REVIEW ARTICLE

Systematic Review and Meta-Analysis of Salt Valproate Preventing Switch Associated with Antidepressants in Chinese Patients With Depressive Episodes

Shen Dong, MD; Wangqiang Lv, MD; Sun Fengli, MD; Jin Weidong, MD

ABSTRACT

Objective • This overview of systematic reviews (SRs) and meta-analyses aims to critically appraise the methodology and reporting quality of relevant SRs and meta-analyses with the aim of identifying whether or not the use of valproate can prevent the switch to mania associated with antidepressant treatment in Chinese patients with depressive episodes.

Methods • Electronic databases China National Knowledge Infrastructure (CNKI), Chinese Scientific Journal Database (VIP database) and Wanfang Database were searched for related SRs and meta-analyses from inception to the search date within Chinese restrictions. A total of 2 reviewers independently selected SRs and meta-analyses and collected related data, and a third reviewer was introduced if any disagreement occurred during the assessment. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) and the US Agency for Healthcare Research and Quality (AHRQ) were employed to evaluate quality of the reporting and methodology.

Results • The switch rate in the sodium valproate group by 99% and was significantly lower than in the antidepressant-only group (0% vs 5.7%; OR = 0.18; 95% CI, 0.04-0.84; Z = 2.18; *P* = .03). The magnesium valproate group was similar to the sodium valproate group in switch rate; the switch rate in the antidepressant group was (2.2% vs 16.92%; OR = 0.11; 95% CI, 0.03-0.39; Z = 3.47; *P* = .0005). The switch rate in the salt valproate combined with a selective serotonin reuptake inhibitor (SSRI) group was lower than in the SSRI group (0.51% vs 8.4%; OR = 0.15; 95% CI, 0.04-0.51; Z = 3.01; *P* = .003). The switch rate in the valproate combined with serotonin noradrenaline reuptake inhibitor (SNRI) group was similar to the valproate combined with SNRI group (2.3% vs 17.5%; OR = 0.12; 95% CI, 0.03-0.53; Z = 2.79; *P* = .05).

Conclusion • Salt valproate can reduce the switch rate related to antidepressant treatment in patients with depression (*Altern Ther Health Med.* 2023;29(3):282-288).

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BACKGROUND

In the treatment of depression, there are 2 issues that require significant attention: the efficacy of the treatment and the switching or turning manic associated with antidepressant use.[1] In particular, turning manic or switching not only indicates that the patient has not received effective treatment, but also makes the disease more complicated and more serious.[2,3] Therefore, avoiding this phenomenon is one of the basic principles of clinical treatment.[4] These patients are often said to have breakthrough episodes,[5,6] and are also diagnosed as having bipolar disorder according to the Diagnostic and Statistic Manual of Mental Disorders V (DSM-5).[7]

In order to avoid this change in status, psychiatrists have adopted some methods in clinical practice such as using mood stabilizers.[8] Lithium carbonate can reduce the manic switch rate by 50%,[8] as can lamotrigine.[9] Does valproate also have this effect on preventing conversion to mania? Therefore, Chinese psychiatrists have carried out a lot of research regarding this question. They found that valproate can enhance the efficacy of antidepressants in the treatment of patients with depression,[10] can be used for refractory depression,[11,12] and can treat agitation and impulsivity[13,14] and anxiety in post-stroke depression.[15] They have also found that valproate can prevent mania associated with antidepressant.[8] Our study aims to perform a systematic review and meta-

Figure 1A. PRISMA flow diagram.

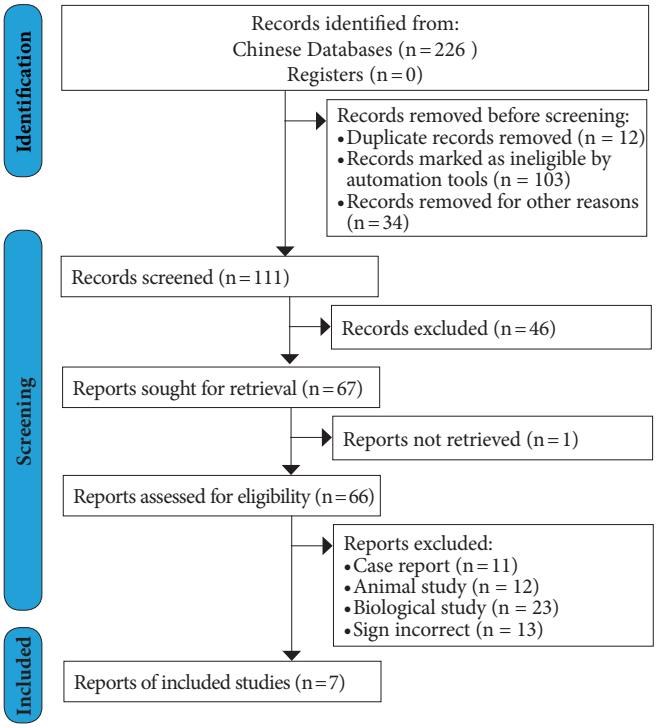
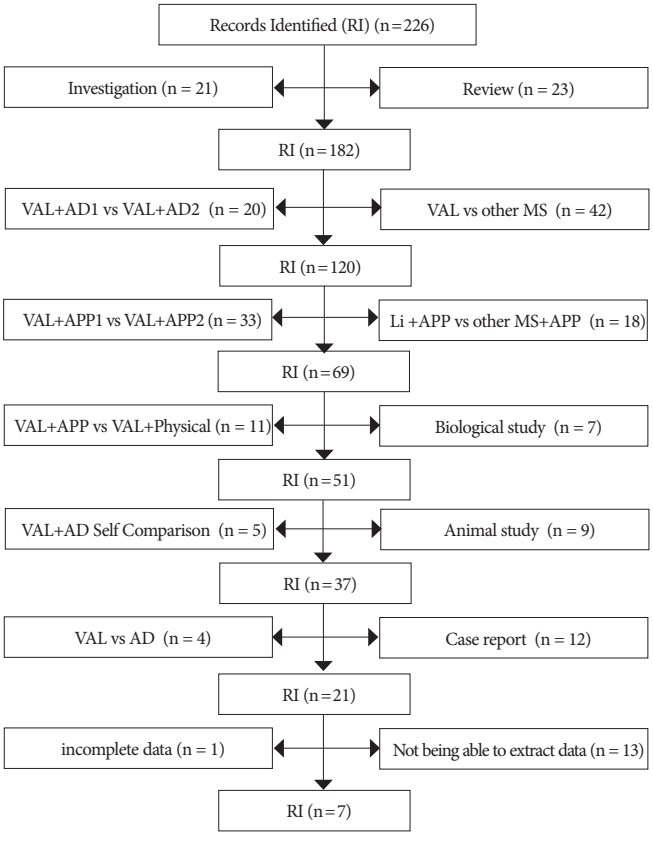


Figure 1B. Search process for studies for analysis.



Abbreviations: AD, antidepressants; APP, atypical antipsychotic; MS, mood stabilizer; VAL, salt vaproate.

analysis regarding the prevention of the switch to mania via the use of salt valproate.

METHODS

Study Registration

The protocol was not registered.

Inclusion and Exclusion Criteria

Inclusion criteria. All randomized controlled trials (RCTs) regarding the combination treatment of salt valproate and an antidepressant compared with monotherapy with antidepressants in patients with depressive episodes were identified. Only papers in Chinese or English were selected. Study status, type and dates had no influence on the systematic review. The switch to mania criteria were: (1) the direct rate of drop off in the study was due to a switch to an excited mood, hypomania or mania; (2) the detection rate or number of cases of switch was reported directly in study; (3) the rate of change in the therapeutic plan was due to psychopathology of mania, hypomania, very irritable or very compulsive behavior; (4) the number of study patients with a score >11 on the YOUNG Mania Rating Scale (YMRS) or the Bech-Rafaelsen Mania Scale (BRMS); (5) cases were reported in the study and became mixed episodes due to bipolar depression.

Exclusion criteria. Exclusion criteria included animal studies, reviews, case series, quasi-RCTs or non-RCTs.

Interventions

The experimental intervention used salt valproate combined with an antidepressant as treatment in patients with depression; the control group used the same antidepressant alone.

Outcome Measures

The outcome measure was the switch rate associated with the use of an antidepressant with or without valproate.

Literature Search Method

Electronic. Relevant papers published as of January 1, 2020 were collected from the Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), WANFANG and Chinese Social Sciences Citation Index (VIP) databases(CSSCI). The papers in Chinese were selected according to the recommendations of the US Agency for Healthcare Research and Quality (AHRQ).[16]

Other Sources. To determine the existence of other RCTs, we searched for relevant systematic reviews and reference lists that contained other potential qualifying studies. In addition, the study investigators were contacted to obtain the latest clinical data for the convenience of ongoing RCTs. Of note, related conference proceedings were also evaluated to identify the studies included in the review. Figure 1A shows the review flowchart.And detail search flowchart was listed in Figure 1B.

Table 1. Characteristics of Studies Included in the Meta-Analysis

Author (year)	Design	Experimental group (EG) cases (n)	Switch Cases in EG (n)	Control group (CG) cases (n)	SwitchCases in CG (n)	Quality score	Drugs
Feng (2001)	RCT	50	1	50	8	8	MV+SSRI
Qian (2008)	RCT	49	1	45	8	8	MV+SNRI
Wang (2014)	RCT	35	1	35	6	8	MV+SNRI
Xie (2013)	RCT	40	0	40	1	8	SV+SSRI
Yang (2008)	RCT	35	0	30	2	8	SV+SSRI
Yu (2008)	RCT	40	0	40	3	8	SV+SSRI
Zhou (2005)	RCT	30	0	30	2	8	SV+SSRI

NOTES:
(1) Experimental group (EG) was treated with a combination of an antidepressant and salt valproate.
(2) Control group (CG) was treated with only an antidepressant.
(3) Switch means that patient switched from depression to mania during treatment.
(4) Quality score was assessed according to Agency for Healthcare Research and Quality (AHRQ). Score of 8 = quality of retrieved article was good.

Abbreviations: RCT, randomized controlled trial; SNRI, serotonin noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; MV, magnesium valproate; SV, sodium valproate.

Search Strategy

Search terms consist of salt vaproate ("sodium valproate," "magnesium valproate,") and depression ("depressive syndrome," "depressive episode," "bipolar depression," "unipolar depression"). Text words and MeSH were used.

Data Collection and Analysis

Study Selection. After the 2 researchers extracted information from the literature included in the study independently, they used it to generate a unified statistical table.

Data Extraction and Management. Data collected from each study were: funding source and type, follow-up duration, primary outcomes, blinding method, allocation concealment method, intervention time, randomization, intervention group sample size, year of publication, the first author, reference ID, patient age range, control group type and outcome measures If the reported data were insufficient, the study lead investigator was contacted. For any disagreement between the 2 researchers, a third-party researcher was invited to make the final determination. A total of 2 psychiatrists reviewed each included article independently, using the 11-item checklist recommended by the AHRQ.[16] An item would be scored 0 if it was answered NO or UNCLEAR, whereas 1 was given to the answer YES. Article quality was assessed as follows: low quality = 0 to 3; moderate quality = 4 to 7; high quality = 8 to 11. Differences in article quality were discussed to reach a consensus final score.

Treatment Effect Measures. Odds ratios (ORs) were adopted to measure treatment effects with regard to dichotomous and continuous outcomes, respectively, which all reported 95% CIs.

Statistical Analysis

All statistical analyses were performed using RevMan 5.2 software (Cochrane, London UK), and a P value <.05 was considered statistically significant. The heterogeneity of all involved studies was assessed by I^2. When it was >50%, the studies with an acceptable heterogeneity were considered, and then the fixed-effects model with Mantel-Haenszel method was used; otherwise, a random effects model with the Der Simonian and Laird (DL) method was adopted. The combined ORs were initially estimated using graphic Forrest plots. For each trial, the OR was estimated from the original article. If not available, we looked at the total numbers of events and number of patients at risk in each group to determine the estimated OR.

Assessment of Publication Bias

Bias was investigated in each of the pooled study groups primarily via the Egger's linear regression test. As a supplemental approach, Begg's rank correlation was also applied to assess potential publication bias; P <.05 was considered to represent no publication bias in the study.

Ethics Approval

Ethics approval and patient consent were not required as this study is an overview based on published systematic reviews and meta-analyses.

RESULTS

Study Characteristics

A total of 7 comparison studies, including 549 patients, met the inclusion criteria and were included for the final meta-analysis.[17-23] The 549 patients comprised 279 patients in the intervention group (combination of valproate and antidepressant) and 270 patients in the control group (antidepressant treatment alone). The sample size of the studies ranged from 30 to 50 patients. The 7 studies were from 2005 to 2015. A total of 33 patients switched from depression to mania (see Table 1).

Figure 2. Comparison of switch rate between the experimental and control groups. The fixed effect model was used. The results showed that the switch rate with salt valproate was 3/279 (0.11%), while the switch rate with an antidepressant alone was 30/270 (11.11%), There was a significant difference (OR=0.13; 95% CI, 0.05-0.35). The switch rate in the experimental group was significantly lower than in the control group (Z=4.11; *P* <.0001)

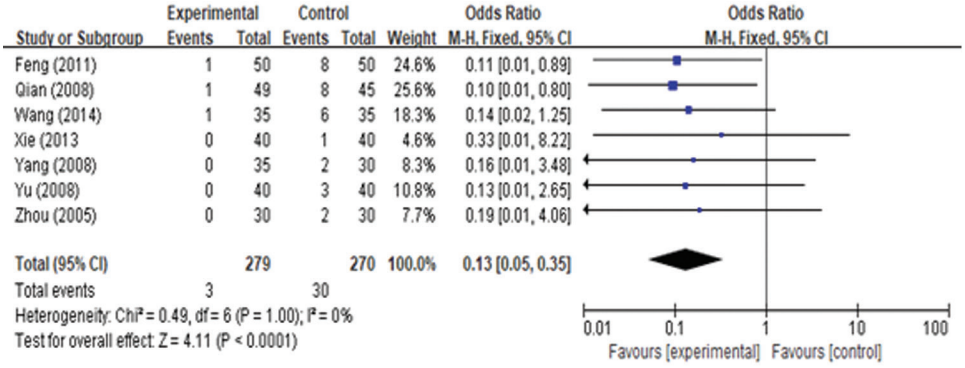
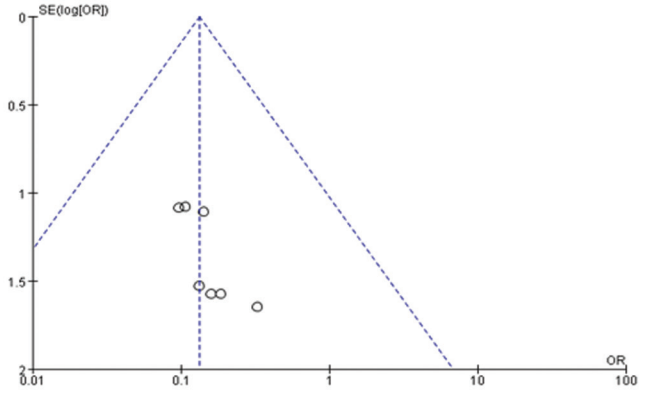


Figure 3. The funnel plot analysis of the study concerning switch rate shows a gap, which indicate there may be a publication bias.



Comparison of Switch Rate in the Experimental and Control Groups

A total of 549 patients were included in the 7 studies. The random effect model was used to account for the data via RevMan 5.2 software (Cochrane, London, UK). The results showed that the switch rate in the valproate plus antidepressant group was 3/279 patients (0.11%) and 30/270 patients (11.11%) in the control (antidepressant alone) group (OR = 0.13; 95% CI, 0.05-0.35). The switch rate in the intervention group was significantly lower than in the control group (Z = 4.11; *P* < .0001). Results also indicated that salt valproate reduced the switch rate by 99% (11.11%-0.11%/11.11%) (see Figure 2).

The funnel plot analysis of our review regarding the switch rate shows a gap, which indicates there may be a publication bias (see Figure 3) present. Because the number of studies included was <9, Egger`s publication bias test and Begg`s publication bias test are not shown.

Subgroup Comparison of Switch Rate in the Sodium and Magnesium Valproate Combination Groups

A total of 285 patients with depression treated with sodium valproate were included in 4 studies. Random effects model was used to account for the data via RevMan 5.2 software. The results showed that the switch rate in the sodium valproate group was 0/145 (0.00%) and the switch rate in the antidepressant alone group was 8/140 (5.7%%), which was a significant difference (OR = 0.18; 95% CI, 0.04-0.84). The switch rate in the intervention group was significantly lower than in the control group (Z = 2.18; *P* = .0033). In the group of patients treated with sodium valproate, the switch rate was reduced by 100% (5.7%-0%/5.7%) (see Figure 4).

A total of 264 patients with depression treated with magnesium valproate were included in 3 studies. Random effects model was used to account for the data via RevMan 5.2 software. The results showed that the switch rate in the magnesium valproate group was 3/134 (2.2%) and the switch rate in the antidepressant along group was 22/130 (16.92%), which was a significant switch rate (OR = 0.11; 95% CI, 0.03-0.39). The switch rate in the experimental group was significantly lower than in the control group (Z = 3.47; *P* = .0005). In the group of patients with depression treated with magnesium valproate, the switch rate was reduced by 98.7% (16.22%-2.2%/16.22%) (see Figure 4).

The switch rate in the salt valproate combined with a selective serotonin reuptake inhibitor (SSRI) group was 1/195 (0.51%) and the switch rate in the SSRI alone group was 16/190 (8.4%), which was significantly different (OR = 0.15; 95% CI, 0.04-0.51). The switch rate in the valproate group was significantly lower than in the control group (Z = 3.01; *P* = .003). The switch rate in the salt valproate plus SSRI group was 2/84 (2.3%), and 14/80 (17.5%) in the SNRI alone group, which was significant (OR = 0.12; 95%CI, 0.03-0.53). The switch rate in the experimental group was significantly lower than in the control group (Z = 2.79; *P* = .005) (see Figure 5).

Figure 4. Subgroup comparison of switch rate according to salt valproate use. The fixed random model was used. The switch rate in the sodium valproate group was 0/145 (0.00%); the switch rate in the antidepressant group was 8/140 (5.7%) which was significant (OR = 0.18; 95% CI, 0.04-0.84). The switch rate in the experimental group was significantly lower than in the control group (Z = 2.18; *P* = .0033); The switch rate in the magnesium valproate group was 3/134 (2.2%) and the switch rate in the antidepressant group was 22/130 (16.92%), which was significant (OR = 0.11; 95% CI, 0.03-0.39). The switch rate in the experimental group was significantly lower than in the control group (Z = 3.47; *P* = .0005)

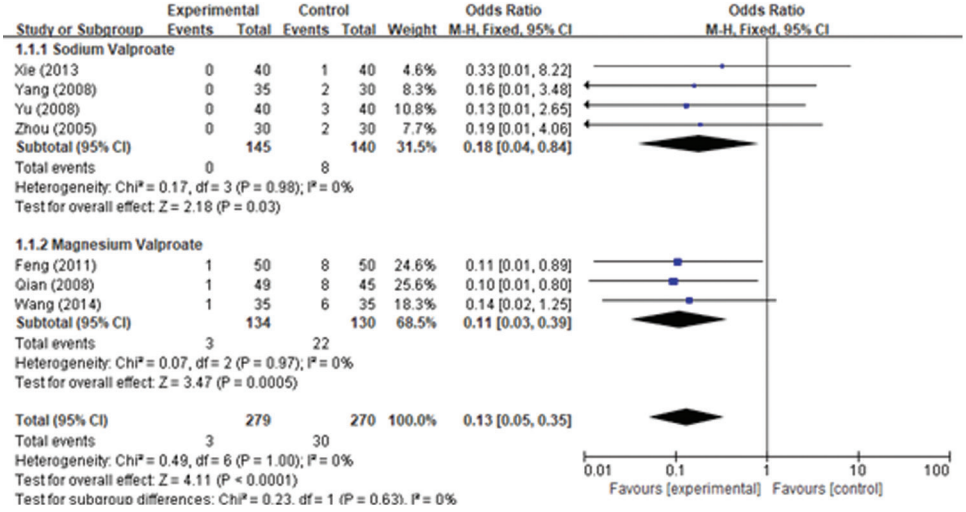
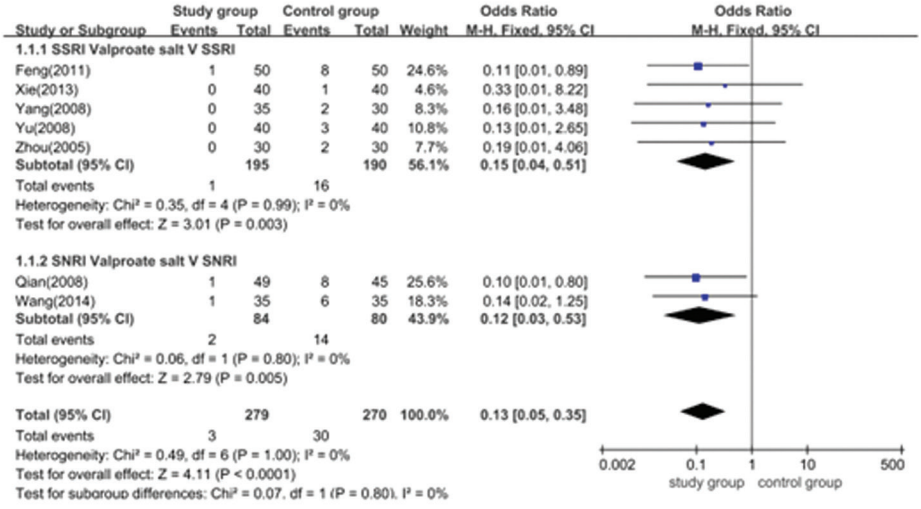


Figure 5. Subgroup comparison of switch rate according to antidepressant. The fixed random model was used. The switch rate in the salt valproate combined with SSRI group was 1/195 (0.51%), the switch rate in the SSRI group was 16/190 (8.4%), which was significant (OR = 0.15; 95% CI, 0.04-0.51). The switch rate in the experimental group was significantly lower than in the control group (Z = 3.01; *P* = .003). The switch rate in the salt valproate plus SNRI group was 2/84 (2.3%), the switch rate in the SNRI group was 14/80 (17.5%), which was significant (OR = 0.12; 95% CI, .03-0.53). The switch rate in the experimental group was significantly lower than in the control group (Z = 2.79; *P* = .005)



DISCUSSION

As a typical mood stabilizer, salt valproate was primarily was used for treatment is bipolar disorder.[24,25] In a study designed to evaluate the efficacy of lurasidone as adjunctive therapy with lithium or valproate, patients with bipolar I depression were randomly assigned to 6 weeks of double-blind treatment with lurasidone (n = 180) or placebo (n = 176) added to background treatment with lithium or valproate.[25] The study found that lurasidone in combination with lithium or valproate demonstrated significant improvement in depressive symptoms based on the Montgomery-Asberg Depression Rating Scale (MADRS) from weeks 2 to 5, but not at the primary week 6 end point.[25] A total of 4 randomized controlled double-blind trials with 142 participants were included for meta-analysis; quality was good in all 4 trials, although individual study sample sizes were small. Meta-analysis showed a significant difference in favor of valproate for the reduction in depressive symptoms, both on depression symptom scales and in effective rate.[24]

Valproate is also used for other types of depression, such as treatment-resistant depression (TRD),[9,10] depression with mixed features, with agitation or with anxiety symptoms.[26,27] Antidepressant augmentation with VPA provided substantial clinical improvement in a subgroup of patients with severe TRD. Overall, these results provide suggestive evidence of beneficial effects of carbamazepine, lamotrigine and valproate that require further study, especially for long-term adjunctive use, particularly in patients with recurring major depressive disorder (MDD) with prominent irritability or agitation.[26,27] It also hints that valproate may be effective in the prevention of switch associated with antidepressants. In fact, the risk for switch associated with antidepressants in patients with depression was treated only with antidepressant monotherapy without the use of a mood stabilizer.[4]

The next question is whether the preventive effect on switching is associated with antidepressants in patients with depression. In this study, regardless of whether sodium valproate or magnesium valproate was used, the possibility of switching associated with antidepressants was decreased. The switch rate in the experimental group was significantly lower than in the control group (Z = 2.18-3.47; P = .0033-.0005; OR = 0.11-0.18). In total, our results showed that the switch rate with salt valproate was 3/279 (0.11%), while the switch rate with antidepressants alone was 30/270 (11.11%), which was a significant difference (OR = 0.13; 95% CI, 0.05-0.35). The switch rate in the intervention group was significantly lower than in the control group (Z = 4.11; P < .0001). And they also indicated that salt valproate reduced the switch rate by 99% (11.11%-0.11%/11.11%). Our meta-analysis further found that salt valproate can prevent the switching associated with antidepressant use in patients with depression. But the funnel plot analysis of the study regarding switch rate was asymmetric due to a gap, which indicate there may be publication bias without applying Egger`s and Begg`s publication bias tests. Therefore, we need to exercise caution with regard to this finding.

A certain number of patients with depression experience a switch to mania or hypomania during antidepressant treatment, which can be diagnosed according to the DSM-5 criteria for bipolar disorder.[7,28] But this is not a successful therapeutic plan for patients to appear mnia during treatent with antidepressant, because it induces the mania ahead.[29] So, avoiding the switch to mania is an important part of the therapeutic plan, whether the patient has unipolar or bipolar depression. In general, 4 stages occur when a patient is going into a switch: first is the switch to mania or hypomania; second the primary rapid cycle becomes accelerated; third is that obvious and serious irritability, compulsive and agitated behavior appear and the clinician has to change treatment methods; and fourth is the development of antidepressant-induced chronic irritable dysphoria (ACID).[3] Salt valproate can prevent this switch.

The mechanism that causes the switch resulting from antidepressant use is unclear. Tricyclic antidepressants have higher risk of causing switching than other classes of antidepressants; this may be due to their higher norepinephrine (NE) function in the central nervous system (CNS). Converging evidence suggests that certain pharmacological and non-pharmacological interventions with different mechanisms of action—such as sleep deprivation, exogenous corticosteroids and dopaminergic agonists—can trigger episodes of mood switches in patients with bipolar disorder or soft bipolar disorder.[30] The arachidonic acid (AA) cascade hypothesis is considered to be associated with manic episodes. Unlike mood stabilizers, antidepressants that increase switching of bipolar depression to mania induced the AA cascade in rat brains.[31]

Study Limitations

Our study had several limitations. First, the sample size of this meta-analysis was relatively small; only 7 studies comprising 549 patients were involved. Second, the methods for collecting data may have influenced the result of the investigation; for example, different switch criteria can result in different rates of switch. So, it is important to establish diagnostic criteria for switch associated with antidepressants. Third, not all the studies included blinded observation. These factors are partly responsible for the source of the pooled switch rate associated with antidepressants, also influence us to see the real risk of switch to mania.

CONCLUSION

As a typical mood stabilizer, salt valproate can reduce the switch rate related to antidepressant use in patients with depressive episodes. In our study, salt valproate reduced the switch rate by 99%. But the ability of valproate to reduce switching is not a reason to use antidepressants in bipolar depression treatment. The 3 principles of antidepressive use for the treatment of bipolar depression need to be taken into account: (1) no first selection of an antidepressant, (2) no monotherapy with antidepressants and (3) no combination of antidepressants. We also need to treat the finding that salt valproate decreases the switch rate induced by antidepressants during treatment in patients with depression cautiously pending further research.

CONFLICT OF INTEREST

None.

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