

Significant Effect of Valproate Augmentation Therapy in Patients With Schizophrenia

A Meta-analysis Study

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Abstract: Valproate is an anticonvulsant, which is also widely used for treating psychiatric disorders. Some clinical trials have demonstrated benefits of valproate augmentation therapy in schizophrenia. Previous meta-analysis showed inconsistent findings because of limited literature at that time.

The aim of this study is to update the newer published data by conducting a meta-analysis of clinical efficacy of valproate augmentation therapy in patients with schizophrenia or schizoaffective disorder.

Data sources include electronic research through platform of PubMed.

Study eligibility criteria, participants, and interventions were as follows: the inclusion criteria included articles discussing comparisons of the treatment effect in schizophrenic patients treated with antipsychotic augmented with valproate and antipsychotics with/without placebo; articles on clinical trials in humans. The exclusion criteria were case reports or series and nonclinical trials. We compared the effect between antipsychotic treatment with valproate augmentation and antipsychotic monotherapy.

Data from clinical trials were pooled by random-effects model, and possible confounding variables were examined through meta-regression and subgroup analysis. Data from 11 articles including 889 patients were included into current meta-analysis.

We found patients treated with antipsychotics with valproate augmentation showed significantly more improvement in total psychopathology than those treated with antipsychotics only ($P=0.02$). Results from open trials, but not from randomized controlled trials ($P=0.20$), showed significant improvement ($P=0.01$). In addition, the significance only persisted in the studies conducted with a shorter treatment duration ($P<0.001$) rather than longer treatment duration

($P=0.23$). There is no difference in the dropout rate between valproate augmentation and antipsychotic treatment only ($P=0.14$).

We could not perform a detailed meta-analysis for every category of antipsychotics, long-term effect, and safety profiles of valproate augmentation therapy in maintenance treatment, safety in pregnant patients, and subtype of schizophrenia.

Our meta-analysis highlights the significantly better treatment effect with valproate augmentation therapy in patients with schizophrenia or schizoaffective disorder, and provides important evidence for supporting the practice of valproate augmentation therapy in these patients.

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Abbreviations: BPRS = Brief Psychiatric Rating Scales, CGI = clinical global impression, CI = confidence interval, ES = effect sizes, GAD67 = glutamic acid decarboxylase 67, MRI = magnetic resonance imaging, PANSS = positive and negative syndrome scales, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses, RCT = randomized control trials, RELN = reelin.

INTRODUCTION

Schizophrenia is one of the most serious mental illnesses worldwide and can result in a heavy economic burden to affected family. Antipsychotics, either typical or atypical, are considered to be the gold standard treatment for schizophrenia. However, not all schizophrenic patients respond well to monotherapy antipsychotic treatment, and about one-fifth to one-third of the patients responds poorly.¹ Augmentation therapy has been developed to improve the limited response rate, including antipsychotic agents combined with mood stabilizers, benzodiazepines, beta-blockers, and antidepressants, especially for treatment-resistant schizophrenia.²

Valproate was first synthesized in 1882, and it was first used as an anticonvulsant in 1962.³ It has also shown as an antiepileptic effect possibly through a weak antagonist effect of sodium channels and a moderating effect on the expression of gamma amino-butyric acid (GABA) transaminase, which in turn enhances central GABAergic tone.^{4,5} In addition, valproate also binds to benzodiazepine receptors which are linked to GABA-A receptors, thereby affecting epileptic activity.⁶

In addition to an anticonvulsant, valproate also plays an important role in the treatment of psychiatric disorders. It is widely used in augmentation therapy for treatment-resistant schizophrenia.^{2,7} Increasing evidence has shown that valproate interacts with coadministered antipsychotics and alters their blood concentrations. For example, the addition of valproate has been reported to increase the plasma or serum levels of haloperidol,⁸ risperidone,^{9,10} and clozapine.^{11,12} In addition to affecting the metabolism of the coadministered antipsychotics,

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valproate may also modify clinical symptoms of schizophrenic disorder through modifying epigenetics. Furthermore, hypermethylation in specific gene promoters such as glutamic acid decarboxylase 67 (GAD67) and reelin (RELN), in GABAergic neurons in schizophrenic patients has been postulated to be a possible pathophysiology of schizophrenia.^{13,14} Other antipsychotics, such as clozapine and sulpiride, activate brain DNA demethylation,¹⁵ and others including clozapine, quetiapine, and olanzapine induce chromatin remodeling in specific GABAergic or glutamatergic neurons.¹⁶ Similarly, valproate has been shown a similar effect to demethylation^{15,17} and chromatin remodeling.^{16,18} Taken together, valproate may improve the clinical symptoms of schizophrenia through mechanisms such as epigenetic modification, and also altering neurotransmission of catecholamine or serotonin. Furthermore, in the functional magnetic resonance imaging (MRI) study, the anatomical abnormality and connection problems in schizophrenia patients had been proven.¹⁹ However, these abnormalities seemed to be relieved by the administration of valproate or psychotropics agents.^{19–21}

In clinical practice, valproate treatment has been shown to have beneficial effects for schizophrenic patients in several case reports,^{22,23} clinical trials,^{24,25} and randomized control trials (RCTs).^{8,26} In addition, the strategy of augmentation therapy with valproate seems to be more beneficial for a rapid response,²⁷ reducing hostility,⁸ aggressive behavior,²⁸ and in global function.²⁹ However, in other clinical trials, the authors did not agree with these findings and instead reported negative results. In the study by Wassef et al,²⁵ changes in clinical global impression (CGI) scores were significantly lower in schizophrenic patients receiving haloperidol and valproate than in those receiving haloperidol only. Similarly, the scores of positive items of positive and negative syndrome scales (PANSS) after 28 days of treatment were significantly higher in patients receiving haloperidol and valproate than in those receiving haloperidol only in another study.³⁰ However, other studies on the treatment effect of antipsychotics augmented with valproate for schizophrenic patients have reported controversial

findings.^{27,31–35} One of the most recent large meta-analysis published by the Cochrane library tried to elucidate the role of valproate augmentation therapy for schizophrenia; however, the results were insignificant.³⁶

Since the meta-analysis conducted by Schwarz et al in 2008,³⁶ several new reports have been published within the past 6 years.^{31,32,37} To update the published data, we conducted this thorough meta-analysis of the role of valproate augmentation therapy in patients with schizophrenia or schizoaffective disorder.

METHODS

Literature Search and Screening

A systematic article search using PubMed was conducted by 2 independent psychiatrists (H-YW and K-YT). If there was an inconsistent selection and lack of agreement, another senior psychiatrist (WC) made the final judgment and decision. The search was performed using the key words “(valproate) AND (schizophrenia) AND (add-on OR augmentation OR antipsychotics OR mood stabilizer OR adjunct)” for all articles available till July 28, 2015. Only articles written in English were chosen. Initially, all articles meeting these inclusion criteria were collected, and the titles and abstracts were screened by H-YW and -YT to determine whether they were potentially eligible for inclusion in this meta-analysis. When there was disagreement on eligibility, we reached agreement through consensus. All reports that were not related to the topics of augmentation of valproate for patients with schizophrenia were excluded. We then screened all of the selected articles using the following inclusion criteria: articles discussing comparisons of the treatment effect in schizophrenic patients treated with antipsychotic augmented with valproate and antipsychotics with/without placebo; and articles on clinical trials in humans. The exclusion criteria were: case reports or series; and non-clinical trials. The screening and search protocol is depicted in Figure 1. In addition, to investigate the quality of clinical trials included in the current meta-analysis, we used the Jadad scores

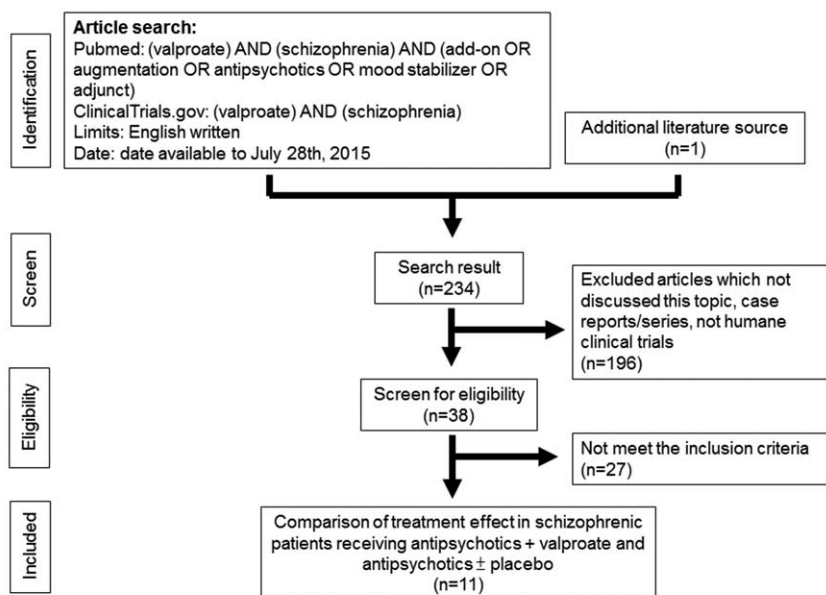


FIGURE 1. Flowchart of the selection strategy and inclusion/exclusion criteria in the current meta-analysis.

to evaluate the quality of clinical trials and applied these scores as one of the variables in procedure of meta-regression.³⁸

Data Extraction

The primary outcome was disease severity rating scale, which varied in every study and included the Brief Psychiatric Rating Scales (BPRS),³⁹ the CGI, and the PANSS.⁴⁰ All of the primary outcomes and other clinical variables were extracted from all of the studies included in the final stage. When data were not available in the literature, we tried to contact the authors to acquire the original data. Among these rating scales, we preferred the PANSS and BPRS rather than the CGI because they are more specific to the psychiatric settings. However, of these 2 scales, we chose the BPRS first because most studies have used it in current meta-analyses. We did not deal with the patient's personal data and only dealt with the statistical data meta-analysis, so the ethical approval was not applicable in the current meta-analysis.

Meta-analytic Methods and Data Extraction

All the effect sizes (ES) expressing changes in disease severity rating scales in each of the enrolled studies were set as the standardized mean difference, based on Hedges adjusted g .⁴¹ In our analysis, ES greater than 0 were considered to indicate greater improvements in the primary outcome in schizophrenic patients who received antipsychotics and valproate augmentation therapy than in patients treated with antipsychotics with/without a placebo, and we tried to derive the ES from other statistical parameters such as the t or P value with the sample size. All of the ES were synthesized using a random-effects model for every meta-analysis in the current study.

All of the meta-analytic procedures were performed using Comprehensive Meta-Analysis software, version 2 (Biostat, Englewood, NJ). Two-tailed P values <0.05 were considered to be statistically significant. We used Q statistics, their related P values, and the I^2 statistic to investigate the heterogeneity of each study. In addition, we used meta-regression to examine possible sources of heterogeneity using the unrestricted maximum likelihood method. We investigated publication bias through funnel plots, and Egger regression analysis was used to test statistically for the significance of any possible publication bias.⁴² In addition, to investigate the possible confounding effects by clinical variables such as disease severity, age, treatment duration, mean valproate dosage, quality of clinical trials, sex proportion, and whether or not the patients were drug-free, we performed meta-regression and subgroup meta-analysis. Finally, to exclude the possible confounding effect of diagnosis entity, we had made further subgroup meta-analysis in different disease entity, including different schizophrenia subtype. The current meta-analytic procedure fulfill with the criteria of Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) compliant (see supplementary information, <http://links.lww.com/MD/A665>).⁴³

RESULTS

Studies Included in Each Meta-analysis

A total of 38 articles reached the screening stage, of which 3 were excluded because of demographic research,^{44–46} 1 which was irrelevant to schizophrenia⁴⁷ and 1 which did not include a direct comparison of valproate augmentation therapy,^{11,48} because they were nonclinical trials such as case report/series, comments, or review articles,^{22,36,49–57}

1 because it used retrospective data,⁵⁸ 4 because of a lack of detailed data on treatment effect,^{12,35,59,60} and 6 because of a lack of a control group.^{29,61–65} After the screening procedure, a total of 11 articles remained for the current meta-analysis (Table 1).^{8,25–27,30–34,37,66}

The Main Results of the Current Meta-analysis

We investigated meta-analysis studies that compared the treatment effect of antipsychotics augmented with valproate or antipsychotics with/without placebo in schizophrenic patients. A total of 436 schizophrenic patients treated with antipsychotics augmented with valproate and 453 treated with antipsychotics with/without placebo were extracted from the 11 studies (Table 1). The treatment effect in the schizophrenic patients was significantly better in those treated with antipsychotics augmented with valproate than in those treated with antipsychotic treatment only (ES = 0.31, 95% confidence interval [CI] 0.05–0.57, $P = 0.020$) (Figure 2A). In addition, a significant heterogeneity within these studies was found ($Q = 24.35$, $df = 10$, $I^2 = 58.93\%$, $P = 0.007$). Also, there was a trend of publication bias detected using Egger test ($t = 2.13$, $df = 9$, 2-tailed $P = 0.062$) and visual examination by the funnel plot (Figure 2C).

We then used meta-regression to investigate any possible confounding clinical variables within these studies, the results of which revealed that treatment duration, mean age, and mean valproate dosage were significantly associated with the treatment effect (slope = -0.06 , $P < 0.001$; slope = -0.06 , $P = 0.014$; slope = -0.0005 , $P = 0.002$, respectively), rather than female sex, BPRS, and Jadad score ($P = 0.497$, 0.051 , and 0.487 , respectively).

Next, we did subgroup analysis by separating the included studies into open trials^{25,33,37,66} and RCTs.^{8,26,27,30–32,34} We found that valproate augmentation resulted in significantly better effect in open trials (ES = 0.60, 95% CI 0.13–1.06, $P = 0.012$), but not in RCT (ES = 0.19, 95% CI -0.10 to 0.47 , $P = 0.201$) (Figure 2B).

We further investigated whether valproate augmentation improved any subset of psychiatric symptoms. It was found that valproate augmentation did not improve positive symptoms (ES = 0.26, 95% CI -0.14 to 0.66 , $P = 0.203$) (Figure 3A) or negative symptoms (ES = 0.24, 95% CI -0.18 to 0.66 , $P = 0.263$) (Figure 3B) to a significant degree. Finally, we did not find any difference in dropout rate between patients with valproate augmentation and without valproate (odds ratio [OR] 0.71, 95% CI 0.45–1.12, $P = 0.141$) (Figure 3C).

The Main Results of the Meta-analysis in Those Who Were Drug-free

We then performed the meta-analysis focusing on the studies using participants who were drug-free. Here, we defined the patients under condition of “drug-free” as those who were drug-naïve or were after an adequate drug wash-out period. The results showed significantly better improvement in patients with valproate augmentation than those without valproate augmentation when including those who were drug-free^{26,30,37} (ES = 0.66, 95% CI 0.11–1.22, $P = 0.020$).

The Main Results of the Meta-analysis of Those With Moderate to Severe Disease

We subdivided the studies included in the current meta-analysis according to their mean scores of disease severity, either in PANSS or BPRS. The criteria of disease severity were based on the report of Leucht et al,^{67,68} which defined as

TABLE 1. Summary of Characteristics of Studies in the Current Meta-analysis

Study	Diagnostic Criteria	Diagnosis	Comparison	N	Dropout Rate	Sex (% Female)	Mean Age (y)	Severity	Primary Outcome	Trials	Country
Dose et al (1998)	DSM-III	Schizophrenia	Haloperidol + valproate	20	30.0%	n/a	n/a	Remit	BPRS	Prospective, DB, RPCT	Germany
Hesslinger et al (1999)	ICD-10	Schizoaffective	Haloperidol + placebo	22	31.8%	44.4	32.3 ± 14.1	n/a	pPANSS	Prospective, SB, RCCT	Germany
		Schizophrenia	Haloperidol + valproate	9	0%						
Wassef et al (2000)	n/a	Schizoaffective	Haloperidol	9	0%	41.7	28.5 ± 7.3	Moderate	BPRS	Prospective, DB, RPCT	USA
		Schizophrenia	Haloperidol + valproate	5	n/a						
Wassef et al (2001)	DSM-IV	Schizophrenia	Haloperidol + placebo	7	n/a	n/a	n/a	Severe	SANS	Prospective, case-control	USA
Casey et al (2003)	DSM-IV	Schizophrenia	Haloperidol	16	4.1%	24.0	38.8 ± 10.2	Severe	PANSS	Prospective, DB, RCCT	USA
Isaac and Isaac (2003)	ICD-10	Schizophrenia	Risperidone/olanzapine + valproate	120	12.5%	0	n/a	Severe	BPRS	Prospective, case-control	UK
Wang (2005)	CCMD-3	Schizophrenia	Antipsychotics + valproate	18	n/a	41.7	32.2 ± 7.3	Moderate	BPRS	Prospective, RCCT	China
Citrome et al (2007)	n/a	Schizophrenia	Risperidone + valproate	30	6.1	6.1	39.6 ± 10.5	Moderate	PANSS	Prospective, RCCT	USA
Casey et al (2009)	DSM-IV	Schizophrenia	Risperidone/olanzapine + valproate	195	62.6%	22.6	40.0 ± 10.5	Severe	BPRS	Prospective, DB, RPCT	USA
Glick et al (2009)	DSM-IV	Schizophrenia	Antipsychotics + valproate	8	n/a	36.0	n/a	n/a	PANSS	Prospective, DB, RPCT	USA
Larrison et al (2011)	DSM-IV	Schizoaffective Schizophrenia	Haloperidol + valproate	9	16.7	16.7	27.5	n/a	PANSS	Prospective, case-control	USA
			Haloperidol	9							

Data presentation: mean ± SD.

BPRS = Brief Psychiatric Rating Scale, CCMD-3 = Chinese Classification of Mental Disorders, 3rd edition, DB = double-blinded, DSM-III = Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, ICD-10 = International Classification of Disease, 10th edition, n/a = not applicable, PANSS = positive and negative syndrome scales, pPANSS = positive subscale of positive and negative syndrome scales, RCCT = randomized case-controlled trials, RPCT = randomized placebo-controlled trials, SANS = Schedule for Assessment of Negative Symptoms, SB = single-blinded, SD = standard deviation.

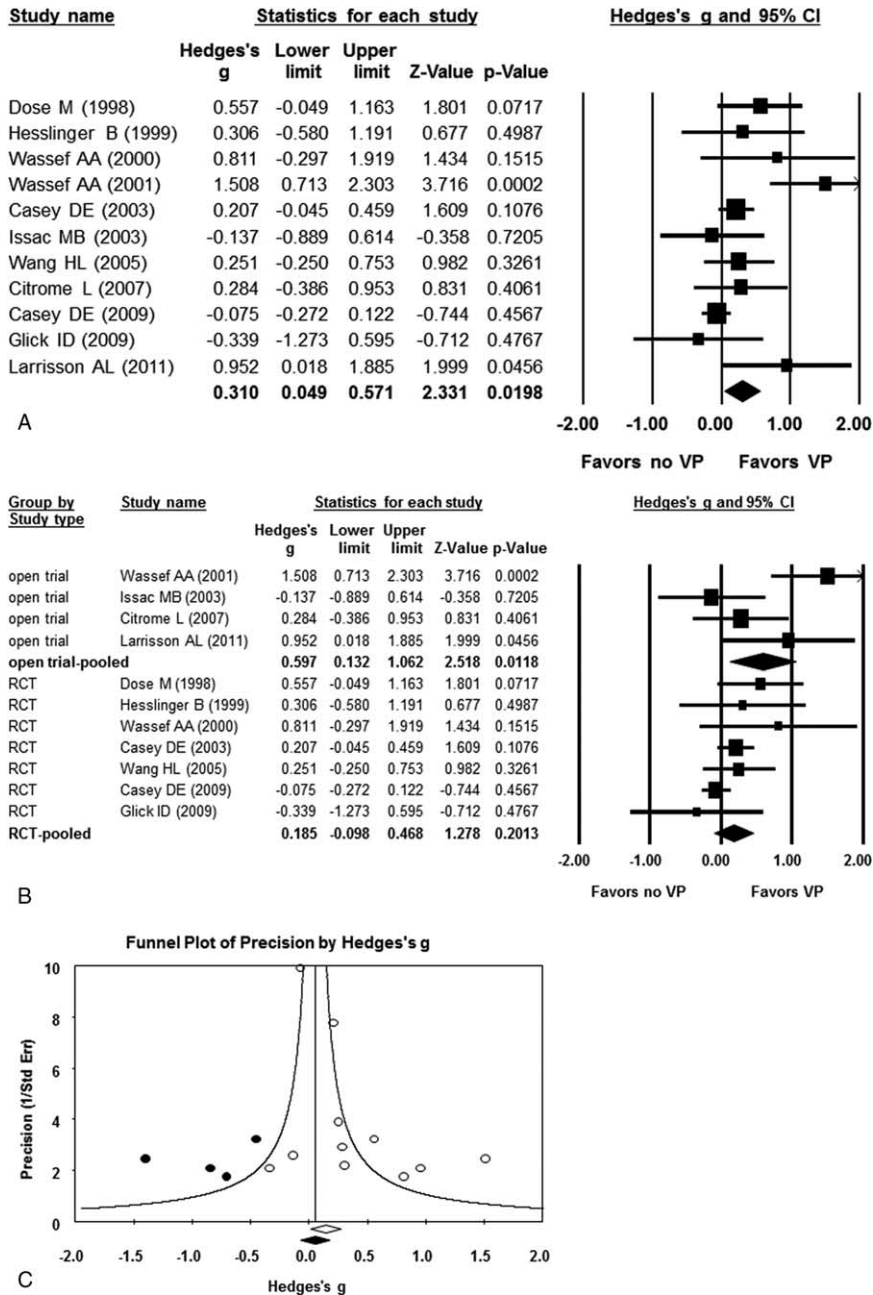


FIGURE 2. (A) Forest plot showing effect sizes (Hedges *g*) and 95% confidence intervals (CIs) from individual studies and pooled result in all included studies, comparing total psychopathology between patients receiving antipsychotics with valproate (VP) augmentation therapy and patients receiving antipsychotics monotherapy only. (B) Forest plot showing effect sizes (Hedges *g*) and 95% CIs from individual studies and pooled result comparing total psychopathology between patients receiving antipsychotics with VP augmentation therapy and patients receiving antipsychotics monotherapy only, separated by study type, open trial, and randomized controlled trial (RCT). (C) Funnel plot examining publication bias in all studies comparing total psychopathology between patients receiving antipsychotics with VP augmentation therapy and patients receiving antipsychotics monotherapy only. The plots describe the effect sizes (Hedges *g*) of studies vs their precision (inverse of standard error). Open dots and open diamond are shown as included studies and effect sizes (Hedges *g*) and 95% CIs of pooled result, separately. Dark dots are shown as imputed studies to counterbalance the publication bias of included studies. Dark diamond is shown as effect sizes (Hedges *g*) and 95% CIs of pooled result of included and imputed studies.

“mildly ill” when PANSS is 58 or BPRS 31, “moderately ill” when PANSS is 75 or BPRS 41, and “severely ill” when PANSS is 95 or BPRS 53. In the current meta-analysis, 1 study recruited schizophrenic patients with only mild disease

severity⁸ and another 3 with unknown disease severity which did not provide definite scores of rating scales.^{30,32,37} Therefore, to rule out possible confounding effects of mild disease severity, we focused on studies performed in patients with

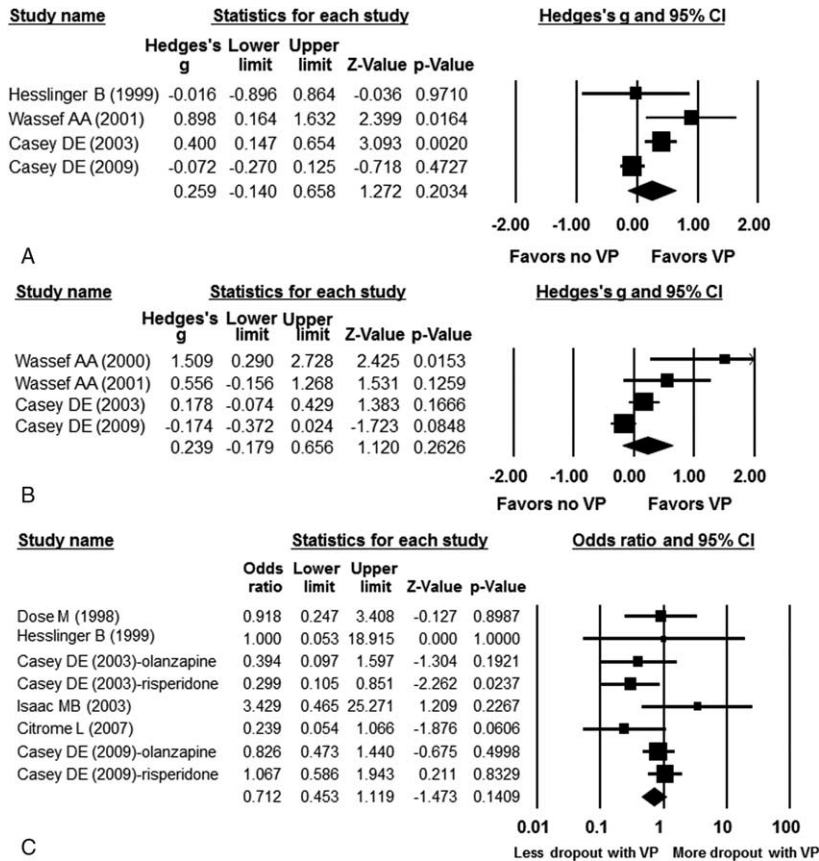


FIGURE 3. Forest plot showing effect sizes (Hedges *g*) and 95% confidence intervals (CIs) from individual studies and pooled result comparing (A) positive symptoms, (B) negative symptoms, and (C) dropout rate between patients receiving antipsychotics with valproate (VP) augmentation therapy and patients receiving antipsychotics monotherapy only.

moderate to severe disease severity.^{25,26,31,34,66} The main results showed that the treatment effect in schizophrenic patients did not have any significant difference between those treated with antipsychotics augmented with valproate and those treated with antipsychotics with/without placebo (ES = 0.28, 95% CI -0.03 to 0.59, *P* = 0.075).

Differences in the Main Results of the Meta-analysis Between Those With Short or Moderate to Long-term Treatment Duration

Because of the inverse association with the ES and the treatment duration, we performed another subgroup meta-analysis as the following procedure. To clarify the possible confounding effect of treatment duration on the treatment effect, we subdivided the studies according to the treatment duration stated in the treatment protocol in each study. There were 2 subgroups including one with a treatment duration of 4 weeks or longer^{8,27,30-34,66} and the other shorter than 4 weeks.^{25,26,37}

The main results remained the same when focusing on the studies, with a treatment duration shorter than 4 weeks (ES = 1.17, 95% CI 0.64-1.70, *P* < 0.001), but the difference was insignificant when focusing on the studies with a treatment duration of 4 weeks or longer (ES = 0.10, 95% CI: -0.06 to 0.26, *P* = 0.228).

The Differences in the Main Results of the Subgroup Meta-analysis in Different Schizophrenia Entities

Because of possible founding effect of better treatment effect of valproate in schizoaffective patients, we made further meta-analysis excluding the studies using patients with schizoaffective disorder. In this part of meta-analysis, the treatment effect was still significantly better in those treated with antipsychotics augmented with valproate than in those treated with antipsychotics treatment only when we focused in studies using schizophrenic patients only (ES = 0.34, 95% CI 0.03-0.65, *P* = 0.032). Furthermore, a significant heterogeneity within these studies was found (*Q* = 21.37, *df* = 7, *I*² = 67.24%, *P* = 0.003). Also, there was a trend of publication bias detected using Egger test (*t* = 2.43, *df* = 6, 2-tailed *P* = 0.051).

On the contrary, we had tried to investigate the treatment effect of valproate in different schizophrenia subtypes. However, most of the studies used subjects with unknown subtype or mixed subtype diagnosis, including paranoid, disorganized, or undifferentiated type. There were only 2 articles using pure diagnosis of schizophrenia subtype.^{25,37} Therefore, the subgroup meta-analysis of different diagnosis of schizophrenia subtype could not be performed. However, among these 2 literatures using patients with diagnosis of schizophrenia, paranoid type, the results were both significantly better treatment

effect in patients receiving valproate augmentation than those without valproate augmentation.

DISCUSSION

Previous studies and meta-analyses on the efficacy of valproate augmentation therapy for schizophrenia or schizoaffective disorder have reported inconsistent conclusions and a lack of evidence to support the use of augmentation strategy in clinical practice. The inconclusive findings might be derived from the limited data available at that time. In recent years, there had been some newer reports about the treatment effect of valproate in schizophrenia published^{31,32,37}; among them, some were well designed, randomized, case-control trials.^{31,32} We conducted a systematic literature search and reviewed all articles available through PubMed, and our main finding was that the treatment effect was significantly better in the patients with schizophrenia or schizoaffective disorder who received antipsychotics and valproate than in those who received antipsychotics with/without placebo. Furthermore, the results remained unchanged when including studies on patients who were drug-free only or including studies using schizophrenic patients only. Meta-regression analysis revealed a significantly inverse association between the treatment effect and the duration of treatment, mean valproate dosage, and the mean age. The results of the meta-analysis remained the same when focusing on studies using a shorter treatment duration, but not in studies using a longer treatment duration.

The result of previous meta-analysis conducted by the Schwarz et al³⁶ revealed inconsistent findings of the treatment effect of valproate augmentation therapy. However, in recent 6 years, there are several trials been published,^{31,32,37} which may attribute new findings in the current knowledge about the treatment strategy of valproate augmentation therapy. In addition, in the meta-analysis by the Schwarz et al, the authors focused on the different rating scales of disease severity and side-effect profiles only. On the contrary, the current meta-analysis raised another finding, which may bring important clinical implication, namely the significantly better treatment effect in the schizophrenic patients who were drug-free.

In current meta-analysis, our results showed still significant better response in patients receiving valproate augmentation therapy who were drug-free when entering the study. This is an interesting finding because the valproate augmentation strategy would be preferred in later stage of treatment or for those patients who are treatment-resistant schizophrenic patients. These phenomena may be due to the side effects of valproate augmentation strategy and the lack of sufficient evidence to prove the efficacy of valproate augmentation.^{2,36,69} However, valproate augmentation therapy for schizophrenia has been reported to be more beneficial in a rapid response and in those with severe hostility and aggression.^{8,27,28} On the contrary, the inverse association with treatment effect, and the duration of treatment and the results of meta-analysis in different periods of treatment revealed that the treatment effect was significantly better in the schizophrenic patients receiving antipsychotics and valproate than in those receiving antipsychotics with/without placebo for a treatment duration of less than 4 weeks rather than more than 4 weeks. The significantly better treatment effect with a shorter rather than a longer treatment duration could also support the phenomenon observed in a study conducted by Casey et al,²⁷ which revealed that valproate augmentation therapy was significantly beneficial for a rapid response. Therefore, taken the evidences together, it

seems as though valproate augmentation strategy should not only be limited to those with treatment-resistant schizophrenia but also for those who need a rapid response or for those with aggression or severe hostility.

With regards to the safety of the long-term use of valproate augmentation therapy, the dropout rate in current meta-analysis revealed insignificant difference between the experimental group (patients receiving valproate augmentation therapy) and the control group (patients without valproate augmentation therapy). Furthermore, in studies included in the current meta-analysis, the 3 studies which used a longer duration^{31–33} revealed no severe side effects in the groups receiving antipsychotics augmented with valproate. One case who received antipsychotics + valproate developed more depressive symptoms and suicide risk in a study conducted by Glick et al³²; however, there was a lack of further information to clarify whether these symptoms were a result of disease progression or a drug side effect. In addition, Casey et al found a significant decrease from baseline in platelet count in patients receiving valproate augmentation therapy compared with the monotherapy group. Nevertheless, there was no evidence of the development of severe or life-threatening thrombocytopenia related to the decreased platelet count.³¹ In contrast, the mean serum level of low-density lipoprotein cholesterol was significantly decreased from baseline in the group receiving valproate augmentation therapy compared with the antipsychotic monotherapy group, suggesting a significantly improved lipid profile in the augmentation group. Compared with the antipsychotic monotherapy, other mild drug side effects of valproate augmentation therapy, including somnolence, weight gain, urinary incontinence, and back pain, have been reported.³¹

Another issue is whether the benefits of valproate augmentation therapy only exist in schizophrenic patients with specific disease severity or not. The results of the current meta-analysis revealed insignificant findings, namely, there was no significant difference in severe/moderate schizophrenic patients receiving valproate augmentation therapy and those without valproate augmentation therapy. On the contrary, there was only 1 study compared valproate augmentation therapy and antipsychotic monotherapy in patients with mild schizophrenia, which reported only some benefits in “hostility belligerence,” but not an overall therapeutic effect.⁸

About the effect of dosage of valproate on the treatment effect, in this meta-analysis, there is a significantly inverse association between the treatment effect and the mean valproate dosage through meta-regression. This phenomenon might be partially explained by the concomitant sedative side effects along with the increased valproate dosage, which would mask the improvement of the psychopathology.³¹

LIMITATION

There are some limitations to this study. First, we did not perform a detailed meta-analysis for every category of antipsychotics used in each study such as traditional and atypical antipsychotics. Second, the significant better response in the schizophrenic patients with valproate augmentation therapy than those without valproate augmentation turned out to be insignificant when focusing studies with RCT design. Third, only 1 study discussed the treatment effect of valproate augmentation therapy in patients with a milder severity of disease. In addition, we performed meta-analysis of dropout rate in these 2 groups, but did not investigate the long-term effect and safety profiles of valproate augmentation therapy in maintenance

treatment for chronic schizophrenia or schizoaffective disorder. Furthermore, we did not analyze the drug side-effect profiles between patients receiving valproate augmentation therapy and antipsychotic monotherapy. In addition, clinicians should be careful when apply the results of the current study in pregnant patients. Actually, most of the studies had excluded pregnant patients from their study participants because the valproate had been proven to have teratogenic effect in pregnant women with schizophrenia.⁵² Therefore, in the current meta-analysis, we could not investigate the safety of valproate in pregnancy because of lack of data. In addition, although we had tried our best to investigate the possible founding effects of the clinical variables through meta-regression test or subgroup metaanalysis, we still could not rule out the confounding effects of the other clinical variables, such as disease subtype, valproate dosage, body mass index, duration of illness, age of onset, and so on because of lack of data.

CONCLUSIONS

The current meta-analysis highlights that the treatment effect was significantly better in patients with schizophrenia or schizoaffective disorder who received valproate augmentation therapy than those receiving antipsychotics monotherapy. This significance persisted in comparison with those who were drug-free. This finding has an important clinical implication because it provides the rationale for valproate augmentation therapy in schizophrenic patients, which is practiced worldwide despite a lack of conclusive evidence. However, further studies are needed to elucidate the treatment effect and safety profile of valproate augmentation therapy for maintenance therapy in patients with chronic schizophrenia or schizoaffective disorder.

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Y-WC, who is a junior neurologist and works equally as the other one of the first author, takes the responsibility of writing down the section of the methods and results and part of the pharmacokinetics of valproate in the section of introduction.

WC, one of the senior psychiatrists, takes the responsibility of both final judgment of literature searching and writing down the part of role of methylation via valproate prescription in the section of introduction.

K-YT, one of the junior psychiatrists, takes the responsibility of both literature searching and providing the excellent comment of possible confounding effect of “drug-free.”

H-YW, one of the junior psychiatrists, takes the responsibility of both literature searching and raising critical comment on the possible confounding effect via the different treatment duration in each study.

C-KW, one of the senior psychiatrists, raises the comparison of adverse effect by valproate augmentation in each study included in current meta-analysis.

Lin P.Y., the other one of the senior psychiatrists and the corresponding author, helps in the procedure of meta-analysis, provides great comment on the role of methylation and demethylation along with the course of schizophrenia, and collects and revises all the information from all the other authors.

All authors reviewed and agreed with the final draft of the manuscript.

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