 3).

Clinical remission: In four studies[39-41, 46], remission was defined as the HAMD total score ≤ 7 or 9. One study[45] defined remission as the MADRS total score ≤ 12. One study[48] defined remission according to DSM-IV. Antidepressant medications did not offer statistical benefits when compared with placebo in the short-term phase [two randomized controlled trials, *n* = 356, *RR* = 0.94, 95%*CI*: 0.71, 1.23, *P* = 0.64][45-46] and in the long-term phase [one randomized controlled trial; *n* = 366, *RR* = 0.86, 95%*CI*: 0.60, 1.22, *P* = 0.40][48] (Figure 3).

Switching to mania: Four studies[39-41, 48] had defined switching to mania as DSM-III-R mania or hypomania, or a score ≥ 8 on YMRS, or HAMD ≥ 14. There was no significant difference in an increased risk of switching to mania [four randomized controlled trials, *n* = 462, *RR* = 1.06, 95%*CI*: 0.63, 1.78, *P* = 0.84][40, 43, 45-46]. Long-term data also failed to show a significant difference [three randomized controlled trials, *n* = 433, *RR* = 0.81, 95%*CI*: 0.50, 1.32, *P* = 0.40][39, 41, 48] (Figure 3).

Tolerability: Patients receiving short-term antidepressant treatment were slightly less likely to drop out compared with those receiving long-term treatment, but the effect did not show a significant difference [three randomized controlled trials, *n* = 445, *RR* = 0.78, 95%*CI*: 0.61,1.00, *P* = 0.05][43, 45-46]. The discontinuation rate was 30.6% in the antidepressant group, and 40.4% in the placebo group. Long-term data did not show a significant difference [two randomized controlled trials, *n* = 421, *RR* = 1.41, 95%*CI*: 0.97, 2.05, *P* = 0.07][41, 48]. There was no significant difference in an increased risk of relapse depression during long-term treatment between the antidepressant and placebo groups [two randomized controlled trials, *n* = 67, *RR* = 0.61, 95%*CI*: 0.37, 1.02, *P* = 0.06][39, 41].

Suicidality: Suicidality occurred in two out of 118 patients who received short-term antidepressant treatment and in three out of 121 patients who received short-term other medications. There was no significant difference in suicidality between antideprassant group and placebo group [one randomized con-trolled trial, *n* = 239, *RR* = 0.68, *CI*: 0.12, 4.02, *P* = 0.67][45]. Long-term data also failed to show a significant difference [one randomized controlled trial, *n* = 366, *RR* = 0.84, 95% *CI*: 0.23, 3.06, *P* = 0.79][48], with suicidality occurring in four out of 179 patients who received antidepressant therapy and in five out of 187 patients who received placebo therapy.

Antidepressant versus other medications

There were no double-blind randomized controlled trials that provided data regarding long-term use of antidepressants versus other antipsychotics.

Clinical response: In two trials[42, 50], response was defined as at least a 50% reduction in baseline HAMD.

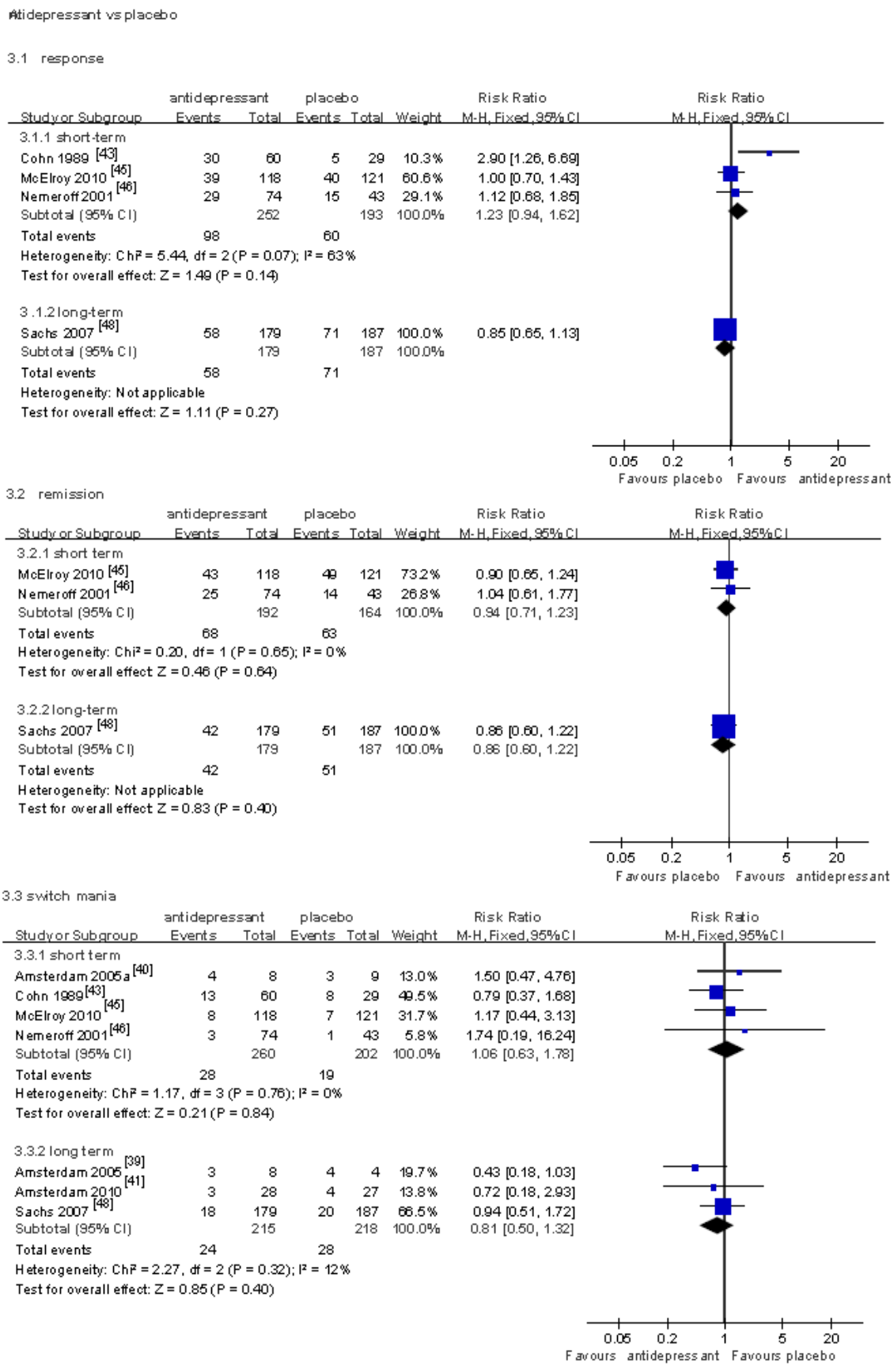
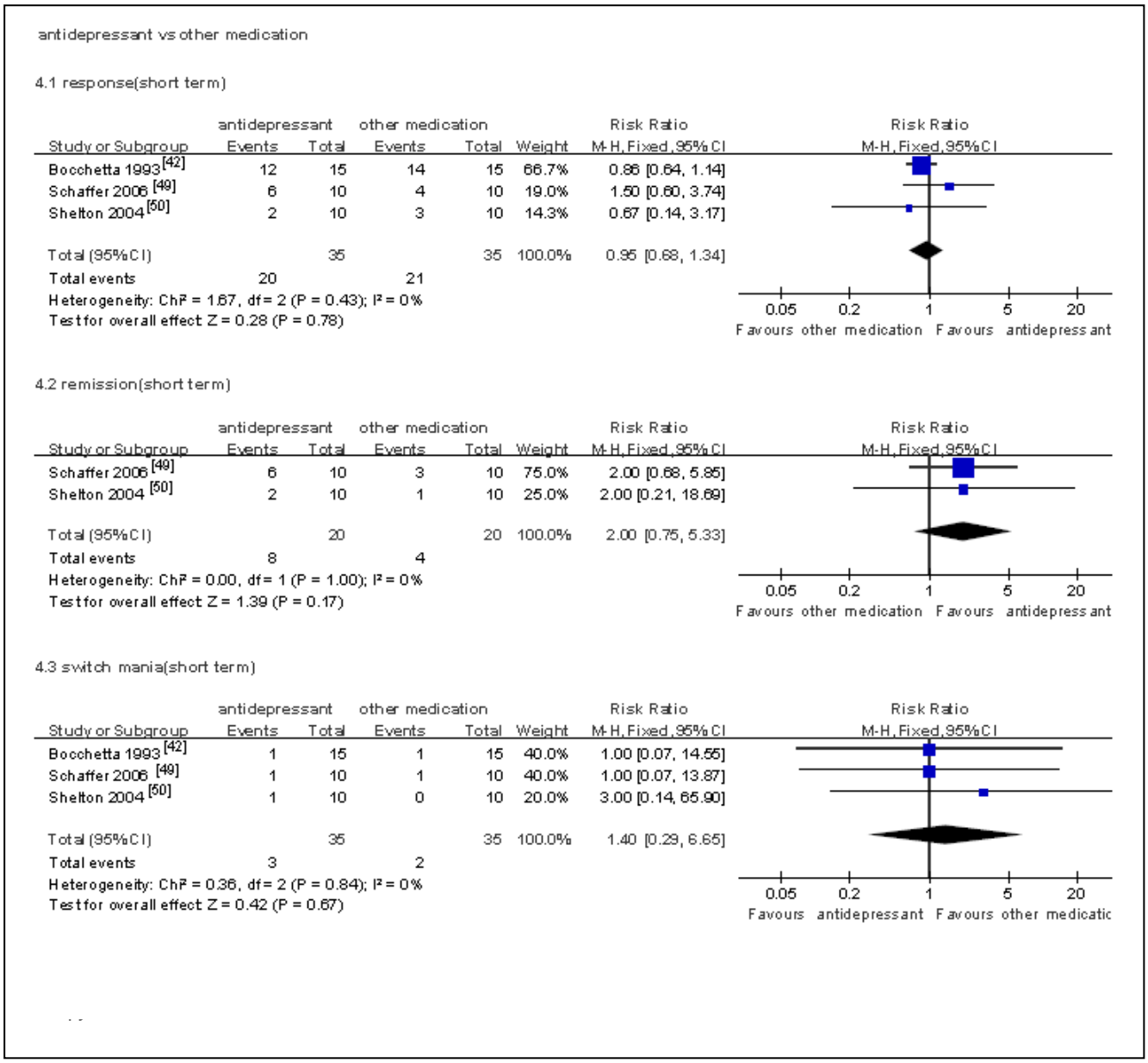


Figure 3 Clinical response, remission, and switching to mania in patients with bipolar disorder who received antidepressant *versus* placebo treatment.



In one study[49], it was defined as at least a 50% reduction in MADRS. There was no significant difference in effect size between short-term antidepressant treatment and other medication treatments [three randomized controlled trials, *n* = 70, *RR* = 0.95, 95%*CI*: 0.68, 1.34, *P* = 0.78][42, 49-50] (Figure 4).

Clinical remission: There was no significant difference in clinical remission between short-term antidepressant treatment and other medication treatments [two randomized controlled trials, *n* = 40, *RR* = 2.00, 95%*CI*: 0.75, 5.33, *P* = 0.17][49-50] (Figure 4).

Switching to mania: There was no significant difference in an increased risk of switching to a manic episode between short-term antidepressant treatment and other medication treatments [three randomized controlled trials, *n* = 70, *RR* = 1.40, 95%*CI*: 0.29, 6.65, *P* = 0.67][42, 49-50] (Figure 4).

Tolerability: The rate of discontinuation was 19.6% in the antidepressant group and 27.5% in the other medication group. The antidepressants did not cause significantly more discontinuation rates than other medications [four randomized controlled trials, *n* = 97, *RR* = 0.73, 95%*CI*: 0.35, 1.50, *P* = 0.39][42, 49-50, 52]. The incidences of relapse were equal between short-term antidepressant treatment and other medications [one randomized controlled trial, *n* = 20, *RR* = 0.50, 95%*CI*: 0.12, 2.14, *P* = 0.35][49], being 20.0% and 40.0%, respectively.

Suicidality: There were no studies in which data on suicidality were described between antidepressant treatment and other medications.

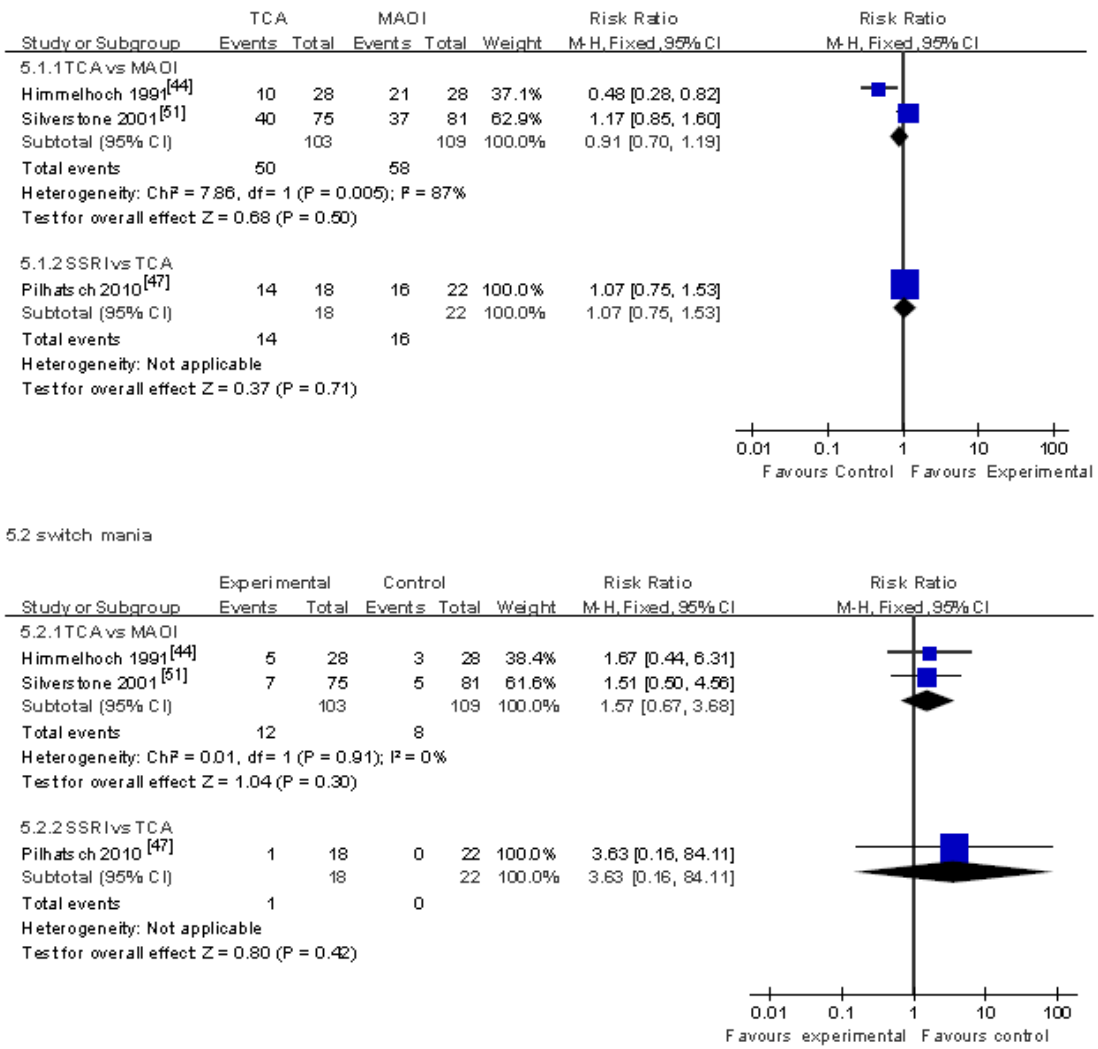


Figure 5 Clinical response and switching to mania in patients with bipolar disorder who received antidepressant treatment *versus* antidepressant treatment.

Antidepressant versus antidepressant

Clinical response: There was no difference in clinical response between TCAs and monoamine oxidase inhibitors (MAOIs) [two randomized controlled trials, *n* = 212, *RR* = 0.91, 95%*CI*: 0.70, 1.19, *P* = 0.50][44, 51], with significant heterogeneity (*P* = 0.005, I^2 = 87%). A suitable interpretation had not been found for the cause of this heterogeneity. There was no significant difference in effect of response rate between SSRI and TCA groups [one randomized controlled trial, *n* = 40, *RR* = 1.07, 95%*CI*: 0.75, 1.53, *P* = 0.71][47] (Figure 5).

Clinical remission: There were no short-term or long-term studies in which data on clinical remission were described.

Switching to mania: There was no evidence of an increased risk of switching to a manic episode between TCA and MAOI treatments [two randomized controlled trials, *n* = 212, *RR* = 1.57, 95%*CI*: 0.67, 3.68, *P* = 0.30][44, 51], and the same effect was observed in SSRI and TCA treatments [one randomized controlled trial, *n* = 40, *RR* = 3.63, 95%*CI*: 0.16, 84.11, *P* = 0.42][47].The risk of switching to a manic episode was 11.7% for TCA treatment, 7.3% for MAOI treatment, and 5.6% for SSRI treatment (Figure 5).

Tolerability: There was no significant difference in the rate of discontinuation between the TCA group and the MAOI group (26.2% *vs*. 26.6%) [two randomized controlled trials, *n* = 212, *RR* = 1.00, 95%*CI*: 0.64, 1.55, *P* = 0.99][44, 51]. Similarly, one randomized controlled trial found no significant difference in the rate of discontinuation between SSRI and TAC treatments [*n* = 40, *RR* =

2.44, 95%*CI*: 0.50, 11.86, *P* = 0.27][47]. One randomized controlled trial[44] showed that the incidence of relapse was similar between the MAOI group and TCA group [*n* = 56, *RR* = 1.00, 95%*CI*: 0.07, 15.21].

Suicidality: There were no studies in which data on suicidality were described.

Sensitivity analysis

Sensitivity analyses were conducted to examine the influence of pharmaceutically funded or affiliated studies on the estimated treatment effects. Two of the 14 trials were industry funded. Sensitivity analysis on the effects of bipolar subtype, adjunct mood stabilizer was also conducted. When these factors were taken into account, there was no change in the overall profile of estimated treatment effects.

DISCUSSION

In this meta-analysis, we tried to elucidate whether there is evidence for or against the clinical efficacy of antidepressants for the treatment of bipolar disorder, using a meta-analysis approach for double-blind randomized controlled trials. Effectiveness criteria including response, remission, and switching to mania, and safety criteria including discontinuation of the study for any reason, relapse and suicidality, probably reflected the most valuable outcome parameters for clinical practice.

Comparison with previous studies

The data are based on 11 short-term and three long-term double-blind randomized controlled trials published up to December 2012. Our analysis excluded several trials that have been cited in recent reviews[31]. One[53] was the single-blind randomized control trial, two of them[54-55] were trials on anti-depressants in comparison with psychiatrics, and another trial[56] compared bupropion with alpha-2 antagonist idazoxan, which did not meet our included criterion. Three new double-blind randomized controlled trials[41, 45, 47] published from 2009 to 2012 were added.

Antidepressant efficacy

The current study showed that antidepressants were not associated with a significant increase in efficacy compared with placebo or other pharmacologic treatments in the acute and maintenance phase therapy of bipolar disorder. In the current analysis, when we controlled for study design factors known to influence therapy effect, the point estimates indicated a slight, but not significant, benefit of antidepressants over placebo in short-term use regarding response. The present analysis was in line with an earlier meta-analysis by Sidor *et al* [31] that focused on trials of short-term use of antidepressants. In addition, our study did not suggest that remission of long-term antidepressant treatment appeared to be better than long-term placebo or other medication treatments.

Recent studies[19] indicated that second-generation antipsychotics significantly improved depressive symptoms in patients with bipolar disorder and second-generation antipsychotics, and combined with second-generation antidepressants, had an even more robust antidepressant effect. To avoid the risks of intervention bias, we narrowed our study to antidepressant monotherapy or antidepressant combined with mood stabilizer. Two open-label design studies that were excluded from this analysis found that the effect was in favor of antidepressants. Amsterdam and Sbults[57] compared the effectiveness of venlafaxine with lithium monotherapy in 83 patients with bipolar II disorder and found that antidepressant monotherapy was superior to lithium with a similar hypomanic symptom. A large-scale study[58] used olanzapine combined with fluoxetine for the treatment of bipolar disorder and found that fluoxetine was more effective than placebo without an increased risk of switching to mania. Contrary to open-label trails, double-blind randomized controlled trials included in this study failed to confirm the efficacy of short-term and long-term antidepressant treatment for the treatment of bipolar disorder. This suggests that the open-label design introduced a study bias, and future study designs should take methodology bias into account.

In the present analysis, we do not have enough evidence to support that antidepressant treatments yield significantly higher response rate and remission rate than placebo, mood stabilizer, or antipsychotic treatments.

Switching to mania

The classes of antidepressants studied here, mostly SSRIs and TCAs, did not increase the risk of switching. This finding is consistent with another previous study[31]. The rates of switching to mania did not support the belief that switching to mania is a common complication of treatment with antidepressants in bipolar disorder in the short-term spans of 4 to12 weeks or in long-term spans of 26 to 50 weeks. Bond *et al* [59] found that the switch rate for bipolar I disorder was 14% and 7% for bipolar II disorder during antidepressant treatment in the short-term. This result suggests that the reported switch rate can be influenced by the ratio of bipolar II to bipolar I disorder patients included in a study. While the current study failed to separate bipolar II disorder and bipolar I disorder, the interpretation of the findings that anti-

depressants did not increase the risk of switching to mania from the study should be care-fully considered.

Tolerability

There was no significant difference in the risk of discontinuation among patients who received antidepressants, other antipsychotic and placebo treatments in doubleblind randomized controlled trials. The rate of discontinuation was 32% for short-term placebo treatment, which was higher than that reported in open-label trials using active drugs (24%). This difference is possibly attributable to the physician's and patient's perception of treatment effectiveness with the active drugs. Our study indicated that compared with short-term placebo treatment, antidepressant treatment tended to yield a slightly, but not significantly, lower discontinuation rate. Double-blind randomized controlled trials included in this study suggest that the use of antidepressants in the treatment of bipolar disorder did not increase the rate of discontinuation for any reason. In addition, there was no significant difference in relapse rate for mania or depressive episode between patients who received short-term or long-term antidepressant, placebo, and other medication treatments.

Suicidality

Few data exist regarding the risk for suicidality in patients receiving antidepressant treatment. No excessive risks were found among short-term antidepressant treatments. Many studies have suggested that antidepressants could cause a generally increased risk for suicidality in teenagers[60], while a recent review indicated that SSRIs decreased the risk for attempted or completed suicidality among adults[61]. The current meta-analyses are consistent with a Food and Drug Administration (FDA) data analysis that the risk of suicide is not in-creased in adults[62].

Differences between antidepressants

Data from this study are inadequate to definitively favor one antidepressant over another antidepressant, and these data also demonstrated that there was no effect on response and remission between SSRIs, TCAs and MAOIs either in short-term or long-term application. Data from this study showed that although SSRIs have been proposed as an antidepressant in the treatment of bipolar disorder because of their lower switching rate than TCAs or MAOIs, there was no significant difference in an increased risk of switching to a manic episode between SSRI and TCA treatments in patients with bipolar disorder. These findings are consistent with those from previous studies[31-32].

Advantage of this analysis

The major advantage of our analysis is the inclusion of double-blind randomized controlled trials to reduce the risks of study bias and confounding factors that influence interpretation of outcome. The previous study[31-32] has been criticized for methodological shortcomings, because they included trials with a high risk for bias and open-label designs. For the current meta-analysis, we retained more rigid methods and excluded studies with a high risk for bias or open-label designs and limited mixed-treatment comparisons of antidepressants and mood stabilizers or other antipsychotics. Furthermore, whenever possible, we used meta-analyses of head-to-head studies to determine the efficacy.

Limitations

The present study suffers from several limitations. First, the limitations of this study relate largely to the quality of the studies. Many studies reported incomplete descriptions of methodology and few reported on, for example, method of randomization, method of concealment, success, or blinding. It is important to acknowledge that to date there have been relatively few high quality double-blind randomized con-trolled trials published and that methodological limitations often reduce the validity of the extant studies. Second, publication bias is a concern for all meta-analyses. Selective availability of studies with positive results can seriously bias conclusions, particularly when a pharmaceutical company compares two of its own drugs (as in the case of olanzapine and fluoxetine). Third, a small number of studies limit the validity of statistical methods to explore publication bias, such as funnel plots. Fourth, the antidepressants in the study differ to a large extent in the way they affect neurotransmitter physiology, and lumping those into one category can obscure the more favorable effectiveness of individual drugs.

In light of currently available data, there is strong support for future large double-blind randomized controlled trials to elucidate the role of short- and long-term use of antidepressants for the treatment of bipolar I disorder and bipolar II disorder. The roles of second-generation antidepressants combined with second-generation antipsychotics, as well as other combinations of antidepressants with lithium, anticonvulsants, or atypical antipsychotics, especially in longer-term follow-up, should be further evaluated in double-blind randomized controlled trials.

Conlusion

There remains a lack of definitive evidence regarding the efficacy of short-term and long-term antidepressant therapy for the treatment of bipolar disorder. Existing evidence does not warrant choosing an antidepressant as therapy for acute phase or maintenance phase bipolar disorder, although better tolerability and safety of antidepressants have been generally acknowledged.

REFERENCES

[1] Bruffaerts R, Vilagut G, Demyttenaere K, et al. Role of common mental and physical disorders in partial disability around the world. Br J Psychiatry. 2012;200(6):454-461.

[2] Kenneson A, Funderburk JS, Maisto SA. Risk factors for secondary substance use disorders in people with childhood and adoles-cent-onset bipolar disorder: Opportunities for prevention. Compr Psychiatry. in press.

[3] Undurraga J, Baldessarini RJ, Valenti M, et al. Suicidal risk factors in bipolar I and II disorder patients. J Clin Psychiatry. 2012;73(6):778-782.

[4] Grande I, Goikolea JM, de Dios C, et al. Occupational disability in bipolar disorder: analysis of predictors of being on severe disablement benefit (PREBIS study data). Acta Psychiatr Scand. 2013;127(5):403-411.

[5] Ebmeier KP. Managing bipolar disorder in primary care. Practitioner. 2010;254(1729):19-22.

[6] Ketter TA. Diagnostic features, prevalence, and impact of bipolar disorder. J Clin Psychiatry. 2010;71(6):e14.

[7] Ferrari AJ, Saha S, McGrath JJ, et al. Health states for schizophrenia and bipolar disorder within the Global Burden of Disease 2010 Study. Popul Health Metr. 2012; 10(1):16.

[8] Magalhaes PV, Kapczinski F, Nierenberg AA, et al. Illness burden and medical comorbidity in the Systematic Treatment Enhancement Program for Bipolar Disorder. Acta Psychiatr Scand. 2012;125(4):303-308.

[9] Angst J, Gamma A, Bowden CL, et al. Evidence-based definitions of bipolar-I and bipolar-II disorders among 5,635 patients with major depressive episodes in the Bridge Study: validity and comorbidity. Eur Arch Psychiatry Clin Neurosci. in press.

[10] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association. 2000.

[11] Baek JH, Park DY, Choi J, et al. Differences between bipolar I and bipolar II disorders in clinical features, comorbidity, and family history. J Affect Disord. 2011;131(1-3):59-67.

[12] Yatham LN, Fountoulakis KN, Rahman Z, et al. Efficacy of aripiprazole versus placebo as adjuncts to lithium or valproate in relapse prevention of manic or mixed episodes in bipolar I patients stratified by index manic or mixed episode. J Affect Disord. 2013;147(1-3):365-372.

[13] Kemp DE, Hert MD, Rahman Z, et al. Investigation into the long-term metabolic effects of aripiprazole adjunctive to lithium, valproate, or lamotrigine. J Affect Disord. 2013; 148(1):84-91.

[14] Fornaro M, Martino M, De Pasquale C, et al. The argument of antidepressant drugs in the treatment of bipolar depression: mixed evidence or mixed states? Expert Opin Pharmacother. 2012;13(14):2037-2051.

[15] Grof P, Duffy A, Alda M, et al. Lithium response across generations. Acta Psychiatr Scand. 2009;120(5):378-385.

[16] Cipriani A, Rendell J, Geddes JR. Olanzapine in the long-term treatment of bipolar disorder: a systematic review and meta-analysis. J Psychopharmacol. 2010;24(12): 1729-1738.

[17] Sanford M, Keating GM. Quetiapine: a review of its use in the management of bipolar depression. CNS Drugs. 2012; 26(5):435-460.

[18] Fountoulakis KN, Kasper S, Andreassen O, et al. Efficacy of pharmacotherapy in bipolar disorder: a report by the WPA section on pharmacopsychiatry. Eur Arch Psychiatry Clin Neurosci. 2012;262 Suppl 1:1-48.

[19] Citrome L. Olanzapine-fluoxetine combination for the treatment of bipolar depression. Expert Opin Pharmacother. 2011;12(17):2751-2758.

[20] Swartz HA, Thase ME. Pharmacotherapy for the treatment of acute bipolar II depression: current evidence. J Clin Psychiatry. 2011;72(3):356-366.

[21] Frankle W, Perlis R, Deckersbach T, et al. Bipolar depression: relationship between episode length and antidepressant treatment. Psychol Med. 2002;32(8):1417-1423.

[22] Malhi GS, Tanious M, Das P, et al. The science and practice of lithium therapy. Aust N Z J Psychiatry. 2012; 46(3):192-211.

[23] Yatham LN, Kennedy SH, Schaffer A, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. Bipolar Disord. 2009;11(3):225-255.

[24] Amsterdam JD, Wang G, Shults J. Venlafaxine monotherapy in bipolar type II depressed patients unresponsive to prior lithium monotherapy. Acta Psychiatr Scand. 2010; 121(3):201-208.

[25] Amsterdam JD, Luo L, Shults J. Efficacy and mood conversion rate during long-term fluoxetine v. lithium monotherapy in rapid- and non-rapid-cycling bipolar II disorder. Br J Psychiatry. 2013;202(4):301-306.

[26] Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. Bipolar Disord. 2013;15(1):1-44.

[27] Nivoli AM, Colom F, Murru A, et al. New treatment guidelines for acute bipolar depression: a systematic review. J Affect Disord. 2011;129(1-3):14-26.

[28] Musetti L, Del Grande C, Marazziti D, et al. Treatment of bipolar depression. CNS Spectr. 2013:1-11.

[29] Podawiltz A. A review of current bipolar disorder treatment guidelines. J Clin Psychiatry. 2012;73(3):e12.

[30] Walpoth-Niederwanger M, Kemmler G, Grunze H, et al. Treatment patterns in inpatients with bipolar disorder at a psychiatric university hospital over a 9-year period: focus on mood stabilizers. Int Clin Psychopharmacol. 2012; 27(5):256-266.

[31] Sidor MM, Macqueen GM. Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry. 2011;72(2):156-167.

[32] 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.
[33] Wilson M. DSM-III and the transformation of American psychiatry: a history. Am J Psychiatry. 1993;150(3):399- 410.
[34] Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960;23:56-62.
[35] Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429-435.
[36] Kirschenfeld JJ. A community medical education program in Montgomery. J Med Assoc State Ala. 1979;48(9):7-8.
[37] Steinberg M. Interviewers Guide to the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D). Washington, DC: American Psychiatric Press. 1994.
[38] Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.1[updated September 2008]. NewYork: John Wiley & Sons, Inc. 2008.
[39] 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.
[40] Amsterdam JD, Shults J. A-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.
[41] Amsterdam JD, Shults J. Efficacy and safety of long-term fluoxetine versus lithium monotherapy of bipolar II disorder: a randomized, double-blind, placebo-substitution study. Am J Psychiatry. 2010;167(7):792-800.
[42] 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.
[43] 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.
[44] Himmelhoch JM, Thase ME, Mallinger AG, et al. Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry. 1991;148(7):910-916.
[45] McElroy SL, Weisler RH, Chang W, et al. A double-blind, placebo-controlled study of quetiapine and paroxetine as monotherapy in adults with bipolar depression (EMBOLDEN II). J Clin Psychiatry. 2010;71(2):163-174.
[46] 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.
[47] Pilhatsch M, Wolf R, Winter C, et al. Comparison of paroxetine and amitriptyline as adjunct to lithium maintenance therapy in bipolar depression: a reanalysis of a randomized, double-blind study. J Affect Disord. 2010; 126(3):453-457.
[48] 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.
[49] 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; 96(1-2):95-99.
[50] Shelton RC, Stahl SM. Risperidone and paroxetine given singly and in combination for bipolar depression. J Clin Psychiatry. 2004;65(12):1715-1719.
[51] Silverstone T. Moclobemide vs. imipramine in bipolar depression: a multicentre double-blind clinical trial. Acta Psychiatr Scand. 2001;104(2):104-109.
[52] 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.
[53] 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.
[54] Brown EB, McElroy SL, Keck PE Jr, et al. A 7-week, randomized, double-blind trial of olanzapine/fluoxetine combination versus lamotrigine in the treatment of bipolar I depression. J Clin Psychiatry. 2006;67(7):1025-1033.
[55] Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I de-pression. Arch Gen Psychiatry. 2003;60(11):1079-1088.
[56] Grossman F, Potter WZ, Brown EA, et al. A double-blind study comparing idazoxan and bupropion in bipolar depressed patients. J Affect Disord. 1999;56(2-3):237-243.
[57] Amsterdam JD, Shults J. Comparison of short-term venlafaxine versus lithium monotherapy for bipolar II major depressive episode: a randomized open-label study. J Clin Psychopharmacol. 2008;28(2):171-181.
[58] Tamayo JM, Sutton VK, Mattei MA, et al. Effectiveness and safety of the combination of fluoxetine and olanzapine in outpatients with bipolar depression: an open-label, randomized, flexible-dose study in Puerto Rico. J Clin Psychopharmacol. 2009;29(4):358-361.
[59] Bond DJ, Noronha MM, Kauer-Sant”Anna M, et al. Antidepressant-associated mood elevations in bipolar II disorder compared with bipolar I disorder and major depressive disorder: a systematic review and meta-analysis. J Clin Psychiatry. 2008;69(10):1589-1601.
[60] Wagner KD, Asarnow JR, Vitiello B, et al. Out of the black box: treatment of resistant depression in adolescents and the antidepressant controversy. J Child Adolesc Psychopharmacol. 2012;22(1):5-10.
[61] Barbui C, Esposito E, Cipriani A. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. CMAJ. 2009;180(3):291-297.
[62] Valluri S, Zito JM, Safer DJ, et al. Impact of the 2004 Food and Drug Administration pediatric suicidality warning on antidepressant and psychotherapy treatment for new-onset depression. Med Care. 2010;48(11):947-954.

(Reviewed by Gautam B, Haase R, Wang GQ, Li NX)
(Edited by Wang LM, Li CH, Song LP, Liu WJ, Zhao M)