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Research Article

# Lithium Carbonate and Lamotrigine for Treatment of Bipolar Depression: Which is Better? Results from Chinese Data in Meta-Analysis

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## Abstract

**Background:** Bipolar depression and its clinical presentation is a frequent but complex psychiatric disease and is difficult to treat. For the present, Many therapeutic methods are different and contentious. To systematically evaluate the difference in efficacy and safety of Lithium carbonate and lamotrigine for treatment of bipolar depression in China is necessary for psychiatrists.

**Methods:** A meta-analysis was performed of all the literatures germane to estimate the bipolar depressive patients treated with lithium carbonate and lamotrigine. Searches were applied to the following electronic databases in china: Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), WANFANG and Chinese Social Sciences Citation Index (VIP) databases. A total of 7 RCTs were included and their meta-analysis was performed to estimate the bipolar depression patients treated with lithium or lamotrigine randomized controlled trials (RCTs) from 2008 to 2014. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated and the meta-analysis was conducted with Revman4.2 software.

**Results:** A total of 7 RCTs were included for meta-analysis. The results of meta-analysis demonstrated by effective rate, remission rate, depressive symptoms change and side effects between two groups of lithium and lamotrigine for therapy of bipolar depression. The results of meta-analysis demonstrated as following: (1) The effective rate was higher in lamotrigine group than that in lithium group (170/239, 134/233, Z = 3.18, P = 0.001, OR = 1.27, 95%CI = 1.27 ~ 2.77). (2) No difference on full remission rate was found between lamotrigine group and lithium group (64/146, 49/143, Z = 1.68, P = 0.09, OR = 1.51, 95%CI = 0.93~2.45). (3) The depressive scale was lower found in lamotrigine group than that in lithium group (Z = 4.08, P < 0.0001). (4) The dropout rate was similar in lamotrigine group compared to lithium group (18/170, 22/165, Z = 0.79, P = 0.43, OR = 0.76, 95%CI = 0.39~1.49). (5) We also found lamotrigine have more erythra (Z = 2.10, P = 0.04, OR = 5.24, 95%CI = 1.12~24.51) and insomnia (Z = 2.75, P = 0.006, OR = 4.03, 95%CI = 1.49~10.85) than that of lithium, and lamotrigine have less tremble (Z = 2.18, P = 0.03, OR = 0.18, 95%CI = 0.04~0.34) and digestive events (Z = 3.14, P = 0.002, OR = 0.32, 95%CI = 0.16~0.65) than that of lithium. These results show that lithium and lamotrigine are different in some aspects of clinical practice.

**Conclusion:** The results indicate that lamotrigine are better than lithium carbonate in effective rate and improving depressive symptoms, their remission rate and dropout are similar, but side effect are different during treatment of bipolar depression in China. So the selection of lithium and lamotrigine may be prescribed for different bipolar depressive patients. These results also reflects chinese psychiatrist's ideas about treatment for bipolar depression.

***Keywords:*** *Lithium Carbonate; Lamotrigine; Bipolar Depression; Meta-Analysis; Chinese Data*

## Introductions

Bipolar depression and its clinical presentation is a frequent but complex psychiatric disease. Despite the high prevalence and the clinical and economic relevance of bipolar depression, few treatments are proven to be highly and consistently effective. In practice, the treatment of bipolar depression typically includes complex treatment decision-making. The best evidence for a pharmacological treatment exists for quetiapine. Alternatives with limitations are lamotrigine (also in the combination with lithium), carbamazepine and olanzapine [1]. In fact, the mood stabilizers are most important in treatment of bipolar disorder, especially in bipolar depression. Because the effectiveness and recommendation of antidepressants in the treatment of bipolar depression remains controversial. Initially, depressive episodes should been treated with one of the named substances with antidepressant properties. In non-responders, a combination of lithium and lamotrigine, or antidepressants in combination with either lithium, an antiepileptic drug or atypical antipsychotics, may be necessary. If a depressive episode occurs under ongoing mood-stabilizing treatment, combination treatments of different substances, even with antidepressants, can be necessary. In the case of treatment-resistant depressive episodes, complex treatment strategies (combination therapies, MAO inhibitors) should be considered. So the antidepressants in therapy for bipolar depression are not first selection.

Lithium is a first line option in the acute and maintenance treatment of bipolar disorder, and only one drug that can prevent suicide because there is a high suicidal risk among BD affected individuals. But this is not only one ration that lithium was used in bipolar disorder. The lithium of choice in treatment of this disorder with special emphasis on pharmacology, and it have both effectiveness in depression and mania. But lithium is known to interact with many types of drugs used to treat different ailments in humans. This could cause either augmentation or minimization of the therapeutic action, causing secondary undesired effects of the agent. This necessitates a search for other alternatives and/or different combinations to lithium in order to decrease the range of unwanted effects for which it has received discredit. These alternatives should be potent mood stabilizers as monotherapy so as to avoid polypharmacy [2]. But the fact is that polypharmacy for bipolar treatment are more often.

Lamotrigine also is a first line option in the acute and maintenance treatment of bipolar disorder, and only one drug called “mood stabilizer for depression” to used often in bipolar disorder because there is a high prevalence of depression among BD affected individuals [3]. A meta-analytically summarize lamotrigine’s effectiveness and safety in unipolar and bipolar depression and found that lamotrigine outperformed placebo regarding depressive symptoms (studies = 11, n = 713 vs n = 696; SMD = -0.15, 95% CI = -0.27, -0.02, p = 0.02, heterogeneity: p = 0.24) and response (after removing one extreme outlier; RR = 1.42, 95% CI = 1.13-1.78; p = 0.003, heterogeneity: p = 0.08). Conversely, lamotrigine did not differ regarding efficacy on depressive symptoms, response, or remission from lithium, olanzapine+fluoxetine, citalopram, or inositol (studies = 6, n = 306 vs n = 318, p-values = 0.85 - 0.92) [4]. So lamotrigine was superior to placebo in improving unipolar and bipolar depressive symptoms, without causing more frequent adverse effects/discontinuations and did not differ from lithium, olanzapine+fluoxetine, citalopram, or inositol. The lamotrigine was used more and more in treatment of bipolar depression.

How about the difference in efficacy between lithium and lamotrigine in therapy for bipolar depression?. The not only effectiveness difference was found that lamotrigine was better than lithium [5], but also side events difference was found that Lamotrigine and placebo were significantly better tolerated than lithium by a systematic review and network meta-analysis [6]. So we can found that lithium use decreased while lamotrigine use increased in bipolar patients. These changes could not be explained by differences in bipolar subtypes; lithium use decreased in both bipolar type I and type II, and the use of lamotrigine increased in bipolar type II. Some study investigated possible changes in the use of mood stabilizers and antidepressants in Sweden during 2007 - 2013 and found in both bipolar subtypes, lithium use decreased steadily during the study period, while the use of lamotrigine and quetiapine increased. The use of valproate decreased in bipolar II disorder and the use of olanzapine decreased among women. The use of antidepressant remained principally unchanged but increased somewhat in bipolar I disorder [7]. These studies indicated changes in mood stabilizer prescription patterns in bipolar disorder was really and also suggested the difference on efficacy between lithium and lamotrigine was really. So we should must understand chinese psychiatrists ideal about lithium and lamotrigine in treatment for bipolar depression.

## Materials and Methods

This review included randomized controlled trials (both individual and cluster randomisation). We were interested in comparisons of treatment of lithium carbonate and lamotrigine in bipolar depressive patients. The primary outcome of our meta-analysis were full remission rate, effective rate, changes of depressive symptom. While the incidence of adverse effect and dropout rate were the second outcome of our meta-analysis.

### Literature Search and Selection

Searches were applied to the following electronic databases, but only in china: Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), WANFANG and Chinese Social Sciences Citation Index (VIP) databases. The search strategy was based on combinations 'lithium and lamotrigine and bipolar depression or depression episode'. We also modified the terms according to the different databases. Last query was updated on 31 December 2016. References of retrieved articles were cross-searched to identify any studies missed by the electronic search strategies.

### Inclusion criteria

Inclusion criteria for original studies were as follows: 1. The patients involved in trial meet bipolar depression diagnostic criteria in DSM-V or DSM-IV or ICD-10. 2. Trial design was comparing lamotrigine and lithium in treatment for bipolar depression, regardless of randomized, blind, follow up and publication status. 3. The trial included scale use, full remission rate, effective rate and side events. 4. The trial observation must last more 4 weeks.

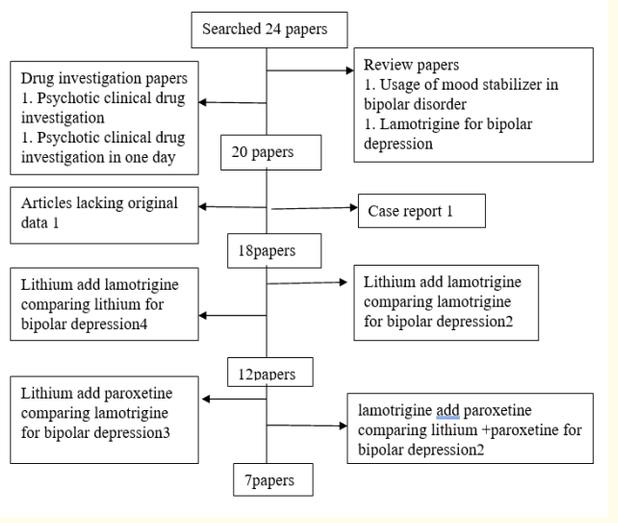
Exclusion criteria for original studies were as follows: 1. When multiple articles were published by the same authors or institutions, the most recent or informative single article was selected. 2. Articles lacking original data for meta-analysis. 3. Review articles. 4. Case report.

### Data extraction

Our initial selection of all candidate articles was relied on careful screening of their abstracts by two independent reviewers, using a standardized data collection form, including the following items: the first author, year of publication, sex, mean or median age, full remission rate, effective rate, dropout rate, the incidence of adverse effect, clinical symptom score, treatment and control group interventions and assessment of outcomes.

We manually searched the reference lists of the some articles. We also screened references from the relevant literature, including all of the identified studies, but no additional reviews and editorials. Disagreements were resolved by consensus between the two readers. In case of persistent disagreement, the final decision was made by our expert.

### Selecting paper process




***Figure***

### Statistical methods

All statistical analyses were performed using Statistical Analysis System software (Revman 5.2), and the P value for the overall effect < 0.05 with two-tailed was considered statistically significant. The heterogeneity of all involved studies was assessed by I2. When it was lower than 50%, the studies with an acceptable heterogeneity were considered, and then the fixed-effects model with Mantel-Haenszel method was used; otherwise, a random effect model with the Der Simonian and Laird (DL) method was adopted. The combined odds ratio (OR) were initially estimated using Forrest plots graphically. For each trial, the OR was estimated from the original article. If not available, we looked at the total numbers of events and the numbers of patients at risk in each group to determine the OR estimate.

The effective rate, symptom changes, dropout rate and side effect rate were the index of this study.

Assessment of publication bias was investigated for each of the pooled study groups mainly by the Egger's linear regression test. As supplement approach, the Begg's rank correlation also was applied to assess the potential publication bias, when P < 0.05 was considered that there was no publication bias in the study.

## Results

### Literature search and eligible studies

7 paper were selected into our study that were published from 2008 to 2014. These papers study design were carried out by randomly, but not double blind [8-14] (See table 1).

| Author | Year | Cases in lamotrigine and dose | | Cases in lithium and dose | | Scale | Time | Random Group | Double Blind |
|---|---|---|---|---|---|---|---|---|---|
| Wu Sheng | 2009 | 36 | 50 - 200 mg | 34 | 500 - 2000 mg | HAMD CGI | 8 Weeks | Yes | No |
| Cong XS | 2011 | 31 | 50 - 250 mg | 31 | 500 - 2000 mg | HAMD CGI | 8 Weeks | Yes | No |
| Li Zhixiang | 2014 | 20 | 100 - 200 mg | 20 | 1000 - 2000 mg | HAMD TESS | 8 Weeks | Yes | No |
| Li Yuming | 2010 | 59 | 100 - 200 mg | 59 | 1000 - 2000 mg | HAMD CGI | 8 Weeks | Yes | No |
| Shi WP | 2008 | 19 | 100 - 150 mg | 18 | 1000 - 2000 mg | HAMD YMRS | 8 Weeks | Yes | No |
| Ma YT | 2008 | 18 | 100 - 200 mg | 16 | 500 - 2000 mg | HAMD CGI | 8 Weeks | Yes | No |
| Zhou JM | 2014 | 50 | 100 - 200 mg | 50 | 1000 - 2000 mg | HAMD CGI | 8 Weeks | Yes | No |

***Table 1:*** *General information of 7 paper.*

### Meta-analysis results

#### Effective rate and full remission rate

These were 7 articles that report effective rate. 170 cases with effectiveness of 239 patients in lamotrigine group and 134 cases with effectiveness of 233 patients in lithium group was found. There was no statistical heterogeneity among the studies ($X^2$ = 12.06, df = 6, P = 0.06, $I^2$ = 50.2%). Thus, the random-effect model was used for statistical analysis. The effective rate was higher in lamotrigine group than that in lithium group (170/239, 134/233, Z = 3.18, P = 0.001) (See figure 1).

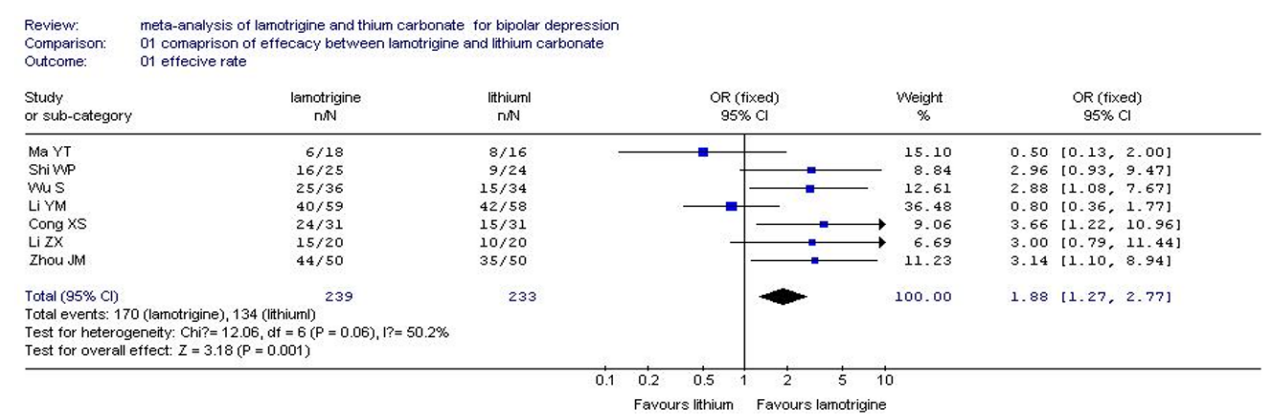



***Figure 1:*** *The effective rate comparison between lamotrigine group and lithium group.*

These were 4 articles that report full remission rate. 64 cases with full remission in lamotrigine group and 49 cases in lithium group was found. There was no statistical heterogeneity among the studies ($X^2$ = 2.55, df = 3,P = 0.06, $I^2$ = 0%). Thus, the fixed-effect model was used for statistical analysis. No difference on full remission rate was found between lamotrigine group than lithium group (64/146, 49/143, Z = 1.68, P = 0.09) (See figure 2).

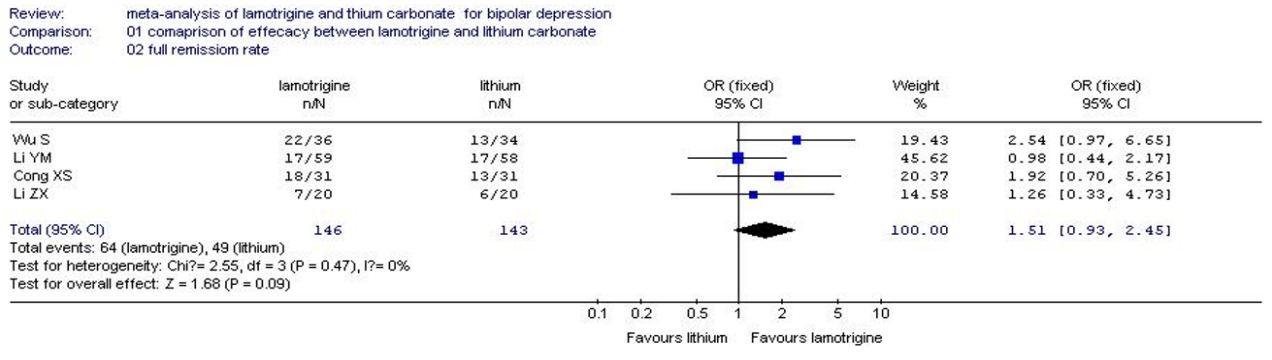



***Figure 2:*** *The full remission rate comparison between lamotrigine group and lithium group.*

**Total changes of symptoms**

We observe 4 weeks depressive symptom changes in our analysis. There was statistical heterogeneity among the studies ($X^2$ = 58.19, df = 19, P < 0.00001, $I^2$ = 67.3%). Thus, the random-effect model was used for statistical analysis. But depressive scale was lower found in lamotrigine group than that in lithium group (Z = 4.08, P < 0.0001) (See figure 3).

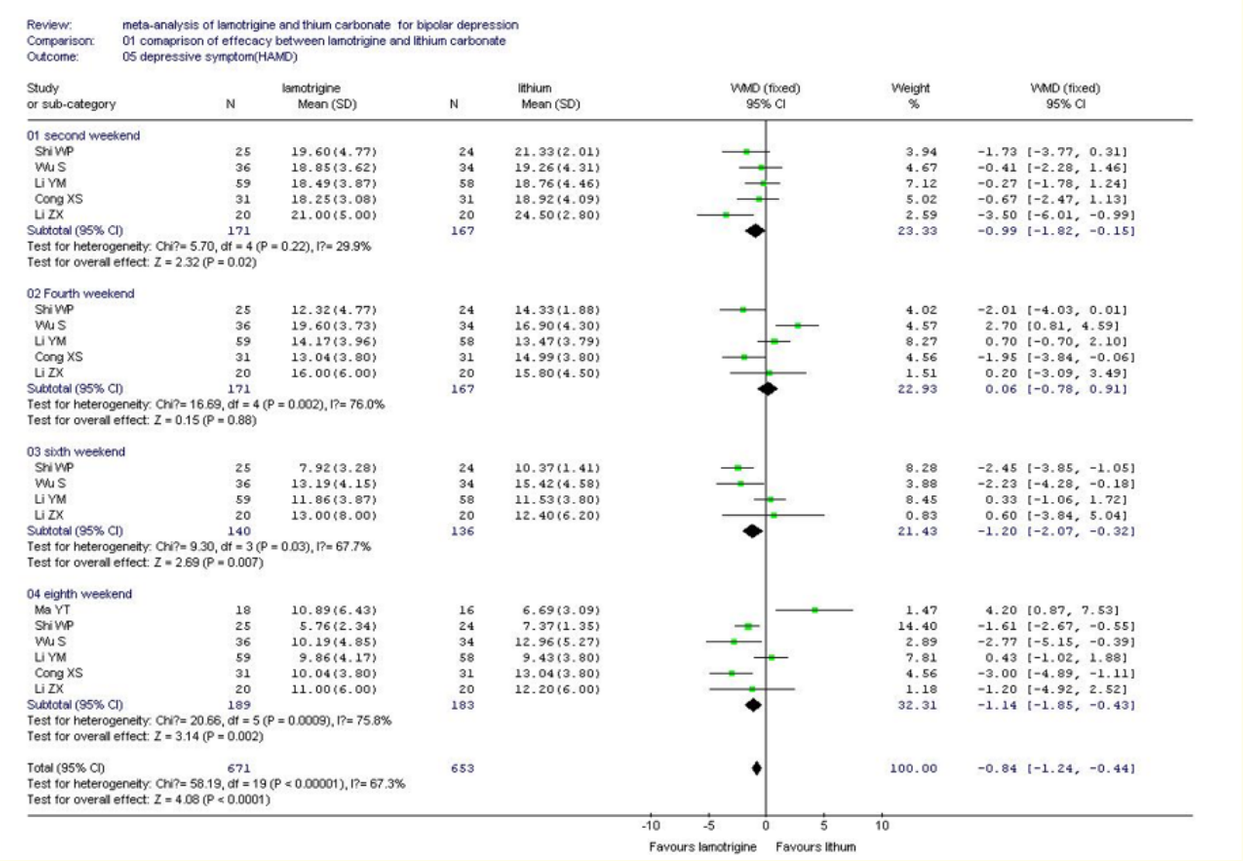



***Figure 3:*** *The depressive scale comparison between lamotrigine group and lithium group.*

**The dropout rate**

These were 5 articles that report dropout rate. 18 cases drop out of 170 patients in lamotrigine group and 22 cases dropout of 165 patients in lithium group was found. There was no statistical heterogeneity among the studies ($X^2 = 4.99$, df = 4, P = 0.29, $I^2 = 19.8\%$). Thus, the fixed-effect model was used for statistical analysis. The dropout rate was similar in lamotrigine group compared to lithium group (18/170, 22/165, Z = 0.79, P = 0.43) (See figure 4).

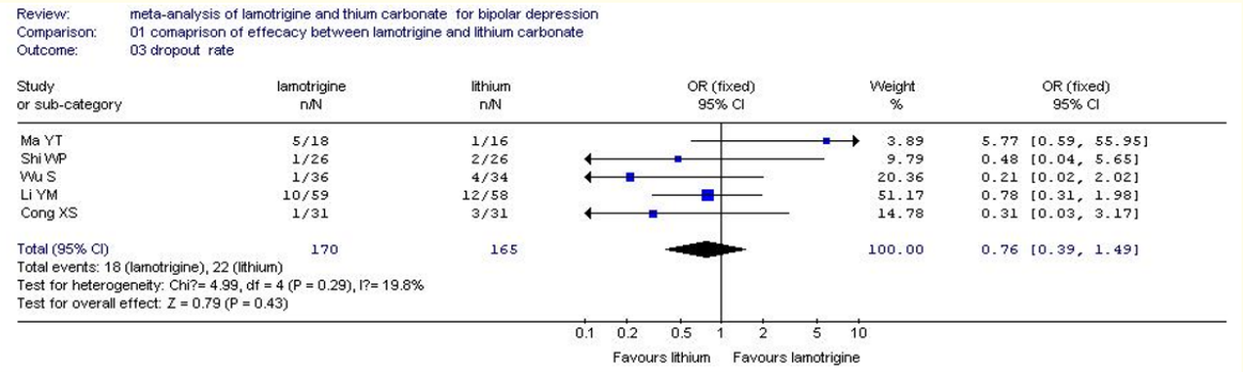



***Figure 4:*** *The dropout rate comparison between lamotrigine group and lithium group.*

**The side events rate**

The 4 side events of erythra, tremble, insomnia and digestive were an anlysed these were 5 articles that report erythra incidence rate. 8 cases with erythra in lamotrigine group and no cases with erythra in lithium group was found. There was no statistical heterogeneity among the studies ($X^2$ = 0, df = 3, P = 0.29, $I^2$ = 0%). Thus, the fixed-effect model was used for statistical analysis. The effective rate was higher in lamotrigine group than that in lithium group (8/164, 0/159, Z = 2.10, P = 0.04) (See figure 5).

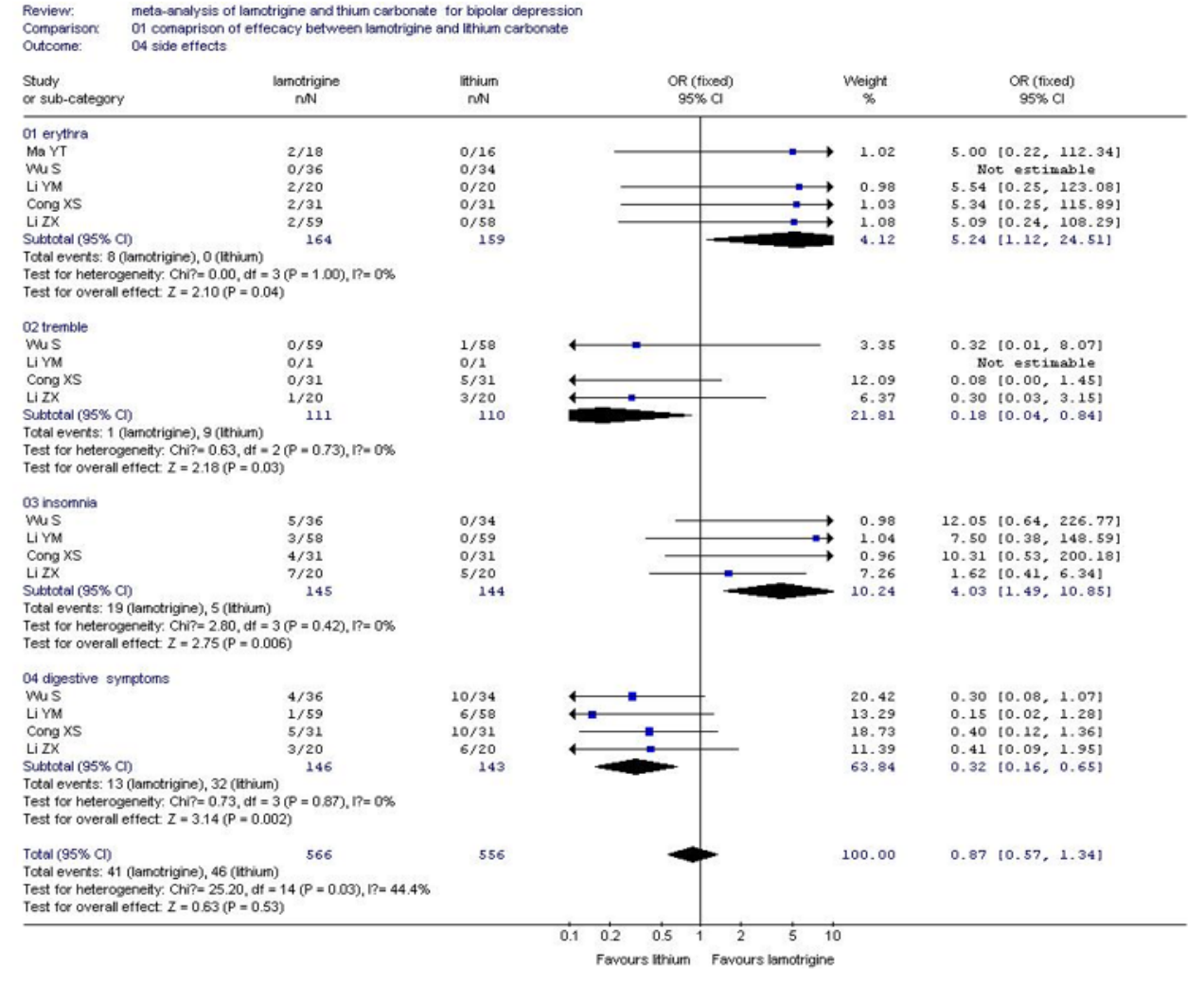



***Figure 5:*** *The side effects comparison between lamotrigine group and lithium group.*

These were 4 articles that report tremble incidence rate. Only 1 case with tremble in lamotrigine group and 9 cases with insomnia in lithium group was found. There was no statistical heterogeneity among the studies ($X^2$ = 0.63, df = 2, P = 0.73, $I^2$ = 0%). Thus, the fixed-effect model was used for statistical analysis. The effective rate was lower in lamotrigine group than that in lithium group (1/111, 9/110, Z = 2.18, P = 0.03) (See figure 5).

These were 5 articles that report insomnia incidence rate. 19 cases with insomnia in lamotrigine group and 5 cases with insomnia in lithium group was found. There was no statistical heterogeneity among the studies ($X^2 = 2.8$, df = 3, P = 0.42, $I^2 = 0\%$). Thus, the fixed-effect model was used for statistical analysis. The effective rate was higher in lamotrigine group than that in lithium group (19/145, 5/144, Z = 2.75, P = 0.006) (See figure 5).

These were 4 articles that report digestive symptoms incidence rate. 13 cases with digestive symptoms in lamotrigine group and 32 cases with digestive symptoms in lithium group was found. There was no statistical heterogeneity among the studies ($X^2 = 0.73$, df = 3, P = 0.87, $I^2 = 0\%$). Thus, the fixed-effect model was used for statistical analysis. The effective rate was lower in lamotrigine group than that in lithium group (13/146, 32/143, Z = 3.14, P = 0.002) (See figure 5).

## Discussion

Recently, mood stabilizers are the first line drugs for treatment of bipolar depression except some atypical antipsychotic. Lamotrigine is one of the mood stabilizers for acute treatment and prevention relapse. The prescription patterns for bipolar disorder are changing [1]. In both bipolar subtypes, lithium use decreased steadily during the study period, while the use of lamotrigine and quetiapine increased. The use of valproate decreased in bipolar II disorder and the use of olanzapine decreased among women. Especially, during the years 2007 - 2011, they found that lithium use decreased while lamotrigine use increased in bipolar patients. These changes could not be explained by differences in bipolar subtypes; lithium use decreased in both bipolar type I and type II, and the use of lamotrigine increased in bipolar type II. Lithium use was more common in men, whereas lamotrigine use was more common in women [7]. Just about lamotrigine and lithium for bipolar depression, increased use of lamotrigine and decreased use of lithium are common in clinical practice. Our results suggest that lamotrigine have higher significant effective rate than that of lithium in bipolar depression (Z = 4.08, P < 0.0001), which maybe one reasons to select lamotrigine than lithium in therapy for bipolar depression.

These results also show that lamotrigine is more effective than that of lithium in improving depressive symptom (Z = 4.08, P < 0.0001). But some result do not support this point. Licht and his colleges directly compared lamotrigine to lithium under conditions similar to clinical routine conditions. They found the crude Hazard Rate Ratio (HRR) (lamotrigine relative to lithium) was 0.92 [95% confidence interval (CI): 0.60 - 1.40] for the primary outcome measure. When the primary endpoints were broken down by polarity, the HRRs (lamotrigine relative to lithium) for mania and depression were, respectively, 1.91 (95% CI: 0.73 - 5.04) and 0.69 (95% CI: 0.41 - 1.22). There was no between-group difference in terms of staying in study [HRR: 0.85 (95% CI: 0.61 - 1.19)]. They find no differences in maintenance effectiveness between lithium and lamotrigine [15]. Miura and their colleagues systematically searched Embase, Medline, PreMedline, PsycINFO, and the Cochrane Central Register of Controlled Trials for randomised controlled trials published before June 28, 2013, that compared active treatments for bipolar disorder (or placebo), either as monotherapy or as add-on treatment, for at least 12 weeks. The primary outcomes were the number of participants with recurrence of any mood episode [6]. They found in view of the efficacy in prevention of both manic episode and depressive episode relapse or recurrence and the better quality of the supporting evidence, lithium should remain the first-line treatment when prescribing a relapse-prevention drug in patients with bipolar disorder. Kessing and their colleagues identified 730 patients who received lamotrigine and 3518 patients received lithium subsequent to a diagnosis of bipolar disorder in psychiatric hospital settings during a period from 1995 to 2006 [5]. The overall rate of switch to or add on of another psychotropic (the opposite drug of interest (lithium or lamotrigine), antidepressants, antipsychotics or other anticonvulsants than lamotrigine) was increased for lamotrigine compared with lithium (HR = 2.60, 95% CI: 2.23 - 3.04), regardless of whether the index episode was depressive, manic, mixed or remission. In addition, the overall rate of psychiatric hospitalization was increased for lamotrigine compared with lithium (HR = 1.45, 95% CI: 1.28 - 1.65), as were the rates for patients with a depressive (HR = 1.31, 95% CI: 1.01 - 1.70) and patients with a manic (HR = 1.65, 95% CI: 1.31 - 2.09) index episode. Rates did not differ significantly between the drugs for patients with a mixed index episode and for patients in remission. It is concluded that in daily clinical practice, treatment with lithium is in general superior to treatment with

lamotrigine. These results at least suggest two aspects that we should attention. One is the difference in effectiveness between lamotrigine and lithium should be assessed carefully. Other is therapy decision should attention to prevention and relapse. In fact our result also show no difference in full remission rate between lamotrigine and lithium (64/146, 49/143, Z = 1.68, P = 0.09).

Hoshmand (2013) found the trends in pharmacotherapy in patients referred to a bipolar specialty clinic during 2000 - 2011 by assessing mood stabilizer (MS) and second-generation antipsychotic (SGA) prescribing trends in bipolar disorder (BD) outpatients referred to a bipolar disorder specialty clinic over the past 12 years [16]. Among 597 BD patients, lamotrigine, quetiapine, and aripiprazole usage more than doubled, from 14.7% to 37.2% ($p < 0.0001$), 7.2% to 19.7% ($p < 0.0001$), and 3.1% to 10.9% ($p = 0.0003$), respectively, while olanzapine and risperidone use decreased by more than half from 15.0% to 6.6% ($p = 0.0043$), and from 8.7% to 3.8% ($p = 0.039$), respectively. SGA use increased from 34.1% to 44.8% ($p = 0.013$), although MS use continued to be more common (in 65.2% for 2006 - 2011). Use of other individual MSs and SGAs and MSs as a class did not change significantly. It means that lamotrigine increased in treatment for bipolar disorder, especially bipolar depression among mood stabilizers. So olanzapine-fluoxetine combination (OFC), quetiapine, and lurasidone are FDA-approved treatment options in bipolar depression, and evidence also supports lamotrigine with compelling evidence as an adjunct to lithium and in recurrence prevention paradigm [16]. Mauer (2014) investigate and found among the 186 subjects enrolled in the International Mood Network (IMN), a majority of subjects were prescribed mood stabilizers including lithium (64%), lamotrigine (37%), valproate (31%), and carbamazepine (3%), which suggest our selection maybe pay attention to personal [17].

The different mood stabilizer have different side effects. The side effects of lithium, valproate, carbamazepine, and lamotrigine related to neurological, gastrointestinal, metabolic, thyroid, dermatological, nephrogenic, cognitive, sexual, hematological, hepatogenic, and teratogenic events. The lithium-treated patients reported diarrhea, tremor, polyuria, and thirst more frequently [15]. Lamotrigine has not been approved for adolescents, but some studies suggest its efficacy for bipolar depression (often a treatment-resistant phase) in this age group. Major side effects are the risk of Lyell or Stevens-Johnsons syndrome (which usually occur within the first eight weeks of treatment). There is no need for biological tests, just clinical monitoring. Pharmacological interactions between lamotrigine and oral contraceptives require caution [18]. Most of those can be transient or dose-related and can be managed by optimizing drug doses to the lowest effective dose. Some rare adverse effects (AEs) can be serious and potentially lethal, and require abrupt discontinuation of medication [19]. In our study, we found lamotrigine have more erythra (Z = 2.10, P = 0.04) and insomnia (Z = 2.75, P = 0.006) than that of lithium, and lithium have more tremble (Z = 2.18, P = 0.03) and digestive events (Z = 3.14, P = 0.002) than that of lamotrigine. All AEs can be managed by striving for the lowest possible dose without losing efficacy by lowering the dose below the therapeutic window [20]. But the erythra induced by lamotrigine should be managed in short time by discontinued drug, because it maybe develop to Lyell or Stevens-Johnsons syndrome, all though lamotrigine was better tolerated than lithium [15].

Licht also found most treatment failures occurred within the first 1.5 years of treatment, and, among patients followed for at least five years, practically no patients were maintained successfully on monotherapy with either of the drugs [15]. It suggested that bipolar patients did not have better drug adhere. Our study did not found the difference in dropout rate between two drugs (Z = 0.79, P = 0.43), all though their dropout rate about 10%.

The differences between lithium and lamotrigine was found. These difference may be related to the their mechanism Lithium's specific mechanism of action in mood regulation is progressively being clarified, such as the direct inhibition on glycogen synthase kinase 3β, and its various effects on neurotrophic factors, neurotransmitters, oxidative metabolism, apoptosis, second messenger systems [2]. The lamotrigine's exact mechanism of action remains unclear. The current study investigated whether lamotrigine might exert its effects through altering the expression of the serotonin transporter (5-HTT) gene and its regulatory transcription factors Y box binding protein 1 (YB-1) and CCCTC-binding factor (CTCF) [3].

Several limitations of the current studies could not be ignored. First, although we don't detect significant publication bias between studies, it is uncertain whether the cases are comparably representative. We attempt to minimise publication bias by making our literature search as complete as possible, however we could not account for unpublished studies, and missing information may reflect "negative" or more conservative outcomes, which represent potential selection bias. Second, most of the included studies are small and without formal sample size calculation. The results were likely to be underpowered. Third, in relapse rate and the incidence of adverse effect were grouped together for analysis. Fourth, the published papers we searched limited only in Chinese mainland. Fifth, the soft mare we used is RenMan4 rather than RenMan5. Sixth, we did not report the sensitiveness. We did not sufficiently assessment the bias.

However, this conclusion should be interpreted cautiously since this analysis was ideally be performed on individual patient data. Further investigation into this subset of patients from other RCTs should pay more attention to the use and description of blinding and allocation concealment. The results should be in accordance with international requirements of the CONSORT statement to conduct a comprehensive specification of the report. In the similar circumstances of safety and efficacy, the economic evaluation is an important indicator to determine the selection of the scheme in order to provide more evidence for the clinical decision. We are looking forward to more high quality researches in this field, the clinical effect of drugs for bipolar disorder will be more clear.

## Competing Interests

The authors have no proprietary interest in any aspect of the study.

## Acknowledgments

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**Volume 7 Issue 12 December 2018**