Lamotrigine and Lithium Combination for Treatment of Rapid Cycling Bipolar Disorder: Results From Meta-analysis

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Abstract

Objective: to observe effect of combination of lithium and lamotrigine in treatment for Rapid-cycling bipolar disorder(RCBD).

Method: We searched both MEDLINE, EMBASE, Cochrane Library in English and CBM, CNKI, WANFANG and CSSCI in Chinese to find literature from January 1 2000 to December 31, 2020 related to combination of lithium carbonate and lamotrigine for treatment of RCBD.

Results: Five comparison studies, with 265 subjects of 131 cases in study group and 134 cases in control group met the inclusion criteria and were included for the final meta-analysis. The comprehensive analysis show that study group had significant lower score of mental symptoms than that of control group ($Z=2.34$, $P=0.02$) by random model ($X^2=33.02$, $df=7$, $P<0.01$). But these differences only were shown in PANSS ($Z=5.18$, $P<0.01$) and BPRS ($Z=3.08$, $P<0.01$). The no difference in response rate (54.9% vs 45.7% OR=1.47, 95% CI: 0.79~2.73, $Z=1.21$, $P>0.05$), and remission rate (47.9% vs 45.9% OR=1.05, 95% CI: 0.49~2.25, $Z=0.13$, $P>0.05$), were found between two groups. The response rate of lamotrigine and lithium combination was significant higher compare to monotherapy of lithium in patients with no treatment-resistant (82% V 54%, OR=4.26, 95% CI: 1.65~10.99, $Z=3.99$, $P<0.01$) by fixed effect model ($X^2=0.89$, $df=1$, $P>0.05$, $I^2=0\%$).

Conclusion: Combination of lithium and lamotrigine have better improvement of psychotic symptoms and higher response rate in patients of RCBP with no treatment-resistant.

Background

long-term course of bipolar disorder is typified by recurring mood episodes of opposite polarity as well as mixed states. Rapid-cycling bipolar disorder refers to the presence of at least 4 mood episodes in the previous 12 months that meet the criteria for manic, hypomanic, or major depressive episode[1]. The rapid cycling were also conclude ultra-rapid(cycle lengths of days to weeks, including 48-h cycling) and and ultra-ultra-rapid(cycling(cycle lengths up to 24 h) according the cycling speed[2,3,4]. But the course is not clear, and antidepressant maybe a extra induced course[2,5]. Rapid-cycling bipolar disorder (RCBD) has been estimated to affect approximately 20% of patients with bipolar disorders[6]. Patients with RCBD are more likely to demonstrate non-response to traditional mood stabilizers and have a poorer prognosis and an increased risk for suicide compared to those without RCBD[7]. Moreover, frequent comorbidities with substance use disorders pose additional negative impact on the treatment outcomes of patients with RCBD, including a greater risk for treatment nonadherence, more hospitalizations more mood episodes lower rates of remission, 13 and decreased quality of life[6]. So most guide about treatment rapid cycling bipolar disorder all suggest stop and prohibit usage of antidepressant, and suggest combination of mood stabilizer.

Lamotrigine is a mood stabilizer, it 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[8]. 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)[9]. 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.

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 reason that lithium was used in bipolar disorder. The lithium of choice in treatment of this disorder with special emphasis on pharmacology, and it has both effectiveness in depression and mania. These alternatives should be potent mood stabilizers as monotherapy so as to avoid polypharmacy[8]. But the fact is that polypharmacy for bipolar treatment are more often, especially for rapid cycling bipolar disorder.

The concept of double mood stabilizer have been suggested for treatment bipolar disorder[11,12,13]. The clinical therapeutic effect is more than that only one mood stabilizer for patients with bipolar disorder with less interaction between drugs. But this is combination of lithium and valproate, which was more common than that of lithium and lamotrigine. However, lamotrigine is called "mood stabilizer for depression" and also can decrease the switch to mania induced by antidepressant[8,14], which may further strengthen the mood stability of lithium to further improve depression symptom that were less likely to respond to the treatment of single lithium or divalproex. And the study also shown that lamotrigine is superior to placebo in treatment of rapid cycling bipolar disorder[15]. Case report addition of lamotrigine to valproic acid had a successful outcome in a case of rapid-cycling bipolar affective disorder[16]. So their combination may play a role on bipolar disorder, especially on rapid cycling bipolar disorder. This study was that meta-analysis about lamotrigine combining with lithium was used for treatment of rapid cycling bipolar disorder.

Methods

1. Literature retrieval methods:

1.1 This study was performed according to the recommendations of the Moose [17]. Two reviewers independently searched the database. The database includes all Chinese databases: Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), WANFANG and Chinese Social Sciences Citation Index (VIP) databases .

1.2 Search key words: lamotrigine, lithium, bipolar disorder, rapid cycling . Their retrieved relationship is "lamotrigine" and "lithium", and "bipolar disorder" and "rapid cycling."

1.3 The search strategy: The search strategy was based on combinations. To retrieve all articles, we search papers by "lamotrigine and lithium and bipolar disorder (or mood disorder or mania or bipolar depression or depression", And then further screen the papers related by add "rapid cycling". Last query was updated on Jan 1 2000 to Jan 1 2021. References of retrieved articles were cross-searched to identify any studies missed by the electronic search strategies. see Fig. 1.

1.4 Inclusion and Exclusion Criteria

The two researchers reviewed the initial retrieved publications independently. The discrepancy was resolved through discussion by all reviewers. Studies that met the following criteria were included: (1) study about combination of lamotrigine and lithium for treatment of rapid cycling bipolar disorder. (2) study design was combination of lamotrigine and lithium compared to only lithium. (3) there was index of therapeutic effects in study design. However, articles had incomplete or unidentified data were excluded, as well as abstracts, reviews, case reports, letters and duplicate publications.

1.5 Two psychiatrists reviewed each included article independently, using the 11-item checklist that was recommended by the Agency for Healthcare Research and Quality (AHRQ) [18]. An item would be scored '0' if it was answered 'NO' or 'UNCLEAR' whereas '1' will be given to the answer 'YES'. Article quality was assessed as follows: low quality = 0–3; moderate quality = 4–7; high quality = 8–11. Differences in article quality were discussed to reach an agreeable final score. The following information was extracted: first author, publication time, the sample size, study population, assessment tools, and index of therapeutic effects. See table 1 [6,7,19,20,21]. See Table 1.

1.6 Statistic analysis: All statistical analyses were performed using software of 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 I^2 . 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.

1.7 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.

Results

1. Study Characteristic

Five comparison studies, with with 265 subjects of 131 cases in study group and 134 cases in control group, who met the inclusion criteria and were included for the final meta-analysis. Five studies consist of 3 study in Chinese and 2 in English [5,25 ~ 38]. The sample size of the studies ranged from 18 to 40. Assessment tools for therapeutic effectiveness used in the studies are list as follows: PANSS, BPRS, YMRS, MADRS, CGI. The main features of the 5 articles were summarized in Table 1. AHRQ scores suggested that all 5 studies scored at eight as high quality.

2. Comparison of mental symptoms between study and control group.

The scale assessment for mental symptom during treatment were used in 4 studies. The PANSS and BPRS was used in 2 studies, YMRS and MADRS was used in other studies. The subgroup analysis was made for mental symptom due to the different way of assessment. The comprehensive analysis show that study group had significant lower score of mental symptoms than that of control group ($Z = 2.34, P = 0.02$) by random model ($X^2 = 33.02, df = 7, P < 0.01$). But these differences only were shown in PANSS ($Z = 5.18, P < 0.01$) and BPRS ($Z = 3.08, P < 0.01$), not shown in MADRS ($Z = 0.39, P > 0.05$) and YMRS ($Z = 0.94, P > 0.05$). See Fig. 2. But the publishing bias was found by the funnel plot analysis, see Fig. 3.

3. Comparison of response and remission between study group and control group.

4 of the 5 studies with 185 subjects were included for the meta-analysis of response rate, which was 54.9% in study group and 45.7% in control group. The random effect model was used for this analysis ($X^2 = 13.02, df = 3, P < 0.01, I^2 = 77\%$). The no difference in response rate was found between two groups (OR = 1.47, 95% CI: 0.79 ~ 2.73, $Z = 1.21, P > 0.05$). See Fig. 4,

3 of the 5 studies with 145 subjects were included for the meta-analysis of remission rate, which was 47.9% in study group and 45.9% in control group. The random effect model was used for this analysis ($X^2 = 4.42, df = 2, P > 0.05, I^2 = 55\%$). The no difference in remission rate was found between two groups (OR = 1.05, 95% CI: 0.49 ~ 2.25, $Z = 0.13, P > 0.05$). See Fig. 5.

Subgroup meta-analysis for response rate also was made according to treatment-resistant or not. The response rate of lamotrigine and lithium combination was significant higher compare to monotherapy of lithium in patients with no treatment-resistant(82% V 54%,OR = 4.26,95% CI: 1.65 ~ 10.99, Z = 3.99,P < 0.01) by fixed effect model($\chi^2 = 0.89, df = 1, P > 0.05, I^2 = 0\%$).But the response rate of lamotrigine, lithium and valproate combination was not significant higher compare to placebo,lithium and valproate combination in patients with treatment-resistant(21.9% V 36.3%,OR = 0.49,95% CI: 0..19 ~ 1.28, Z = 1.46,P > 0.05) by random effect model($\chi^2 = 3.81, df = 1, P = 0.05, I^2 = 77\%$).See Fig. 6.

Discussion

Rapid-cycling bipolar disorder represents a frequent severe subtype of illness which has been associated with poor response to pharmacological treatment.To our knowledge, this is first meta-analysis of lamotrigine and lithium combination in treatment for RCBd,which conclude 5 studies of only two randomized, parallel-group, placebo-controlled trials to evaluate the efficacy of a triple medication combination in RCBd [6,7] in English and of only three randomized controlled trial in Chinese[19,20,21]. The 2 studies in English are controlled study to evaluate the role of lamotrigine in combination with lithium and divalproex in presentations of RCBd not accompanied by a co-occurring substance use disorder,which in fact are treatment-resistant RCBd.

4 of the 5 studies with 185 subjects were included for the meta-analysis of response rate, which was 54.9% in study group and 45.7% in control group.3 of the 5 studies with 145 subjects were included for the meta-analysis of remission rate, which was 47.9% in study group and 45.9% in control group.There was no difference both in response and remission.But the lamotrigine and lithium combination play role on more improving mental symptoms,especially in psychotic symptom rather than depressive and manic symptom,compared to control group.But subgroup meta-analysis show that lamotrigine and lithium combination had higher response rate compared to monotherapy of lithium in patients with no TR-RCBD.This result also show that lamotrigine and lithium combination can play important role in treatment of RCBd,especially in patient with no-TR-RCBD,which may suggest that the patients with no-TR-RCBD should be treated with lamotrigine and lithium combination.

The controlled study about treatment of RCBd indeed are less.The search returned 206 papers and ultimately 25 papers were selected for review[22]. Only six randomized, controlled trials specifically designed to study a rapid cycling population were found. Most data were derived from post hoc analyses of trials that had included rapid cyclers. The literature find that: (i) most patients with rapid cycling patients perform worse in the follow-up period; (ii) lithium have same efficacy comparable anticonvulsants; (iii) there is inconclusive evidence on the comparative acute or prophylactic efficacy of the combination of anticonvulsants versus anticonvulsant monotherapy; (iv) antipsychotic, such as aripiprazole, olanzapine, and quetiapine are effective against acute bipolar episodes; (v) olanzapine and quetiapine appear to be equally effective to anticonvulsants during acute treatment; (vi) aripiprazole and olanzapine appear promising for the maintenance of response of rapid cyclers; and (vii) presence of rapid cycling might be an association with antidepressant use.According this review and this study result, atypical antipsychotic maybe relative better selection for treatment of RCBd,although lamotrigine and lithium combination show better improvement mental symptoms and higher response in no-TR-RCBD. Other therapeutic was also useful selection,such as Vagus nerve stimulation (VNS)[23],levothyroxine augmentation therapy[24].

According to monotherapy, lamotrigine are similar to lithium in treatment of patients with RCBd in a small sample trial[25].Also according to monotherapy,both lamotrigine and lithium were superior to placebo at prolonging the time to intervention for any mood episode (lamotrigine vs placebo, P = .02; lithium vs placebo, P = .006). Lamotrigine was superior to placebo at prolonging the time to a depressive episode (P = .02). Lithium was superior to placebo at prolonging the time to a manic, hypomanic, or mixed episode (P = .006)[26].It was obvious that study about

combination of lamotrigine and lithium in treatment for RCBP should be carried out. It was pity there were few clinical trials about combination of lamotrigine and lithium in treatment for RCBP. Update now, only the 5 study trial were found. So this meta-analysis was seen as a supplement of few trial. In fact, the combination study was proved to be superior to monotherapy of lithium for RCBP.

This study had several limitations. Firstly, the sample size of this meta-analysis was relatively small. Only 5 studies and 265 subjects were involved. Secondly, collecting data style may influence the result of investigation, for example, different criteria of RCBP can get different response. The different response and remission was found between no TR and TR patients. Thirdly, the dose and level in blood of drug was not cared. Fourth, the side effects related to drug, especially to combination therapy of lamotrigine and lithium. Fifth, not all the studies had blind observation. These factors are partly responsible for the source of pool response and remission rate of the study, also affect us to see the real significance of their combination.

Abbreviations

EMBASE=Excerpta Medical Database

CBM=Chinese Biomedical Database

CNKI=China National Knowledge Infrastructure

CSSCI=Chinese Social Sciences Citation Index (VIP)

YMRS=Yung Manic Rating Scale

BRMS=Beck-Rafaelsdn Mania Rating Scale

SPSS=Statistic product and service solutions

PANSS=positive and negative symptom scale

BPRS=Brief Psychotic Rating Scale

TR=treatment-resistant

RR=relative risk

BD=bipolar disorder

CI=confidence interval

MADRS=Montgomery-Asberg Depression Rating Scale

CGI=Clinical Global Impression

Declarations

1. Ethics approval and consent to participate

Not Available

2. Consent to publication

All authors agree to publish our paper and no conflict in any interests.

3. Availability of data and material.

See Table1

4. Competing interests

There were not any financial and non-financial competing interests.

5. Funding

Not Available

6. Authou's contribution

All authors have read and approved the manuscript

Our authors have different contributions to this article. Dr GZH participated in collection of data and the writing of the article, Dr GZH, Dr LWQ and Dr SFL assessed the quality of researched papers. Dr SD and Dr SFL complete most statistic analysis. All authors reviewed researched whole paper. Prof JWD participated in the design, statistical processing and final revision of the article.

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Table

Table 1

Characteristics of studies included in the meta-analysis

Author(year)	Study design	Experimental group(EG) cases	Drugs of EG	Control group(CG) cases	Drugs of CG	Quality score	Index for Therapeutic Effect
Chen(2006)	Comparison	20	Lithium+ lamotrigine	20	lithium	8	Response rate PANSS,BPRS
Wang(2010)	Comparison	18	Lithium+ Valproate+ lamotrigine	18	Lithium+ Valproate	8	Response rate Remission rate YMRS,MADRS CGI
Kemp(2012)	Comparison	23	Lithium+ Valproate+ lamotrigine	26	Lithium+ Valproate+ Placebo	8	Response rate Remission rate YMRS,MADRS CGI
Cai(2012)	Comparison	30	Lithium+ lamotrigine	30	lithium	8	Response rate Remission rate
Liu(2020)	Comparison	40	Lithium+ lamotrigine	40	lithium	8	PANSS,BPRS
PANSS = positive and negative symptom scale; BPRS = Brief Psychotic Rating Scale, BPRS; YMRS = Yung Manic Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; CGI = Clinical Global Impression							

Figures

Figure 1

Flowchart of selection of studies for inclusion in meta-analysis

Figure 2

Comparison of different mental symptom between study and control group. The comprehensive analysis show that study group had significant lower score of mental symptoms than that of control group($Z=2.34, P=0.02$) by random model($\chi^2=33.02, df=7, P<0.01$). But these differences only were shown in PANSS($Z=5.18, P<0.01$) and BPRS($Z=3.08, P<0.01$), not shown in MADRS($Z=0.39, P>0.05$) and YMRS($Z=0.94, P>0.05$).

Figure 3

The funnel plot analysis of mental symptom The publishing bias was found by the funnel plot analysis.

Figure 4

The comparison of response rate between study and control group. The random effect model was used for this analysis($\chi^2=13.02, df=3, P<0.01, I^2 = 77\%$). The no difference in response rate was found between two groups($OR=1.47, 95\% CI: 0.79\sim2.73, Z=1.21, P>0.05, .$).

Figure 5

The comparison of remission rate between study and control group. 3 of the 5 studies with 145 subjects were included for the meta-analysis of remission rate, which was 47.9% in study group and 45.9% in control group. The random effect model was used for this analysis ($\chi^2=4.42, df=2, P>0.05, I^2 = 55\%$). The no difference in remission rate was found between two groups ($OR=1.05, 95\% CI: 0.49\sim2.25, Z=0.13, P>0.05$).

Figure 6

Subgroup analysis of response between study and control group. Subgroup meta-analysis for response rate also was made according to treatment-resistant or not. The response rate of lamotrigine and lithium combination was significant higher compare to monotherapy of lithium in patients with no treatment-resistant (82% V 54%, $OR=4.26, 95\% CI: 1.65\sim10.99, Z=3.99, P<0.01$) by fixed effect model ($\chi^2=0.89, df=1, P>0.05, I^2 = 0\%$). But the response rate of lamotrigine, lithium and valproate combination was not significant higher compare to placebo, lithium and valproate combination in patients with treatment-resistant (21.9% V 36.3%, $OR=0.49, 95\% CI: 0.19\sim1.28, Z=1.46, P>0.05$) by random effect model ($\chi^2=3.81, df=1, P=0.05, I^2 = 77\%$).