Neuropsychiatric Disease and Treatment

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Efficacy and tolerability of topiramate-augmentation therapy for schizophrenia: a systematic review and meta-analysis of randomized controlled trials

This article was published in the following Dove Press journal:
Neuropsychiatric Disease and Treatment
15 December 2016
Number of times this article has been viewed

Yuji Okuyama*
Kazuto Oya*
Shinji Matsunaga
Taro Kishi
Nakao Iwata

Department of Psychiatry, Fujita Health University School of Medicine, Toyoake, Japan

*These authors contributed equally to this work

Abstract: This study aimed to perform a comprehensive meta-analysis of topiramate-augmentation therapy in patients with schizophrenia receiving antipsychotic agents. Data published up to June 20, 2016 were obtained from the PubMed, PsycINFO, and Cochrane Library databases. Twelve randomized controlled trials comparing topiramate to placebo or antipsychotic only were included (n=676 patients). The primary outcome was change in overall symptoms. Relative risk (RR) and standardized mean difference (SMD), along with 95% confidence intervals, were calculated using random effects model for each outcome. Topiramate-augmentation therapy was superior to the control for decreasing overall symptoms (SMD –0.55, 95% confidence interval –0.86 to –0.24; P=0.001; I^2=55%, eight comparisons, n=380), positive symptoms (SMD –0.4), negative symptoms (SMD –0.47), and Positive and Negative Syndrome Scale general subscale scores (SMD –0.67). Furthermore, topiramate-augmentation therapy decreased weight (SMD –0.69) and body mass index (SMD –0.95) compared with the control. Topiramate was similar to the control with respect to discontinuation due to all causes (RR 1.19), inefficacy (RR 1.71), and adverse events (RR 1.09). Topiramate was associated with higher incidence of paresthesia (RR 2.67) and attention difficulty (RR 8.97) compared with the control. Our results seemed to suggest that topiramate-augmentation therapy improves the psychopathology of schizophrenia with good tolerability and has the additional advantage of weight maintenance. However, because there were some limitations (numbers of studies and patients included in the meta-analysis were small, some studies used completer analysis, Chinese studies were included in the meta-analysis, and studies that had a risk of bias were included in the meta-analysis) in this study, we cannot apply the results of this study in daily clinical practice.

Keywords: schizophrenia, topiramate, efficacy, safety, systematic review, meta-analysis

Introduction

Schizophrenia is characterized by positive symptoms, such as hallucinations and delusions, negative symptoms, such as abulia and autism, and cognitive impairments.[1] At its 15-year follow-up, a Dutch cohort study of psychotic disorder reported that two-thirds of patients suffered at least one relapse. Of those patients, one in six failed to recover fully and one in ten committed suicide.[2] A previous meta-analysis that compared relapse rates between antipsychotic and placebo groups at 7–12 months found that antipsychotics significantly reduced relapse rates at 1 year over placebo, measured by the number needed to treat to benefit, which was three.[3] Nonetheless, it appears difficult to maintain drug adherence by outpatients, which leads to relapse and readmission to hospital.[4] In an anonymous online-survey study (n=113), patients with schizophrenia reported discontinuing medication for the following

Correspondence: Taro Kishi
Department of Psychiatry, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi 470-1192, Japan
Tel +81 562 939 250
Fax +81 562 931 831
Email tarok@fujita-hu.ac.jp

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/NDT.S125367

reasons: side effects (80%), stigma (31%), mistrusting the physician/therapist (31%), and rejection of medication in general (28%).[5] Therefore, side effects are considered the cardinal reason for poor compliance or noncompliance with antipsychotic medication.[6]

A recent network meta-analysis comparing 15 antipsychotics to placebo found that antipsychotics were superior for reducing overall symptoms of schizophrenia.[7] However, all individual effect sizes were moderate, with the exception of clozapine, which had a large effect size compared with placebo.[7] On the other hand, olanzapine and clozapine have been demonstrated to have a higher risk of metabolic abnormalities compared with other second-generation antipsychotics.[8] For example, olanzapine revealed a higher risk of weight gain compared with amisulpride, aripiprazole, asenapine, lurasidone, paliperidone, and risperidone.[8] Risperidone was also associated with the need for more use of antiparkinsonian medication compared with clozapine, olanzapine, quetiapine, and ziprasidone.[9] When comparing antipsychotics (regarding overall symptoms as efficacy, and weight gain as safety), because the effect size of efficacy is smaller than that of safety, such as weight gain, several guidelines for the management of schizophrenia have recommended that the safer antipsychotic should be used for patients with schizophrenia.[10] However, not all patients with schizophrenia respond to the safer antipsychotics.

Topiramate is approved for the treatment of epilepsy and prophylaxis of migraine by the US Food and Drug Administration.[11] A previous review suggested that topiramate effects on psychopathology may be mediated through glutamatergic neurons, especially those expressing kainic acid and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, and by inhibition of nitric oxide production.[12] Although the mechanisms for improving metabolic disturbances are unclear, a previous report demonstrated that topiramate enhances insulin action and glucose transport in adipose cells from obese and insulin-resistant rodents.[13] Further, appetite suppression through hypothalamic AMPA-receptor antagonism is thought to contribute to weight loss.[14]

To our knowledge, 12 randomized controlled trials (RCTs) of topiramate have been conducted for the treatment of schizophrenia and related psychoses.[15–26] There were inconsistent results among these RCTs, however, regarding psychopathology and metabolic outcomes. Although four studies[15,19,21,25] reported that topiramate was superior to control in improving psychopathological outcomes, six studies[16–18,20,23,26] reported that topiramate was similar to the control in this aspect, and the remaining studies[22,24] did not report any psychopathological outcomes. To date, two meta-analyses have evaluated topiramate for the treatment of schizophrenia.[27,28] Sommer et al[27] reviewed three RCTs,[15,20,23] and reported that topiramate augmentation for clozapine showed trend-level improvement regarding overall symptoms compared with placebo. Mizuno et al[28] conducted a meta-analysis of multiple pharmacological strategies to combat weight gain in antipsychotic-treated schizophrenia patients that included two RCTs[19,21] of topiramate augmentation. The pooled result showed that topiramate significantly lowered weight compared with the placebo (mean difference –5.20 kg).[28] However, these meta-analyses focused on topiramate augmentation as a strategy only for psychopathology or metabolic adverse events (including weight gain), and the number of topiramate trials included was small. In this updated systematic review and meta-analysis of topiramate-augmentation therapy for patients with schizophrenia and its related disorders, we have incorporated all relevant findings involving various antipsychotics from the 12 published RCTs.[15–26] Because a meta-analysis can increase the statistical power for group comparisons and overcome the limitation of sample size when larger trials are lacking (http://www.cochrane.org), a systematic review and meta-analysis is considered to provide the "best evidence" for clinical practice. Moreover, safety outcomes are critical for adherence; therefore, we also evaluated topiramate-discontinuation rates and individual adverse events.

Materials and methods

Inclusion criteria, search strategy, data extraction, and outcomes

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[29] We performed a systematic literature review according to the PICO (patients, intervention, comparison, outcome) strategy: patients, schizophrenia and schizophrenia-related disorders; intervention, topiramate in addition to an antipsychotic agent; comparison, versus placebo in addition to an antipsychotic agent or antipsychotic only; and outcome, primary outcome (improvement in overall symptoms) and secondary outcomes (improvement in positive and negative symptoms and Positive and Negative Syndrome Scale [PANSS] general subscale scores,[30] decreasing weight and body mass index [BMI], improvement in Clinical Global Impression – Severity [CGI-S],[31] and depressive symptoms, discontinuation rate, and individual adverse events).

Only those RCTs involving the use of topiramate in patients with schizophrenia and its related disorders were included.

Relevant studies were identified through searches of PubMed, the Cochrane Library, and PsycINFO citations. There were no language restrictions, and we accepted studies retrieved using the keywords "topiramate" and "schizophrenia" published up to June 20, 2016. Additional eligible studies were sought by scrutiny of the reference lists from primary articles and relevant reviews. Two authors (YO and KO) checked the inclusion and exclusion criteria for each of the identified studies, and resolved discrepancies in coding by discussion. The same authors independently extracted, checked, and entered data into RevMan version 5.3 for Windows (Cochrane Collaboration, London, UK). When data required for the meta-analysis were missing, the first/corresponding authors were contacted for additional information. We also assessed the risk of bias in the trials using the Cochrane risk-of-bias criteria (domains of random-sequence generation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias) (http://www.cochrane.org).

Data synthesis

The primary efficacy measure was overall symptom reduction as measured by PANSS total scores and Brief Psychiatric Rating Scale (BPRS)[32] total scores (Table 1). Secondary outcomes were as follows: 1) positive symptoms as measured by PANSS positive subscale scores and Scale for the Assessment of Positive Symptoms[33] (Table 1), 2) negative symptoms as measured by PANSS negative subscale scores and Scale for the Assessment of Negative Symptoms[34] (Table 1), 3) PANSS general subscale scores (Table 1), 4) CGI-S[31] (Table 1), 5) depressive symptoms as measured by the Calgary Depression Scale for Schizophrenia[35] or Montgomery–Åsberg Depression Rating Scale[36] (Table 1), 6) weight (Table 1), 7) BMI (Table 1), and discontinuation rates due to 8) all causes, 9) inefficacy, and 10) adverse events.

In addition, we pooled the data for individual adverse events. With regard to tolerability, discontinuations due to worsening mental condition and unsatisfactory response[17,23] were considered "discontinuation due to inefficacy", and discontinuation due to low leukocyte levels[23] was considered "discontinuation due to adverse events". For estimation of missing data from individual studies, we imputed the standard deviation (SD) of BPRS-change scores from baseline to end point in Ko et al,[19] from the data of Muscatello et al,[20] and SD of CGI-S and BMI-change scores from baseline to

Table 1 Data synthesis

	Afshar et al[15]	Behdani et al[16]	Chen et al[24]	Chengappa et al[17]	Kim et al[18]	Ko et al[19]	Liu[25]	Muscatello et al[20]	Narula et al[21]	Nickel et al[22]	Tiihonen et al[23]	Yang[26]
Overall symptoms	PANSS total change scores	NR	NR	PANSS total change scores	NR	BPRS total change scores	PANSS total end point scores	BPRS total end point scores	PANSS total end point scores	NR	PANSS total change scores	PANSS total end point scores
Positive symptoms	PANSS positive change scores	PANSS positive change scores	NR	PANSS positive change scores	NR	NR	PANSS positive end point scores	SAPS total end point scores	PANSS positive end point scores	NR	PANSS positive change scores	PANSS positive end point scores
Negative symptoms	PANSS negative change scores	PANSS negative change scores	NR	PANSS negative change scores	NR	NR	PANSS negative end point scores	SANS total end point scores	PANSS negative end point scores	NR	PANSS negative change scores	PANSS negative end point scores
PANSS general subscale scores	PANSS general change scores	PANSS general change scores	NR	NR	NR	NR	PANSS general end point scores	NR	PANSS general end point scores	NR	PANSS general change scores	PANSS general end point scores
Depressive symptoms	NR	NR	NR	MADRS change scores	NR	NR	NR	CDSS end point scores	NR	NR	NR	NR
CGI-S	NR	NR	NR	Change scores	NR	Change scores	NR	NR	NR	NR	NR	End point scores
Weight	NR	NR	Change scores	Change scores	Change scores	Change scores	End point scores	NR	Change scores	End point scores	Change scores	Change scores
BMI	End point scores	NR	Change scores	Change scores	NR	Change scores	End point scores	NR	End point scores	NR	NR	Change scores

Abbreviations: BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression – Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; NR, not reported; PANSS, Positive and Negative Syndrome Scale; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms.

end point in the study of Ko et al[19] from the SD of Chengappa et al.[17] We converted weights from pounds to kilograms for Chengappa et al.[17] We assumed that the number of patients required for evaluating efficacy outcomes in Behdani et al[16] was the same as the number of patients required for evaluating safety outcomes and the number of patients required for evaluating efficacy outcomes in Afshar et al[15] was the same number of randomized patients for each treatment arm, because the trial used general linear model analysis. We used those estimations to increase sample size for analysis to gain as much statistical power as possible. The median highest topiramate dose for all studies except Ko et al[19] was 238 mg/day, so data from the 200 mg/day topiramate group but not the 100 mg/day topiramate group were used for meta-analysis. For individual adverse events, we considered memory disturbances[23] and forgetfulness[17] as "memory loss", and sedation[17,23] and drowsiness[16] as "somnolence".

Statistical analysis

We based our data analyses on intention to treat, observed cases, and crossover studies. This meta-analysis was performed using RevMan. To combine studies, we used the random-effect model described by DerSimonian and Laird.[37] We used this conservative model to address the possibility that underlying effects differed across studies and populations were heterogeneous. For continuous data, we used standardized mean difference (SMD), combining effect size (Hedges' *g*) data and 95% confidence interval (CI). For dichotomous data, relative risk (RR) was estimated along with the 95% CI. When the random-effect model revealed significant between-group differences in dichotomous outcomes, the number needed to harm (NNH) was calculated. Study heterogeneity was measured using χ^2 and I^2 statistics, with values of $P<0.05$ and $I^2\geq 50\%$ indicating heterogeneity.[38] In cases where I^2 values were ≥50% for primary outcome, sensitivity analyses were performed to determine the reasons for heterogeneity. Finally, funnel plots were visually inspected to explore the possibility of publication bias.

Results

Study characteristics

Searches of the PubMed, Cochrane Library, and PsycINFO databases yielded 116 hits. We excluded eight duplicate studies, 81 studies based on title or abstract review, and 20 studies after full-text reading. Five additional articles[17,22,24–26] were identified by manually searching the review articles.[17,39] Finally, 12 eligible studies[15–26] were accepted (Figure 1). Mean study duration was 13.4 (range 8–24) weeks, and 676 patients were included (schizophrenia 579, schizoaffective disorder 48, psychosis and unipolar or bipolar disorder 49). Patient numbers in each treatment arm were 358 for topiramate and 318 for control (consisting of 258 placebo-treated and 60 treatment as usual). The mean number of patients included in the individual studies was 56. Three studies were published in Chinese.[24–26] We evaluated the methodological quality of the individual studies based on Cochrane risk-of-bias criteria (Figures S1 and S2). Three studies did not employ a placebo control.[18,24,25] One study was a crossover design.[23] Seven studies used a completer analysis.[19–22,24–26] Five studies were at high risk of selective reporting bias.[15,18,20,21,24] One study was sponsored by the pharmaceutical industry.[15] The characteristics of the studies are summarized in Table 2.

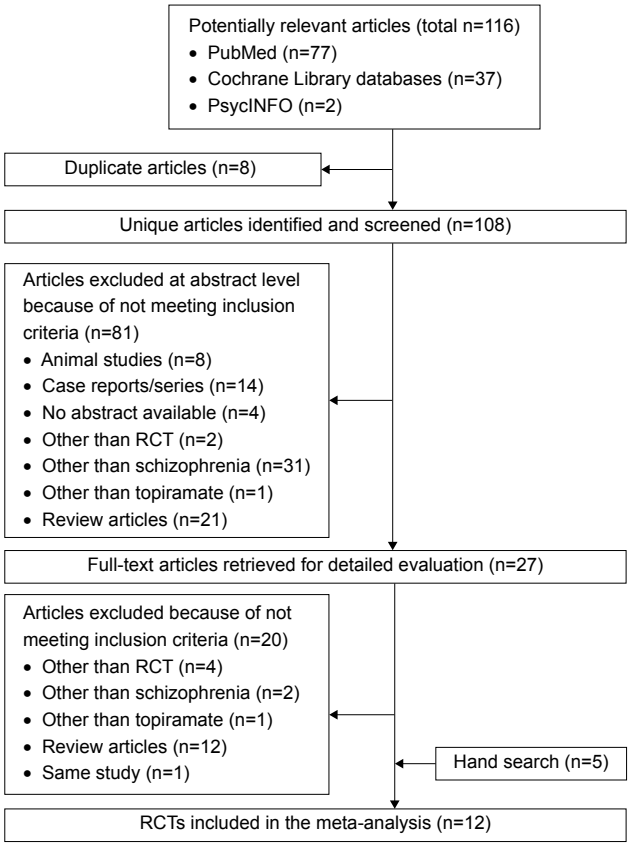


Figure 1 Literature search results.
Abbreviation: RCT, randomized controlled trial.

Meta-analysis

Efficacy

Topiramate as augmentation to antipsychotic therapy was superior to control (antipsychotic alone or placebo plus antipsychotic) for the reduction of overall symptoms (SMD −0.55,

Table 2 Study, patient, and treatment characteristics of the included double-blinded and open label randomized controlled trials of topiramate augmentation therapy for antipsychotic-treated schizophrenia patients

Study	Study design/ total n	Patients (1) diagnosis, (2) age, (3) status	Diagnostic criteria/duration	Age (mean ± SD)	Male (%)	Drug dose, range, mean ± SD, (mg/day)	n	Concomitant drugs (%)	Efficacy outcomes: psychopathology and metabolic symptoms[e]
CLO trials									
Afshar et al[15] Industry, Iran	DB-RCT, ITT/32	(1) SZ, (2) 18–45 years, (3) inefficient with long-term APs and treatment with CLO (≥100 mg) for the previous 2 months	DSM-IV-TR/ 8 weeks	TOP: 37.5±5.7 PBO: 38.1±4.6	TOP: 56 PBO: 68	TOP: start with 50 and up to 300 (highest tolerable dose) CLO: ≥100 PBO CLO: ≥100	16 16	CLO: 100 Lorazepam: NR	PANSS total: TOP > PBO PANSS positive: TOP > PBO PANSS negative: TOP > PBO PANSS general: TOP > PBO BMI loss: TOP = PBO
Behdani et al[16] Nonindustry, Iran	DB-RCT, ITT/80	(1) SZ, (2) 25–65 years, (3) inefficient with at least 2 APs other than CLO	DSM-IV-TR/ 17 weeks	TOP: 45.12±9.82 PBO: 46.93±9.83	TOP: 93 PBO: 78	TOP: start with 50 and up to 300, 243 (SD: NR) CLO: ≤300 PBO CLO: ≤300	40 40	CLO: 100	PANSS positive: TOP = PBO PANSS negative: TOP = PBO PANSS general: TOP = PBO
Muscatello et al[20] Nonindustry, Italy	DB-RCT, CA/60	(1) SZ, (2) 23–58 years, (3) inefficient with CLO (150–650 mg/day) ≥1 year	DSM-IV/24 weeks	TOP: 32.3±4.6 PBO: 31.5±4.9	TOP: 74 PBO: 71	TOP: start with 25 and up to 200 (fixed) CLO: 150–650 (highest tolerable dose) PBO CLO: 150–650 (highest tolerable dose)	30 30	CLO: 100 Lorazepam: NR	BPRS: TOP = PBO SAPS: TOP = PBO SANS: TOP = PBO CDSS: TOP = PBO
OLA trials									
Chen et al[24] Nonindustry, China	DB-RCT, CA/44	(1) SZ, (2) NR, (3) inpatients, first episode, drug-naïve, BMI ≤30	CCMD-3/10 weeks	TOP: 36.9±5.3 Only OLA: 37.1±5.1	TOP: 43 Only OLA: 42	TOP: start with 50 and up to 100–150 (flexible), 100.3±30.3 OLA: 15–20 (flexible), 12.5±7.2 PBO OLA: 15–20 (flexible), 12.5±7.2	23 21	OLA: 100	Weight loss: TOP > only OLA BMI loss: TOP > only OLA WHR reduction: TOP > only OLA
Kim et al[18] Nonindustry, South Korea	OL-RCT, ITT/60	(1) SZ, (2) NR, (3) treated with SGAs (>3 months)	DSM-IV/12 weeks	TOP: NR	100	TOP: start with 50 and up to 100 (fixed) OLA: 10–20 (flexible), 12.29±4.26 OLA: 10–20 (flexible), 12.43±4.45	30 30	OLA: 100	PANSS total: TOP + OLA = OLA Weight loss: TOP + OLA > OLA

(Continued)

Table 2 (*Continued*)

Study	Study design/ total n	Patients (1) diagnosis, (2) age, (3) status	Diagnostic criteria/duration	Age (mean ± SD)	Male (%)	Drug dose, range, mean ± SD, (mg/day)	n	Concomitant drugs (%)	Efficacy outcomes: psychopathology and metabolic symptoms[e]
Liu[25] Nonindustry, China	OL-RCT, CA/60	(1) SZ, (2) 18–45 years, (3) treated without SGAs before enrollment for >3 months, BMI <30	ICD-10/12 weeks	TOP: 24.52±5.35 Only OLA: 25.63±6.21	TOP: 33.3 Only OLA: 38.5	TOP: start with 25 and up to 200 (fixed) OLA: 10–20 (flexible), 13.76±3.68 OLA: 10–20 (flexible), 13.34±3.75	30 30	OLA: 100	PANSS total: TOP > only OLA PANSS positive: TOP = only OLA PANSS negative: TOP = only OLA PANSS general: TOP > only OLA Weight loss: TOP > only OLA BMI loss: TOP > only OLA
Narula et al[21] Nonindustry, India	DB-RCT, CA/72	(1) SZ, (2) 18–65 years, (3) first episode, drug-naïve	ICD-10/12 weeks	TOP: 31.21±9.70 PBO: 31±10.09	TOP: 67 PBO: 65	TOP: start with 50 and up to 100 (fixed) OLA: 5–20 (flexible), 11.47±0.4 PBO OLA: 5–20 (flexible), 11.52±0.41	36 36	OLA: 100	PANSS total: TOP > PBO PANSS positive: TOP = PBO PANSS negative: TOP = PBO PANSS general: TOP > PBO Weight loss: TOP > PBO BMI loss: TOP > PBO
Nickel et al[22] Nonindustry, Germany	DB-RCT, CA/49	(1) Psychosis, unipolar and bipolar disorder, (2) ≥18 years, (3) treated with OLA (≥3 months), weight gain (≥5 kg)	NR/10 weeks	TOP: 35.2±8.2 PBO: 34.5±9.2	0	TOP: start with 50 and up to 250 within 5 weeks (fixed) OLA: 7.8±3.6 PBO OLA: 7.2±3.1	25 24	OLA: 100	Weight loss: TOP > PBO
Yang[26] Nonindustry, China	DB-RCT, CA/60	(1) SZ, (2) 18–55 years, (3) first-episode outpatients, treated without AP before enrollment for >3 months, BMI <30	CCMD-3/ 12 weeks	TOP: 25.3±6.3 PBO: 27.0±7.0	TOP: 48 PBO: 46	TOP: start with 25 and up to 200 (fixed) OLA: 10–20 (flexible), 12.96±3.47 PBO OLA: 10–20 (flexible), 12.78±3.76	30 30	OLA: 100	PANSS total: TOP = PBO PANSS positive: TOP = PBO PANSS negative: TOP = PBO PANSS general: TOP > PBO CGI: TOP = PBO Weight loss: TOP > PBO BMI loss: TOP > PBO WHR: TOP > PBO
Various AP trials									
Chengappa et al[17] Nonindustry, USA	DB-RCT, ITT/48	(1) SA, (2) ≥18 years, (3) PANSS total ≥60, CGI-S ≥4, receiving fixed dose and therapeutic levels of Li, VAL, or both (≥2 weeks)	DSM-IV-TR/ 8 weeks	TOP: 42.6±8.9 PBO: 42.8±6.7	TOP: 44 PBO: 50	TOP: start with 50 and up to 400 (highest tolerable dose or ≥20% reduction of PANSS total) (fixed), 276±108 Li and VAL: within therapeutic levels[a] APs: NR	32	FGAs: 25 SGAs: 69 VAL: 63 Li: 28 VAL + Li: 9 Anxiolytic: NR Hypnotic: NR	PANSS total: TOP = PBO PANSS positive: TOP = PBO PANSS negative: TOP = PBO YMRS: TOP = PBO MADRS: TOP = PBO CGI-S: TOP = PBO Weight loss: TOP > PBO BMI loss: TOP > PBO Waist loss: TOP = PBO

						PBO Li and VAL: within therapeutic levels[b] APs: NR	16	FGAs: 38 SGAs: 56 VAL: 63 Li: 31 VAL + Li: 6 Anxiolytic: NR Hypnotic: NR	
Ko et al[19] Nonindustry, South Korea	RCT,[c] CA/66	(1) SZ, (2) 18–60 years, (3) maintenance therapy with an AP, BMI ≥25 kg/m^2	DSM-IV/12 weeks	TOP (100): 34.2±7.62 TOP (200): 35.3±9.75 PBO: 37.6±7.98	TOP (100): 38 TOP (200): 41 PBO: 60	TOP: 100[d] APs: 5.7±2.6 (RIS equivalent)	22[f]	RIS: 12.5 OLA: 31.3 QUE: 18.8 CLO: 37.5	BPRS: TOP (200) > PBO; TOP (100) > PBO CGI-S: TOP (200) > PBO; TOP (100) > PBO
						TOP: 200[d] APs: 5.4±2.5 (RIS equivalent)	22[f]	RIS: 23.5 OLA: 23.5 QUE: 17.6 CLO: 35.3	Weight loss: TOP (200) > TOP (100); TOP (200) > PBO BMI loss: TOP (200) > TOP (100)
						PBO APs: 5.1±1.7 (RIS equivalent)	22[f]	RIS: 15 OLA: 10 QUE: 10 CLO: 65	TOP (200) > PBO Waist loss: TOP (200) > TOP (100); TOP (200) > PBO Hip loss: TOP (200) > TOP (100); TOP (200) > PBO
Tiihonen et al[23] Nonindustry, Finland	DB-CO-RCT, ITT/26	(1) SZ, (2) 18–60 years, (3) inefficient with CLO, OLA, QUE, or RIS ≥4 months	DSM-IV/24 weeks	TOP: 42±11.4 PBO: 45.5±14.4	81	TOP: start with 25 and up to 300 (fixed) CLO: 598±179 OLA: 26±5 QUE: 633±208	22	CLO: 54 OLA: 19 QUE: 11.5, CLO + OLA: 11.5	PANSS total: TOP = PBO PANSS positive: TOP = PBO PANSS negative: TOP = PBO PANSS general: TOP > PBO Weight loss: TOP = PBO
						PBO CLO: 598±179 OLA: 26±5 QUE: 633±208	23	OLA + QUE: 4	

Notes: [a]Blood levels – VAL 61±7 mg/mL, Li 0.7±0.15 mEq/L; [b]blood levels – VAL 69.4±15 mg/mL, Li 0.69±0.13 mEq/L; [c]because the study did not show detailed information regarding blinding to patients and/or assessors, we included the study as an OL RCT in the meta-analysis; [d]50 mg/day for the first week, 100 mg/day in week 2, and titrated upward 25 mg/day until the target dose in each treatment arm; [e]results shown as original study reported; [f]number of patients confirmed by a previous study.[47]

Abbreviations: APs, antipsychotics; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CA, complete analysis; CCMD, Chinese Classification of Mental Disorders; CDSS, Calgary Depression Scale for Schizophrenia; CGI-S, Clinical Global Impression – Severity; CLO, clozapine; CO, crossover; DB, double-blind; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; DSM-IV-TR. DSM-IV, text revision; FGAs, first generation antipsychotics; ICD, International Classification of Diseases; ITT, intention to treat; Li, lithium carbonate; MADRS, Montgomery–Åsberg Depression Rating Scale; n, number of patients; NR, not reported; OL, open-label; OLA, olanzapine; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; QUE, quetiapine; RCT, randomized controlled trial; RIS, risperidone; SA, schizoaffective disorder; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SD, standard deviation; SGAs, second-generation antipsychotics; SZ, schizophrenia; TOP, topiramate; VAL, valproic acid; WHR, waist hip ratio; YMRS, Young Mania Rating Scale.

95% CI −0.86 to −0.24; P=0.001; I^2=55%, eight comparisons, n=380) (Figure 2A). Visual inspection of the funnel plot for primary outcome did not suggest publication bias (Figure S3). Topiramate was superior to control for the following secondary outcomes: positive symptoms (SMD −0.4, 95% CI −0.63 to −0.17; P=0.001; I^2=29%, eight comparisons, n=423) (Figure 2B), negative symptoms (SMD −0.47, 95% CI −0.82 to −0.12; P=0.01; I^2=67%, eight comparisons, n=423) (Figure 2C), PANSS general subscale scores (SMD −0.67, 95% CI −1.06 to −0.28; P=0.001; I^2=66%, six comparisons, n=332) (Figure 3A), weight loss (SMD −0.69, 95% CI −0.88 to −0.49; P<0.0001; I^2=32%, nine comparisons, n=447) (Figure 3B), and BMI reduction (SMD −0.95, 95% CI −1.23 to −0.66; P<0.0001; I^2=32%, seven comparisons, n=331) (Figure 3C). Topiramate was not different from control for depressive symptoms (SMD 0.15, 95% CI −0.71 to 1.01; P=0.73; I^2=75%, two comparisons, n=91) or CGI-S (SMD −0.24, 95% CI −0.65 to 0.18; P=0.26; I^2=31%, three comparisons, n=140).

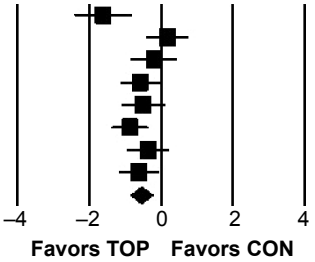
Sensitivity/subgroup analysis

There was significant heterogeneity in overall symptoms among studies (I^2=55%, P=0.03), so we performed 13 sensitivity analyses for primary outcome (antipsychotic class, blinding, analyzed population, region, control, study duration, topiramate dose, publication year, diagnosis, number of patients, patient status, language, and sponsorship) (Table 3). Significant heterogeneity in overall symptoms among the

A Overall symptoms

Study	SMD	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afshar et al[15]	−1.62	0.41	0.17	−2.42	−0.82	−3.97	0
Chengappa et al[17]	0.17	0.31	0.09	−0.43	0.77	0.56	0.58
Ko et al[19]	−0.20	0.33	0.11	−0.85	0.45	−0.61	0.54
Liu[25]	−0.59	0.28	0.08	−1.14	−0.04	−2.09	0.04
Muscatello et al[20]	−0.50	0.31	0.10	−1.12	0.11	−1.62	0.11
Narula et al[21]	−0.87	0.26	0.07	−1.37	−0.37	−3.41	0
Tiihonen et al[23]	−0.37	0.30	0.09	−0.96	0.22	−1.22	0.22
Yang[26]	−0.62	0.28	0.08	−1.16	−0.08	−2.25	0.02
Pooled studies	−0.55	0.16	0.03	−0.86	−0.24	−3.44	0

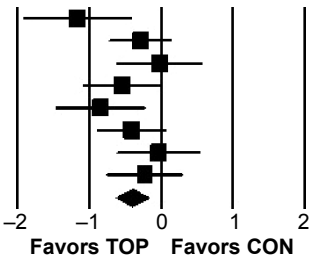
SMD and 95% CI



B Positive symptoms

Study	SMD	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afshar et al[15]	−1.17	0.38	0.15	−1.92	−1.42	−3.05	0
Behdani et al[16]	−0.29	0.22	0.05	−0.73	0.15	−1.28	0.20
Chengappa et al[17]	−0.02	0.31	0.09	−0.62	0.58	−0.08	0.94
Liu[25]	−0.55	0.28	0.08	−1.10	0	−1.96	0.05
Muscatello et al[20]	−0.84	0.32	0.10	−1.47	−0.22	−2.63	0.01
Narula et al[21]	−0.41	0.25	0.06	−0.89	0.07	−1.66	0.10
Tiihonen et al[23]	−0.03	0.30	0.09	−0.62	0.55	−0.12	0.91
Yang[26]	−0.23	0.27	0.07	−0.76	0.30	−0.85	0.40
Pooled studies	−0.40	0.12	0.01	−0.63	−0.17	−3.35	0

SMD and 95% CI



C Negative symptoms

Study	SMD	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afshar et al[15]	−1.40	0.39	0.16	−2.18	−0.63	−3.55	0
Behdani et al[16]	−0.37	0.23	0.05	−0.81	0.07	−1.63	0.10
Chengappa et al[17]	−0.06	0.31	0.09	−0.66	0.54	−0.20	0.84
Liu[25]	−0.14	0.28	0.08	−0.68	0.40	−0.51	0.61
Muscatello et al[20]	−0.88	0.32	0.10	−1.52	−0.25	−2.75	0.01
Narula et al[21]	−0.36	0.25	0.06	−0.85	0.12	−1.47	0.14
Tiihonen et al[23]	0.28	0.30	0.09	−0.31	0.87	0.93	0.35
Yang[26]	−1.08	0.29	0.08	−1.65	−0.52	−3.75	0
Pooled studies	−0.47	0.18	0.03	−0.82	−0.12	−2.65	0.01

SMD and 95% CI

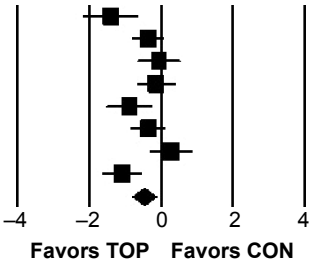


Figure 2 Forest plots of psychopathological outcomes.
Abbreviations: SMD, standardized mean difference; CI, confidence interval; TOP, topiramate; CON, control.

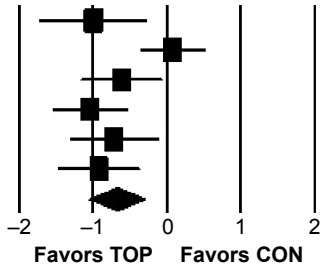
various-antipsychotic subgroup, open-label subgroup, Europe–US subgroup, and older publication year (before 2008) subgroup disappeared without significant difference when comparing topiramate to control. On the other hand, significant heterogeneity in the olanzapine subgroup, non-intention-to-treat population subgroup, Asia subgroup, the long-duration subgroup (13 weeks or more), low-dose topiramate subgroup (200 mg/day or less), newer publication year (after 2008) subgroup, diagnosis (schizophrenia) subgroup, not treatment-refractory subgroup, and large number of patients (more than 55) subgroup disappeared when comparing topiramate to control. One study was unique, because it was the only study that was sponsored by the pharmaceutical industry (Table 3).

Safety

Topiramate and control did not differ regarding discontinuation rate due to all causes (RR 1.19, 95% CI 0.79–1.79; P=0.4; I^2=1%, ten comparisons, n=561), discontinuation rate due to inefficacy (RR 1.71, 95% CI 0.52–5.66; P=0.38; I^2=0, seven comparisons, n=377), or discontinuation rate due to adverse events (RR 1.09, 95% CI 0.14–8.49; P=0.93; I^2=0, seven comparisons, n=377). Although topiramate was associated with a lower incidence of weight gain (RR 0.31, 95% CI 0.15–0.64; P=0.002; I^2=62%, NNH −2, three comparisons, n=165) (Figure 4A), ≥7% weight gain (RR 0.25, 95% CI 0.12–0.51; P=0.0002; I^2=0, NNH −2, two comparisons, n=97) (Figure 4B), and increased appetite (RR 0.26,

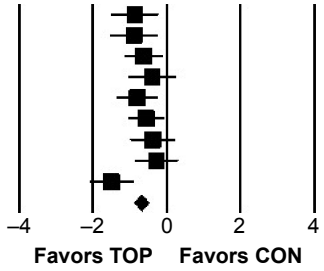
A PANSS general subscale scores

Study	SMD	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afshar et al[15]	–0.99	0.37	0.14	–1.73	–0.26	–2.65	0.01
Behdani et al[16]	0.08	0.22	0.05	–0.36	0.52	0.37	0.71
Liu[25]	–0.61	0.28	0.08	–1.16	–0.06	–2.16	0.03
Narula et al[21]	–1.03	0.26	0.07	–1.54	–0.52	–3.96	0
Tiihonen et al[23]	–0.71	0.31	0.09	–1.32	–0.11	–2.32	0.02
Yang[26]	–0.92	0.28	0.08	–1.48	–0.36	–3.24	0
Pooled studies	–0.67	0.20	0.04	–1.06	–0.28	–3.40	0



B Weight loss

Study	SMD	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Chen et al[24]	–0.86	0.33	0.11	–1.50	–0.22	–2.64	0.01
Chengappa et al[17]	–0.89	0.33	0.11	–1.54	–0.23	–2.65	0.01
Kim et al[18]	–0.62	0.26	0.07	–1.14	–0.10	–2.35	0.02
Ko et al[19]	–0.39	0.33	0.11	–1.04	0.27	–1.16	0.25
Liu[25]	–0.80	0.29	0.08	–1.36	–0.24	–2.80	0.01
Narula et al[21]	–0.56	0.25	0.06	–1.05	–0.07	–2.24	0.03
Nickel et al[22]	–0.38	0.31	0.10	–0.99	0.23	–1.21	0.23
Tiihonen et al[23]	–0.28	0.30	0.09	–0.86	0.31	–0.92	0.36
Yang[26]	–1.50	0.31	0.09	–2.09	–0.90	–4.90	0
Pooled studies	–0.69	0.10	0.01	–0.88	–0.49	–6.95	0



C BMI reduction

Study	SMD	Standard error	Variance	Lower limit	Upper limit	Z-value	P-value
Afshar et al[15]	–0.53	0.36	0.13	–1.23	0.18	–1.47	0.14
Chen et al[24]	–1.28	0.34	0.12	–1.96	–0.61	–3.74	0
Chengappa et al[17]	–0.93	0.33	0.11	–1.58	–0.27	–2.77	0.01
Ko et al[19]	–1.04	0.35	0.12	–1.72	–0.35	–2.95	0
Liu[25]	–0.76	0.28	0.08	–1.32	–0.21	–2.69	0.01
Narula et al[21]	–0.60	0.25	0.06	–1.09	–0.12	–2.42	0.02
Yang[26]	–1.58	0.31	0.10	–2.18	–0.97	–5.11	0
Pooled studies	–0.95	0.14	0.02	–1.23	–0.66	–6.55	0

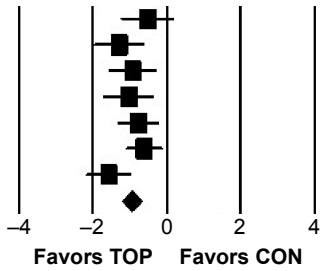


Figure 3 Forest plots of psychopathological and anthropometric outcomes.
Abbreviations: PANSS, Positive and Negative Syndrome Scale; SMD, standardized mean difference; CI, confidence interval; TOP, topiramate; CON, control; BMI, body mass index.

Table 3 Sensitivity analysis for overall symptoms of topiramate-augmentation therapy

Variable	Subgroup	Studies (n)	Patients (n)	I^2 (%)	SMD	95% CI	*P*-value	Test for subgroup differences	
								P-value	I^2 (%)
Antipsychotic class	Clozapine	2	75	77	−1	−2.06 to 0.06	0.06	0.04	69.7
	Olanzapine	3	175	0	−0.69	−1 to −0.39	<0.00001		
	Various APs	3	130	0	−0.13	−0.48 to 0.22	0.47		
Blinding	Double-blind	6	367	69	−0.64	−1.13 to −0.16	0.009	0.49	0
	Open	2	90	0	−0.42	−0.84 to 0	0.05		
Analyzed population	ITT	2	80	91	−0.68	−2.39 to 1.03	0.43	0.78	0
	Non-ITT	5	255	0	−0.59	−0.84 to −0.33	<0.00001		
	Crossover	1	45	NA	−0.36	−0.95 to 0.23	0.23		
Region	Asia	5	244	47	−0.72	−1.09 to −0.36	0.0001	0.07	69.2
	Europe and USA	3	136	23	−0.23	−0.62 to 0.17	0.26		
Control	PBO	7	327	59	−0.54	−0.89 to −0.18	0.003	0.9	0
	Non-PBO	1	53	NA	−0.58	−1.13 to −0.03	0.04		
Study duration	<13 weeks	6	292	65	−0.58	−1 to −0.17	0.006	0.6	0
	≥13 weeks	2	88	0	−0.43	−0.85 to 0	0.05		
Topiramate dose	≤200 mg	5	255	0	−0.59	−0.84 to −0.33	<0.00001	0.95	0
	>200 mg	3	125	83	−0.55	−1.47 to 0.36	0.24		
Publication year	<2008	3	130	0	−0.13	−0.48 to 0.22	0.47	0.008	85.7
	≥2008	5	250	28	−0.76	−1.07 to −0.45	<0.00001		
Diagnosis	Schizophrenia	7	332	32	−0.63	−0.91 to −0.36	<0.00001	0.02	82.4
	Schizoaffective disorder	1	48	NA	0.17	−0.43 to 0.77	0.58		
Number of patients	n≤55	3	125	83	−0.55	−1.47 to 0.36	0.24	0.95	0
	n>55	5	255	0	−0.59	−0.84 to −0.33	<0.00001		
Patient status	Treatment-refractory	3	120	68	−0.76	−1.44 to −0.08	0.03	0.41	0
	Not treatment-refractory	5	260	48	−0.44	−0.8 to −0.09	0.01		
Language	English	6	272	66	−0.53	−0.96 to −0.09	0.02	0.81	0
	Chinese	2	108	0	−0.6	−0.98 to −0.21	0.003		
Sponsorship	Industry	1	32	NA	−1.58	−2.38 to −0.77	0.0001	0.009	85.5
	Nonindustry	7	348	24	−0.45	−0.7 to −0.2	0.0004		

Abbreviations: APs, antipsychotics; CI, confidence interval; ITT, intention to treat; NA, not applicable; PBO, placebo; SMD, standardized mean difference.

95% CI 0.1–0.66; P=0.005; I^2=0, NNH −4, two comparisons, n=120) (Figure 4C) than the controls, it was associated with a higher incidence of paresthesia (RR 2.67, 95% CI 1.15–6.19; P=0.02; I^2=0, NNH not significant, four comparisons, n=248) (Figure 5A) and attention difficulty (RR 8.97, 95% CI 1.17–68.63; P=0.03; I^2=0, NNH 8, two comparisons, n=120) (Figure 5B) than the controls. There were no significant differences in individual adverse events reported (asthenia, constipation, diarrhea, dizziness, dry mouth, fatigue, headache, insomnia, memory loss, muscle weakness, nausea, psychomotor slowing, psychosis exacerbation, or somnolence) between topiramate and control (Table 4).

Discussion

To the best of our knowledge, the current study is the largest comprehensive systematic review and meta-analysis of topiramate-augmentation therapy for schizophrenia and related diseases. Topiramate augmentation was more efficacious than control (antipsychotic alone or antipsychotic plus placebo) for reducing overall, positive, and negative symptoms, PANSS general subscale scores, weight, and BMI. We did not find any cause for the heterogeneity among individual studies, despite performing 13 sensitivity analyses of overall symptoms. Based on the results of the sensitivity analyses, low-dose topiramate (≤200 mg/day)-augmentation therapy for olanzapine may be useful. The prevalence of metabolic syndrome is at least twice as high in schizophrenia patients compared with the age-adjusted population.[40] Given the importance of maintaining medication adherence for schizophrenia, it is often necessary to use a safer but less efficacious antipsychotic. Augmentation therapy should be considered before changing from the safer antipsychotic to one with greater potential efficacy but also higher metabolic risk.[41,42] In a prospective study, 27% of patients with schizophrenia

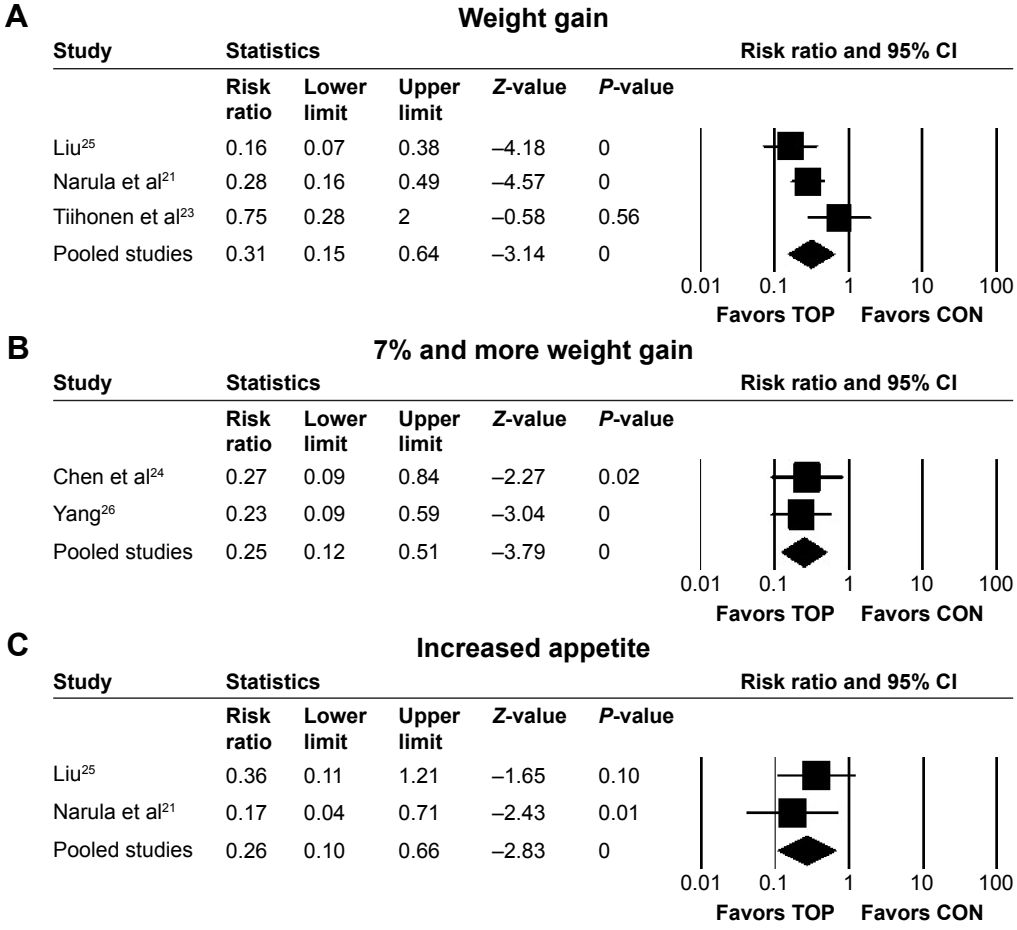


Figure 4 Forest plots of individual adverse events.
Abbreviations: CI, confidence interval; TOP, topiramate; CON, control.

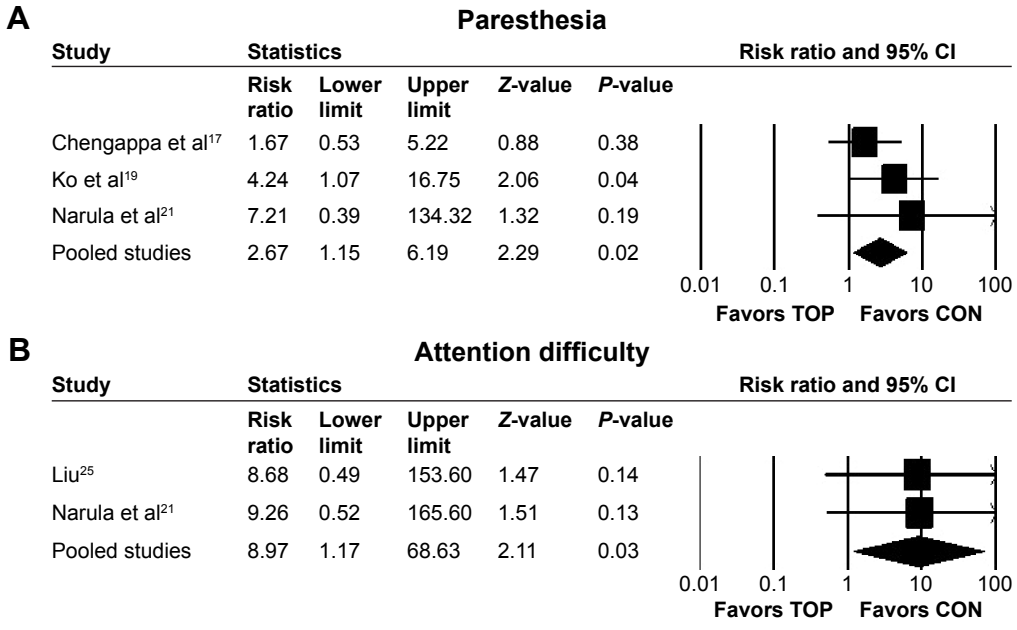


Figure 5 Forest plots of individual adverse events.
Abbreviations: CI, confidence interval; TOP, topiramate; CON, control.

Table 4 Discontinuation rates and individual adverse events

	Studies (n)	Patients (n)	I^2 (%)	Risk ratio	95% CI	*P*-value
Discontinuation due to inefficacy	7	377	0	1.71	0.52–5.66	0.38
Discontinuation due to adverse events	7	377	0	1.09	0.14–8.49	0.93
Asthenia	2	112	0	0.98	0.54–1.77	0.95
Constipation	3	195	49	0.43	0.05–3.68	0.44
Diarrhea	2	101	0	1.10	0.36–3.4	0.87
Dizziness	5	308	0	0.56	0.29–1.09	0.09
Fatigue	2	106	0	0.87	0.51–1.47	0.59
Headache	4	236	6	0.89	0.3–2.64	0.83
Insomnia	2	127	0	0.68	0.2–2.27	0.53
Memory loss	3	148	0	0.99	0.46–2.13	0.97
Nausea	4	241	0	0.55	0.2–1.5	0.24
Psychomotor slowing	2	120	0	3.30	0.58–18.93	0.18
Psychosis exacerbation	2	123	NA	5.00	0.25–100.97	0.29
Somnolence	6	348	4	1.09	0.81–1.45	0.57

Abbreviations: CI, confidence interval; NA, not applicable.

eventually developed poor adherence.[43] Moritz et al[44] studied the reasons for antipsychotic nonadherence, and concluded that side effects were the most common reason. Weight gain is also a well-known side effect, especially with second-generation antipsychotics, which are more widely used throughout the world than first-generation antipsychotics for treating schizophrenia.[45] Furthermore, augmentation therapy for clozapine may be particularly important, since clozapine is thought to be the final option for treatment-resistant schizophrenia (alongside modified electroconvulsive therapy). If clozapine efficacy is still insufficient, effective augmentation drugs should be considered.[27]

However, we cannot apply the results of this study in daily clinical practice because of the following. There are some limitations to this meta-analysis. The main limitation is the paucity of RCTs, despite updating from previous meta-analyses.[27,28] All the trials included were small, and it is well documented that small trials exaggerate effects. Second, although we utilized a funnel plot to assess potential publication bias, these are generally used only if ten or more studies are included. The third limitation is the short follow-up period (8–24 weeks). Fourth, we did not investigate the optimal topiramate dose for augmentation therapy. Future research should investigate the long-term efficacy of multiple doses and generate more safety data using larger samples. Fifth, although several of our included studies were from China, it has been reported that many Chinese studies are problematic.[46] Some studies included in the meta-analysis did not report detailed information about sequence generation or allocation concealment. Moreover, seven studies used a completer analysis.

Conclusion

Our results indicate that topiramate-augmentation therapy is well tolerated, can improve the psychopathology of schizophrenia, and reduces weight gain associated with antipsychotics. Since there were some limitations in this study, we could not apply the results of this study in daily clinical practice. Future research should investigate long-term efficacy and generate more safety data for schizophrenia patients receiving topiramate augmentation of antipsychotics.

Disclosure

The authors report no conflicts of interest in this work, but report the following interests: Dr Okuyama has received speaker's honoraria from Janssen; Dr Oya has received honoraria from Eisai, Eli Lilly, Janssen, Meiji, Otsuka, and Tanabe-Mitsubishi; Dr Matsunaga has received honoraria from Eisai, Janssen, Novartis, Daiichi Sankyo, Ono, Eli Lilly, Takeda, and Otsuka and has a Fujita Health University School of Medicine research grant and Grant-in-Aid for Young Scientists (B); Dr Kishi has received speaker's honoraria from Abbvie, Astellas, Daiichi Sankyo, Dainippon Sumitomo, Eisai, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Mochida, Shionogi, Tanabe-Mitsubishi, Tsumura, Novartis, and Pfizer and has a Fujita Health University School of Medicine research grant and Grant-in-Aid for Young Scientists (B); and Dr Iwata has received honoraria from Astellas, Dainippon Sumitomo, Eli Lilly, GlaxoSmithKline, Janssen, Yoshitomi, Otsuka, Meiji, Shionogi, Novartis, and Pfizer.

References

1. MacDonald AW, Schulz SC. What we know: findings that every theory of schizophrenia should explain. *Schizophr Bull*. 2009;35(3):493–508.
2. Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull*. 1998;24(1):75–85.
3. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379(9831):2063–2071.

4. Valenstein M, Copeland LA, Blow FC, et al. Pharmacy data identify poorly adherent patients with schizophrenia at increased risk for admission. *Med Care*. 2002;40(8):630–639.
5. Moritz S, Favrod J, Andreou C, et al. Beyond the usual suspects: positive attitudes towards positive symptoms is associated with medication noncompliance in psychosis. *Schizophr Bull*. 2013;39(4):917–922.
6. Haddad PM, Brain C, Scott J. Nonadherence with antipsychotic medication in schizophrenia: challenges and management strategies. *Patient Relat Outcome Meas*. 2014;5:43–62.
7. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet*. 2013;382(9896):951–962.
8. Rummel-Kluge C, Komossa K, Schwarz S, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res*. 2010;123(2–3):225–233.
9. Rummel-Kluge C, Komossa K, Schwarz S, et al. Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. *Schizophr Bull*. 2012;38(1):167–177.
10. National Institute for Health and Care Excellence. *Psychosis and Schizophrenia in Adults: Treatment and Management*. London: NICE; 2014.
11. Topamax (topiramate) [package insert]. Beerse, Belgium: Janssen Pharmaceutica; 2005.
12. Hahn MK, Cohn T, Teo C, Remington G. Topiramate in schizophrenia: a review of effects on psychopathology and metabolic parameters. *Clin Schizophr Relat Psychoses*. 2013;6(4):186–196.
13. Wilkes JJ, Nelson E, Osborne M, Demarest KT, Olefsky JM. Topiramate is an insulin-sensitizing compound in vivo with direct effects on adipocytes in female ZDF rats. *Am J Physiol Endocrinol Metab*. 2005;288(3):E617–E624.
14. Berelowitz M, Matthews J, Pimstone BL, Kronheim S, Sacks H. Immunoreactive somatostatin in rat cerebral cortical and hypothalamic synaptosomes. *Metabolism*. 1978;27(9 Suppl 1):1171–1173.
15. Afshar H, Roohafza H, Mousavi G, et al. Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. *J Psychopharmacol*. 2009;23(2):157–162.
16. Behdani F, Hebrani P, Ardani AR, Rafee E. Effect of topiramate augmentation in chronic schizophrenia: a placebo-controlled trial. *Arch Iran Med*. 2011;14(4):270–275.
17. Chengappa KN, Kupfer DJ, Parepally H, et al. A placebo-controlled, random-assignment, parallel-group pilot study of adjunctive topiramate for patients with schizoaffective disorder, bipolar type. *Bipolar Disord*. 2007;9(6):609–617.
18. Kim JH, Yim SJ, Nam JH. A 12-week, randomized, open-label, parallel-group trial of topiramate in limiting weight gain during olanzapine treatment in patients with schizophrenia. *Schizophr Res*. 2006;82(1):115–117.
19. Ko YH, Joe SH, Jung IK, Kim SH. Topiramate as an adjuvant treatment with atypical antipsychotics in schizophrenic patients experiencing weight gain. *Clin Neuropharmacol*. 2005;28(4):169–175.
20. Muscatello MR, Bruno A, Pandolfo G, et al. Topiramate augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. *J Psychopharmacol*. 2011;25(5):667–674.
21. Narula PK, Rehan HS, Unni KE, Gupta N. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. *Schizophr Res*. 2010;118(1–3):218–223.
22. Nickel MK, Nickel C, Muehlbacher M, et al. Influence of topiramate on olanzapine-related adiposity in women: a random, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2005;25(3):211–217.
23. Tiihonen J, Halonen P, Wahlbeck K, et al. Topiramate add-on in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. *J Clin Psychiatry*. 2005;66(8):1012–1015.
24. Chen ZX, Xia ML, Xia WJ, Huang HG, Jin L. [Topiramatefor prevention of olanzapine associated weight gain]. *Modern Pract Med*. 2012;24:979–980. Chinese.
25. Liu JJ. [The efficacy of topiramate in the treatment of antipsychotic-induced weight gain and lipid disorders]. *Modern Pract Med*. 2011;23:665–667. Chinese.
26. Yang Y. *The studying about the effects of topiramate in preventing olanzapine-induced weight gain and glucose and lipid metabolic dysfunction* [dissertation]. Chongqing: Chongqing Medical University; 2008. Available at: http://cdmd.cnki.com.cn/Article/CDMD-10631-2008176780.htm.dissertation.
27. Sommer IE, Begemann MJ, Temmerman A, Leucht S. Pharmacological augmentation strategies for schizophrenia patients with insufficient response to clozapine: a quantitative literature review. *Schizophr Bull*. 2012;38(5):1003–1011.
28. Mizuno Y, Suzuki T, Nakagawa A, et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull*. 2014;40(6):1385–1403.
29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
30. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
31. Guy W, Bonato RR. *Manual for the ECDEU Assessment Battery*. 2nd ed. Chevy Chase (MD): National Institute of Mental Health; 1970.
32. Overall J, Gorham D. The brief psychiatric rating scale. *Psychol Rep*. 1962;10:799–812.
33. Andreasen N. *Scale for the Assessment of Positive Symptoms (SAPS)*. Iowa City: University of Iowa; 1984.
34. Andreasen N. *Scale for the Assessment of Negative Symptoms (SANS)*. Iowa City: University of Iowa; 1984.
35. Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophr Res*. 1990;3(4):247–251.
36. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134:382–389.
37. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177–188.
38. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.
39. Liang H, Li H, Hu Y, Li S, Lu L, Song X. [Effects of topiramate for atypical antipsychotic-induced body weight gain and metabolic adversities: a systematic review and meta-analysis]. *Zhonghua Yi Xue Za Zhi*. 2016;96(3):216–223. Chinese.
40. De Hert MA, van Winkel R, Van Eyck D, et al. Prevalence of the metabolic syndrome in patients with schizophrenia treated with antipsychotic medication. *Schizophr Res*. 2006;83(1):87–93.
41. Kishi T, Mukai T, Matsuda Y, Moriwaki M, Iwata N. Efficacy and safety of noradrenalin reuptake inhibitor augmentation therapy for schizophrenia: a meta-analysis of double-blind randomized placebo-controlled trials. *J Psychiatr Res*. 2013;47(11):1557–1563.
42. Kishi T, Meltzer HY, Iwata N. Augmentation of antipsychotic drug action by azapirone 5-HT1A receptor partial agonists: a meta-analysis. *Int J Neuropsychopharmacol*. 2013;16(6):1259–1266.
43. Brain C, Sameby B, Allerby K, et al. Twelve months of electronic monitoring (MEMS) in the Swedish COAST-study: a comparison of methods for the measurement of adherence in schizophrenia. *Eur Neuropsychopharmacol*. 2014;24(2):215–222.
44. Moritz S, Hünsche A, Lincoln TM. Nonadherence to antipsychotics: the role of positive attitudes towards positive symptoms. *Eur Neuropsychopharmacol*. 2014;24(11):1745–1752.
45. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009;373(9657):31–41.
46. Woodhead M. 80% of China's clinical trial data are fraudulent, investigation finds. *BMJ*. 2016;355:i5396.
47. Correll CU, Maayan L, Kane J, Hert MD, Cohen D. Efficacy for psychopathology and body weight and safety of topiramate-antipsychotic cotreatment in patients with schizophrenia spectrum disorders: results from a meta-analysis of randomized controlled trials. *J Clin Psychiatry*. 2016;77:e746–e756.

Supplementary materials

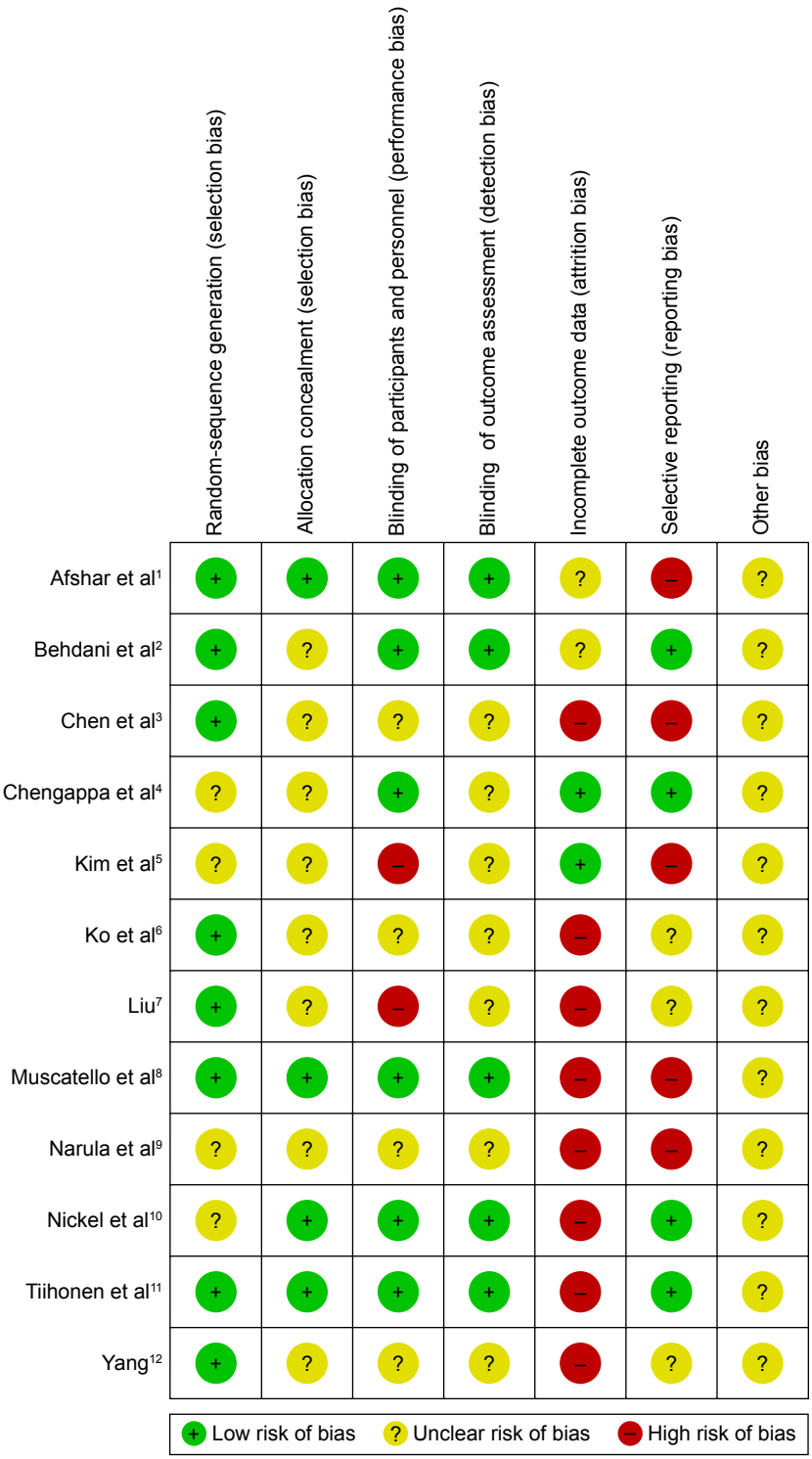


Figure S1 Risk-of-bias summary.

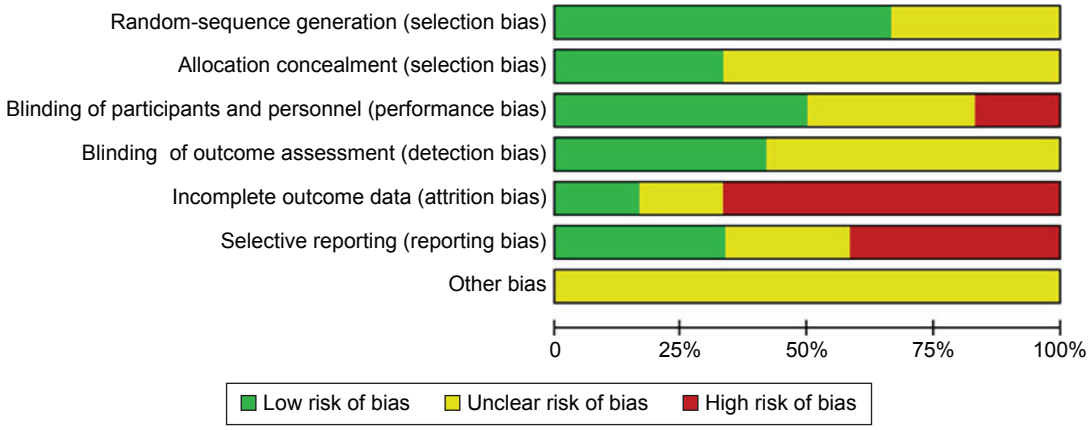


Figure S2 Risk-of-bias graph.

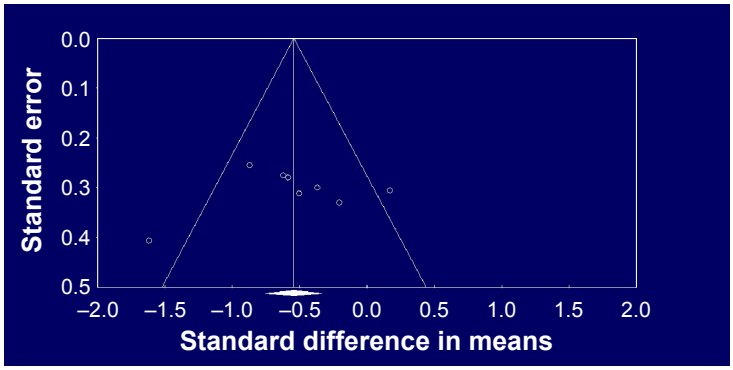


Figure S3 Funnel plot of standard error by standard difference in means.

References

1. Afshar H, Roohafza H, Mousavi G, et al. Topiramate add-on treatment in schizophrenia: a randomised, double-blind, placebo-controlled clinical trial. *J Psychopharmacol*. 2009;23(2):157–162.
2. Behdani F, Hebrani P, Ardani AR, Rafee E. Effect of topiramate augmentation in chronic schizophrenia: a placebo-controlled trial. *Arch Iran Med*. 2011;14(4):270–275.
3. Chen ZX, Xia ML, Xia WJ, Huang HG, Jin L. [Topiramatefor prevention of olanzapine associated weight gain]. *Modern Pract Med*. 2012; 24:979–980. Chinese.
4. Chengappa KN, Kupfer DJ, Parepally H, et al. A placebo-controlled, random-assignment, parallel-group pilot study of adjunctive topiramate for patients with schizoaffective disorder, bipolar type. *Bipolar Disord*. 2007;9(6):609–617.
5. Kim JH, Yim SJ, Nam JH. A 12-week, randomized, open-label, parallel-group trial of topiramate in limiting weight gain during olanzapine treatment in patients with schizophrenia. *Schizophr Res*. 2006;82(1):115–117.
6. Ko YH, Joe SH, Jung IK, Kim SH. Topiramate as an adjuvant treatment with atypical antipsychotics in schizophrenic patients experiencing weight gain. *Clin Neuropharmacol*. 2005;28(4):169–175.
7. Liu JJ. [The efficacy of topiramate in the treatment of antipsychotic-induced weight gain and lipid disorders]. *Modern Pract Med*. 2011;23: 665–667. Chinese.
8. Muscatello MR, Bruno A, Pandolfo G, et al. Topiramate augmentation of clozapine in schizophrenia: a double-blind, placebo-controlled study. *J Psychopharmacol*. 2011;25(5):667–674.
9. Narula PK, Rehan HS, Unni KE, Gupta N. Topiramate for prevention of olanzapine associated weight gain and metabolic dysfunction in schizophrenia: a double-blind, placebo-controlled trial. *Schizophr Res*. 2010;118(1–3):218–223.
10. Nickel MK, Nickel C, Muehlbacher M, et al. Influence of topiramate on olanzapine-related adiposity in women: a random, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2005;25(3):211–217.
11. Tiihonen J, Halonen P, Wahlbeck K, et al. Topiramate add-on in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. *J Clin Psychiatry*. 2005;66(8): 1012–1015.
12. Yang Y. *The studying about the effects of topiramate in preventing olanzapine-induced weight gain and glucose and lipid metabolic dysfunction* [dissertation]. Chongqing: Chongqing Medical University; 2008. Available at: http://cdmd.cnki.com.cn/Article/CDMD-10631-2008176780.htm.dissertation.