

How About Effect of Lithium Carbonate on Preventive Switch Induced by Antidepressants in Patients With Depressive Episode? Chinese Data Analysis

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Primary research

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Abstract

Background: Although mania or hypomania was defined as indispensable for bipolar disorder, depressive episodes are more common and impairing, with proven response to treatments. So the prevention switch was an important affair in clinical psychiatry.

Methods: We searched CBM, CNKI, WANFANG and CSSCI in Chinese to find literature from July 1 2000 to July 31 2020 related to the study in model of “comparison of switch rate between combination treatment of lithium and antidepressant and monotherapy of antidepressant in patients with depressive episode”, among which results such as comments, letters, reviews and case reports were excluded. The rate of switch between groups was synthesized and discussed.

Result: A total of 695 subjects were included in 9 studies. Random effect model is used to account for the data by Revman 5.2. The results showed that the switch rate of lithium carbonate was 8.28% (29/350), switch rate of antidepressant was 25.29% (87/344), which was very different in switch rate (OR=0.25, 95% CI: 0.16–0.39) and also indicated that lithium reduced switch rate was 67.25% (25.29%–8.28%/25.29%). In bipolar depression group, lithium reduced switch rate was 68.11% (25.84%–8.24%/25.84%). In depression group, lithium reduced switch rate was 67.34% (25.29%–8.26%/25.29%). In group of patients treated by SSRI, lithium reduced switch rate was 60.3% (29.85%–11.85%/29.85%). In group of patients treated by TCA, lithium reduced switch rate was 73.14% (22.28%–6.01%/22.28%).

Conclusion: As typical mood stabilizer, lithium carbonate can reduce switch rate related to antidepressant in patients with depressive episode.

Background

As a classic mood stabilizer, lithium carbonate can be used in depressive episode for the following reasons. First, lithium carbonate has an obvious action of anti-suicide [1,2], because suicide is an emergency in psychiatric clinic, especially in adolescent bipolar disorder, which always is with trait of suicide [2]. Second, lithium has an anti-depressant role. Taking into account good adherence to drug treatment, in clinical practice settings, long-term lithium salts seem to have a preventive effect on depressive symptoms [3]. Third, lithium can strengthen the role of antidepressant in treatment for depression. This point of view was proven in STAR*D, although more participants discontinued lithium due to adverse effects than discontinued others [4]. Fourth, lithium had the same anti-depressant role as lamotrigine in bipolar depression, and was called “mood stabilizer for depression” and they all are recommended for bipolar depression in the treatment guideline of bipolar disorder [5,6]. So many studies' results are the reasons of lithium in treatment for depressive episode.

Another important reason is that lithium carbonate can prevent switch induced by antidepressant, which is a special phenomenon in the clinical process of psychiatry. This is neither a side effect of the antidepressant [7]. The risk factors associated

switch included age of onset, personality characteristics, family history, type of antidepressants, type of depression, combination without mood stabilizers, previous history, severe suicide attempts, amphetamine use and some combination of pharmacological treatments. During the current depressive episode, the identified risk factors were any possible mood elevation, multiple mania-associated symptoms with at least moderate severity, and comorbid panic attacks.[8,9]. In general, adjunctive antidepressants are associated with reduced symptoms of acute bipolar depression, but the magnitude of benefit is small because they do not increase clinical response or remission rates. However, these medications should be used only in the short term because prolonged use is associated with an increased risk of treatment-emergent mania or hypomania[10]. It had been found switch rate of bipolar depression had very higher than that in "unipolar" depression[11]. Patients with bipolar depression present very heterogeneous responses to the use of ADs. Some improve significantly, while others, especially those with concomitant manic symptoms, have had previous episodes of treatment-emergent mania or are rapid cyclers, exhibit manic switches or cycle acceleration[12]. The one of methods in avoidance switch was use of mood stabilizer, especially lithium carbonate[3,10,11,12].

Mood stabilizer can reduce the risk of developing antidepressant-induced manic form states in acute treatment of bipolar I depressed patients[13]. In 2007, we found that classic mood stabilizer, lithium carbonate can reduced 62% switch rate associated with antidepressant[14]. The following study continuously indicated that lithium carbonate reduced 66.4% switch rate associated with antidepressant by meta-analysis[15]. These results show use of lithium carbonate can reduce the switch in depression, which not all are bipolar depression in China. In recent years, the research has increased about comparison between combination treatment of lithium and antidepressant and monotherapy of antidepressant in patients with depressive episode, in which the switch rate was noticed. The further study is necessary comparing switch rate between combination treatment of lithium and antidepressant and monotherapy of antidepressant in patients with depressive episode by meta-analysis and assessment of prevention about switch rate of lithium in patients with depressive episode.

Methods

1. Literature retrieval methods:

1.1 This study was performed according to the recommendations of the Moose [16]. Two reviewers independently searched the database. The database includes just Chinese databases; Searches were applied to the following Chinese electronic databases: Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), WANFANG and Chinese Social Sciences Citation Index (VIP) databases .

1.2 Search key words: Depression (bipolar depression, depressive episode); lithium carbonate;

1.3 The search strategy: The search strategy was based on combinations. We also modified the terms according to the different databases. To retrieved all articles, we first search papers by "lithium carbonate

and depression”, And then further screen the papers related to lithium carbonate and depression. Last query was updated on late 1 January 2000 to 31 July 2020. References of retrieved articles were cross-searched to identify any studies missed by the electronic search strategies.

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 general criteria were “comparison between combination treatment of lithium and antidepressant and monotherapy of antidepressant in patients with depressive episode”. (1) detection rate of mania or hypomania was reported during study; or (2) detection rate of psychopathology of very irritable or very compulsive to have to change therapeutic plan or treated as drop off cases or (3) cases changed mixed episode from bipolar depression or (4) YMRS or BRMS was higher 11 score. However, articles had incomplete or unidentified data were excluded, as well as abstracts, reviews, case reports, letters and duplicate publications.

1.5 Switch detection criteria: (1) The direct rate of drop off in study was due to shift of exciting or hypomania or mania. (2) The detection rate of or cases of switch was reported directly in study. (3) The rate of changing therapeutic plan was due to psychopathology of mania or hypomania or very irritable or very compulsive. (4) The the case numbers of study patients with higher 11 score of YMRS or FMRS . (5) The cases were reported in study, which became mixed episode from bipolar depression.

1.6 Two psychiatrists reviewed each included article independently, using the 11-item checklist that was recommended by the Agency for Healthcare Research and Quality (AHRQ) [16]. 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 the number of people who had anxiety and depression, yes or no comparison.

1.7 Statistic analysis: 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 Simonian 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.

1.8 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

Results

1. Study Characteristic

Nine comparison studies, with 695 subjects, met the inclusion criteria and were included for the final meta-analysis[17,18,19,20,21,22,23,24,25]. The 695 subjects consist of 351 cases in experimental group and 344 cases in control group. The sample size of the studies ranged from 44 to 105. The years of nine studies are from 2001 to 2015. 117 cases switch from depression to mania in total.

2. Comparison of switch rate between experimental group and control group.

A total of 695 subjects were included in 9 studies. Random effect model is used to account for the data by Revman 5.2. The results showed that the switch rate of lithium carbonate was 8.28%(29/350), switch rate of antidepressant was 25.29%(87/344), which was very different in switch rate(OR=0.25 ,95% CI: 0.16–0.39). The switch rate in experimental group was significantly lower than in that in control group (Z=5.9,P<0.00001). And it also indicated that lithium reduced switch rate was 67.25%(25.29%-8.28%/25.29%). See figure2.

The funnel plot analysis of study about switch rate show a gap, which indicate there maybe a bias of publication. see figure3. But the Eggers *publication bias test* (P = 0.16) and *Begg's publication bias test* (P=0.62) all show there not were publication bias. see figure4 and figure5.

3. Subgroup comparison of switch rate

3.1 Subgroup comparison of switch rate according to type of depression.

A total of 186 bipolar subjects were included in 3 studies. Random effect model is used to account for the data by Revman 5.2. The results showed that the switch rate of lithium carbonate group was 8.25% (8/97), switch rate of antidepressant group was 25.84%(23/89) in bipolar patients, which was very different in switch rate(OR=0.24 ,95% CI: 0.10–0.58). The switch rate in experimental group was significantly lower than in that in control group (Z=3.19,P=0.001). In bipolar depression group, lithium reduced switch rate was 68.11%(25.84%-8.24%/25.84%). See figure6.

A total of 509 unipolar subjects were included in 6 studies. Random effect model is used to account for the data by Revman 5.2. The results showed that the switch rate of lithium carbonate group was 8.26% (21/254), switch rate of antidepressant group was 25.09%(64/255) in unipolar patients, which was very different in switch rate(OR=0.25 ,95% CI: 0.15–0.43). The switch rate in experimental group was significantly lower than in that in control group (Z=4.96,P<0.0001). In depression group, lithium reduced switch rate was 67.07%(25.09%-8.26%/25.09%). See figure6.

3.2 Subgroup comparison of switch rate according to type of antidepressant.

A total of 426 subjects were included in 5 studies according to TCA treatment study. Random effect Loading [MathJax]/jax/output/CommonHTML/fonts/TeX/fontdata.js results showed that the switch rate of lithium

carbonate group was 6.01%(13/216),switch rate of antidepressant group was 22.38%(47/210) , which was very different in switch rate(OR=0.20 ,95% CI: 0.10–0.40).The switch rate in experimental group was significantly lower than that in control group (Z=4.66,P<0.00001). Lithium reduced switch rate was 73.14%(22.38%-6.01%/22.38%) in patients treated with TCA. See figure7.

A total of 269 subjects were included in 4 studies according to SSRI treatment study. Random effect model is used to account for the data by Revman 5.2. The results showed that the switch rate of lithium carbonate group was 11.85%(16/135),switch rate of antidepressant group was 29.85%(40/134), which was very different in switch rate(OR=0.30 ,95% CI: 0.16–0.58).The switch rate in experimental group was significantly lower than that in control group (Z=3.62,P=0.0003). Lithium reduced switch rate was 60.30% (29.85%-11.85%/29.85%). See figure7.

Discussion

Lithium has been an intriguing treatment option in psychiatry for over a century. While seemingly just a simple elemental compound, it has powerful treatment effects for both depression and bipolar disorder. Lithium is still one of few drugs that have been proven to reduce the risk of suicidality and prevention for depressive symptoms, and it may have utility in illnesses beyond affective disorders in recent years[2,3]. Practically, as a primary agent or as an adjunct, lithium continues to claim a rightful place in the treatment for adjunctive for depression[17,18,19,20,21,22].In China,many studies have proven that lithium carbonate combination with antidepressant is more effective than that monotherapy by antidepressant in management of depression,especially in irritability,compulsive behavior[17-22].

The certain number of depressive patients switch to mania or exciting status during treatment by antidepressant,of which could be diagnosed by criteria of bipolar disorder in DSM-5[26].But this is not successful therapeutic plan for patient duo to switch,because it induce the mania ahead[7].So avoiding switch to mania is important part of therapeutic plan,whereas the patients is unipolar or bipolar depression.In general ,four status indicate the patients come into switch.First is mania or hypomania.Second is primary rapid cycle become acceleration,Third is obvious and serious behavior of irritability,compulsive,agitated behavior to have to change manege methods during treatment,Fourth is antidepressant induced chronic irritability(AICD)[8]. These all indicate the patients switch to mania,which suggest that the therapeutic plan should be changed.

To recognize the risk of switch was one of prevention methods before treatment[8,9].And therapeutic drug was also very important. In Cox proportional hazard analyses, both antidepressant monotherapy and polytherapy exhibited higher risk of manic switch than their alternatives (antidepressant monotherapy vs. SGA monotherapy, hazard ratio [HR]=2.87 [95% CI: 1.10-7.49][27].So establishing of correct management program is necessary.The add on mood stabilizer,such as lithium carbonate maybe one important methods in treatment of patients with depressive episode if possible.

This meta-analysis found switch rate of lithium carbonate group was 8.26%(21/254), switch rate of Loading [MathJax]/jax/output/CommonHTML/fonts/TeX/fontdata.js patients, which was very different in switch

rate(OR=0.25 ,95% CI: 0.15–0.43).The switch rate in experimental group was significantly lower than in that in control group ($Z=4.96,P<0.0001$). But the funnel plot analysis of study about switch rate show asymmetric due to a gap,which indicate there maybe a bias of publication.Whereas the Egger *publicationbiastest*($P = 0.16$) and *Begg's publication bias test*($P=0.62$) all show the there not were publication bias. This suggest lithium carbonate do decrease the switch rate induced by antidepressant during treatment for patients with episode of depression.

It was known to all that different depression and different antidepressant were accompanied different switch rate[7,8,9].So the subgroup analysis was made. The result also show lithium carbonate can decreased the switch rate both in patients with unipolar depression and bipolar depression, although bipolar disorder have higher switch rate than that in unipolar disorder[28,29].The result also show lithium carbonate can decreased the switch rate both in patients treated with TCA and SSRI, although switch rate related to TCA was higher than that related to SSRI[29,30]. These all means that lithium carbonate reduce switch rate regardless of the type of antidepressant and the type of depressive episode.

The switch-inducing potential of antidepressants is unclear, although tricyclic antidepressants, which confer higher risk of switching than other classes of antidepressants, with higher NE function in CNS, are a possible exception. Converging evidence suggests that certain pharmacologic and nonpharmacologic interventions with very different mechanisms of action, such as sleep deprivation, exogenous corticosteroids, and dopaminergic agonists, can trigger mood episode switches in patients with bipolar disorder or soft bipolar disorder[31]. But lithium carbonate may displace Na^+ from the allosteric Na^+ -binding sites in neurotransmitter transporters and G-protein coupled receptors (GPCRs),which can stabilize the unsettle of mood[32].

This study had several limitations. Firstly, the sample size of this meta-analysis was relatively small. Only 9 studies and 695 subjects were involved. Secondly, collecting data style may influence the result of investigation, for example,different criteria of switch can get different detection rate of switch. so it was very import to establish a diagnostic criteria for switch associated with antidepressant.Thirdly, not all the studies had blind observation. .These factors are partly responsible for the source of pool rate of switch associated with antidepressant, also affect us to see the real significance and risk of switch.

Conclusion

As typical mood stabilizer, lithium carbonate can reduced switch rate related to antidepressant in patients with depressive episode. In this study, lithium carbonate reduce 67.25% switch rate regardless of the type of antidepressant and the type of depressive episode.But the ability of lithium carbonate in reducing switch is not the reason of use about antidepressant in bipolar depression. The 3 principles should be taken during treatment for bipolar depression,which are no first selection of antidepressant,no monotherapy by antidepressant,no combination of antidepressants.

Abbreviations

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MEDLINE=The National Library of Medicine

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

Declarations

Ethics approval and consent to participate

Not Available

Consent to publication

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

Availability of data and material.

See Table1

Competing interests

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

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Not Available

Authou's contribution

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

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Figures

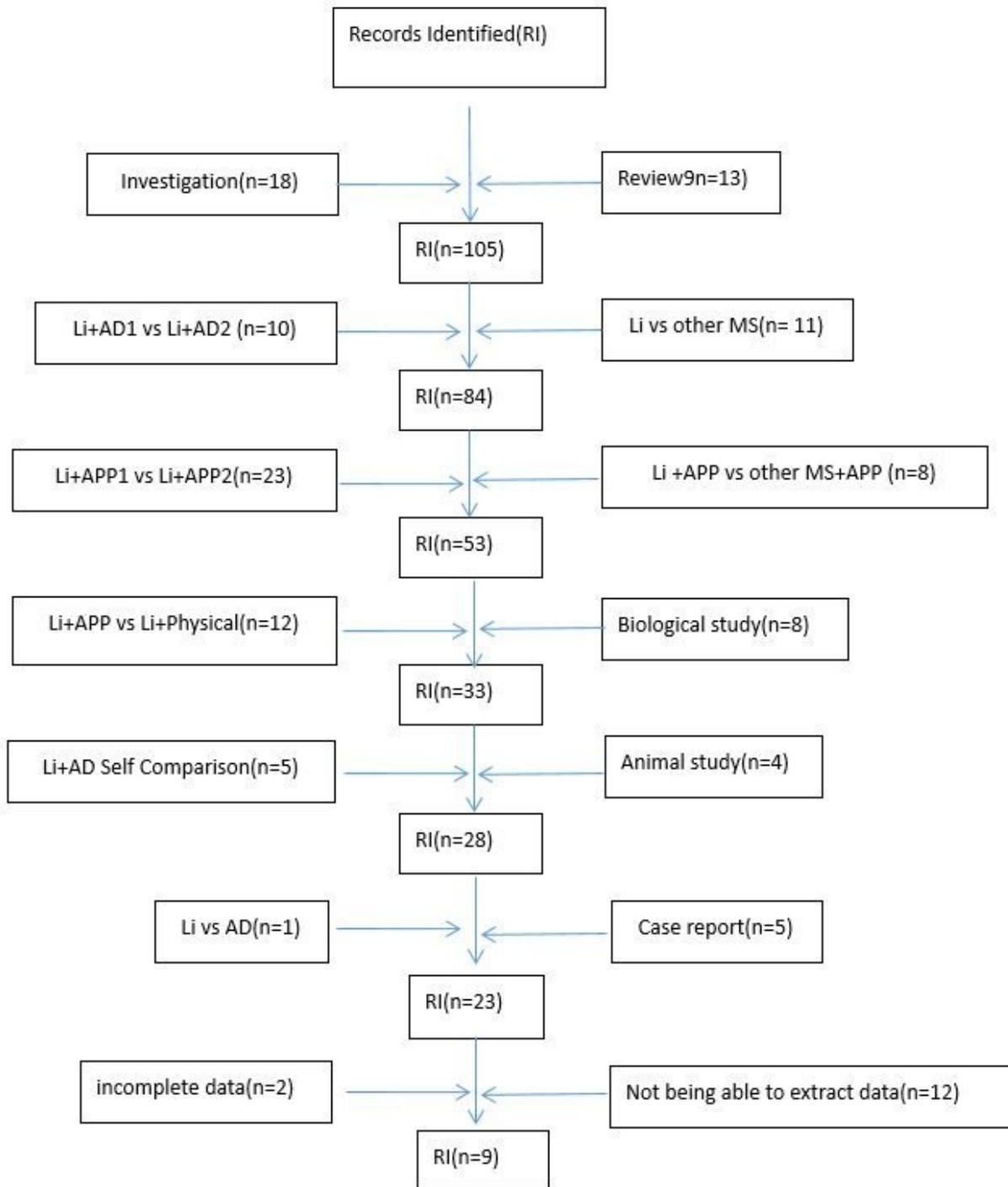


Figure 1

Search process Li=Lithium Carbonate; AD=Antidepressants; APP=Atypical antipsychotic; MS=Mood Stabilizer

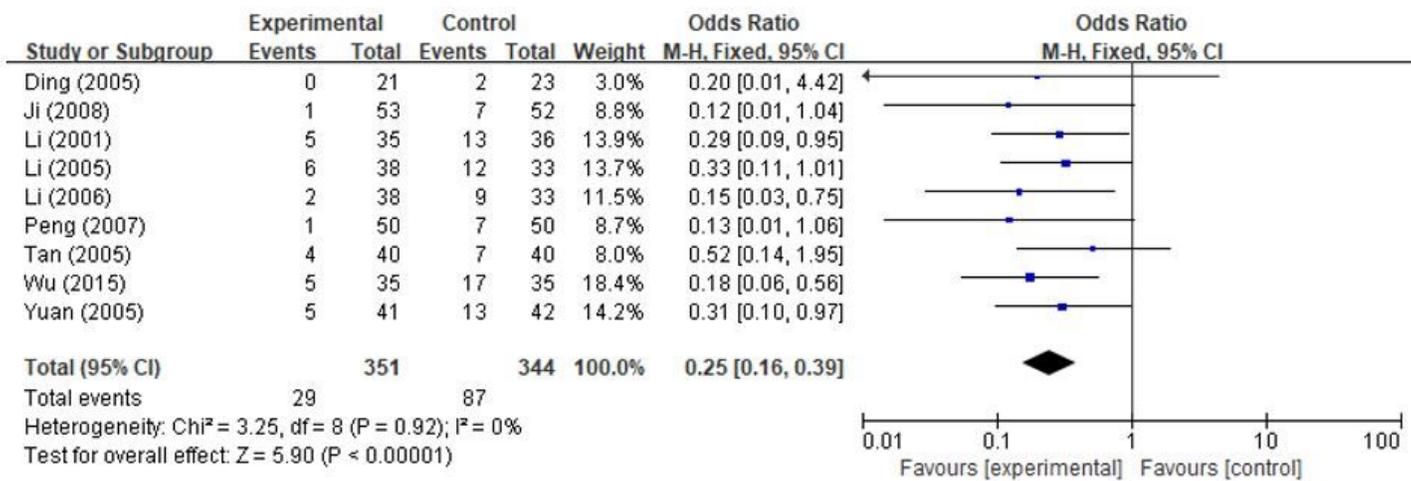


Figure 2

Comparison of switch rate between experimental group and control group.

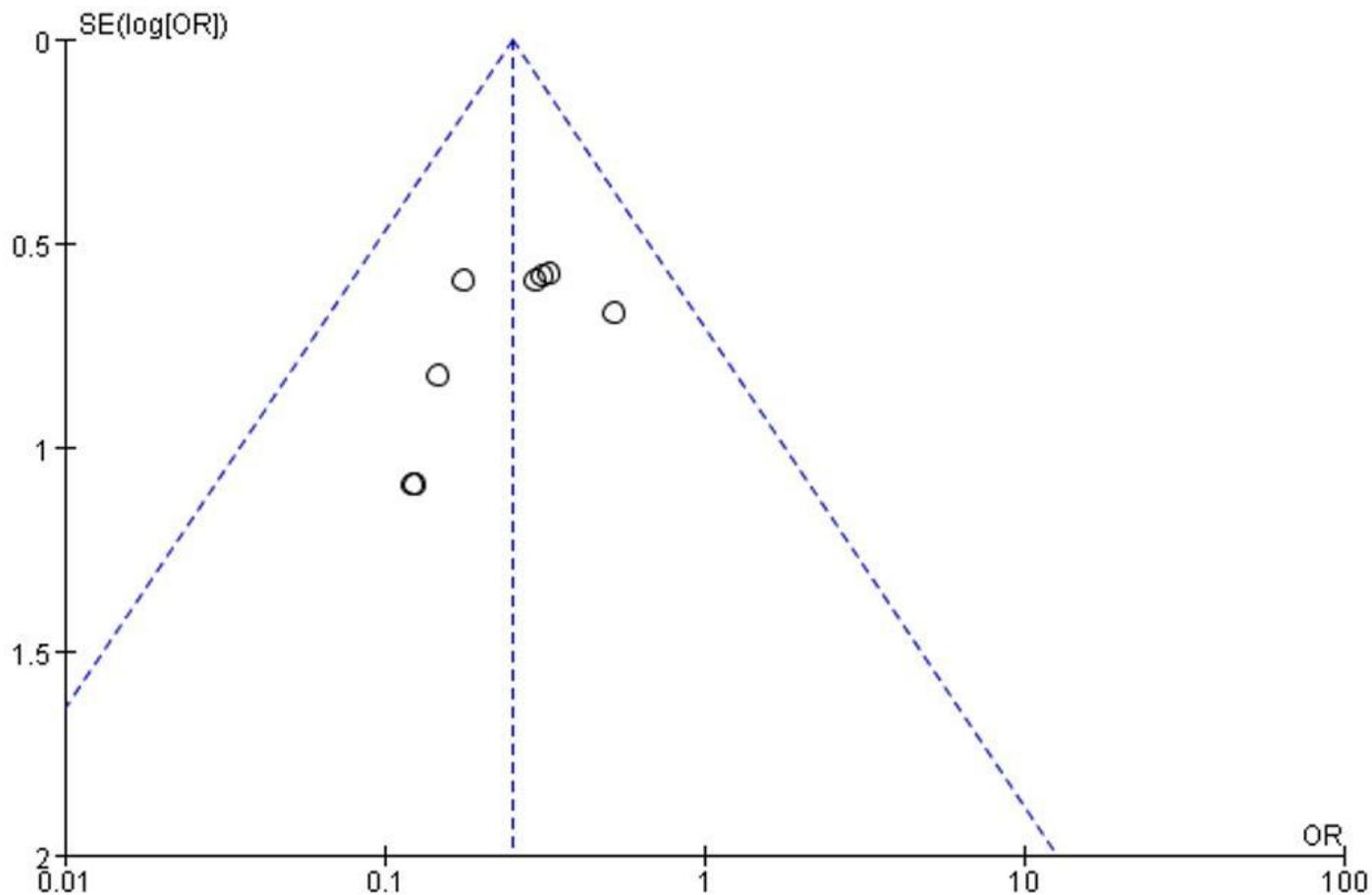


Figure 2

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The funnel plot analysis of study about switch rate

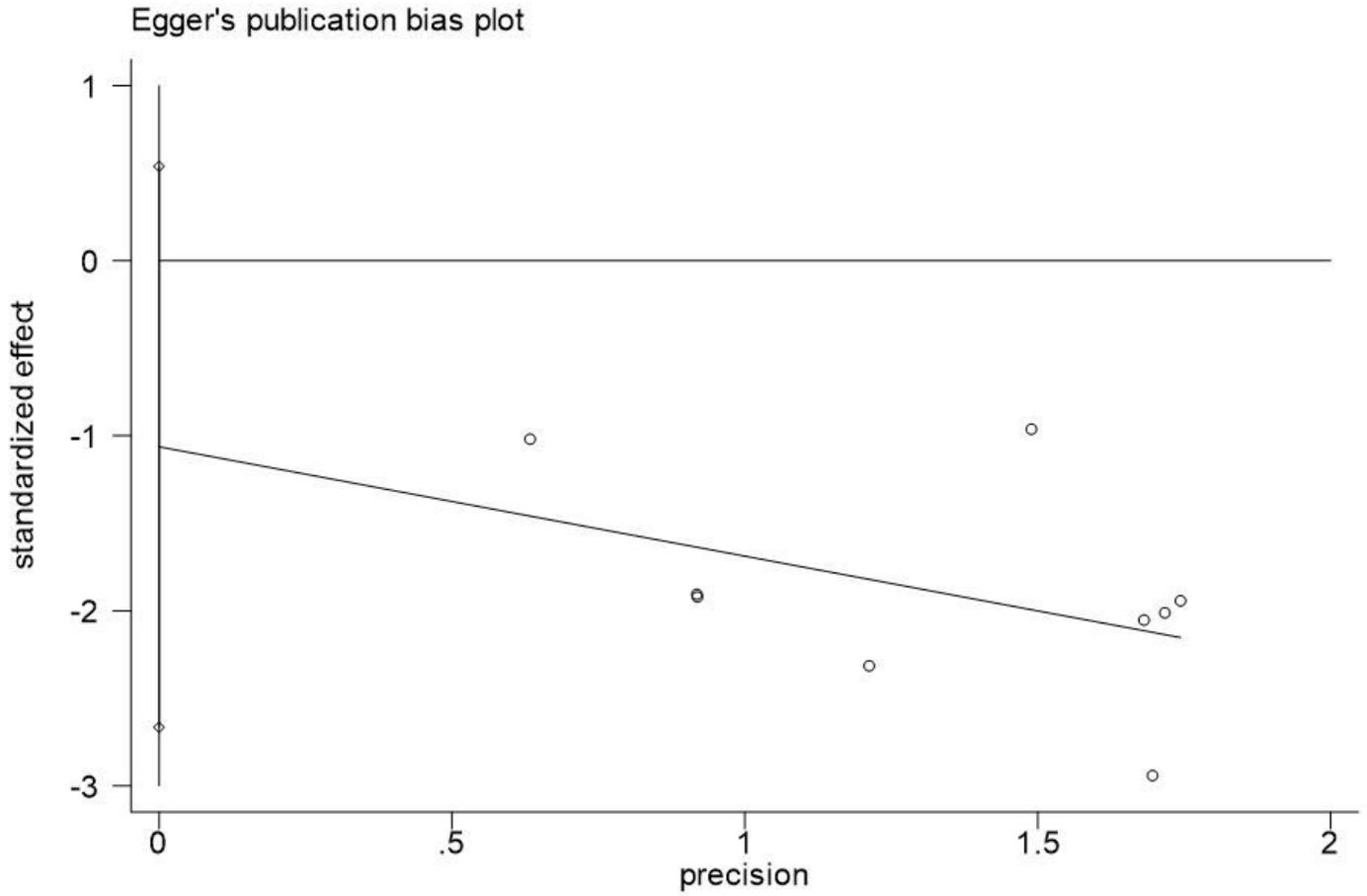


Figure 4

Egger's publication bias test

Begg's funnel plot with pseudo 95% confidence limits

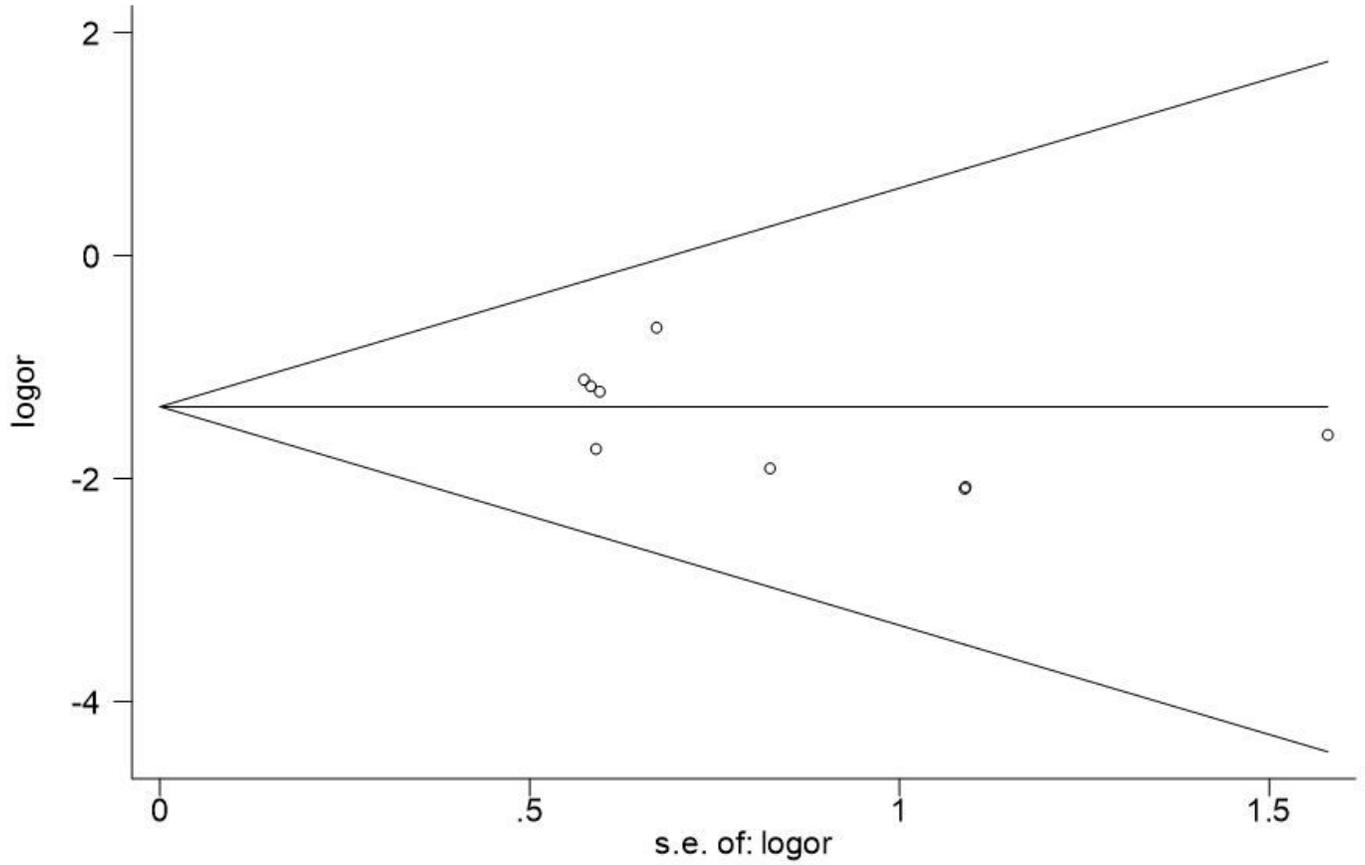


Figure 5

Begg's publication bias test

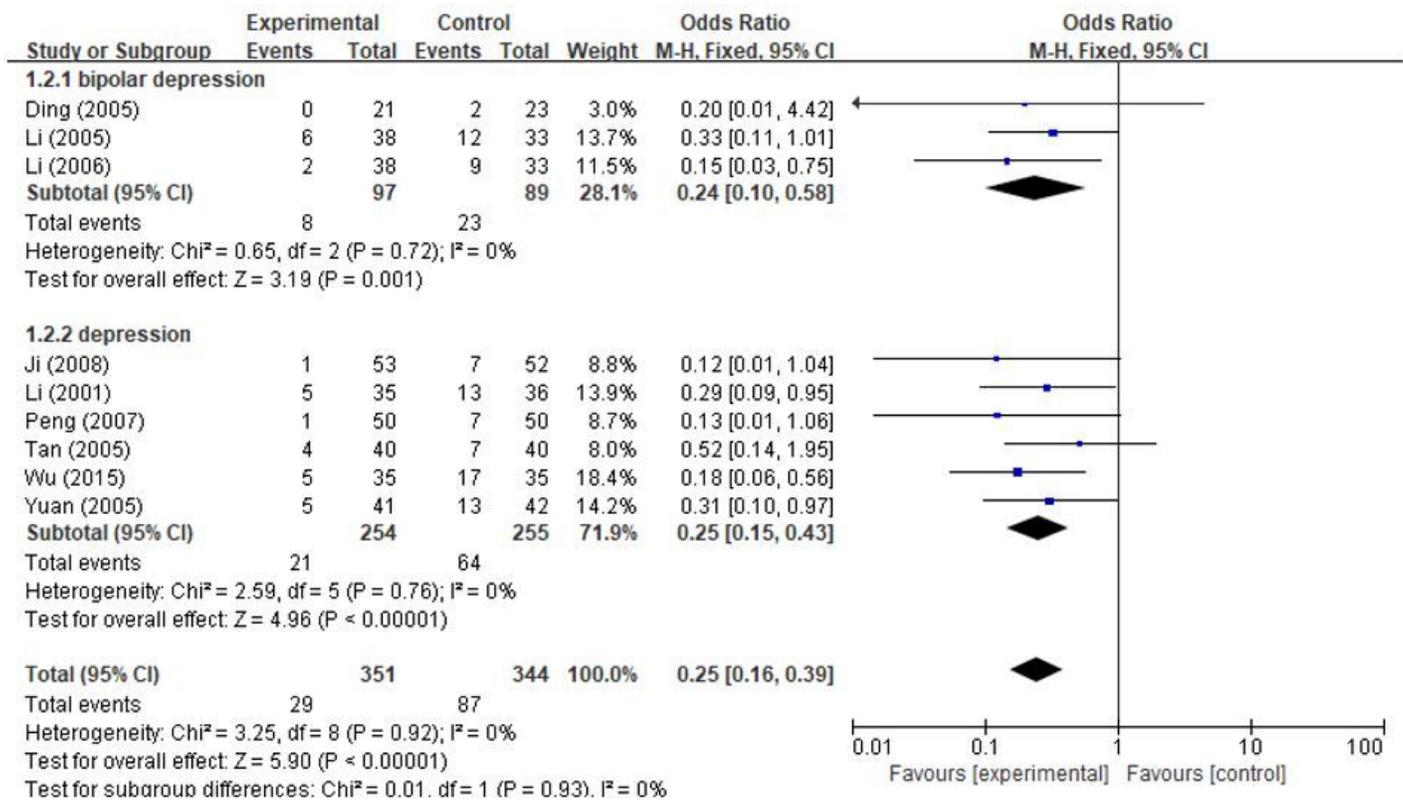


Figure 6

Subgroup comparison of switch rate according to type of depression.

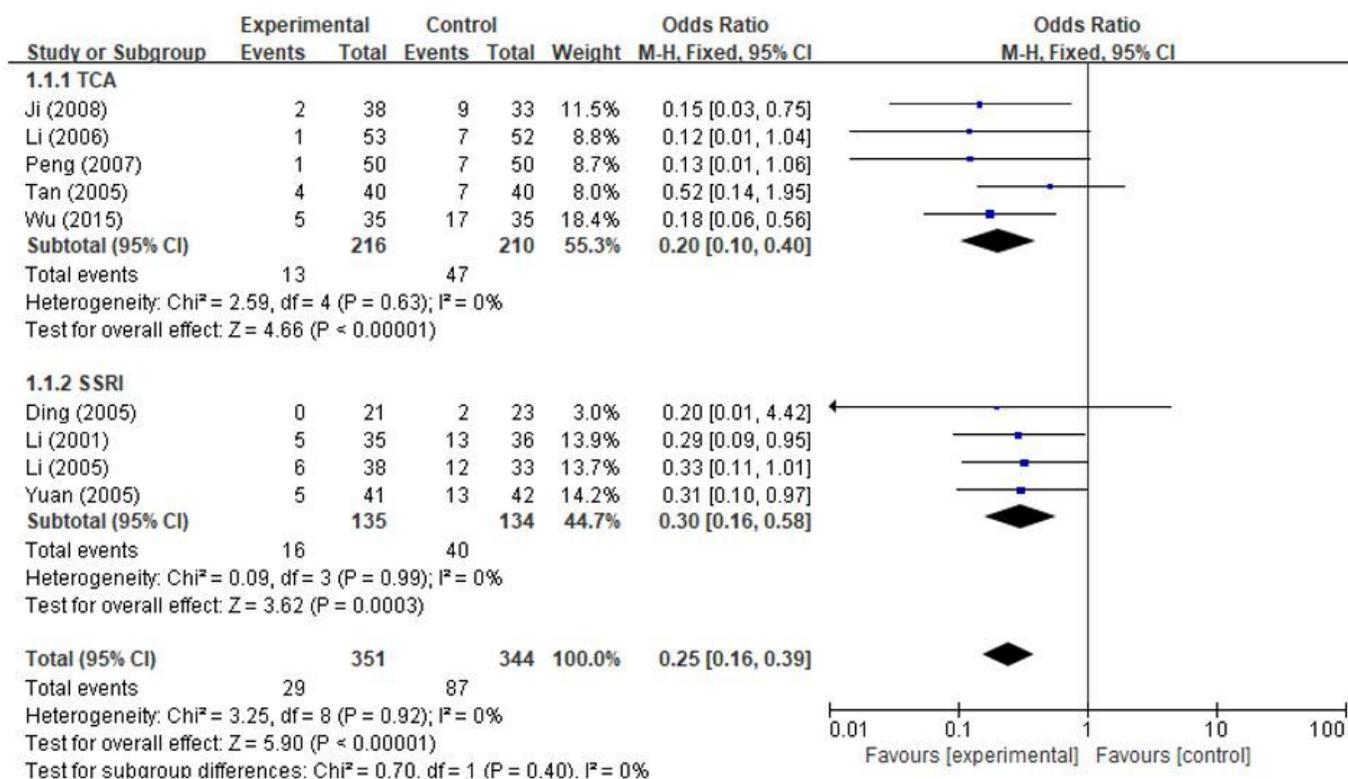


Figure 7

Subgroup comparison of switch rate according to type of antidepressant.