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

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ABSTRACT

Objective: To meta-analyze the efficacy and tolerability of topiramate-antipsychotic cotreatment in schizophrenia.

Data Sources: PubMed/MEDLINE database were searched until September 5, 2015, using the keywords *topiramate* AND *antipsych** OR *neurolept** OR specific antipsychotic names.

Study Selection: Randomized controlled trials (RCTs) of topiramate-antipsychotic cotreatment versus placebo and ongoing antipsychotic treatment in patients with schizophrenia spectrum disorders were included.

Data Extraction: Two evaluators extracted data. Standardized mean difference (SMD), weighted mean difference (WMD), and risk ratio (RR) ± 95% CIs were calculated.

Results: In 8 RCTs, lasting a mean ± SD of 13.6 ± 4.9 weeks, 439 patients were randomized to topiramate (100–400 mg/d) versus placebo (trials = 7) or ongoing antipsychotic treatment (trial = 1). Topiramate outperformed the comparator regarding total psychopathology (trials = 6, n = 269, SMD = −0.57 [95% CI, −1.01 to −0.14], *P* = .01), positive symptoms (trials = 4, n = 190, SMD = −0.56 [95% CI, −1.0 to −0.11], *P* = .01), negative symptoms (trials = 4, n = 190, SMD = −0.62 [95% CI, −1.13 to −0.10], *P* = .02) general psychopathology (trials = 3, n = 179, SMD = −0.69 [95% CI, −1.27 to −0.11], *P* = .02), body weight (trials = 7, n = 327, WMD = −3.14 kg [95% CI, −5.55 to −0.73], *P* = .01), and body mass index (BMI) (trials = 4, n = 198, WMD = −1.80 [95% CI, −2.77 to −0.84], *P* = .0003). Topiramate's efficacy for total psychopathology and weight reduction effects were not mediated/moderated by trial duration, topiramate dose, sex, age, inpatient status, baseline Positive and Negative Syndrome Scale, or baseline BMI. Conversely, clozapine-topiramate cotreatment moderated greater efficacy, but less weight loss, compared to topiramate-nonclozapine antipsychotic combinations. All-cause discontinuation was similar between topiramate and control groups (trials = 7, RR = 1.24 [95% CI, 0.76 to 2.02], *P* = .39). Topiramate trended only toward more paresthesia than placebo (trials = 4, RR = 2.03 [95 % CI, 0.99 to 4.18], *P* = .05).

Conclusions: Topiramate-antipsychotic cotreatment significantly reduced total, positive, negative, and general psychopathology and weight/BMI in patients with schizophrenia spectrum disorder while being well tolerated. However, larger studies are needed to confirm and extend these findings.

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Despite treatment advances, patients with schizophrenia spectrum disorders are still frequently struggling with significant residual psychopathology and functional impairment.[1] This is even true for patients who use clozapine, which, when dosed appropriately,[2] was found in meta-analyses to be superior to other antipsychotics in treatment-refractory patients.[3,4] Augmentation with a second antipsychotic,[5,6] lithium,[7] valproic acid,[8] carbamazepine,[9] lamotrigine,[10,11] benzodiazepines,[12] or β-blockers[13] did not succeed in consistently and robustly decreasing total psychopathology and positive symptoms, while negative and/or cognitive symptoms did not sufficiently improve with augmentation of antipsychotics with *N*-methyl-D-aspartate modulators,[14,15] antidepressants,[16–19] acetylcholinesterase inhibitors,[20] omega-3 fatty acids,[21] or modafinil.[22] Addition of electroconvulsive therapy,[23] nonsteroidal anti-inflammatory drugs,[24] testosterone,[25] estrogen,[26] and cannabidiol[27] are potentially promising strategies, but these have been examined only in few and small studies.

Augmentation strategies can also aim at reducing antipsychotic-related adverse effects. Recently, cardiometabolic adverse effects of antipsychotics have gained more attention than any other side effect cluster.[28–30] While nonpharmacologic weight loss programs have been more effective than a control condition,[31,32] many patients are unwilling or unable to take advantage of these programs. Successful pharmacologic strategies to reduce antipsychotic-related weight gain include, for most, metformin and topiramate, as well as d-fenfluramine, sibutramine, and reboxetine.[33–35]

Topiramate, a sulfamate-substituted monosaccharide that is related to fructose, is approved by the US Food and Drug Administration as an antiepileptic and antimigraine treatment (http://dailymed.nlm.nih.gov/dailymed/index.cfm). Also, topiramate is approved by the European Medicines Agency (http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Topamax_30/WC500018620.pdf) for the monotherapy and adjunctive therapy of seizures and as prophylactic treatment of migraine headaches. The exact mechanisms of

Clinical Points

- Insufficient response and resistance to antipsychotic treatment as well as significant weight gain are common clinical problems for which no approved and few clinically useful combination options exist.
- Results from this meta-analysis suggest that the addition of topiramate 100–400 mg/d to ongoing antipsychotic treatment may help improve total, positive, negative, and general symptoms and reduce body weight in patients with schizophrenia who derive insufficient benefit from first-line antipsychotics or clozapine, while being well tolerated except for a greater likelihood of paresthesia.
- Although more and larger studies are needed, preliminary data suggest that the efficacy of topiramate augmentation may be enhanced in patients on clozapine treatment, whereas the weight-reducing effect may be enhanced in patients treated with antipsychotics other than clozapine.

action of topiramate are unknown but include the blockage of voltage-dependent sodium channels, stimulation of the γ-aminobutyric acid-A ($GABA_A$) receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate glutamate receptor antagonism, and inhibition of the carbonic anhydrase enzyme, particularly isozymes II and IV.[36] In epilepsy, topiramate has been associated with weight loss.[37] Topiramate has been associated with significantly greater advantages than placebo regarding body weight loss, improvement in glucose homeostasis, and blood pressure, both in nonpsychiatric patients with obesity[38–42] and/or type 2 diabetes.[43–46] Much of topiramate's benefits are ascribed to its ability to reduce appetite and daily energy intake and, consequently, fat stores.[41,43] However, the use of topiramate as a weight-loss agent or augmentation strategy for the treatment of type 2 diabetes has been precluded by its adverse effect profile.[43–45] A chart review[47] of 431 patients showed that adverse psychiatric side effects occurred in as many as 103 patients (23.9%). A psychiatric history has been found to be a risk factor for the development of psychiatric adverse events during topiramate treatment.[48,49] Worsening of preexistent psychosis has been reported[50–52] as well as cases of topiramate-induced psychosis in nonpsychiatric patients.[53–56] Consistent with its status as an AMPA/kainate receptor antagonist, topiramate has also been associated with cognitive adverse effects.[41–45] Conversely, both case reports[57,58] and case series[59,60] of weight loss with topiramate when initiated after weight gain associated with olanzapine or clozapine have been reported without exacerbation of the underlying psychiatric symptoms. Additionally, individual randomized controlled trials (RCTs) reported improved psychopathology after augmentation of antipsychotics with topiramate.[61–63]

There is no lack of reviews on topiramate augmentation in schizophrenia, but their scope of studies and specificity for schizophrenia is limited. Alt hough 1 recent review[64] summarized separately the results of 3 adjunctive topiramate trials targeting symptom reduction, 3 topiramate trials targeting body weight reduction in patients with schizophrenia were not included in this review. Another recent meta-analysis[35] was conducted regarding topiramate's weight loss effects in antipsychotic-treated patients, but studies in patients with schizophrenia and nonschizophrenia diagnoses were mixed together, and in an even more recent, targeted meta-analysis[34] of adjunctive weight loss agents in schizophrenia, only 3 topiramate trials were included. Finally, the only 2 meta-analyses[26,65] of topiramate's efficacy as an augmentation agent for improving psychopathology focused exclusively on studies of clozapine-treated patients. This selection, although defendable, excludes the great majority of patients because most treatment-resistant patients do not receive clozapine.[66] Therefore, we decided to conduct a systematic review and comprehensive meta-analysis of all randomized trials of topiramate addition to any antipsychotic in patients with schizophrenia spectrum disorders. On the basis of the results from single studies, we hypothesized that topiramate is more effective than placebo for reducing both psychopathology and body weight.

METHODS

Search

We conducted a systematic PubMed/MEDLINE database search, from inception of the database until September 5, 2015, and without language restrictions, using the following keywords: (*topiramate* OR *topamax*) AND (*antipsych** OR *neurolept** OR *risperidone* OR *olanzapine* OR *aripiprazole* OR *quetiapine* OR *perospirone* OR *ziprasidone* OR *clozapine* OR *amisulpride* OR *asenapine* OR *blonanserin* OR *clothiapine* OR *iloperidone* OR *lurasidone* OR *mosapramine* OR *paliperidone* OR *remoxipride* OR *sertindole* OR *sulpiride* OR *tiapride* OR *chlorpromazine* OR *thioridazine* OR *mesoridazine* OR *loxapine* OR *molindone* OR *perphenazine* OR *thiothixene* OR *trifluoperazine* OR *haloperidol* OR *fluphenazine* OR *droperidol* OR *zuclopenthixol* OR *pimozide* OR *flupenthixol* OR *prochlorperazine*). We also hand searched reference lists from identified and relevant review articles for additional studies and contacted authors for unpublished data.

Study Selection

We included randomized, placebo-controlled trials or open trials with an untreated control group (for adverse effect outcomes only) of antipsychotic augmentation with topiramate in patients with schizophrenia spectrum disorders (ie, schizophrenia, schizophreniform disorder, schizoaffective disorder). Randomized crossover studies were included when data for the first randomized, pre–crossover study phase were obtainable.[67]

Data Extraction

Two independent evaluators extracted data (L.M. and C.U.C.). Any inconsistencies were resolved by discussion.

Data Synthesis and Statistical Analysis

To minimize the effect of chance, we meta-analyzed only outcomes for which data from ≥3 studies were available.

The primary outcome was Positive and Negative Syndrome Scale (PANSS)[68]/Brief Psychiatric Rating Scale (BPRS)[69] total score change/end point difference. Secondary outcomes included positive, negative, and general psychopathology symptoms; all-cause discontinuation; body weight; body mass index (BMI); glucose and lipid parameters; and adverse effect frequencies. Whenever change score and end point values of a continuous outcome were available, we preferred change data, as often in smaller randomized trials the baseline values differ, biasing the analysis of end point results. However, we excluded skewed data from the analyses, defined by a standard deviation ≥ 2 times the mean in ≥ 1 treatment group. To assess potential dose effects, we entered the 2 fixed-dose topiramate treatment arms from 1 study[62] separately but assigned only half of the total number of patients randomized to placebo to each topiramate arm so that the number of placebo-treated patients would not be inflated.

The meta-analysis was performed using Review Manager (RevMan) version 5.1 for Windows (Review Manager version 5.0, Cochrane Collaboration; http://tech.cochrane.org/revman).

To combine studies, the random-effects model[70] was used in all cases. For continuous data, standardized mean difference (SMD) ± 95% CI was calculated, which allows for pooling of data across studies using differently scaled rating instruments that assess the same outcome domain. In order to also provide clinically more intuitive results, we also calculated in an exploratory fashion weighted mean differences (WMDs) for absolute point change in PANSS total scores, as the PANSS was the most used instrument, as well as for body weight difference between groups in kilograms and BMI units. For dichotomous data, pooled relative risk (RR) was calculated.

We analyzed data following the intention-to-treat (ITT) (≥ 1 dose) or modified ITT (≥ 1 follow-up) assessment principle, including 1 study[62] reporting observed cases results. To test the robustness of the results for the primary outcome, PANSS/BPRS total score change/end point difference, we conducted 2 sensitivity analyses repeating the analyses after removing the 2 studies[62,71] that used observed cases and after removing the 1 study[61] that had an outlying effect size of > −1.5, as each of these factors could potentially have biased the results.

Study heterogeneity was measured using the χ^2 and I^2 statistics, with χ^2 $P < .05$ and $I^2 \geq 50\%$ indicating heterogeneity.[72] For cases in which I^2 was ≥ 50% for the effect of topiramate on PANSS/BPRS score or body weight, the following exploratory, a priori–defined 2 subgroup and 7-step meta-regression analyses were conducted in order to seek reasons for the heterogeneity. Subgroup analyses conducted with RevMan included (1) timing of topiramate addition (concurrent with antipsychotic initiation vs after established antipsychotic treatment) and (2) antipsychotic treatment (clozapine [> 65%] vs antipsychotics other than clozapine). Additionally, we conducted a post hoc sensitivity analysis excluding a study not using a placebo control that contributed meta-analyzable weight gain, but no efficacy data.

Random-effects meta-regression analyses were conducted using Comprehensive Meta-Analysis Version 3 (Biostat; http://www.meta-analysis.com) to examine the potentially moderating effect of (1) mean age of study participants, (2) percentage of males, (3) percentage of inpatients, (4) baseline BMI, and (5) baseline PANSS scores (for end point PANSS only) and to examine the potential mediating effect of (6) trial duration and (7) topiramate dose on PANSS/BPRS total score change/end point difference and weight change difference between topiramate and placebo.

Finally, publication bias was evaluated with funnel plots, Egger regression coefficient, and the Trim Safe method, which estimates the number of studies needed to change the findings to meet or not meet 2-tailed α = .05, using Comprehensive Meta-Analysis.

RESULTS

Search

The last electronic search conducted on September 5, 2015, yielded 309 hits. Two hundred seventy-three studies were excluded on the basis of title or abstract. Of the remaining 36 references, 28 were excluded after full text review (review article [11], nonrandomized study [9], no schizophrenia spectrum disorder diagnosis [3], no placebo/antipsychotic continuation arm [3], duplicate data publication [2]) yielding 8 studies that were included in the meta-analysis (Figure 1).

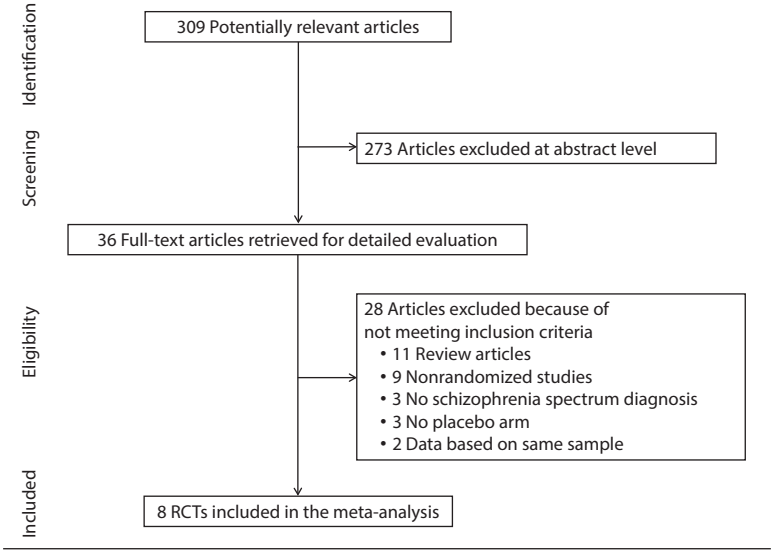
Study and Patient Characteristics

In 8 RCTs,[61–63,67,71,73–75] lasting 8–24 weeks (mean ± SD = 13.6 ± 4.9), 439 patients were randomized to topiramate (100–400 mg/d) or a comparison group consisting of placebo (7 trials) or continuation of open-label antipsychotic treatment without placebo addition (1 trial).[75] Six studies[61–63,71,73,74] were double-blind, placebo-controlled; 1 study[75] was a randomized, open-label trial; and 1 study[67] was a randomized, placebo-controlled, crossover trial (Table 1). Patients were 38.5 ± 5.5 years old, 63.7% ± 14.9% were male, and 55.1% ± 46.3% were inpatients. Most patients had schizophrenia (n = 391, 89.1%), and 48 (10.9%) had schizoaffective disorder. The mean baseline PANSS score was 85.3 ± 13.6, the mean baseline BPRS score was 29.3 ± 7.5, and the mean baseline BMI was 27.1 ± 4.5. One study[63] included acute, first-episode schizophrenia patients; the remaining studies were conducted in chronically ill patients. In 2 studies,[63,75] topiramate was started concurrently with the newly initiated antipsychotic; in the remaining 6 studies, topiramate was added to stable antipsychotics (Table 1).

Psychopathology Outcomes

PANSS/BPRS total scores. Compared to placebo/antipsychotic monotherapy, adjunctive topiramate outperformed placebo augmentation of antipsychotics with regard to change/end point in PANSS/BPRS total score

Figure 1. PRISMA Flow Diagram of Excluded and Included Studies



(trials = 6, n = 269, SMD = −0.57 [95% CI, −1.01 to −0.14], $P = .01$; $I^2 = 64\%$; Figure 2). When results from the 4 studies reporting PANSS total scores were pooled in a partial post hoc analysis, the WMD difference in favor of topiramate was −4.68 points (95% CI, −9.31 to −0.05; $P = .05$; $I^2 = 84\%$). When results from the 2 studies[61,74] including clozapine-treated patients and reporting PANSS score changes were pooled, the WMD difference in favor of topiramate was −10.73 points (95% CI, −25.36 to 3.90; $P = .15$; $I^2 = 91\%$). There was no indication of publication bias (Egger regression coefficient: $P = .81$), and the Trim Safe method indicated that 30 additional studies would be required to lead to a nonsignificant finding.

Results for PANSS/BPRS total score remained significant when the 2 studies[62,71] using completer analyses were removed (SMD = −0.77 [95% CI, −1.46 to −0.07], $P = .03$; $I^2 = 77\%$) and when the 1 strong outlying study[61] was removed (SMD = −0.43 [95% CI, −0.82 to −0.04], $P = .03$; $I^2 = 50\%$). When clozapine was the antipsychotic in > 65% of patients, topiramate had a particularly robust effect (SMD = −0.96 [95% CI, −1.59 to −0.32], $P = .003$; $I^2 = 54\%$), remaining significant when the 1 outlier[61] was removed (SMD = −0.65 [95% CI, −1.14 to −0.16], $P = .009$; $I^2 = 0\%$). By contrast, topiramate augmentation was not significantly different from placebo in patients treated with antipsychotics other than clozapine (SMD = −0.30 [95% CI, −0.86 to 0.25], $P = .28$; $I^2 = 64\%$) (see Supplementary eFigure 1). Nevertheless, in a direct comparison between studies of clozapine and studies of antipsychotics other than clozapine, no statistically significant subgroup difference based on baseline clozapine use versus nonuse was found ($P = .13$, $I^2 = 57\%$). The overall beneficial effect of topiramate on PANSS/BPRS total score was not moderated by concurrent versus later topiramate addition to the antipsychotic treatment ($P = .35$, $I^2 = 56.6\%$). In exploratory meta-regression analyses, none of the examined variables were significantly related to PANSS/BPRS total score change (trial duration: $P = .86$; age: $P = .64$; sex: $P = .44$; inpatient status: $P = .63$; topiramate dose: $P = .28$; baseline BMI: $P = .17$; baseline PANSS: $P = .20$).

Positive and Negative Symptoms and General Psychopathology

Compared to placebo/antipsychotic monotherapy, adjunctive topiramate outperformed placebo augmentation regarding positive symptoms (trials = 4, n = 190, SMD = −0.56 [95% CI, −1.00 to −0.11], $P = .01$; $I^2 = 53\%$; Figure 3A), negative symptoms (trials = 4, n = 190, SMD = −0.62 [95% CI, −1.13 to −0.10], $P = .02$; $I^2 = 64\%$; Figure 3B) and general psychopathology (trials = 3, n = 179, SMD = −0.69 [95% CI, −1.27 to −0.11], $P = .02$; $I^2 = 70\%$).

Body Weight, Blood Pressure, and Metabolic Outcomes

Furthermore, topiramate led to significantly reduced/lower end point body weight (trials = 7, n = 327, SMD = −0.71 [95% CI, −1.24 to −0.19], $P = .008$; $I^2 = 80\%$; WMD = −3.14 kg [95% CI, −5.55 to −0.73], $P = .01$; $I^2 = 86\%$) as well as BMI (trials = 4, n = 198, SMD = −1.04 [95% CI: −1.74 to −0.34], $P = .003$; $I^2 = 79\%$; WMD = −1.80 kg/m^2 [95% CI, −2.77 to −0.84], $P = .0003$; $I^2 = 69\%$) (Figure 4). Excluding the 1 study[71] using a randomized, open-label, untreated control group without placebo addition did not change the results for body weight (trials = 6, n = 287, SMD = −0.73 [95% CI, −1.36 to −0.09], $P = .02$; $I^2 = 82\%$; WMD = −3.49 kg [95% CI, −6.27 to −0.72], $P = .01$; $I^2 = 81\%$; no BMI data were reported). There was no indication of publication bias (Egger regression coefficient: $P = .80$), and the Trim Safe method indicated that 69 additional studies would be required to lead to a nonsignificant finding.

Weight loss was significantly greater in the control group than in patients treated with antipsychotics other than clozapine ($P = .02$). Conversely, weight loss with topiramate was not significantly greater in clozapine-treated individuals ($P = .49$) (Supplementary eFigure 2),

Table 1. Design, Patient, Illness, and Treatment Characteristics[a]

Study	Design	Duration, wk	Population; Treatment Setting	Illness Phase + Duration	Antipsychotic (mean daily dose)	Treatment Group (mean dose [mg/d])	n	Age, y	Male, %	Baseline Score: P = PANSS B = BPRS	Baseline BMI (kg/m^2)
Clozapine augmentation											
Afshar et al, 2009[61]	Double-blind, placebo-controlled	8	Schizophrenia; inpatients	Chronic; 17.9 ± 6.8 y	Clozapine (≥ 100 mg)	Topiramate, 50–300 (139 ± 63)	16	37.5 ± 5.7	56.3	P: 96.9 ± 22.0	24.1 ± 3.4
						Placebo	16	38.1 ± 4.6	68.8	P: 101.9 ± 23.1	25.2 ± 4.4
Behdani et al, 2011[74]	Double-blind, placebo-controlled	17	Schizophrenia; inpatients	Chronic; …	Clozapine (≤ 300 mg)	Topiramate, 200–300	40	45.1 ± 9.8	92.5	P: 68.3	…
						Placebo	40	46.9 ± 9.8	77.5	P: 69.7	
Muscatello et al, 2011[71]	Double-blind, placebo-controlled	24	Schizophrenia; outpatients	Chronic; 5.5 ± 2.2 y	Clozapine (333.3 ± 61.2 mg)	Topiramate, 200	30[b]	32.3 ± 4.6	73.7	B: 35.6 ± 9.7	…
					Clozapine (327.3 ± 84.7 mg)	Placebo	30[b]	31.5 ± 4.9	70.8	B: 36.1 ± 9.4	
Antipsychotic augmentation with and without clozapine											
Tiihonen et al, 2005[67]	Double-blind, placebo-controlled, crossover[c]	12	Schizophrenia; inpatients	Chronic; 18.1 y	Clozapine (598 ± 179 mg), n = 14 Olanzapine (26 ± 5 mg), n = 5 Quetiapine (633 ± 208 mg), n = 3 Clozapine + olanzapine, n = 3 Olanzapine + quetiapine, n = 1	Topiramate, 300	13	42.0 ± 11.4	…	P: 79.5 ± 4.2	31.1 ± 6.7
						Placebo	13	45.5 ± 14.4	…	P: 78.9 ± 5.1	28.9 ± 4.9
Antipsychotic augmentation without clozapine											
Roy Chengappa et al, 2007[73]	Double-blind, placebo-controlled	8	Schizoaffective disorder, bipolar type; inpatients (n = 20) and outpatients (n = 28)	Chronic; …	FGA: n = 14 SGA: n = 31 (all on valproic acid, n = 30; lithium, n = 14; or valproic acid + lithium, n = 4)	Topiramate, 100–400 (276 ± 108)	32	42.6 ± 8.9	43.8	P: 74.8 ± 8.4	33.8 ± 7.7
						Placebo	16	42.8 ± 6.7	50.0	P: 76.3 ± 10.3	30.8 ± 3.9
Kim et al, 2006[75]	Randomized, open-label	12	Schizophrenia; without SGA treatment for at least 3 months; outpatients	Chronic; …	Newly initiated: Olanzapine (12.3 ± 4.3 mg)	Topiramate, 100	30	"Adults"	…	…	…
					Olanzapine (12.4 ± 4.5 mg)	Olanzapine alone	30				
Ko et al, 2005[62]	Double-blind, placebo-controlled	12	Schizophrenia; inpatients	Chronic; …	Risperidone (5.7 ± 2.6 mg)	Topiramate, 100	22[d]	34.2 ± 7.6	37.5	B: 21.6 ± 3.3	27.2 ± 2.4
						Topiramate, 200	22[d]	35.3 ± 9.8	41.2	B: 24.8 ± 3.2	29.3 ± 2.9
					Risperidone (5.1 ± 1.7 mg)	Placebo	22[d]	37.6 ± 8.0	60.0	B: 22.4 ± 6.0	27.8 ± 2.5
Narula et al, 2010[63]	Double-blind, placebo-controlled	12	Schizophrenia; first episode, antipsychotic-naive; inpatients (n = 18) and outpatients (n = 49)	Acute	Newly initiated: Olanzapine (11.5 ± 0.41 mg)	Topiramate, 100	33	31.2 ± 9.7	66.7	P: 102.9 ± 17.5	20.6 ± 3.9
					Olanzapine (11.5 ± 0.40 mg)	Placebo	34	31.0 ± 10.1	64.7	P: 103.8 ± 12.7	20.2 ± 3.9
Total	Double-blind, placebo-controlled: 6 trials Randomized, open-label: 1 trial Randomized, placebo-controlled, cross-over: 1 trial	14.6 ± 6.4	Schizophrenia, n = 391 (89.1%) Schizoaffective disorder, n = 48 (10.9%) Inpatients, n = 242 (55.1%) Outpatients, n = 197 (44.9%)	Acute: 1 trial Chronic: 6 trials	Clozapine: 4 trials[e] Olanzapine: 3 trials Quetiapine: 1 trials[e] Risperidone: 2 trials FGAs or SGAs: 1 trial	Topiramate ≤ 100 mg/d: 3 trials[f] Topiramate > 100 mg/d: 6 trials[f] Topiramate ≤ 200 mg/d: 4 trials Topiramate > 200 mg/d: 4 trials	439	38.5 ± 5.5	63.7 ± 14.9	P: 85.3 ± 13.6 B: 29.3 ± 7.5	27.1 ± 4.5

[a]All values represent mean ± SD unless otherwise stated. [b]Thirty patients were randomized each to topiramate and placebo, but demographic and outcome results are based on only patients completing the 24-week trial, ie, 19 patients randomized to 200-mg topiramate and 24 patents randomized to placebo. [b]During this crossover trial, 13 patients received topiramate, and 13 patients received placebo during the first phase (12 weeks). After dropouts during the first phase were accounted for, 9 patients received topiramate and 10 received placebo during the second phase (12 weeks). The values and differences presented in the table are based on phase 1 end point. [c]Twenty-two patients were randomized to each of the 3 treatment groups, but demographic and outcome results are based on only patients completing the 12 week trial, ie, 16 patients randomized to 100-mg topiramate, 17 patients randomized to 200-mg topiramate, and 20 patients randomized to placebo. [d]One trial from a study with mixed clozapine and antipsychotics other than clozapine. [e]One trial had 2 fixed-dose arms of 100-mg and 200-mg topiramate.

Abbreviations: BPRS = Brief Psychiatric Rating Scale, FGA = first-generation antipsychotic, NOS = not otherwise specified, PANSS = Positive and Negative Syndrome Scale, SGA = second-generation antipsychotic.

Symbol: … = data not provided.

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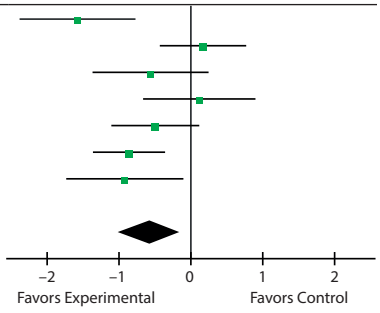
Figure 2. Standardized Mean Differences in Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) Total Score (change or end point)

Study	Scale	Topiramate Mean	Topiramate SD	Topiramate n	Placebo Mean	Placebo SD	Placebo n	Weight, %	Standardized Mean Difference, IV, Random Effects (95% CI)
Afshar et al, 2009[61]	PANSS	−20	11.96	16	−1.31	11.13	16	12.7	−1.58 (−2.38 to −0.77)
Roy Chengappa et al, 2007[73]	PANSS	−13	11.9	32	−15.1	12.9	16	15.8	0.17 (−0.43 to 0.77)
Ko et al, 2005 (100 mg)[62]	BPRS	19.31	3.24	16	22.1	6.66	10	12.7	−0.56 (−1.37 to 0.25)
Ko et al, 2005 (200 mg)[62]	BPRS	22.71	3.87	17	22.1	6.66	10	13.1	0.12 (−0.66 to 0.90)
Muscatello et al, 2010[71]	BPRS	32.1	7.5	19	36.6	9.9	24	15.6	−0.49 (−1.11 to 0.12)
Narula et al, 2010[63]	PANSS	31.21	2.1	33	33.32	2.7	34	17.4	−0.86 (−1.36 to −0.36)
Tiihonen et al, 2005[67]	PANSS	−2.83	3.93	13	0.9	3.93	13	12.6	−0.92 (−1.73 to −0.10)
Total				146			123	100.0	−0.57 (−1.01 to −0.14)

Heterogeneity: $\tau^2 = 0.22$; $\chi_6^2 = 16.80$ ($P = .01$); $I^2 = 64\%$

Test for overall effect: $Z = 2.59$ ($P = .010$)



Abbreviation: IV = inverse variance.

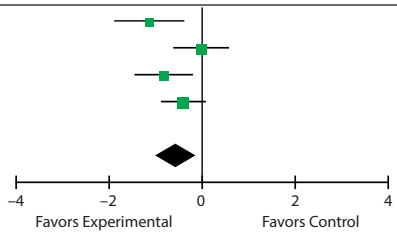
Figure 3. Standardized Mean Difference in Positive and Negative Syndrome Scale (PANSS) Positive and Negative Symptoms Subscores (change or end point)

A. Positive Symptoms

Study	Topiramate Mean	Topiramate SD	Topiramate n	Placebo Mean	Placebo SD	Placebo n	Weight, %	Standardized Mean Difference, IV, Random Effects (95% CI)
Afshar et al, 2009[61]	−5.68	4.36	16	−0.56	4.41	16	20.0	−1.14 (−1.89 to −0.38)
Roy Chengappa et al, 2007[73]	−5.1	4.4	32	−5	4	16	25.4	−0.02 (−0.62 to 0.58)
Muscatello et al, 2010[71]	10.7	14.5	19	23.8	16.3	24	24.3	−0.83 (−1.46 to −0.20)
Narula et al, 2010[63]	7.18	0.6	33	7.47	0.8	34	30.4	−0.40 (−0.89 to 0.08)
Total			100			90	100.0	−0.56 (−1.00 to −0.11)

Heterogeneity: $\tau^2 = 0.11$; $\chi_3^2 = 6.35$ ($P = .10$); $I^2 = 53\%$

Test for overall effect: $Z = 2.47$ ($P = .01$)

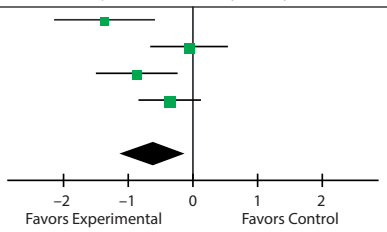


B. Negative symptoms

Study	Topiramate Mean	Topiramate SD	Topiramate n	Placebo Mean	Placebo SD	Placebo n	Weight, %	Standardized Mean Difference, IV, Random Effects (95% CI)
Afshar et al, 2009[61]	−5.87	3.73	16	0	4.6	16	20.6	−1.37 (−2.15 to −0.59)
Roy Chengappa et al, 2007[73]	−1.9	3.4	32	−1.7	3	16	25.6	−0.06 (−0.66 to 0.54)
Muscatello et al, 2010[71]	20.7	15.7	19	41	27.3	24	24.6	−0.87 (−1.50 to −0.24)
Narula et al, 2010[63]	7.33	0.8	33	7.68	1.1	34	29.2	−0.36 (−0.84 to 0.12)
Total			100			90	100.0	−0.62 (−1.13 to −0.10)

Heterogeneity: $\tau^2 = 0.17$; $\chi_3^2 = 8.35$ ($P = .04$); $I^2 = 64\%$

Test for overall effect: $Z = 2.36$ ($P = .02$)



Abbreviation: IV = inverse variance.

and the subgroup difference based on baseline clozapine versus other antipsychotics was marginally significant ($P = .05$; $I^2 = 73\%$). The weight-loss effect of topiramate was not moderated by concurrent versus later topiramate addition to the antipsychotic treatment ($P = .24$; $I^2 = 26\%$). In exploratory meta-regression analyses, none of the examined variables were significantly related to body weight change (trial duration: $P = .56$; age: $P = .34$; sex: $P = .78$; inpatient status: $P = .63$; topiramate dose: 0.42; baseline BMI: $P = .14$; baseline PANSS: $P = .26$).

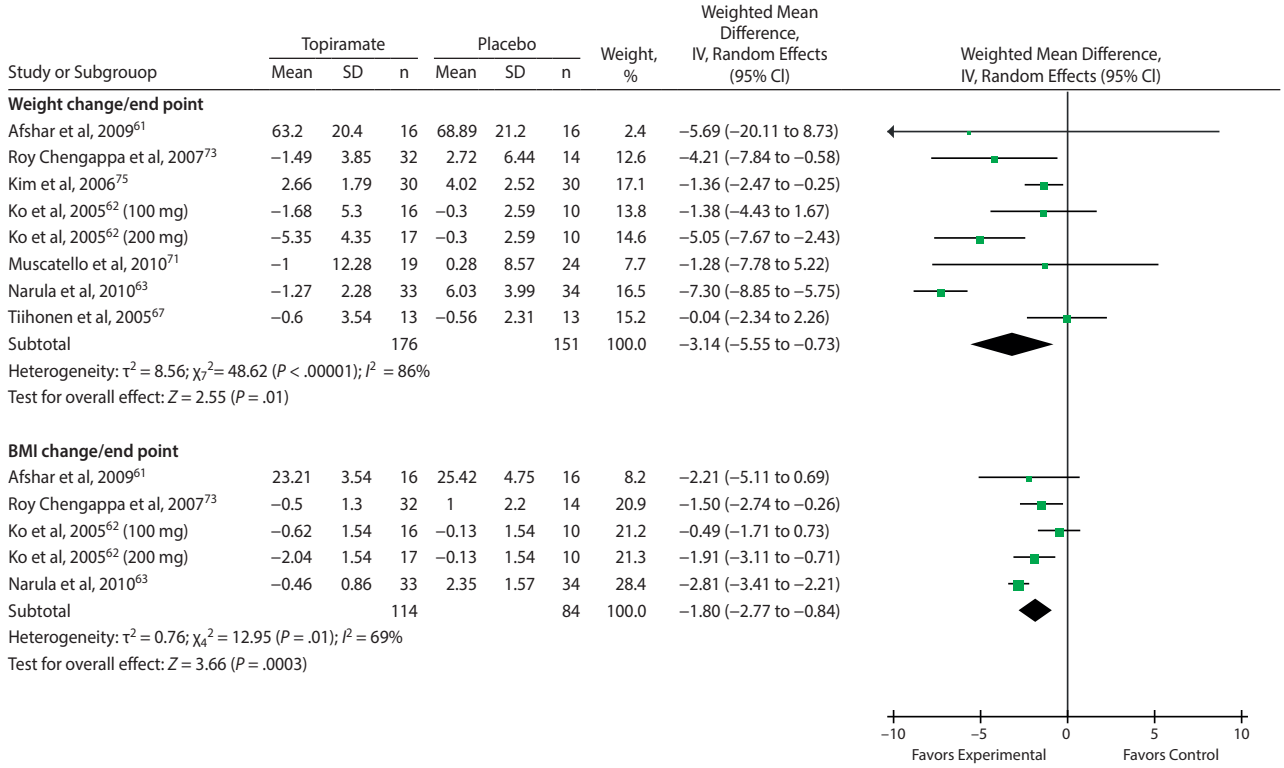
Only 1 study reported on waist circumference[73] or blood pressure and glucose and lipid parameters,[63] observing significant advantages ($P < .05$) for topiramate regarding insulin, glucose, total cholesterol, and low-density lipoprotein cholesterol.

Treatment Discontinuation and Adverse Effects

All-cause discontinuation was similar between topiramate and control group (trials = 7, n = 435, RR = 1.24 [95% CI, 0.76 to 2.02], $P = .39$, $I^2 = 20\%$), as was discontinuation due to inefficacy (trials = 3, n = 164, $P = .53$) and intolerability (trials = 4, n = 212, $P = .50$).

Topiramate users had, at a trend level, more paresthesia than placebo users (trials = 4, n = 248, RR = 2.03 [95% CI, 0.99 to 4.18], $P = .05$; $I^2 = 0\%$). No differences between topiramate and control groups were found regarding any other adverse effects that were reported in ≥ 3 studies, including headache (trials = 3, n = 181, $P = .33$), somnolence (trials = 3, n = 195, $P = .18$), orthostasis (trials = 3, n = 200, $P = .30$), and constipation (trials = 3, n = 195, $P = .44$). Only 1 study[71] assessed cognitive effects, finding either no difference

Figure 4. Weighted Mean Difference in Body Weight and Body Mass Index (BMI) (change or end point)



Abbreviation: IV = inverse variance.

between topiramate and control (phonemic and semantic fluency, Wisconsin card sorting errors and categories) or an advantage of topiramate (Stroop test).

DISCUSSION

In this first comprehensive meta-analysis of 8 randomized trials of topiramate augmentation of antipsychotics in patients with schizophrenia spectrum disorders, treatment with topiramate 100–400 mg/d for 8–24 weeks (mean = 14.6) was significantly superior regarding total, positive, negative, and general psychopathology symptoms and was also associated with a significantly greater reduction in body weight. Moreover, all-cause discontinuation was similar to the control condition, and the only adverse effect with a trend toward more frequency in topiramate users was paresthesia ($P = .05$).

The significant superiority of topiramate for total psychopathology and all traditionally measured subdomains may come as a surprise: case reports have not only implicated topiramate in the emergence of psychiatric symptoms,[53–56] with psychiatric history being a risk factor for the development of psychiatric adverse events,[49] but also described worsening of psychosis.[50–52] The different findings of improved outcomes in our meta-analysis could very well be due to a protective effect of the antipsychotic treatment. A second explanation is a positive interaction of topiramate with the efficacy of antipsychotics, potentially particularly that of clozapine. In subgroup analyses, topiramate separated from placebo regarding PANSS/BPRS total scores in studies with >65% clozapine-treated patients, while topiramate efficacy was diminished and not significant in patients treated with other antipsychotics.

Our finding of clozapine being a moderator of superior efficacy for topiramate addition is similar to that in a meta-analysis[5] of antipsychotic cotreatment strategies, which found clozapine to be a moderator of greater frequency of treatment response. Another meta-analysis found lamotrigine augmentation significantly superior to placebo in decreasing total schizophrenia psychopathology in studies of patients exclusively treated with clozapine[11] but not in studies of patients on other antipsychotics (including some patients on clozapine),[10,76] suggesting either a specific pharmacodynamic interaction with clozapine or a truly treatment refractory status in clozapine-treated patients. Likewise the absence of comparable results in patients not treated with clozapine in our meta-analysis could be due to insufficient power and/or to true treatment resistance in clozapine-treated patients, reducing the chance of a placebo response in the control condition.

Several mechanistic explanations of topiramate's efficacy as an antipsychotic augmenting agent should be considered.[77–79] Schizophrenia has been associated with excessive stimulation of the AMPA/kainite glutamate receptor that may lead to oxidative stress and apoptosis.[79] Here, topiramate's AMPA/kainate glutamate receptor antagonism[34] could counter this effect. Further, impaired cortical inhibition via hyperactive GABA interneuronal

functioning may lead to psychosis.[80] In this context, topiramate's stimulation of $GABA_A$ receptors[34] may help restore the inhibitory imbalance.

Our findings of topiramate's efficacy as an augmenting agent of clozapine contrast with 2 prior meta-analyses that focused on 3[26] or 4[65] studies of clozapine augmentation[26,65] and that did not find topiramate addition to clozapine to be superior to placebo. This difference may be due to the inclusion of the published results of both phases of the topiramate crossover study.[67] Moreover, the most recent meta-analysis[65] apparently included data from 1 study[74] that were highly skewed and from which total PANSS scores could not be calculated. Since it is generally accepted that crossover studies are inappropriate for meta-analyses due to carryover effects that very likely bias the results, we contacted the authors[67] and were able to include the results from only the first phase of the randomized study prior to the patient crossover, yielding significant results for topiramate in our analyses, even when results from an outlier study[61] were removed.

In addition to the superior efficacy for psychotic symptomatology, topiramate was also associated with significant weight loss, consistent with prior reviews and meta-analyses.[33–35,64,81–84] Since weight gain and metabolic adverse effects associated with antipsychotics have become a major limitation of antipsychotic treatment,[27–30] interventions that can safely reduce weight gain and thereby improve cardiovascular health are extremely welcome. A combination with improved efficacy is obviously even more desirable. The observed 3.14 kg and 1.80 BMI weight reduction compared to the control group across 7 studies and 327 subjects is clinically relevant and similar to weight reduction observed across 10 metformin augmentation studies.[34] Moreover, like metformin,[85] topiramate can be started after weight gain has already occurred and need not be initiated concurrently with a weight gain–inducing antipsychotic. However, to date, head-to-head or combination trials directly comparing metformin and topiramate in antipsychotic-treated patients are lacking.

Nevertheless, topiramate did not seem to significantly reduce weight in clozapine-treated patients. Thus, it needs to be studied whether this finding is due to patient characteristics in the 3 studies with clozapine or whether topiramate's countering of increased appetite signaling is restricted to antipsychotics other than clozapine. Furthermore, due to the efficacy[86–88] and increased use of antipsychotics in bipolar disorder,[89] initial findings of weight loss with topiramate in bipolar disorder patients[86,90] should also be followed up, even if topiramate does not seem to have antimanic efficacy.[86–89]

Apart from clozapine treatment, subgroup and meta-regression analyses did not identify additional baseline moderators or mediators of topiramate's efficacy or beneficial effects on body weight, including topiramate dose. These results suggest that the observed findings may generalize to different subgroups and settings.

Although in our meta-analysis, topiramate was not associated with a significantly greater discontinuation (all-cause discontinuation, discontinuation due to inefficacy, and discontinuation due to intolerability) than the control conditions, concern in the nonpsychiatric obese and type 2 diabetes populations has been raised about topiramate's potential to cause cognitive impairment, such as difficulties with attention, concentration, memory, and word finding.[38,40,43,45] Only 1 study[71] examined cognitive effects, but no significant difference in cognitive measures compared to placebo were found; in fact, topiramate-treated patients did better than placebo-treated patients on the Stroop test. However, it is unclear whether this lack of cognitive impairment is a chance finding, due to a type II error, or whether patients with schizophrenia spectrum disorder already have such impaired cognitive functions that a floor effect might minimize further cognitive impairment. On the other hand, it is also possible that the cognitive burden could be more detectable had patients undergone cognitive remediation, as seen, for example, with antihistaminergic effects.[91] Clearly, more data are needed to clarify the extent of cognitive burden conferred by topiramate in schizophrenia spectrum patients. Finally, as expected, based on studies in nonpsychiatric populations,[38,40,43,45] paresthesia was nearly significantly greater ($P = .05$) in topiramate-treated psychiatric patients compared to those taking placebo.

The results of this meta-analysis have to be interpreted within its limitations. For example, the number of studies and included patients was small. Furthermore, studies, populations, and main results were heterogeneous, even in subgroup analyses. Although we used a random-effects model to deal with the heterogeneity and did not see a clear indication of publication bias, additional and larger studies are clearly needed to yield more stable results. Even though we included 1 trial[75] without a placebo comparator, this study did not contribute any psychopathology data to the analyses, and the weight change data remained the same after removal of this study in a post hoc sensitivity analysis. Moreover, 2 studies[62,71] used observed cases analyses and another study[61] in clozapine-treated patients was an outlier, having an unusually large effect size (−1.58) for total psychopathology change. However, the results remained significant, both for clozapine-treated patients and, overall, after removal of the 2 studies reporting only observed cases and after removal of the 1 outlier study. Furthermore, the dose of topiramate varied across the studies, and compliance was not routinely assessed or reported. In particular, data regarding the potential adverse cognitive effects of topiramate are limited to 1 small study.[71] While the beneficial effects regarding body weight and BMI were moderate and comparable to metformin[33–35] and to nonpharmacologic weight loss interventions,[31] studies were mostly of short duration, and effects beyond 6 months require further study. Only 1 study followed patients originally randomized to topiramate or placebo beyond the initial 10 weeks of blind treatment, finding that over the next 18 months, the benefits increased further from −4.4 versus +1.2 kg at 10 weeks[92] to −9.4 versus +5.5 kg at 18 months.[93] However, 37% of the original 43 patients dropped out, and antipsychotic treatment did not

seem to have been kept stable. Finally, the data regarding the important lipid and glucose metabolism parameters were scarce and clearly require further study. This is especially relevant, as antipsychotics appear to cause metabolic adverse effects not only indirectly via weight gain but also, in a dose-dependent fashion, partly independently of body weight change[94–97] that can result in severe dysregulation of the glucohomeostasis.[28]

In conclusion, findings from this meta-analysis suggest that topiramate may be a useful augmentation agent in patients with schizophrenia spectrum disorders for total psychopathology, positive, negative, and general symptoms, at least in clozapine-treated patients, and for body weight reduction, at least in patients not treated with clozapine. However, we consider these findings preliminary, as several questions following from these results need to be investigated further. First, larger studies of topiramate's efficacy and tolerability should focus on the relevance of the distinction between clozapine and antipsychotics other than clozapine. The central question is whether clozapine is a marker for greater degrees of treatment resistance, with a subsequently lower likelihood of placebo response, which would increase hopes that one could generalize the findings to more persistently or profoundly treatment-resistant patients failing to respond to antipsychotics other than clozapine or whether there is a specific pharmacodynamic interaction between topiramate and clozapine that enhances topiramate's efficacy, a possibility for which clear data are lacking. Studies targeting this important question should use strict criteria for treatment resistance that would ideally be prospectively assessed. Furthermore, such studies should include both patients who failed clozapine and those who failed antipsychotics other than clozapine, stratifying randomization to topiramate or placebo, in order to compare topiramate's efficacy on psychopathology and body weight in these 2 important subsamples in the same study applying the same methodology. Second, studies should seek to characterize subgroups of patients benefiting the most from topiramate augmentation. The fact that the mean change in PANSS total score was only around 5 points, which most likely corresponds to less than 10% of the baseline severity, indicates that there is variability in response. This fact is also suggested by the preliminary finding that clozapine-treated patients had a more than 10-point drop in total PANSS scores. Third, since the meta-analyzed studies were relatively short, long-term maintenance effects of topiramate augmentation on psychopathology and body weight as well as on metabolic variables deserve further study. Fourth, predictive factors (such as dose-response relationships and earlier vs later illness phase) and the role of the glutamate pathway for the therapeutic response with topiramate should be examined. Fifth, more studies are needed to rule out a potentially significant and clinically relevant adverse effect on cognition. Sixth, the combined treatment of topiramate with metformin[44,45] in patients with insufficient weight and cardiometabolic risk reduction despite monotherapy with either agent deserves further study.[64] Finally, on the basis of these encouraging results with topiramate, other treatments affecting the glutamatergic system should be explored and developed for the treatment of schizophrenia.[98]

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Drug names: aripiprazole (Abilify and others), asenapine (Saphris), carbamazepine (Tegretol, Epitol, and others), clozapine (Clozaril, FazaClo, and others), iloperidone (Fanapt), lamotrigine (Lamictal and others), lithium (Lithobid and others), modafinil (Provigil and others), olanzapine (Zyprexa and others), paliperidone (Invega and others), pimozide (Orap and others), prochlorperazine (Procomp and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), thiothixene (Navane and others), topiramate (Topamax and others), valproic acid (Depakene and others), ziprasidone (Geodon and others).

Potential conflicts of interest: **Dr Correll** has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Actavis, Alkermes, Bristol-Myers Squibb, Eli Lilly, Genentech, Gerson-Lehrman Group, IntraCellular Therapies, Janssen/Johnson & Johnson, Lundbeck, MedAvante, Medscape, Otsuka, Pfizer, ProPhase, Reviva, Roche, Sunovion, Supernus, and Takeda; and has received grant support from Bristol-Myers Squibb, Otsuka, and Takeda. **Dr Kane** has received honoraria for lectures and/or consulting from Alkermes, Bristol-Myers Squibb, Eli Lilly, Forrest Laboratories, Forum, Genentech, Intracellular Therapies, Janssen, Johnson & Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Reviva, Roche, Sunovion; has received grant support from Genentech, Johnson & Johnson, and Otsuka; and is a shareholder of MedAvante and Vanguard Research Group. **Dr De Hert** has received honoraria as an advisory board member or speaker for Janssen, Lundbeck, Sunovion, and Takeda. **Dr Cohen** has received honoraria from AstraZeneca and grant funding from Fonds Nutsohra and Hemocue. **Dr Maayan** has nothing to disclose.

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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: 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

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List of Supplementary Material for the article

1. eFigure 1 — Standardized Mean Difference in Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) Total Score (Change or Endpoint) By Clozapine vs. Non-Clozapine Antipsychotic Treatment

2. eFigure 2 — Weighted Mean Difference in Body Weight (Change or Endpoint) By Clozapine vs. Non-Clozapine Antipsychotic Treatment

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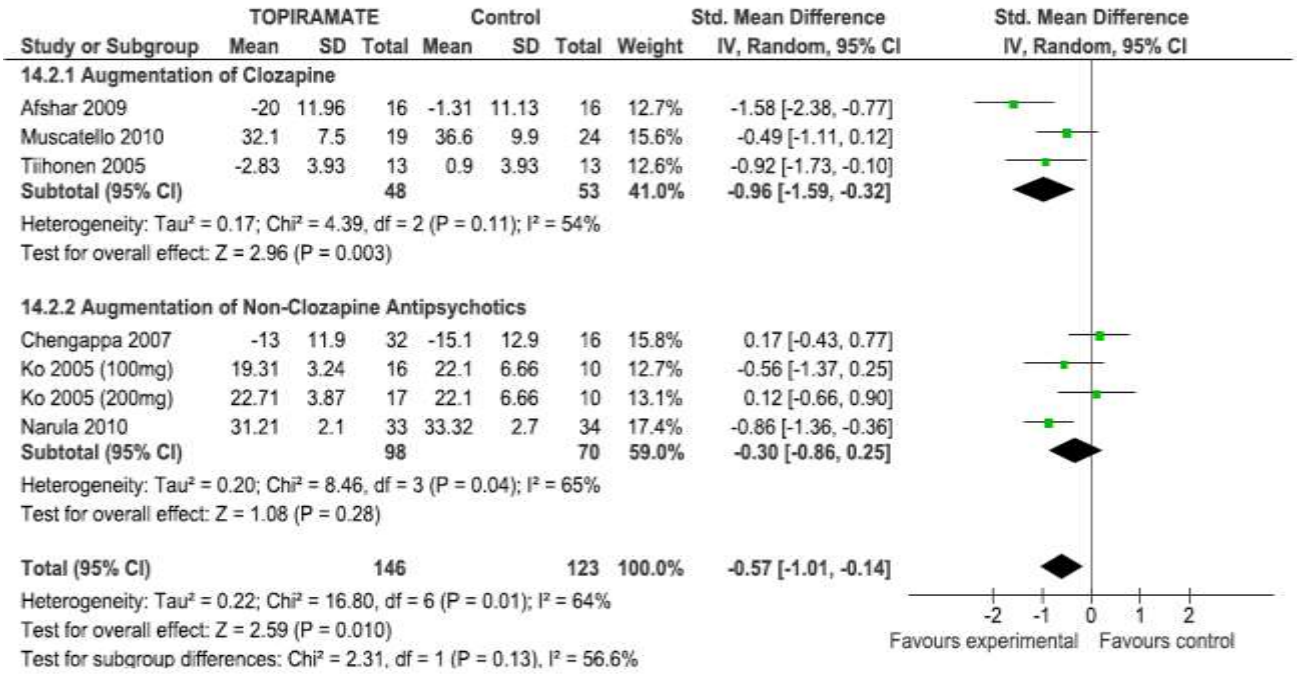
Supplementary eFigure 1. Standardized Mean Difference in Positive and Negative Syndrome Scale (PANSS) or Brief Psychiatric Rating Scale (BPRS) Total Score (Change or Endpoint) By Clozapine vs. Non-Clozapine Antipsychotic Treatment



Supplementary eFigure 2. Weighted Mean Difference in Body Weight (Change or Endpoint) By Clozapine vs. Non-Clozapine Antipsychotic Treatment