Meta-analysis of Salt Valproate Prevent Switch Associated with Antidepressants in Chinese Depressive Patients

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Research Article

Abstract

Objective: to study the efficacy of valproate in preventing switch rate related to antidepressant in depressive patients.

Methods: The related literature were searched in Chinese Biomedical Database(CBM), China National Knowledge Infrastructure(CNKI) , WANFANG database,and Chinese Social Sciences Citation Index(CSSCI) from 1 January 2005 to 1 January 2020 The rate of switch between groups was synthesized and discussed.

Result:

A total of 549 subjects were included in 7 studies,in which in 279 cases are in combination group and 270 cases are in group of monotherapy by antidepressant . The results showed switch rate of valproate group was 0.11%,switch rate of antidepressant group was 11.11%, which was very different (OR=0.13 ,95% CI: 0.05−0.35) and also indicated that valproate reduced switch rate was 99%[(11.11%-0.11%)/11.11%]. In sodium valproate group, switch rate was 0%while switch rate in antidepressant was 5.7%(OR=0.18,95%CI=0.04-0.84,Z=2.18,P=0.03). In magnesium valproate group, switch rate was 2.2%,while switch rate in antidepressant was16.92% (OR=0.11,95%CI=0.03-0.39,Z=3.47, P=0.0005).

Conclusion: The salt valproate can reduced switch rate related to antidepressant in depressive patients.

Background

Valproate may be applied to depression for the following reasons: First, in the study, as an important intensive treatment, it is used in the treatment of depression [1]. Second, valproate can improve the symptoms of refractory depression[2, 3]. Third, valproate is beneficial to the improvement of irritability, impulse and anxiety symptoms of irritable depression [4, 5]. Fourth, valproate is widely used in post-stroke depression in China [6, 7].

In the consensus of experts on the psychiatric application of valproate, the prevention of manic conversion is also one of the important roles of valproate [8]. During the treatment ,manic symptoms may appear, which are related to antidepressant ,patients were diagnosed as bipolar disorder [9,10,11]. In fact, one of the principles is to avoid turning manic as the treatment of bipolar depression [12]. However, since most bipolar disorder often starts with depression, which often treated with antidepressant and switch [13,14].The lithium can prevent the switch and decrease the more 50% switch rate[15].As valproate can improve the irritable,compulsive and mixed symptom in depression,so the avoidance of switch.This study just is a meta-analysis about prevention of switch by valproate.

Methods

1. Literature retrieval methods:

1.1 This study was performed according to the recommendations of the Moose [16] The database includes Chinese Biomedical Database (CBM), China National Knowledge Infrastructure (CNKI), WANFANG and Chinese Social Sciences Citation Index (VIP) databases .

1.2 Search key words and strategy: Depression (depression,depressive episode); salt valproate(sodium or magnesium).Last query was updated on late 1 January 2005 to 1 January 2020.

1.3 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].

1.4 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.

Results

1.Study Characteristic

7 comparison studies, with 549 subjects, met the inclusion criteria and were included for the final meta-analysis[17,18,19,20,21,22,23,],see table1.

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

A total of 549 subjects were included in 7 studies. The results showed that the switch rate of salt valproate was 0.11%(3/279),switch rate of antidepressant was 11.11%(30/270), which was very different in switch rate(OR=0.13 ,95% CI: 0.05–0.35) .The switch rate in experimental group was significantly lower than in that in control group (Z=4.11,P<0.0001). And it also indicated that salt valproate reduced switch rate was 99%(11.11%-0.11%/11.11%).See figure2.

The funnel plot analysis of study about switch rate show a gap,which indicate there maybe a bias of publication.see figure3.

3.Subgroup comparison of switch rate

Subgroup comparison of switch rate according to salt valproate,which conclude sodium and magnesium valproate. A total of 285 depressive subjects treated and compared by sodium valproate were included in 4 studies. The switch rate of sodium valproate group was 0.00%(0/145),switch rate of antidepressant group was 5.7%%(8/140) , which was very different in switch rate(OR=0.18,95%CI=0.04-0.84,Z=2.18,P=0.0033). The sodium valproate reduced switch rate was 100%(5.7%-0%/5.7%). See figure4.

A total of 264 depressive subjects treated and compared by magnesium valproate were included in 3 studies. The switch rate of magnesium valproate group was 2.2%(3/134),switch rate of antidepressant group was 16.92%(22/130), which was very different in switch rate(OR=0.11,95%CI=0.03-

0.39,Z=3.47,P=0.0005). The magnesium valproate reduced switch rate was 98.7%(16.22%-2.2%/16.22%). See figure4.

Discussion

The salt valproate primarily was used for bipolar disorder. Just according to type of depressive episode,salt valproate more was used in treatment bipolar depression[24,25],In a study, lurasidone adjunctive with lithium or valproate demonstrated significant improvement in depressive symptoms based on the MADRS from weeks 2–5 but not at the primary week 6 endpoint[25].Meta-analysis showed a significant difference in favour of valproate for reduction in depressive symptoms, both on depression symptom scales (standardized mean difference (SMD) -0.35 (95% confidence interval, -0.69, -0.02)), and participants with at least 50% improvement in symptoms - relative risk (RR) 2.00 (1.13, 3.53)[24].

But valproate also was used for other type depression,such as TRD[2, 3],depression with mixed future,with agitated or anxiety symptoms[26,27].It also hint valproate maybe effective in prevention of switch associated with antidepressant.In fact,the risk of switch associated with antidepressant in patients with depression was monotherapy by antidepressant and without use of mood stabilizer[12].

In this study,valproate can decrease the possibility of switch associated with antidepressant. The switch rate in experimental group was significantly lower than in that in control group (Z = 2.18 ~ 3.47,P = 0.0033 ~ 0.0005,OR = 0.11−0.18). In total,the results showed that the switch rate of salt valproate was 0.11% (3/279),switch rate of antidepressant was 11.11%(30/270), which was very different in switch rate(OR = 0.13 ,95% CI: 0.05−0.35,Z = 4.11,P < 0.0001). And it also indicated that salt valproate reduced switch rate was 99%(11.11%-0.11%/11.11%).So we need cautiously regard this results that salt valproate decrease the switch rate induced by antidepressant during treatment for patients with depression.

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[28].But this is not successful therapeutic plan for patient duo to switch,because it induce the mania ahead[29].So avoiding switch to mania is important part of therapeutic plan,whereas the patients is unipolar or bipolar depression.

The switch-inducing potential of antidepressants is unclear, which can trigger mood episode switches in patients with bipolar disorder or soft bipolar disorder[30].

This study had several limitations. Firstly, the sample size of this meta-analysis was relatively small. Only 7 studies and 549 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 mood stabilizer,the both sodium valproate and magnesium valproate can reduced switch rate related to antidepressant in depressive patients. The salt valproate can reduced switch rate was 99%.

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 SD participated in collection of data and the writing of the article, Dr SD,Dr ZY and Dr LY assessed the quality of researched papers. Dr LJ complete most statistic analysis.All authors reviewed researched whole paper. Prof JWD participated in the design , statistical processing and the final revision of the article.

7.Acknowledgment

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Tables

Table1: Characteristics of studies included in the meta-analysis

Author(year)	Study design	Experimental group(EG) cases	Cases of switch in EG	Control group(CG) cases	Cases of switch in CG	Quality score	Salt Valproate
Feng(2001)	Comparison	50	1	50	8	8	Sodium
Qian(2008)	Comparison	49	1	45	8	8	Sodium
Wang(2014)	Comparison	35	1	35	6	8	Sodium
Xie(2013)	Comparison	40	0	40	1	8	Magnesium
Yang(2008)	Comparison	35	0	30	2	8	Magnesium
Yu(2008)	Comparison	40	0	40	3	8	Magnesium
Zhou(2005)	Comparison	30	0	30	2	8	Magnesium

Figures
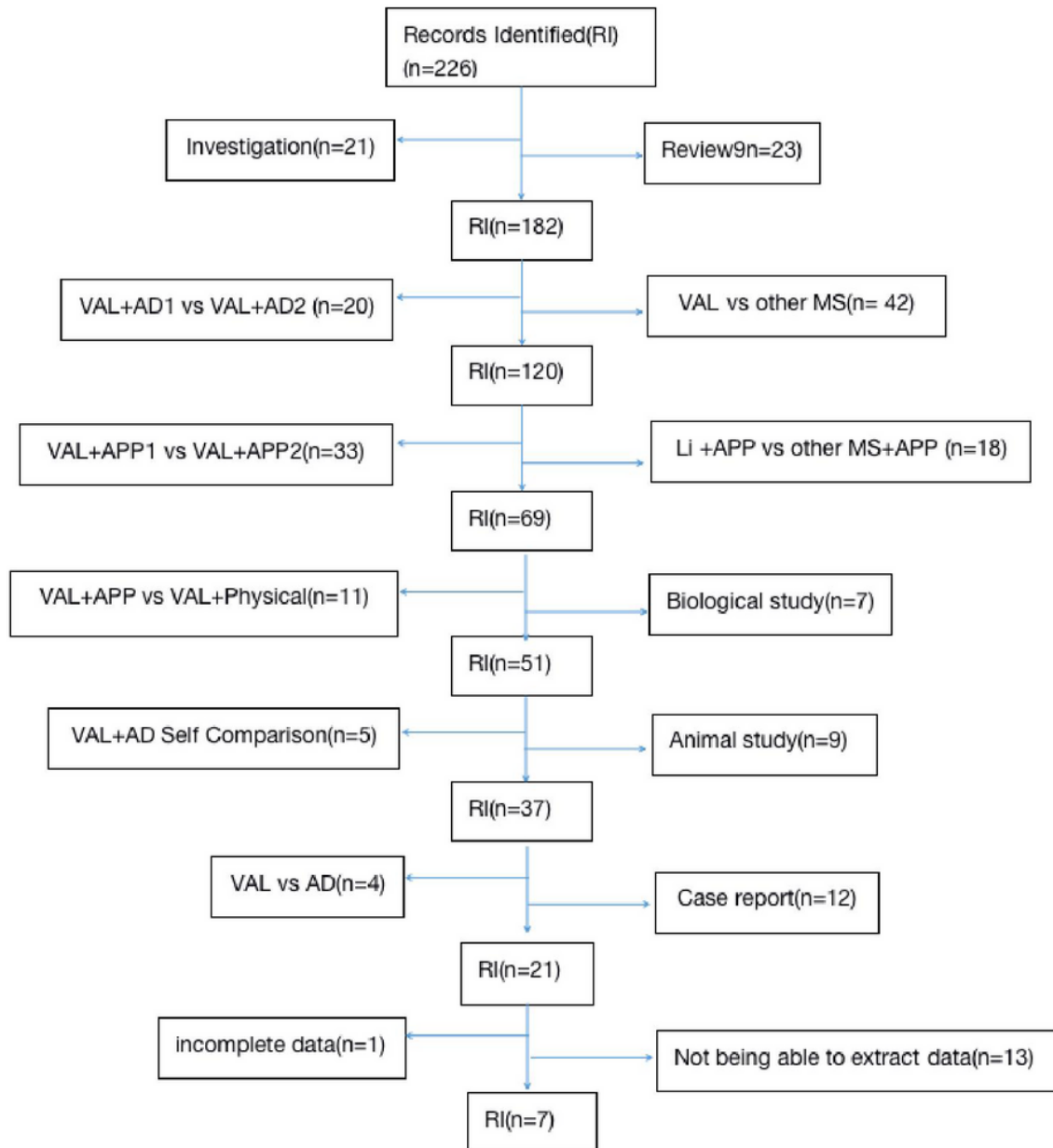
Figure 1

Search process VAL=Salt Valproate; AD=Antidepressants; APP=Atypical antipychotic; MS=Mood Stabilizer

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Feng (2011)	1	50	8	50	24.6%	0.11 [0.01, 0.89]
Qian (2008)	1	49	8	45	25.6%	0.10 [0.01, 0.80]
Wang (2014)	1	35	6	35	18.3%	0.14 [0.02, 1.25]
Xie (2013	0	40	1	40	4.6%	0.33 [0.01, 8.22]
Yang (2008)	0	35	2	30	8.3%	0.16 [0.01, 3.48]
Yu (2008)	0	40	3	40	10.8%	0.13 [0.01, 2.65]
Zhou (2005)	0	30	2	30	7.7%	0.19 [0.01, 4.06]
Total (95% CI)		279		270	100.0%	0.13 [0.05, 0.35]
Total events	3		30			

Heterogeneity: Chi² = 0.49, df = 6 (P = 1.00); I² = 0%
Test for overall effect: Z = 4.11 (P < 0.0001)

Figure 2

Comparison of switch rate between experimental group and control group. The fixed random model was used. The results showed that the switch rate of salt valproate was 0.11%(3/279), switch rate of antidepressant was 11.11%(30/270), which was very different in switch rate(OR=0.13, 95% CI: 0.05-0.35). The switch rate in experimental group was significantly lower than in that in control group (Z=4.11,P<0.0001).

Figure 3

The funnel plot analysis of study about switch rate. switch rate show a gap, which indicate there maybe a bias of publication.

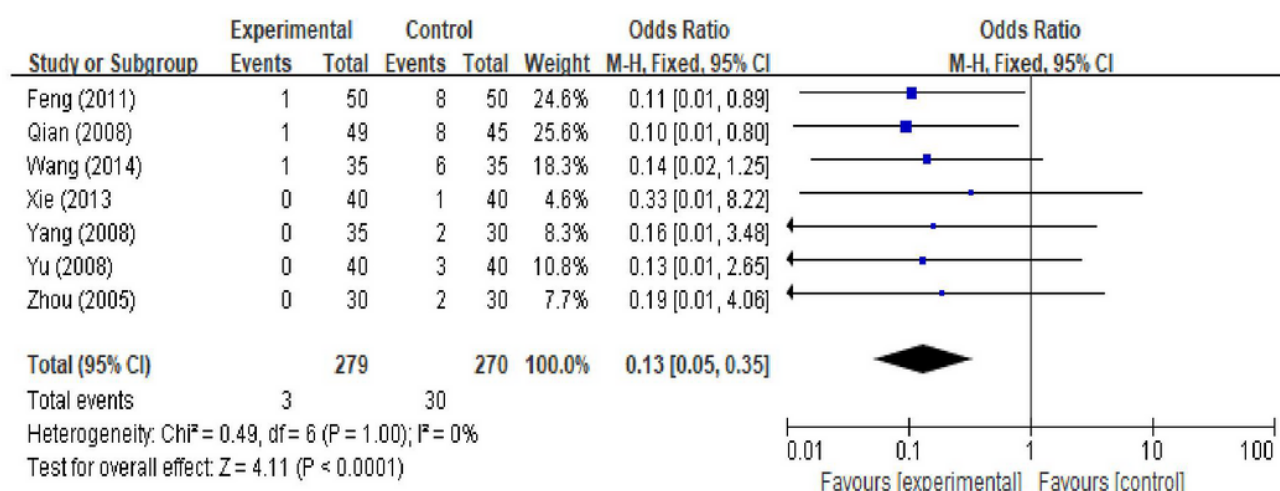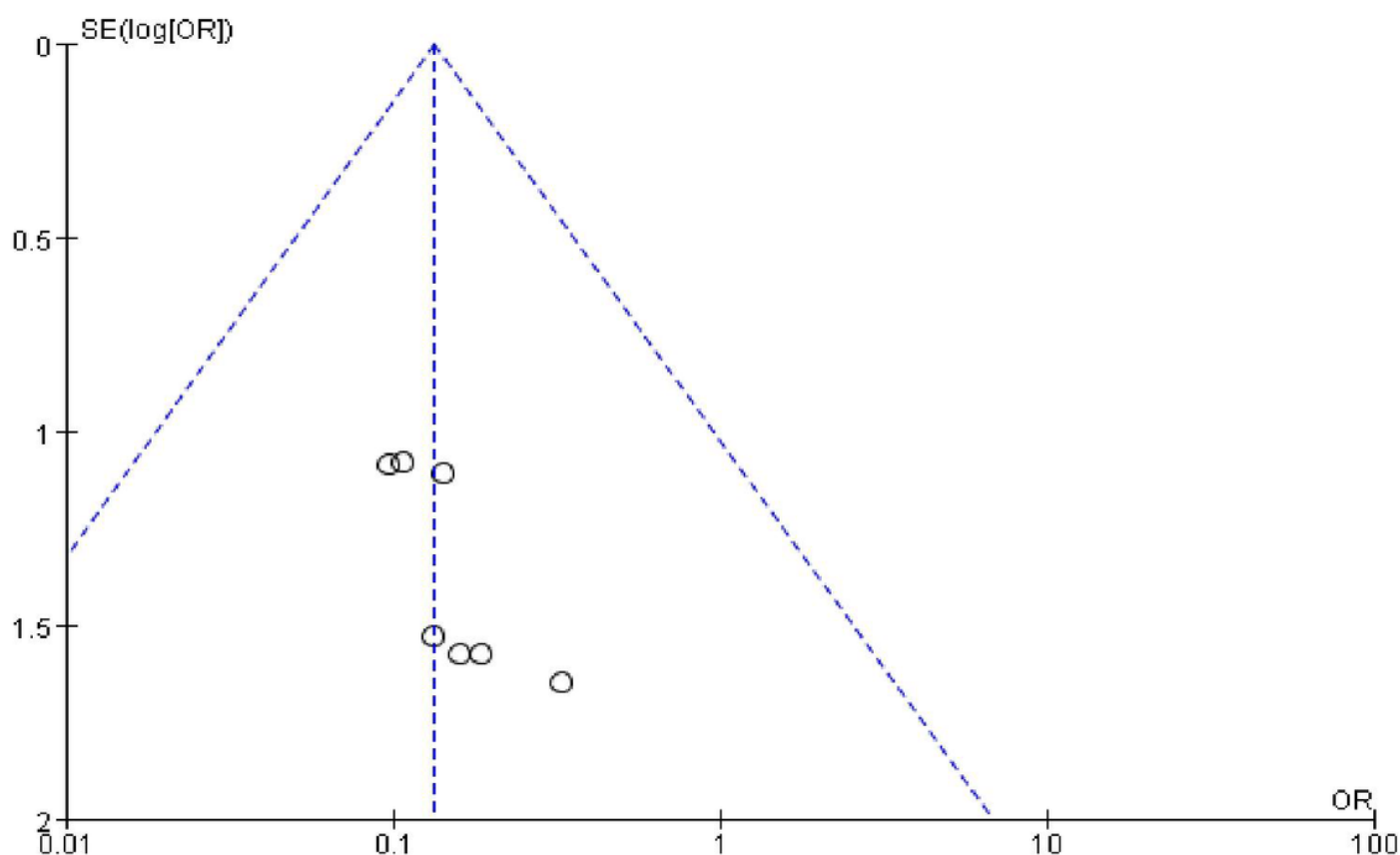| Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
1.1.1 Sodium Valproate						
Xie (2013	0	40	1	40	4.6%	0.33 [0.01, 8.22]
Yang (2008)	0	35	2	30	8.3%	0.16 [0.01, 3.48]
Yu (2008)	0	40	3	40	10.8%	0.13 [0.01, 2.65]
Zhou (2005)	0	30	2	30	7.7%	0.19 [0.01, 4.06]
Subtotal (95% CI)		145		140	31.5%	**0.18 [0.04, 0.84]**
Total events	0		8			
Heterogeneity: Chi² = 0.17, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 2.18 (P = 0.03)						
1.1.2 Magnesium Valproate						
Feng (2011)	1	50	8	50	24.6%	0.11 [0.01, 0.89]
Qian (2008)	1	49	8	45	25.6%	0.10 [0.01, 0.80]
Wang (2014)	1	35	6	35	18.3%	0.14 [0.02, 1.25]
Subtotal (95% CI)		134		130	68.5%	**0.11 [0.03, 0.39]**
Total events	3		22			
Heterogeneity: Chi² = 0.07, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 3.47 (P = 0.0005)						
Total (95% CI)		279		270	100.0%	**0.13 [0.05, 0.35]**
Total events	3		30			
Heterogeneity: Chi² = 0.49, df = 6 (P = 1.00); I² = 0%						
Test for overall effect: Z = 4.11 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						

0.01   0.1   1   10   100
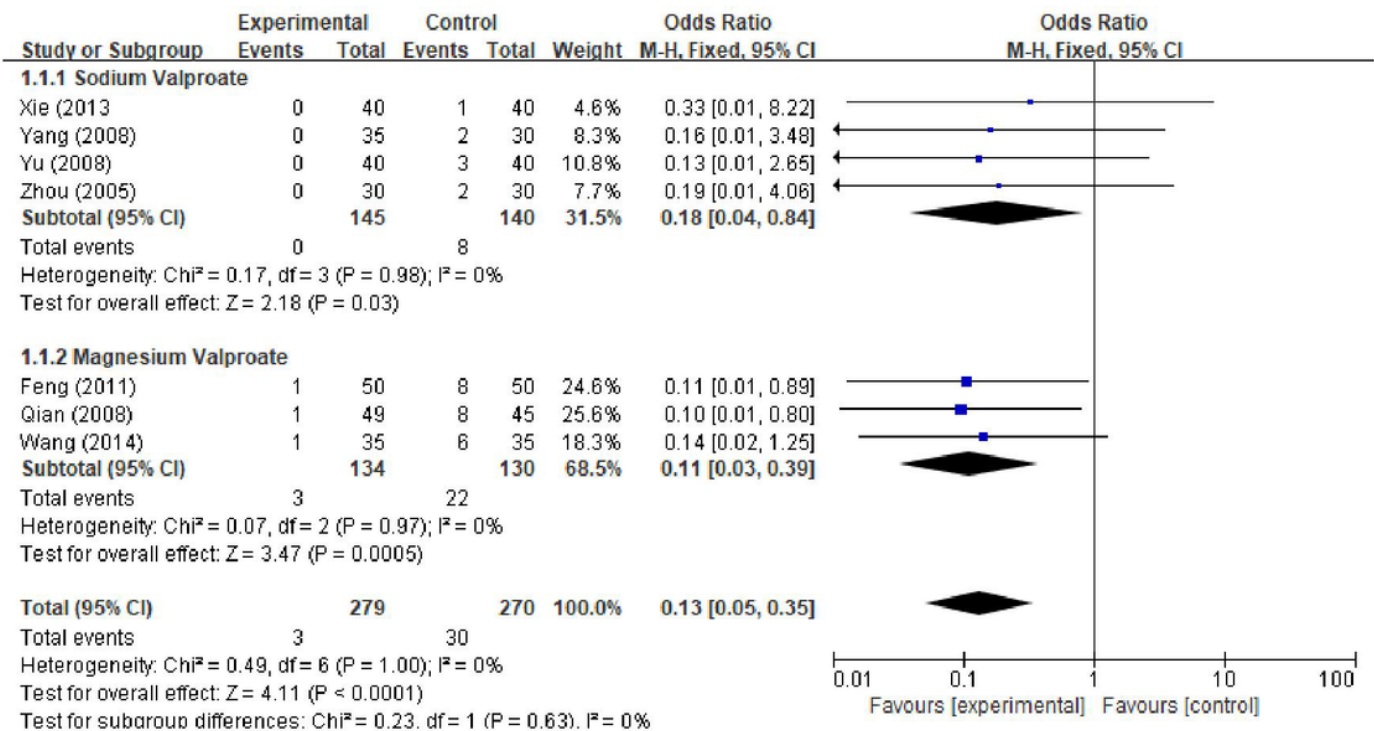Favours [experimental]   Favours [control]

Figure 4

Subgroup comparison of switch rate according to salt valproate. The fixed random model was used. The switch rate of sodium valproate group was 0.00%(0/145), switch rate of antidepressant group was 5.7%% (8/140), which was very different in switch rate(OR=0.18, 95% CI=0.04-0.84). The switch rate in experimental group was significantly lower than in that in control group (Z=2.18, P=0.0033). he switch rate of magnesium valproate group was 2.2%(3/134), switch rate of antidepressant group was 16.92%(22/130), which was very different in switch rate(OR=0.11, 95% CI=0.03-0.39). The switch rate in experimental group was significantly lower than in that in control group (Z=3.47, P=0.0005)