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The Role of Lithium Carbonate in Concept of Double Mood Stabilizer for Treatment of Bipolar Mania

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ABSTRACT

Background: *To systematically evaluate the difference in efficacy of valproate and valproate combination with lithium carbonate for therapy of bipolar mania in China. And to provide evidences for double mood stabilizer in therapy of bipolar disorder.*

Methods: *A meta-analysis was performed of all the literatures germane to estimate the bipolar mania patients treated with valproate combination with lithium and only valproate randomized controlled trials (RCTs) from 2007 to 2014. Odds ratios (ORs) and 95% confidence intervals (CIs) of, effective rate and remission rate were calculated and the meta-analysis was conducted with Revman5.1 software. And symptoms changes and times of relapse were also analyzed by Revman 5.1 software.*

Results: *A total of 5 RCTs were included. The results of meta-analysis demonstrated as following: (1). The effective rate was lower in valproate group than that of valproate combination with lithium group t(24/65vs49/65, Z=4.05, P<0.0001, OR=0.49, 95CI=0.35~0.69). (2). The remission rate was lower in valproate group than that of valproate combination with lithium group (21/100vs45/100, Z=3.62, P<0.0003,. OR=0.31, 95CI=0.17~0.59). (3). The manic scale was lower found in combination group than that in valproate group (Z=6.19, P<0.0001, WMD=-2.07, 95%CI=-2.73~ -1.42). (4). The times of relapse was less found in combination group than that in valproate group, but no statistic significance (Z=1.54, P =0.10, WMD=-1.00, 95%CI=-2.37~ 0.21).*

Conclusion: *The results indicate that valproate combination with lithium was better than valpoate monotherapy in treatment of bipolar disorder. The double mood stabilizer concept should be enlarged for therapeutic ideas in treatment of bipolar disorder.*

Keywords

Valproate, Lithium carbonate, Double mood stabilizer Bipolar mania, Meta-analysis, Chinese data.

Background

The mood stabilizer is usually defined as these drugs which at least have three effects at clinical practice [1]. The first is that these drugs have both therapeutic effectiveness for depression and mania, which was called therapeutic bipolarity. The second is that interrupted switching manic and depressive phase, which means it can prevent depression to mania, from mania to depression and because speed and frequentness of rapid cycling. Third is preventing effect that decrease onset of any mood events, including depression, mania, mixed episode, suicide and also decrease onset

of rapid cycling.

But it is also vague in mechanism in definition of mood stabilizer [2]. Pharmacogenetics of mood stabilizers has provided valuable hints toward the involvement of genes and pathways in modulating response. However, with the exception of lithium, the number of studies is still too sparse to draw definite conclusions. Moreover, the mechanism of action of these drugs has yet to be completely elucidated. At present, mood stabilizer usually include lithium carbonate, and some antiepilepsy drugs, such as valproate, carbarmazepine, Oxcarbazepine, lamotrigine [3].

The mood stabilizer are primary drugs for treatment and prevention of bipolar disorder, which means two aspects. One is that mood stabilizer can be used for any kind of episode, such as depression, mania, mixed, or rapid cycling. Other is that mood stabilizer can be used for any period, such as acute, consolidate and maintain [4].

The guideline for therapy of bipolar disorder also put stress on the usage of mood stabilizer, thought as some antipsychotics more and more important [5]. But mood stabilizer always is the core of all guideline, which refer to all guideline putout the importance of mood stabilizer for bipolar disorder. But about 1/3 bipolar patients belong to resistant-treatment case [6]. So Chinese psychiatrist's putout a new concept of double mood stabilizer [7,8]. Some psychiatrists found double mood stabilizer is more effective than only one mood stabilizer in clinical practice [9-13]. and found no interaction between lithium carbonate and valproater in animal study [14] and clinical study [15]. They summary their theory [16] and report a serious case treated by double mood stabilizer [7] and also introduce this new concept to other psychiatrists [8]. Their meta-analysis also indicated valproate combing lithium is more effective than only lithium in treatment of bipolar disorder [17]. These results suggested double mood stabilizer are better for bipolar disorder. So, they putout treatment indication of double mood stabilizer for bipolar disorder [18].

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 [19]. But the fact is that polypharmacy for bipolar treatment are more often [9-13,17,18]. The double mood stabilizer concept has been put out in the facts which are both of resistant-treatment case and polypharmacy of bipolar disorder [7,8].

The double mood stabilizer often refers to the combination of lithium carbonate and valproate [7,8]. The fact has been proved that valproate combing lithium is more effective than only lithium in treatment of bipolar disorder by clinical study and meta-analysis [9-11,13,17]. The question is the role of lithium carbonate in concept of double mood stabilizer for treatment of bipolar disorder. The meta-analysis of the comparison of lithium carbonate combination with sodium valproate to sodium valproate monotherapy for bipolar disorder in China should been done.

Materials and Methods

This review included randomized controlled trials which were comparisons of adjunctive lithium carbonate with sodium valproate to sodium valproate monotherapy treatment of bipolar manic patients. The primary outcome of our meta-analysis were full remission rate, effective rate, changes of manic symptom and time to relapse. While the incidence of adverse effect and dropout rate were not the 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 of sodium valproate with lithium carbonate treatment to sodium valproate monotherapy of bipolar mania. We also modified the terms according to the different databases. Last query was updated on 31 Des 2018. References of retrieved articles were cross-searched to identify any studies missed by the electronic search strategies. Search terms are bipolar disorder, mood stabilizer, lithium carbonate, valproate.

Inclusion and Exclusion criteria

Inclusion criteria for original studies were as follows: 1. The patients involved in trial meet bipolar mania. 2. Trial design was adjunctive sodium valproate with lithium carbonate comparing to sodium valproate in treatment for bipolar mania, 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. 5. The paper was published in Chinese.

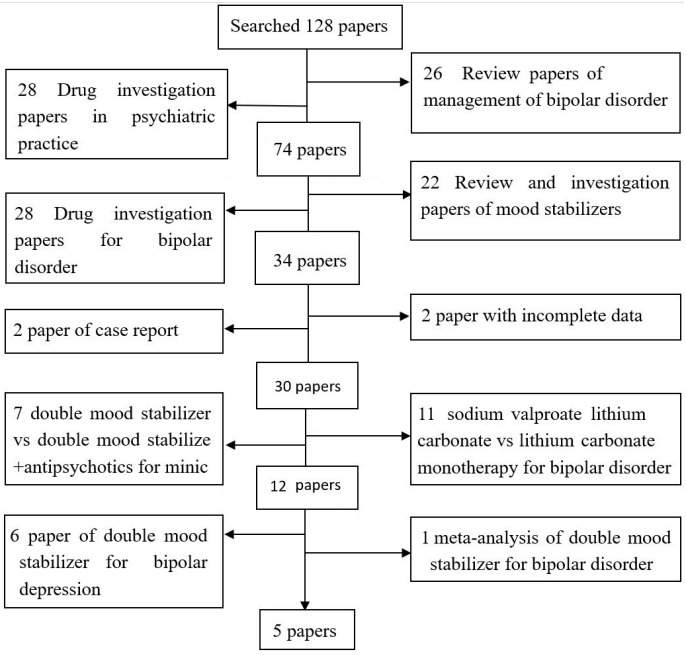
Exclusion criteria for original studies were as follows: 1. when multiple articles were published by the same authors or institutions, the most recent or informative single article was selected. 2.Articles lacking original data for meta-analysis. 3. Review articles. 4. Case report.

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 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



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 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 Sionian and Laird (DL) method was adopted. The combined odds ratio (OR) were initially estimated using Forrest plots raphically. 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.

Results

Materials

5 articles were selected [20-24]. The author studied group, control group, scale, random, blind, follow-up are following as (Table 1).

Effective rate

There were 2 articles report effective rate. 24 cases with effectiveness in valproate group and 49 cases with effectiveness in valproate combining with lithium carbonate group (combination group) was found. There was no statistical heterogeneity among the studies (X^2=1.13, df=1, P=0.29, I^2=12%). Thus, the fixed-effect model was used for statistical analysis. The effective rate was lower in valproate group compared to combination group (24/65vs49/65, Z=4.05, P<0.0001). OR=0.49, 95CI (0.35~0.69)(Figure 1).

Remission rate

There were 3 articles report remission rate. 21 cases with remission in valproate group and 45 cases with remission in combination group was found. There was no statistical heterogeneity among the studies (X^2=0.13, df=2, P=0.93, I^2=0%). Thus, the fixed-effect model was used for statistical analysis. The remission rate was lower in valproate group compared to combination group (21/100vs45/100, Z=3.62, P<0.0003). OR=0.31, 95CI (0.17~0.59) (Figure 2).

Symptom changes

The continuous 6 weeks manic symptom changes in meta-analysis was observed. There was no statistical heterogeneity among the studies (X^2=15.24, df=11, P=0.17, I^2=20%). Thus, the fixed-effect model was used for statistical analysis. But manic scale was lower found in combination group than that in valproate group (Z=6.19, P <0.0001). WMD=-2.07, 95%CI (-2.73~ -1.42) (Figure 3).

Times of relapse

There were 2 articles and 4 index report time of relapse. There was statistical heterogeneity among the studies (X^2=14.52, df=3, P=0.002, I^2=79%). Thus, the random-effect model was used for statistical analysis. The times of relapse was less found in combination group than that in valproate group, but no statistical significance (Z=1.54, P =0.10). WMD=-1.00, 95%CI (-2.37~ 0.21) (Figure 4).

Discussion

Lithium has been used for the treatment of bipolar disorder (BD) for the last sixty or more years, and recent studies with more reliable designs and updated guidelines have recommended lithium to be the treatment of choice for acute manic, mixed and depressive episodes of BD, along with long-term prophylaxis. Bipolar disorder (BD) is a severe and recurrent psychiatric disorder. The severity of prognosis in BD is mainly linked to the high rate of suicide in this population. Indeed, patients with BD commit suicide 20 to 30 times more frequently than the general population, and half of the BD population with an early age of onset have a history of suicide

Author	Studied case	Group drug	Control case	Group drug	Scale	Random	Blind	Followup
Xu (2007)	35	VAL+Li	35	VAL	BRMS	Yes	No	Yes
Weina (2014)	30	VAL+Li	30	VAL	BRMS	Yes	No	Yes
Jin (2014)	31	VAL+Li	31	VAL	BRMS	Yes	No	No
Liu (2013)	34	VAL+Li+APP	34	VAL+APP	BRMS	Yes	No	No
Ma (2010)	34	VAL+Li+APP	35	VAL+APP	BRMS	Yes	No	No

Table 1: General information of studied. VAL = Valproate, Li = Lithium carbonate, APP = Atypical antipsychotics.

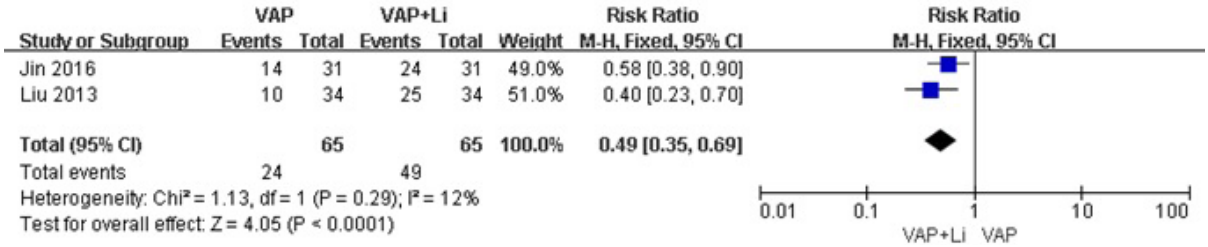


Figure 1: Effective rate between lithium carbonate combination with valproate and valproate monotherapy.

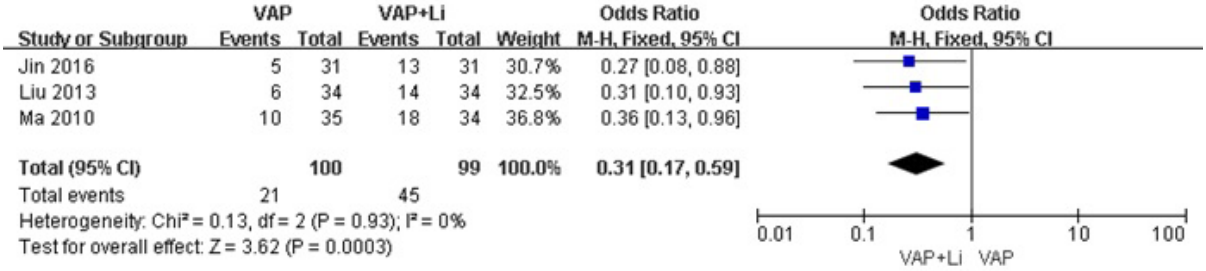


Figure 2: Remission rate between lithium carbonate combination with valproate and valproate monotherapy.

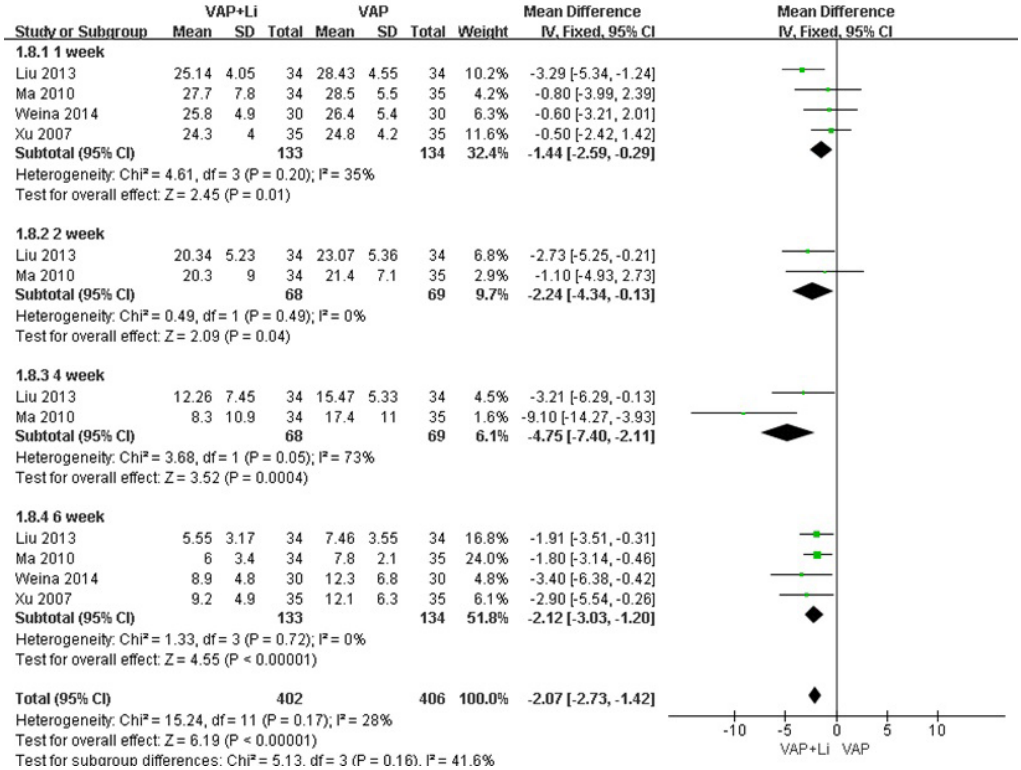


Figure 3: Manic symptoms change between lithium carbonate combination with valproate and valproate monotherapy.

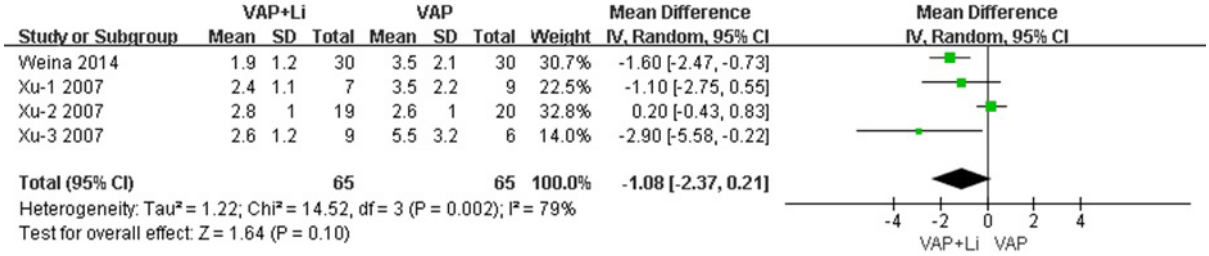


Figure 4: Times of relapse between lithium carbonate combination with valproate and valproate monotherapy. Xu1: (patients=recrudesce mania), Xu2: (patients=bipolar mania), Xu3: (patients=rapid cycling).

attempt. International therapeutic guidelines recommend lithium (Li) as the first-line treatment in BD for its prophylactic action on depressive or manic episodes. In addition, Li is the only mood stabilizer that has demonstrated efficacy in suicide prevention. This effect of Li is unfortunately often unknown to psychiatrists [25]. Self-harm is not only a symptom, but also a prominent cause of morbidity in patients with bipolar disorder and is strongly associated with suicide. There is evolving evidence that lithium use may reduce suicidal behavior, in addition to concerns that the use of anticonvulsants may increase self-harm [26]. Conclusions regarding lithium's antisuicidal effect for bipolar disorder have been limited due to nonrepresentative subjects and potential confounding factors, including varying severity of illness. Findings regarding the effect of valproate, the most common alternative to lithium, are inconsistent for suicidal behavior. They found during follow-up, 10, 648 suicide-related events occurred. The incidence rate was significantly decreased by 14% during lithium treatment (hazard ratio 0.86, 95% confidence interval [CI] 0.78-0.95) but not during valproate treatment (hazard ratio 1.02, 95% CI 0.89-1.15). The difference in hazard ratios of suicide-related events between lithium and valproate was statistically significant. Estimates of the population attributable fraction suggested that 12% (95% CI 4%-20%) of suicide-related events could have been avoided if patients had taken lithium during the entire follow-up. So lithium carbonate maybe a good drug in treatment and prevention [27].

But about 1/3 bipolar patients belong to resistant-treatment case [6]. More stabilizer combination therapy become usually more and more in treatment for bipolar disorder, especially for manic episode. In some especially case, two mood stabilizer and antipsychotics or two antichotics and mood stabilizer were also management for bipolar disorder [7-18]. BALANCE study found 59 (54%) of 110 people in the combination therapy group, 65 (59%) of 110 in the lithium group, and 76 (69%) of 110 in the valproate group had a primary outcome event during follow-up. Hazard ratios for the primary outcome were 0.59 (95% CI 0.42-0.83, p=0.0023) for combination therapy versus valproate, 0.82 (0.58-1.17, p=0.27) for combination therapy versus lithium, and 0.71 (0.51-1.00, p=0.0472) for lithium versus valproate. 16 participants had serious adverse events after randomization: seven receiving valproate monotherapy (three deaths); five lithium monotherapy (two deaths); and four combination therapy (one death). For people with bipolar I disorder, for whom long-term therapy is clinically indicated, both combination therapy with lithium plus valproate and lithium monotherapy are more likely to prevent relapse than is valproate monotherapy. This benefit seems to be irrespective of baseline severity of illness and is maintained for up to 2 years [9]. In clinical practise, Ma also found that combination of lithium and valproate were higher in effective rate andremission rate [12]. These results indicated that lithium carbonate and valproate combination is more effective than valproate monotherapy for therapy of bipolar mania. To assess further role of lithium carbonate in double mood stabilizer concept for treatment of bipolar manic patients, the Chinese data was analyzed.

The results show in 4 aspects. 1. The effective rate was lower in valproate group compared to combination group (24/65vs49/65, Z=4.05, P<0.0001). OR=0.49, 95CI (0.35~0.69).2. The remission rate was lower in valproate group compared to combination group (21/100vs45/100, , Z=3.62, P<0.0003). OR=0.31, 95CI (0.17~0.59). 3. But manic scale was lower found in combination group than that in valproate group (Z=6.19, P <0.0001). WMD=-2.07, 95%CI (-2.73~ -1.42). 4. The times of relapse was less found in combination group than that in valproate group, but no statistical significance (Z=1.54, P =0.10). WMD=-1.00, 95%CI (-2.37~ 0.21). These results show that combination of lithium and valproate were better in improvement of bipolar mania.

The mechanisms of lithium and valproate are similar. The same mechanism may play cooperation. 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, and biological systems are also being revealed. Furthermore, lithium has been proposed to exert its treatment effects through mechanisms associated with neuronal plasticity [28]. In study of effects of lithium and valproate on oxidative stress and behavioral changes induced by administration of methamphetamine (m-AMPH), it was found that hyperactivity was prevented and reverted by Li and VPA only when m-AMPH was administered in the dose of 0.25mg/kg [29]. The further study also found lithium and valproate reversed m-AMPH-induced energetic metabolism dysfunction, however, the effects of lithium and valproate were dependent on the brain region analyzed, which suggested that the decreased Krebs cycle enzymes activity induced by m-AMPH may be inhibiting mitochondrial respiratory chain complexes. Therefore, changes in the Krebs cycle enzymes may also be involved in bipolar disorder. So double mood stabilizer plays a better role than mood stabilizer monotherapy for bipolar disorder.

This study has some deficiency: (1) limitation of literatures: our data not contained articles in English and other language, just in Chinese, and also not contained articles published in Taiwan, Hongkong and Macao. (2) Assessment of articles quality was not done well. (3) The side effects of lithium carbonate and their combination was not estimated. (4). The concentration of lithium and valproate was not analyzed, because mood-dependent changes of serum lithium concentration [30].

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