Clozapine Augmentation With Antiepileptic Drugs for Treatment-Resistant Schizophrenia:

A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Objective: To meta-analyze randomized controlled trials (RCTs) for the efficacy and safety of adjunctive antiepileptic drugs (AEDs) to augment clozapine therapy for treatment-resistant schizophrenia.

Data Sources: The search included databases in English (PubMed, PsycINFO, Embase, and Cochrane Library databases and the Cochrane Controlled Trials Register) and in Chinese (China Journal Net [CJN], WanFang, and China Biology Medicine [CBM]) and references from retrieved articles. The databases were searched using dates inclusive from their onset until January 1, 2016, for terms reflecting (*a*) schizophrenia, (*b*) clozapine, and (*c*) adjunctive drugs.

Study Selection: From 1,969 potentially relevant articles, 21 articles describing 22 RCTs were selected.

Data Extraction: Two independent investigators extracted data for a random-effects meta-analysis and assessed the quality of the studies using risk of bias and the Jadad scale. Standard mean difference, risk ratio (RR) ± 95% confidence intervals (CIs), and the number needed to harm (NNH) were used.

Results: A total of 22 RCTs (N = 1,227) with 4 AEDs (topiramate [5 RCTs, n = 270], lamotrigine [8 RCTs, n = 299], sodium valproate [6 RCTs, n = 430], and magnesium valproate [3 RCTs, n = 228]) were analyzed. The means weighted by sample size were 12.1 weeks for treatment duration, 36.2 years for age, and 61% for male frequency. Significant superiority in total psychopathology was observed for topiramate ($P < .0001$), lamotrigine ($P = .05$), and sodium valproate ($P = .002$), compared to clozapine monotherapy. After removing outliers, the positive effect of sodium valproate remained, but the positive effect of lamotrigine disappeared ($P = .40$). Significantly improved efficacy in positive and general symptom severity was observed for topiramate ($P = .04$ and $P = .02$, respectively) and sodium valproate ($P = .009$ and $P = .003$, respectively). There were no significant differences regarding adverse drug reactions and all-cause discontinuations except for topiramate, which was associated with more all-cause discontinuations (RR = 1.99; 95% CI, 1.16 to 3.39; $P = .01$; $I^2 = 0\%$; NNH = 7).

Conclusions: Sodium valproate augmentation was efficacious and safe. Topiramate augmentation had a too-high discontinuation rate. High-quality RCTs are needed to inform clinical recommendations.

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Schizophrenia is a severe chronic psychiatric disorder associated with social impairment, lower quality of life, and great direct and indirect costs.[1] In spite of the advances in psychopharmacologic treatment, up to 70% of patients with schizophrenia who receive antipsychotics still suffer from unremitting psychotic symptoms.[2]

Traditionally, clozapine has been considered significantly superior to other antipsychotics in improving psychotic symptoms and social functioning and reducing the number of hospitalizations.[3,4] A Bayesian-framework, multiple-treatment meta-analysis of randomized controlled trials (RCTs)[5] and a review of effectiveness trials[6] demonstrated the superiority of clozapine over other antipsychotics in schizophrenia. More recently, a network meta-analysis[7] has questioned this traditional belief, but this recent network meta-analysis has been criticized, particularly regarding the generalizability of the samples that were enrolled in the blinded RCTs.[8]

Clozapine has been recommended for treatment-resistant schizophrenia after the failure of 2 adequate antipsychotic trials.[9,10] However, in spite of the superior efficacy of clozapine, only 30% to 60% of patients with treatment-resistant schizophrenia benefit from clozapine monotherapy.[10] Therefore, different clozapine augmentation strategies have been tried including electroconvulsive therapy (ECT), conventional or second-generation antipsychotics, mood stabilizers/antiepileptic drugs (AEDs), antidepressants, benzodiazepines, and glutamatergic compounds.[2,11–16]

Prior reviews and meta-analyses of clozapine augmentation with AEDs for treatment-resistant schizophrenia focused on adjunctive topiramate and lamotrigine in English-language databases.[2,11–14,17] Thus, we conducted this meta-analysis of RCTs to assess the efficacy and safety of all adjunctive AEDs as a pharmacologic augmentation strategy for clozapine for treatment-resistant schizophrenia identified in databases in the English and Chinese languages. For many years, clozapine has been the most frequently used antipsychotic in China.[18]

METHODS

Search Strategy and Selection Criteria

Two independent investigators (W.Z. and X.-H.Y.) systematically searched databases in English (PubMed,

Clinical Points

- There is no agreement in the literature on which adjunctive antiepileptic drug is best for augmenting clozapine in treatment-resistant schizophrenia.
- The limited published randomized controlled trials for clozapine augmentation suggest that augmenting with sodium valproate may be efficacious and safe.

PsycINFO, Embase, and Cochrane Library databases and the Cochrane Controlled Trials Register) and Chinese (China Journal Net [CJN], WanFang, and China Biology Medicine [CBM]) for RCTs concerning the efficacy and safety of any AED for clozapine augmentation in patients with treatment-resistant schizophrenia. We found RCTs using topiramate, lamotrigine, sodium valproate, and magnesium valproate. The databases were searched using dates inclusive from their onset until January 1, 2016, using the following search terms: (*schizophrenic disorder* OR *disorder*, *schizophrenic* OR *schizophrenic disorders* OR *schizophrenia* OR *dementia praecox*) AND (*leponex* OR *clozapine* OR *clozaril*) AND (*valproate* OR *topiramate* OR *lamotrigine* OR *carbamazepine* OR *gabapentin* OR *vigabatrin*). Additionally, the reference lists of the retrieved articles and relevant review articles were examined for cross references. When necessary, authors were contacted for additional information.

According to the acronym *PICOS*, we used the following selection criteria—***P***articipants: patients with treatment-resistant schizophrenia using any diagnostic criteria, ***I***ntervention: antiepileptic medication plus clozapine, ***C***omparison: clozapine plus placebo or clozapine monotherapy, ***O***utcomes: efficacy and safety, and ***S***tudy design: only RCTs. Case series, nonrandomized studies, and nonoriginal research (reviews and meta-analyses) were excluded.

The protocol for this systematic review was registered on PROSPERO (CRD42015016227) and is available at http://www.crd.york.ac.uk/PROSPERO/.

Data Extraction and Outcome Measures

Data extraction was based on intent-to-treat (ITT) analysis or modified ITT data (ie, at least 1 dose or at least 1 follow-up assessment) if provided; data synthesis and assessment of study quality were conducted by 2 independent investigators (W.Z. and X.-H.Y.). Inconsistencies were resolved by consensus or the involvement of a third reviewer (Y.-T.X.).

The primary outcome measure was the change in total score of the Positive and Negative Syndrome Scale (PANSS)[19] or the Brief Psychiatric Rating Scale (BPRS).[20] The key secondary outcomes included Positive, Negative, and General Psychopathology Symptoms subscales of the PANSS or the BPRS or the total scores on the Scale for the Assessment of Positive Symptoms (SAPS)[21] and the Scale for the Assessment of Negative Symptoms (SANS)[22]; response or remission as defined by each study; all-cause discontinuations; and adverse drug reactions (ADRs).

Assessment of Study Quality

The quality of each study was assessed with the Jadad scale[23]; high and low quality were defined as Jadad score ≥ 3 and < 3, respectively. The methodological quality of RCTs was assessed by using risk of bias.[24]

Data Synthesis and Statistical Analyses

The meta-analysis was performed using Review Manager version 5.3 software (http://www.cochrane.org) for statistical analyses. To combine studies, we used the random effects model by DerSimonian and Laird[25] in all cases. For continuous data and dichotomous data, standard mean difference (SMD) and risk ratio (RR) ± 95% confidence intervals (CIs) were calculated, respectively. Furthermore, the number needed to treat (NNT) and the number needed to harm (NNH) were calculated by dividing 1 by the risk difference when RR was significant. Study heterogeneity was measured using the χ^2 and I^2 values, with values of $P < .1$ and ≥ 50%, respectively, indicating heterogeneity.[26] In cases where I^2 values were ≥ 50% for primary outcome, sensitivity analyses were performed to determine the reasons for the heterogeneity. Furthermore, we conducted 4 subgroup analyses for total psychopathology including (1) Chinese versus non-Chinese studies, (2) studies describing versus those not describing randomization details, (3) double-blind/rater-masked versus nonblinded studies, and (4) Jadad score ≥ 3 (high quality) versus Jadad score < 3 (low quality). Publication bias was assessed using funnel plots and Egger intercept[27] using STATA version 12.0 software (http://www.stata.com). All statistical differences were considered significant at the level of $P < .05$.

RESULTS

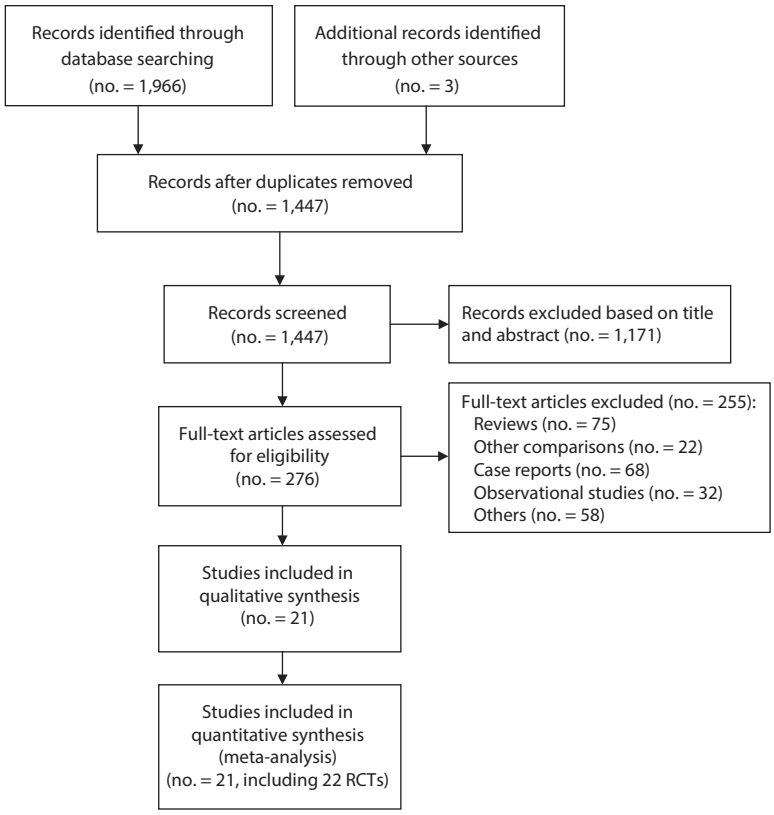
Literature Search

Figure 1 describes the literature search. Of the 1,969 potentially relevant articles, 21 articles[1,28–47] with 22 RCTs (see Supplementary eTable 1 at PSYCHIATRIST.COM) met the selection criteria for meta-analysis. One of the 21 articles[31] included 2 RCTs.

RCTs and Patient and Treatment Characteristics

Supplementary eTable 1 shows 22 RCTs comprising 1,227 patients (sample size range, 4–100 patients). The mean of the treatment duration weighted by sample size was 12.1 weeks (range, 4–24 weeks) comparing the clozapine augmentation (n = 614) with topiramate (n = 270 in 5 RCTs), lamotrigine (n = 299 in 8 RCTs), sodium valproate (n = 430 in 6 RCTs), or magnesium valproate (n = 228 in 3 RCTs) versus clozapine alone (n = 613). From the data available, we calculated means weighted by sample size for age (36.2 years [range, 28.8–46.0 years]), for illness duration (9.2 years [range, 4.3–18.3 years]), and for male frequency (61%; range, 0%–100%). Among the 22 RCTs, 12 RCTs were conducted in China (n = 834); 2 RCTs each in the United States (n = 63), Italy (n = 120), Iran (n = 112), and Finland (n = 60); and 1 RCT each in Japan (n = 34) and Israel (n = 4).

Figure 1. PRISMA Flow Diagram



Abbreviation: RCT = randomized controlled trial.

Quality Assessment and Publication Bias

Supplementary eFigure 1 presents the quality of studies using risk of bias. While 12 RCTs described an adequate method of random sequence generation, only 4 RCTs reported the allocation concealment methods, and only 3 RCTs employed a protocol registration. Among the 22 RCTs, 11 RCTs were double-blind, 10 RCTs were open-label, and 1 RCT used masked assessors. Regarding outcome data, 44% (4/9 RCTs) used ITT analysis for incomplete outcome data. The mean Jadad score weighted by sample size was 2.8 (range, 1–5). Furthermore, due to the limited number (below 10) of RCTs included in each analysis, we cannot conduct a funnel plot analysis to explore publication bias.

Psychotic Symptoms

Figures 2 and 3 present the efficacy of 4 AEDs (topiramate, lamotrigine, sodium valproate, and magnesium valproate) as clozapine augmentation options for treatment-resistant schizophrenia. When combined together, the 4 AEDs showed significant superiority in PANSS/BPRS total scores (19 RCTs, n = 944) (SMD = −0.82; 95% CI, −1.14 to −0.50; $P < .00001$; $I^2 = 81\%$; Figure 2) and study-defined response (6 RCTs, n = 456) (SMD = 1.57; 95% CI, 1.16 to 2.14; $P = .003$; $I^2 = 24\%$; Figure 3) for treatment-resistant schizophrenia.

Topiramate. The pooled effect of 4 RCTs[28,34,35,39] showed that topiramate-clozapine augmentation (n = 75) was associated with a significant reduction in total score for PANSS (2 RCTs) or BPRS (2 RCTs), compared to clozapine monotherapy (n = 84) (SMD = −0.89; 95% CI, −1.30 to −0.47; $P < .0001$; $I^2 = 33\%$; Figure 2). The same was true in all subgroup analyses (Table 1).

Regarding Positive (SMD = −0.49; 95% CI, −0.97 to −0.02; $P = .04$; $I^2 = 64\%$; Supplementary eTable 2), Negative (SMD = −0.70; 95% CI, −1.14 to −0.27; $P = .002$; $I^2 = 56\%$; Supplementary eTable 2), and General Psychopathology Symptoms scores (SMD = −0.52; 95% CI, −0.93 to −0.10; $P = .02$; $I^2 = 42\%$; Supplementary eTable 2), the meta-analyses showed significant superiority of topiramate-clozapine augmentation over clozapine monotherapy.

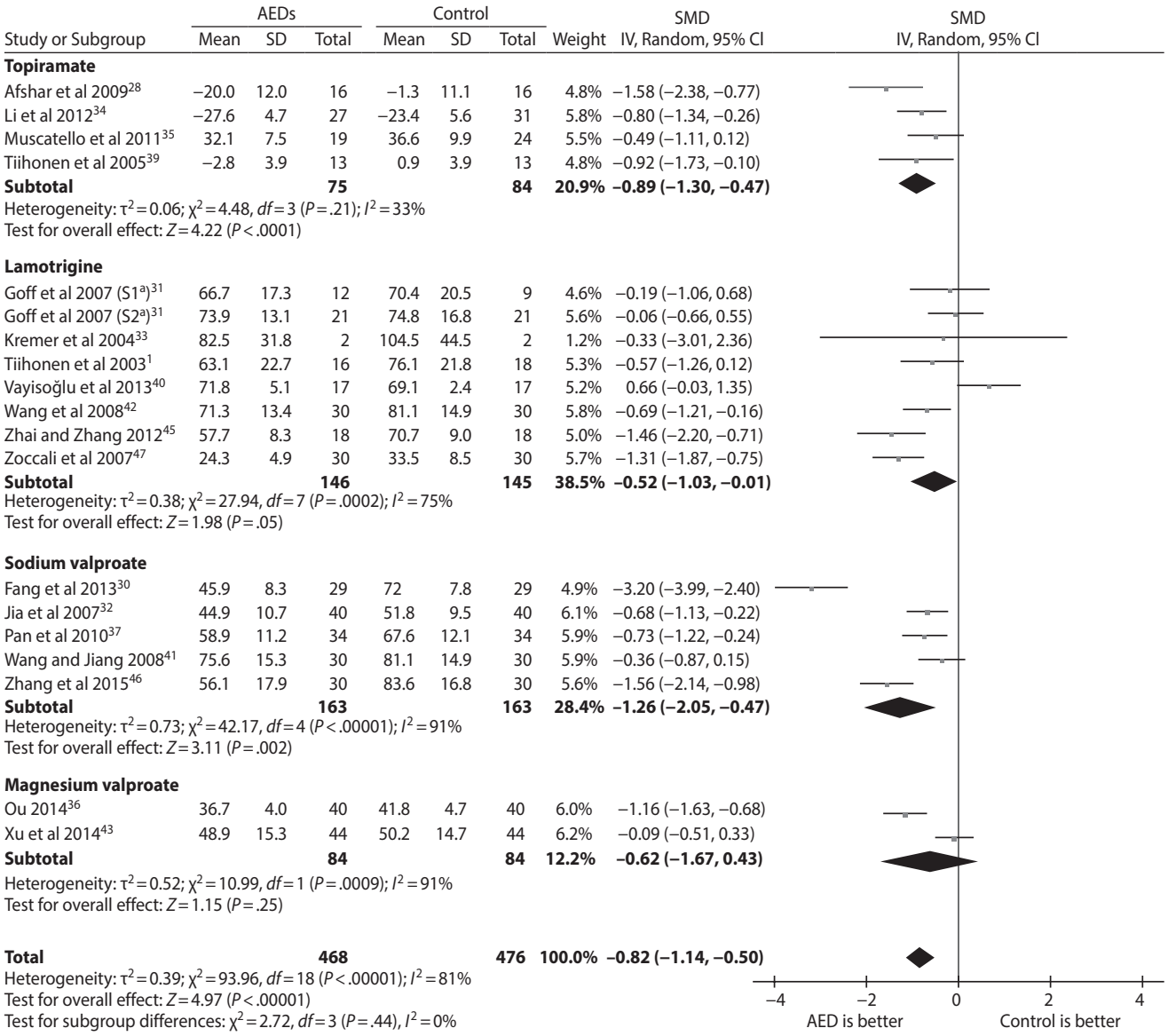
Lamotrigine. The pooled effect of 8 RCTs[1,31,33,40,42,45,47] showed that lamotrigine-clozapine augmentation (n = 146) was associated with a marginally significant reduction in the total score of PANSS (7 RCTs) or BPRS (1 RCT) compared to clozapine monotherapy (n = 145) (SMD = −0.52; 95% CI, −1.03 to −0.01; $P = .05$; $I^2 = 75\%$; Figure 2). However, the significance disappeared when the 2 outliers (SMD < −1.0)[45,47] were excluded from analysis (SMD = −0.19; 95% CI, −0.64 to 0.26; $P = .40$; $I^2 = 53\%$). When lamotrigine-clozapine augmentation was compared with clozapine monotherapy, the results of all subgroup analyses demonstrated a significant difference when pooling data from Chinese RCTs ($P = .0008$) but not in non-Chinese RCTs ($P = .35$) (Table 1).

Regarding Positive, Negative, and General Psychopathology Symptoms scores, the meta-analyses showed no significant difference between lamotrigine-clozapine cotreatment and clozapine monotherapy (SMD = −0.52 to −0.35; 95% CI, −1.56 to 0.53; $P = .06$ to $.33$; $I^2 = 57\%$–87%; Supplementary eTable 2). Additionally, regarding study-defined response (reduction in PANSS total score was ≥ 50%), the effect of 1 RCT[42] showed no significant difference between lamotrigine-clozapine augmentation versus clozapine monotherapy (RR = 2.40; 95% CI, 0.96 to 5.98; $P = .06$; Figure 3).

Sodium valproate. The pooled effect of 5 RCTs[30,32,37,41,46] showed that sodium valproate–clozapine augmentation (n = 163) was associated with a significant reduction in PANSS total score (5 RCTs) compared with clozapine monotherapy (n = 163) (SMD = −1.26; 95% CI, −2.05 to −0.47; $P = .002$; $I^2 = 91\%$; Figure 2). The results remained significant when the 2 outliers (SMD < −1.0)[32,46] were excluded from the analysis (SMD = −0.60; 95% CI, −0.88 to −0.32; $P < .0001$; $I^2 = 0\%$). The results were consistent in all subgroup analyses (Table 1).

Regarding Positive and General Psychopathology Symptoms scores, the meta-analyses showed significant superiority of sodium valproate–clozapine augmentation over clozapine monotherapy (respective values were SMD = −0.78 and

Figure 2. AED Augmentation of Clozapine for Treatment-Resistant Schizophrenia: Forest Plot for Total Score of the PANSS and the BPRS[1,28,30–35,37,39,40,41–43,45–47]



[a]This article included 2 studies called Study 1 (S1) and Study 2 (S2). In the article, the authors provide specific labels to identify them: SCA30926 for S1 and SCA101464 for S2.

Abbreviations: AED = antiepileptic drug, BPRS = Brief Psychiatric Rating Scale, IV = inverse variance, PANSS = Positive and Negative Syndrome Scale, SMD = standard mean difference.

−1.14; 95% CI, −1.36 to −0.20 and −1.90 to −0.38; $P = .009$ and .003; $I^2 = 84\%$ and 87%; Supplementary eTable 2), but not in Negative Symptoms (SMD = −0.26; 95% CI, −0.55 to 0.03; $P = .08$; $I^2 = 43\%$; Supplementary eTable 2). Regarding study-defined response, defined as a reduction in PANSS total score ≥ 50% (2 RCTs) or BPRS total score ≥ 30% (1 RCT), the pooled effect of 3 RCTs[37,41,44] showed that sodium valproate–clozapine augmentation was not associated with a significant difference compared to clozapine monotherapy (RR = 1.36; 95% CI, 0.91 to 2.03; $P = .13$; $I^2 = 36\%$; Figure 3).

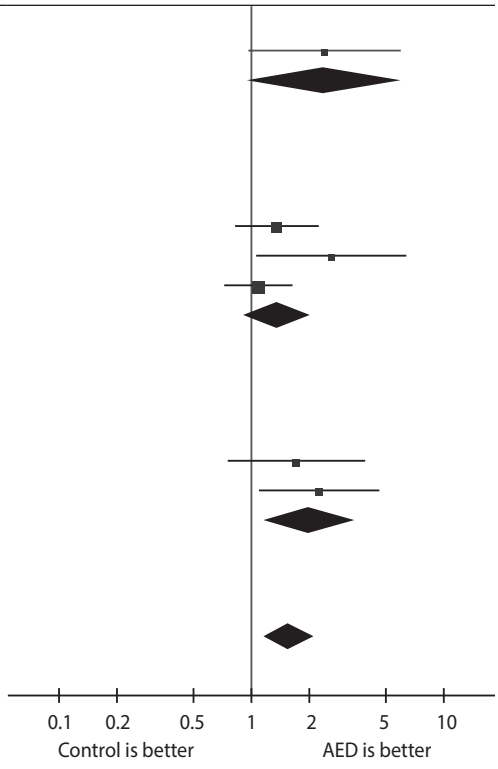
Magnesium valproate. The pooled effect of 2 RCTs[36,43] showed no significant difference between magnesium valproate–clozapine augmentation (n = 84) and clozapine monotherapy (n = 84) regarding the total score of PANSS (1 RCT) or BPRS (1 RCT) (SMD = −0.62; 95% CI, −1.67 to 0.43; $P = .25$; $I^2 = 91\%$; Figure 2). Furthermore, there were no available data regarding Positive and General Psychopathology Symptoms scores between the 2 groups. Regarding study-defined response, defined as a reduction in PANSS total score ≥ 50% (1 RCT) or BPRS total score ≥ 30% (1 RCT), the pooled effect of 2 RCTs[36,43] showed significant superiority of magnesium valproate–clozapine augmentation over clozapine monotherapy (RR = 2.00; 95% CI, 1.16 to 3.44; $P = .01$; $I^2 = 0\%$; NNT = 6; Figure 3).

Treatment Discontinuation and ADRs

Figure 4 shows all-cause discontinuation (RR = 1.47; 95% CI, 0.97 to 2.22; $P = .07$; $I^2 = 0\%$) for AEDs (topiramate,

Figure 3. AED Augmentation of Clozapine for Treatment-Resistant Schizophrenia: Forest Plot for Response Defined by Each Study[36,37,41–44]

Study or Subgroup	AEDs Events	AEDs Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Lamotrigine						
Wang et al 2008[42]	12	30	5	30	9.6%	2.40 (0.96, 5.98)
Subtotal		**30**		**30**	**9.6%**	**2.40 (0.96, 5.98)**
Total events	12		5			
Heterogeneity: Not applicable						
Test for overall effect: $Z = 1.88$ ($P = .06$)						
Sodium valproate						
Pan et al 2010[37]	19	34	14	34	24.1%	1.36 (0.82, 2.24)
Wang and Jiang 2008[41]	13	30	5	30	9.8%	2.60 (1.06, 6.39)
Yuan et al 1994[44]	25	50	23	50	30.8%	1.09 (0.72, 1.64)
Subtotal		**114**		**114**	**64.8%**	**1.36 (0.91, 2.03)**
Total events	57		42			
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 3.14$, $df = 2$ ($P = .21$); $I^2 = 36\%$						
Test for overall effect: $Z = 1.51$ ($P = .13$)						
Magnesium valproate						
Ou 2014[36]	12	40	7	40	11.4%	1.71 (0.75, 3.90)
Xu et al 2014[43]	18	44	8	44	14.2%	2.25 (1.09, 4.62)
Subtotal		**84**		**84**	**25.6%**	**2.00 (1.16, 3.44)**
Total events	30		15			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.24$, $df = 1$ ($P = .63$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.51$ ($P = .01$)						
Total		**228**		**228**	**100.0%**	**1.57 (1.16, 2.14)**
Total Events	99		62			
Heterogeneity: $\tau^2 = 0.03$; $\chi^2 = 6.60$, $df = 5$ ($P = .25$); $I^2 = 24\%$						
Test for overall effect: $Z = 2.92$ ($P = .003$)						
Test for subgroup differences: $\chi^2 = 2.02$, $df = 2$ ($P = .36$), $I^2 = 1.1\%$						



Abbreviations: AED = antiepileptic drug, M-H = Mantel-Haenszel.

lamotrigine, and sodium valproate) used as a clozapine augmentation strategy. Supplementary eTable 3 describes the meta-analysis of the available ADRs; no significant group differences were found in each analysis.

Regarding all-cause discontinuation in the individual medication, the results showed that topiramate-clozapine augmentation had more discontinuations than clozapine monotherapy (RR = 1.99; 95% CI, 1.16 to 3.39; $P = .01$; $I^2 = 0\%$; NNH = 7), while lamotrigine and sodium valproate were similar.

DISCUSSION

This is the most comprehensive meta-analysis of clozapine therapy augmented with AEDs for treatment-resistant schizophrenia; it included 22 RCTs (n = 1,227) and 4 AEDs. Compared with clozapine monotherapy, topiramate, lamotrigine, and sodium valproate showed significant improvement in total symptom severity. The positive efficacy of lamotrigine disappeared after 2 outliers were removed, and the superior effect of sodium valproate remained after 2 outliers were removed in the meta-analysis. Significantly improved efficacy in Positive and General Psychopathology Symptoms severity was found for topiramate and sodium valproate. Topiramate showed improved efficacy for Negative Symptoms over clozapine monotherapy. Augmentation with AEDs was well tolerated in patients with treatment-resistant schizophrenia, except for topiramate, which was associated with more all-cause discontinuations (NNH = 7).

The significant effect size of topiramate was found in total and Positive, Negative, and General Psychopathology Symptoms severity, and the results were significant for total psychopathology in all subgroup analyses. Sommer et al[2] reviewed augmentation strategies for treatment-resistant schizophrenia, which included 3 RCTs of topiramate. As Sommer et al[2] did not include the study by Li et al,[34] published in Chinese, they came to a negative conclusion when they excluded the study by Afshar et al[28] as an outlier.

Lamotrigine showed effects similar to clozapine monotherapy in Positive, Negative, and General Psychopathology Symptoms severity, except for a marginally significant reduction in total symptom severity, as in a prior review.[48] In the Chinese studies, lamotrigine had greater effects on total psychopathology, consistent with earlier reviews[2,49] on the combination of clozapine and lamotrigine for treatment-resistant schizophrenia.

Augmentation with sodium valproate showed more improvement than the control group in total symptom severity and both Positive and General Psychopathology subscores of the PANSS with high heterogeneity, but not in the Negative subscore. Furthermore, the results of exploratory analysis from all subgroup analyses were

Table 1. Subgroup Analysis of the Effect of Variables Mediating Total Symptom Severity

Antiepileptic Drug	No. of Patients (no. of RCTs)	SMD (95% CI)	I^2 (%)	*P* Value[a]
Topiramate				
Origin				
Chinese	58 (1)	−0.82 (−1.34 to −0.26)	NA	**.004**
Non-Chinese	101 (3)	−0.96 (−1.59 to −0.32)	54	**.003**
Description of randomization details				
Yes	158 (4)	−0.89 (−1.30 to −0.47)	33	**<.0001**
Blinded studies				
Yes	101 (3)	−0.96 (−1.59 to −0.32)	54	**.003**
No	58 (1)	−0.82 (−1.34 to −0.26)	NA	**.004**
Jadad score				
≥3 (high quality)	101 (3)	−0.96 (−1.59 to −0.32)	54	**.003**
<3 (low quality)	58 (1)	−0.82 (−1.34 to −0.26)	NA	**.004**
Lamotrigine				
Origin				
Chinese	96 (2)	−1.02 (−1.78 to −0.27)	64	**.0008**
Non-Chinese	195 (6)	−0.31 (−0.96 to 0.34)	76	.35
Description of randomization details				
Yes	195 (6)	−0.31 (−0.96 to 0.34)	76	.35
No	96 (2)	−1.02 (−1.78 to −0.27)	64	**.0008**
Blinded studies				
Yes	195 (6)	−0.31 (−0.96 to 0.34)	76	.35
No	96 (2)	−1.02 (−1.78 to −0.27)	64	**.0008**
Jadad score				
≥3 (high quality)	195 (6)	−0.31 (−0.96 to 0.34)	76	.35
<3 (low quality)	96 (2)	−1.02 (−1.78 to −0.27)	64	**.0008**
Sodium valproate				
Origin				
Chinese	326 (5)	−1.26 (−2.05 to −0.47)	91	**.002**
Description of randomization details				
Yes	58 (1)	−3.20 (−3.99 to −2.40)	NA	**<.00001**
No	268 (4)	−0.81 (−1.27 to −0.36)	69	**.0005**
Blinded studies				
Yes	58 (1)	−3.20 (−3.99 to −2.40)	NA	**<.00001**
No	268 (4)	−0.81 (−1.27 to −0.36)	69	**.0005**
Jadad score				
≥3 (high quality)	58 (1)	−3.20 (−3.99 to −2.40)	NA	**<.00001**
<3 (low quality)	268 (4)	−0.81 (−1.27 to −0.36)	69	**.0005**
Magnesium valproate				
Origin				
Chinese	168 (2)	−0.62 (−1.67 to 0.43)	91	.25
Description of randomization details				
No	168 (2)	−0.62 (−1.67 to 0.43)	91	.25
Blinded studies				
No	168 (2)	−0.62 (−1.67 to 0.43)	91	.25
Jadad score				
<3 (low quality)	168 (2)	−0.62 (−1.67 to 0.43)	91	.25

[a]Bolded values indicate significance.
Abbreviations: CI = confidence interval, NA = not applicable, RCT = randomized controlled trial, SMD = standard mean difference.

consistent for total psychopathology. In addition, the available data regarding magnesium valproate did not show any improvement in total symptom severity on the PANSS or the BPRS. Therefore, current evidence does not support topiramate, lamotrigine, or magnesium valproate as effective augmentation strategies for treatment-resistant schizophrenia.

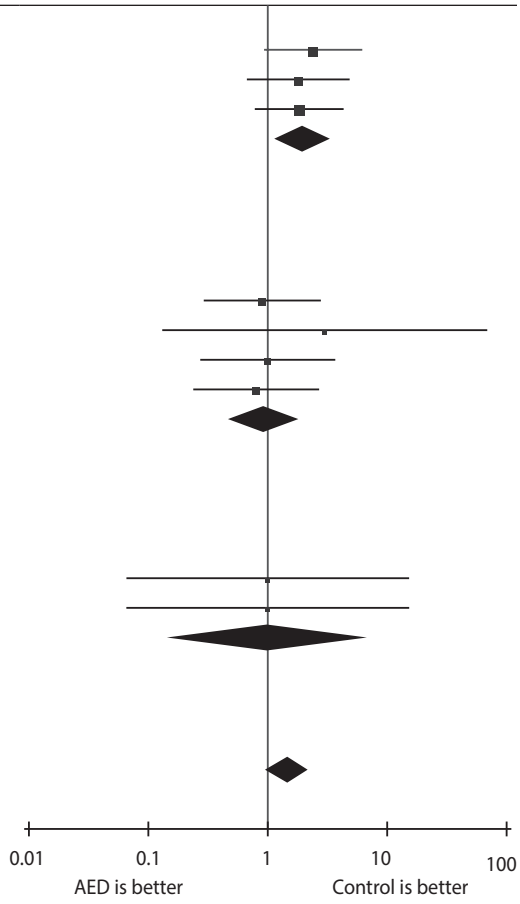
The strengths of the current meta-analysis, compared to prior meta-analyses, are the inclusion of RCTs with sodium valproate and magnesium valproate and the 11 RCTs published in Chinese databases. In addition, we included safety measurement, sensitivity analyses, data synthesis, and the assessment of quality of studies using risk of bias and the Jadad scale.

Limitations

First, 22 RCTs were identified and analyzed, but some RCTs provided incomplete information, which limited comprehensive data exploration. Second, there was significant heterogeneity of meta-analyzable results of outcomes; therefore, we used a random-effects model and conducted sensitivity analyses to compensate for the risk of heterogeneity. When combined, the 4 AEDs had significant superiority on PANSS/BPRS total scores in 19 RCTs (SMD = −0.82; 95% CI, −1.14 to −0.50; $P < .00001$), but the I^2 of 81% indicated that this SMD may not represent the average well since there was substantial heterogeneity. Third, the meta-analysis has limited power, especially for topiramate and magnesium valproate augmentation, but really for all AED augmentation, given the small sample sizes and heterogeneity in the design of the individual RCTs. Fourth, all included RCTs of sodium valproate and magnesium valproate were conducted in China. Therefore, the relevant results need to be replicated in non-Chinese clinical settings. Fifth, we were not able to compare AED augmentation across RCTs. We cannot calculate NNTs for topiramate because data for study-defined response or remission were not available, while we can calculate NNH only for all discontinuations in topiramate (NNH = 7) and NNT for study-defined response in magnesium valproate (NNT = 6). Sixth, the studies did not provide enough information to distinguish between pharmacodynamic and/or pharmacokinetic means of augmentation. We assume that most of the RCT authors assumed that augmentation occurred by pharmacodynamic mechanisms, and many RCTs did not measure clozapine therapeutic drug monitoring before and after adding AEDs to rule out a pharmacokinetic augmentation. As a matter of fact, only 3 of the 22 RCTs established that patients had at least 350 ng/mL of serum clozapine concentration[50] before starting augmentation (Supplementary eTable 1). The limited information available suggests that topiramate and lamotrigine have no relevant pharmacokinetic effects on clozapine metabolism.[50] Valproate is more complicated, since both mild inductive and inhibitory effects have been described.[51,52] Therefore, it is possible that valproate, particularly in nonsmokers,[52] may augment clozapine actions by increasing serum clozapine concentrations. Future studies of clozapine augmentation should establish that all clozapine patients, before entering an augmentation RCT, have at least 350 ng/mL

Figure 4. AED Augmentation of Clozapine for Treatment-Resistant Schizophrenia: Forest Plot for Discontinuation Rates Due to All Causes[1,29,30,34,35,40–42,47]

Study or Subgroup	AEDs Events	AEDs Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Topiramate						
Behdani et al 2011[29]	12	40	5	40	18.8%	2.40 (0.93, 6.19)
Li et al 2012[34]	9	36	5	36	17.2%	1.80 (0.67, 4.85)
Muscatello et al 2011[35]	11	30	6	30	23.0%	1.83 (0.78, 4.32)
Subtotal		**106**		**106**	**59.1%**	**1.99 (1.16, 3.39)**
Total events	32		16			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.23$, $df = 2$ ($P = .89$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.52$ ($P = .01$)						
Lamotrigine						
Tiihonen et al 2003[1]	4	16	5	18	13.2%	0.90 (0.29, 2.78)
Vayisoğlu et al 2013[40]	1	17	0	17	1.7%	3.00 (0.13, 68.84)
Wang et al 2008[42]	4	34	4	34	10.0%	1.00 (0.27, 3.68)
Zoccali et al 2007[47]	4	30	5	30	11.5%	0.80 (0.24, 2.69)
Subtotal		**97**		**99**	**36.4%**	**0.94 (0.48, 1.87)**
Total events	13		14			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.61$, $df = 3$ ($P = .89$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.16$ ($P = .87$)						
Sodium valproate						
Fang et al 2013[30]	1	30	1	30	2.3%	1.00 (0.07, 15.26)
Wang and Jiang 2008[41]	1	31	1	31	2.3%	1.00 (0.07, 15.28)
Subtotal		**61**		**61**	**4.5%**	**1.00 (0.15, 6.87)**
Total events	2		2			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.00$, $df = 1$ ($P = 1.00$); $I^2 = 0\%$						
Test for overall effect: $Z = 0.00$ ($P = 1.00$)						
Total		**264**		**266**	**100.0%**	**1.47 (0.97, 2.22)**
Total events	47		32			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 3.83$, $df = 8$ ($P = .87$); $I^2 = 0\%$						
Test for overall effect: $Z = 1.84$ ($P = .07$)						
Test for subgroup differences: $\chi^2 = 2.99$, $df = 2$ ($P = .22$), $I^2 = 33.1\%$						



Abbreviations: AED = antiepileptic drug, M-H = Mantel-Haenszel.

of serum clozapine to verify that the clozapine dosage in each patient is sufficient to allow for a clozapine response.[53] Moreover, that will eliminate possible differences in clozapine dosing between Chinese and Western studies. Clozapine is used in lower doses in China. This is probably explained by a lower clozapine metabolic capacity in the average Chinese person compared to the average Westerner, as described almost 20 years ago.[54,55] After controlling for confounding factors, such as sex and smoking, the average Chinese person probably has half the average clozapine metabolic capacity as the average Westerner and may need half the clozapine dose prescribed for a Westerner.[56]

CONCLUSIONS

Our review shows that, as a pharmacologic augmentation strategy for clozapine, sodium valproate was efficacious and safe for treatment-resistant schizophrenia. Topiramate augmentation appeared efficacious only when psychotic symptoms were considered, but its discontinuation rate was higher than clozapine monotherapy. More augmentation RCTs with higher quality, including confirmation of serum clozapine concentrations > 350 ng/mL in patients before entering RCTs, are needed and, furthermore, warranted for informing clinical recommendations for treatment-resistant schizophrenia.

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Drug names: carbamazepine (Tegretol, Epitol, and others), clozapine (Clozaril, FazaClo, and others), gabapentin (Neurontin, Gralise, and others), lamotrigine (Lamictal and others), topiramate (Topamax and others), vigabatrin (Sabril).

Author contributions: Drs Zheng and Yang selected studies and conducted statistical analysis. Dr Yu-Tao Xiang reviewed all the data and helped mediate disagreements. Dr Zheng wrote the first draft. Dr de Leon provided suggestions for statistical analysis and for accommodating the journal's style. All authors contributed to the interpretation of data and approved the final manuscript.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Clozapine Augmentation With Antiepileptic Drugs for Treatment-Resistant Schizophrenia: A Meta-Analysis of Randomized Controlled Trials

Author(s): Wei Zheng, MD; Yu-Tao Xiang, MD, PhD; Xin-Hu Yang, MD; Ying-Qiang Xiang, MD, PhD; and Jose de Leon, MD

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List of Supplementary Material for the article

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Supplementary eTable 1. Study, Patient and Treatment Characteristics

		Design				Schizophrenia patients					Concentration	Dosing (mg/day)			Risk	Jadad
		Duration					Age	Male	Diagnostic	TRS	Illness	of CLO	Intervention		Control	of
Author	Country	Total (C/I) weeks		Blinding	Analyses	Setting	years	%	criteria	criteria	duration	in serum	AED	CLO	CLO	bias[a]	score
Topiramate (5 RCTs, N=270)																	
Afshar et al. 2009[28]	Iran	32 (16/16)	8	DB	ITT	Inpatients	37.8	63	DSM-IV	NR	17.9	NR	139	NR	NR	6	4
Behadni et al. 2011[29]	Iran	80 (40/40)	17	DB	ITT	Inpatients	46.0	85	DSM-IV	≥2 APs	NR	NR	NR	NR	NR	5	4
Li et al. 2012[34]	China	72 (36/36)	24	OL	OC	Both	28.8	55	ICD-10	NR	NR	NR	NR	338	311	2	2
Muscatello et al. 2010[35]	Italy	60 (30/30)	24	DB	OC	Outpatients	31.8	72	DSM-IV	CLO (650)[b]	5.5	NR	200	333	327	5	4
Tiihonen et al. 2005[39]	Finland	26 (13/13)	12	DB	ITT	Inpatients	43.8	81	DSM-IV	CLO (NR)[b]	18.1	589[c]	NR	598	598	6	5
Lamotrigine (8 RCTs, N=299)																	
Goff (S1[d]) et al. 2007[31]	USA	21 (12/9)	12	DB	ITT	Both	NR	NR	DSM-IV	NR	NR	≥350[c]	NR	NR	NR	6	4
Goff (S2[d]) et al. 2007[31]	Several[e]	42 (21/21)	12	DB	ITT	Both	NR	NR	DSM-IV	NR	NR	≥350[c]	NR	NR	NR	6	4
Kremer et al. 2004[33]	Israel	4 (2/2)	10	DB	ITT	Inpatients	NR	NR	DSM-IV	≥2 APs	NR	NR	NR	350	400	5	4
Tiihonen et al. 2003[1]	Finland	34 (18/16)	14	DB	ITT	Inpatients	38.3	100	DSM-IV	≥2 APs	13.6	580[c]	NR	508	603	6	5
Wang et al. 2008[42]	China	68 (34/34)	12	OL	OC	Both	33.2	65	CCMD-3	≥2 APs	4.7	NR	NR	NR	NR	1	1
Vayısoğlu et al. 2013[40]	Japan	34 (17/17)	12	DB	ITT	Outpatients	40.9	68	DSM-IV	NR	18.3	506[c]	NR	426	515	5	4
Zoccali et al. 2007[47]	Italy	60 (30/30)	24	DB	ITT	Outpatients	31.4	57	DSM-IV	NR	9.9	344[c]	NR	300	335	6	5
Zhai et al. 2012[45]	China	36 (18/18)	6	OL	ITT	Inpatients	30.6	0	CCMD-3	≥2 APs	4.3	NR	NR	NR	NR	2	2
Sodium valproate (6 RCTs, N=430)																	
Fang et al. 2013[30]	China	60 (30/30)	12	DB	OC	Inpatients	36.7	NR	ICD-10	≥3 APs	11.9	NR	1125	NR	NR	6	5
Jia et al. 2007[32]	China	80 (40/40)	4	OL	ITT	Inpatients	38.9	100	ICD-10	CLO (NR)[b]	15.3	≥350	NR	NR	NR	2	2
Pan et al. 2010[37]	China	68 (34/34)	8	OL	ITT	Inpatients	32.4	41	CCMD-3	≥2 APs	11.2	NR	800	NR	NR	2	2
Wang et al. 2008[41]	China	62 (31/31)	12	OL	OC	Both	34.1	62	CCMD-3	≥2 APs	4.9	NR	961	265	397	1	1
Yuan et al. 1994[44]	China	100 (50/50)	8	RM	ITT	Inpatients	33.8	80	CCMD-2	NR	8.4	NR	NR	NR	NR	3	2
Zhang et al. 2015[46]	China	60 (30/30)	8	OL	ITT	NR	39.0	62	ICD-10	≥3 APs	15.1	NR	800	421	411	2	2
Magnesium Valproate (3 RCTs, N=228)																	
Shu et al. 2014[38]	China	60 (30/30)	4	OL	ITT	Inpatients	37.2	58	CCMD-3	NR	6.3	NR	NR	350	345	2	2
Ou et al. 2014[36]	China	80 (40/40)	8	OL	ITT	Inpatients	36.8	58	CCMD-3	NR	5.9	NR	NR	NR	NR	2	2
Xu et al. 2014[43]	China	88 (44/44)	12	OL	ITT	Inpatients	41.0	0	CCMD-3	≥3 APs	16.7	NR	NR	NR	NR	2	2

[a]Number of low risk judgements.

[b]Daily dosage of clozapine.

[c]Serum baseline concentration in ng/ml. Tihonen reported 1.8 µmol/L which was multiplied by 327 to obtain 589 ng/ml.

[d]This article included two studies: called Study 1 (S1) and 2 (S2). In the article, the authors provide specific labels to identify them: SCA30926 for S1and SCA101464 for S2.

[e]Canada, United Kingdom and USA.

Abbreviations: AP = antipsychotic, AED = antiepileptic drug, Both = in and outpatients, CCMD-2 = China's Mental Disorder Classification and Diagnosis Standard 2nd edition, CCMD-3 = China's Mental Disorder Classification and Diagnosis Standard, 3rd edition, C = control, CLO = clozapine, DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th edition, DB = double blind, I = intervention, ITT = intent to treat; NR = not reported, ICD-10 = International Classification of Diseases, 10th edition, OC = observed cases, RM = rater masked, USA = United States of America.

Supplementary eTable 2. Antiepileptic Drugs Combined with Clozapine for Treatment-Resistant Schizophrenia: Secondary Outcomes

Antiepileptic	Positive Subscores				Negative Subscores				General Subscores			
Drug	RCT (N)	SMD	95% CI	I^2	RCT (N)	SMD	95% CI	I^2	Studies (N)	SMD	95% CI	I^2
Topiramate	4 (213)	**-0.49**[a]	**-0.97 to -0.02**	64	4 (213)	**-0.70**[b]	**-1.14 to -0.27**	56	3 (205)	**-0.52**[c]	**-0.93 to -0.10**	42
Lamotrigine	8 (291)	-0.35	-0.73 to 0.03	57	8 (291)	-0.38	-0.85 to 0.08	71	3 (130)	-0.52	-1.56 to 0.53	87
Sodium valproate	5 (326)	**-0.78**[d]	**-1.36 to -0.20**	84	5 (326)	-0.26	-0.55 to 0.03	43	4 (246)	**-1.14**[e]	**-1.90 to -0.38**	87
Magnesium valproate		No data				No data				No data		

[a]p=.04
[b]p=.002
[c]p=.02
[d]p=.009
[e]p=.003
Abbreviations: CI = confidence interval, N = number of patients, RCT = randomized controlled trial, SMD = standard mean difference.

Supplementary eTable 3. ADRs during RCTs for Treatment-Resistant Schizophrenia Using Clozapine Augmentation with AEDs

ADRs	RCTs	Augmentation Group	Control Group	RR (95% CI)[a]	I^2 (%)	P value
Topiramate:						
Memory difficulty	2	20% (10/49)	37% (20/54)	0.57 (0.28 to 1.16)	11	.12
Lamotrigine:						
Somnolence	2	23% (11/48)	31% (15/48)	0.74 (0.38 to 1.44)	0	.37
Headache	2	21% (10/48)	15% (7/48)	1.44 (0.61 to 3.39)	0	.41
Constipation	3	16% (12/77)	19% (15/78)	0.81 (0.41 to 1.62)	0	.55
Extrapyramidal symptoms	2	14% (8/59)	10% (6/60)	1.34 (0.49 to 3.66)	0	.57
Elevated liver enzymes	2	6% (3/48)	6% (3/48)	0.99 (0.19 to 5.13)	0	.99
Sialorrhea	3	44% (34/77)	45% (35/78)	1.00 (0.71 to 1.41)	0	.98
Dizziness	3	22% (17/77)	19% (15/78)	1.16 (0.62 to 2.18)	0	.64
Fatigue	2	27% (16/59)	28% (17/60)	0.96 (0.54 to 1.72)	0	.90
Sodium valproate:						
Sialorrhea	5	30% (52/173)	39% (68/173)	0.82 (0.51 to 1.31)	55	.40
Elevated liver enzymes	2	10% (7/70)	4% (3/70)	2.31 (0.62 to 8.61)	0	.21
Dizziness	5	14% (24/173)	16% (27/173)	0.87 (0.53 to 1.41)	0	.57
Drowsiness	5	31% (54/173)	28% (48/173)	1.09 (0.80 to 1.49)	0	.59
Nausea/vomiting	4	16% (23/144)	10% (15/144)	1.36 (0.76 to 2.43)	0	.31
Constipation	3	11% (12/109)	21% (23/109)	0.77 (0.16 to 3.65)	72	.74
Magnesium valproate:						
Dizziness	2	11% (8/70)	9% (6/70)	1.33 (0.49 to 3.59)	0	.58
Constipation	2	9% (6/70)	10% (7/70)	0.86 (0.30 to 2.42)	0	.77

[a]Random effects model

Abbreviations: ADR = adverse drug reaction, AED = antiepileptic drug, CI = confidence interval, RCT = randomized controlled trial, RR = risk ratio.

Supplementary eFigure 1. Risk of Bias

	Random sequence generation (selection bias)	*Allocation concealment (selection bias)*	*Blinding of participants and personnel*	*Blinding of outcome assessment (Symptom reduction, response)*	*Incomplete outcome data addressed (attrition bias)*	*Selective reporting (reporting bias)*	*Other sources of bias*
Topiramate							
Afshar et al. 2009[28]	+	?	+	+	+	+	+
Behadni et al. 2011[29]	+	?	+	+	+	?	+
Li et al. 2012[34]	+	?	-	-	?	?	?
Muscatello et al. 2010[35]	+	?	+	+	?	?	+
Tiihonen et al. 2005[39]	+	?	+	+	+	?	+
Lamotrigine							
Goff (S1[a]) et al. 2007[31]	+	?	+	+	+	+	+
Goff (S2[a]) et al. 2007[31]	+	?	+	+	+	+	+
Kremer et al. 2004[33]	+	?	+	+	+	?	+
Tiihonen et al. 2003[1]	+	+	+	+	+	?	+
Wang et al. 2008[42]	?	?	-	-	?	?	+
Vayısoğlu et al. 2013[40]	+	?	+	+	+	?	+
Zoccali et al. 2007[47]	+	+	+	+	+	?	+
Zhai et al. 2012[45]	?	?	-	-	+	?	+
Sodium valproate							
Fang et al. 2013[30]	+	+	+	+	?	?	+
Jia et al. 2007[32]	?	?	-	-	+	?	+
Pan et al. 2010[37]	?	?	-	-	+	?	+
Wang et al. 2008[41]	?	?	-	-	?	?	+
Yuan et al. 1994[44]	-	?	?	+	+	?	+
Zhang et al. 2015[46]	?	?	-	-	+	?	+
Magnesium valproate							
Shu et al. 2014[38]	?	?	-	-	+	?	+

Ou et al. 2014[36]	?	?	-	-	+	?	+
Xu et al. 2014[43]	?	?	-	-	+	?	+

[a]This article included two studies: called Study 1 (S1) and 2 (S2). In the article, the authors provide specific labels to identify them: SCA30926 for S1and SCA101464 for S2.
Abbreviations: + = low risk of bias, - : high risk of bias, ? : unclear risk of bias.