Bipolar Disorders 2007: 9: 609–617

BIPOLAR DISORDERS

Original Article

A placebo-controlled, random-assignment, parallel-group pilot study of adjunctive topiramate for patients with schizoaffective disorder, bipolar type

Chengappa KNR, Kupfer DJ, Parepally H, John V, Basu R, Buttenfield J, Schlicht P, Houck P, Brar JS, Gershon S. A placebo-controlled, random-assignment, parallel-group pilot study of adjunctive topiramate for patients with schizoaffective disorder, bipolar type.
Bipolar Disord 2007: 9: 609–617. © Blackwell Munksgaard, 2007

Objectives: This pilot study evaluated the efficacy and safety of adjunctive topiramate compared with placebo in the treatment of patients with a diagnosis of schizoaffective disorder, bipolar type (SAD-BT).

Methods: A sample of 48 adult patients with a *Diagnostic and Statistical Manual of Mental Disorders*, *4th Edition*, *Text Revision* (DSM-IV-TR) diagnosis of SAD-BT (supported by the *Structured Clinical Interview for DSM-IV Axis I Disorder*, *Patient Edition*) were randomly assigned in a 2:1 ratio (favoring topiramate) to 8 weeks of double-blind treatment with topiramate (100–400 mg/day) or placebo. Patients who had achieved a ≥20% decrease from baseline in their Positive and Negative Syndrome Scale (PANSS) total scores were given the opportunity to continue for an additional 8 weeks of double-blind treatment. The dosage of the study medicine was continued unchanged from the earlier 8-week study period. At the end of the study period, the study medicine was tapered and discontinued over a 2-week period. Primary efficacy was assessed at 8 weeks using the mean change between treatment groups of the PANSS total scores in the intent-to-treat population of randomized patients. Several secondary measures were also assessed. Safety analyses included monitoring of adverse events, vital signs, electrocardiogram (ECG) and laboratory values.

Results: Even though both treatments reduced scores on various psychopathology rating scales, adjunctive topiramate treatment (nearly 275 mg/day) did not show increased efficacy relative to placebo on the primary outcome measure (PANSS scale) or any of the secondary outcome measures. Topiramate-treated patients lost significantly more body weight than placebo-treated patients, which led to a significant reduction in body mass index (BMI). Relative to adjunctive placebo, topiramate-treated patients experienced higher rates of paresthesia, sedation, word-finding difficulty, sleepiness, and forgetfulness, but these differences were not statistically significant. There were no clinically

KN Roy Chengappa[a,b], David J Kupfer[a], Haranath Parepally[a,b], Vineeth John[a], Ranita Basu[a], Joan Buttenfield[a], Patricia Schlicht[a,b], Patricia Houck[a], Jaspreet S Brar[a] and Samuel Gershon[a]

[a]Western Psychiatric Institute and Clinic, School of Medicine, University of Pittsburgh, [b]Mayview State Hospital, Pittsburgh, PA, USA

Key words: bipolar type – body mass index – body weight – clinical trial – placebo – schizoaffective disorder – topiramate

Received 30 September 2005, revised and accepted for publication 30 April 2006

Corresponding author: KN Roy Chengappa, MD, Associate Professor of Psychiatry, Western Psychiatric Institute and Clinic, 3811 O'Hara Street, Pittsburgh, PA 15213-2593, USA.
Fax: +1 412 246 6116;
e-mail: chengappakn@upmc.edu

This research was supported by an investigator-initiated study grant from Ortho-McNeil Neurologics, Inc., which provided financial support and study medication. KNRC has received grant support and has been a consultant to Ortho-McNeil Neurologics. DJK, HP, VJ, RB, JB, PS, PH, JSB, and SG have no reported conflicts of interest. KNRC and SG, as co-editors of this journal, have not had any influence on the acceptance or rejection of the manuscript, which was overseen by other senior Editorial Board members.

significant abnormalities in either the ECG or laboratory results. There were no serious adverse events in the study. Further, there was no worsening of the PANSS total scores (to ≥10% from baseline), and no significant differences between the treatments on worsening of total Montgomery–Asberg Depression Rating Scale (MADRS) scores [1/13 (7.7%) for placebo; 1/25 (4.0%) for topiramate].

Conclusions: This pilot study did not support clinical efficacy for adjunctive topiramate treatment in patients with SAD-BT. There were no major safety or tolerability issues in this study. Confirming the results of other studies, topiramate-treated patients did experience greater body weight loss and reduction in BMI.

Several open-label studies have suggested that topiramate, a novel anticonvulsant drug, may have clinical benefits as an adjunctive treatment for bipolar or schizoaffective disorder (1, 2). Two controlled studies have indicated that two anticonvulsants, valproate and lamotrigine, provide benefits when added to antipsychotic drugs in persons with schizophrenia (3, 4). Topiramate augments the inhibitory neurotransmitter γ-aminobutyric acid via different mechanisms and also inhibits the excitatory neurotransmitter glutamate via the kainate/AMPA receptor (5). Furthermore, topiramate is known to block voltage-sensitive sodium and calcium channels (5). These mechanisms have been considered therapeutically useful in the treatment of bipolar disorder (6). Consequently, it was hypothesized that topiramate may benefit patients with a diagnosis of schizoaffective disorder, bipolar type (SAD-BT) who continued to have symptoms despite treatment with lithium, valproate and/or antipsychotic agents.

The primary objective of this study was to evaluate whether topiramate was efficacious [improvement in Positive and Negative Syndrome Scale (PANSS) (7) total scores and other measures of psychopathology] and safe to add to standard pharmacologic treatment in patients with a diagnosis of SAD-BT. In addition if there were significant differences between the treatment groups, it was intended to estimate the size of the treatment effect.

Methods

Design

A parallel-group, random-assignment (2:1 assignment favoring topiramate), placebo-controlled, double-blind study design was used to evaluate the efficacy and safety of adjunctive topiramate treatment in patients meeting inclusion/exclusion criteria and receiving their care in ambulatory clinics/hospitals affiliated with the University of Pittsburgh, Western Psychiatric Institute and Clinic, or Mayview State Hospital. The study protocol and consent forms were reviewed and approved by the Institutional Review Board of the University of Pittsburgh, the Research Review Committee of Mayview State Hospital, and the Office of Mental Health and Substance Abuse Services, Harrisburg, PA.

Inclusion and exclusion criteria

Men and women aged 18 years or older with a primary *Diagnostic and Statistical Manual of Mental Disorders*, *4th Edn*, *Text Revision* (DSM-IV-TR) (8) diagnosis of SAD-BT [affirmed by the *Structured Clinical Interview for DSM-IV Axis I disorders*, *Patient Edition*) (9)], a total score ≥60 on the PANSS, and a Clinical Global Impression-Severity of Illness scale (CGI-S) score ≥4 were eligible for the study. Each patient provided written informed and competent consent. Patients were required to have received stable doses of lithium, valproate or both within therapeutic levels (lithium 0.6–1.2 mEq/L; valproate 50–125 mg/L) for at least 2 weeks prior to study entry; certain psychotropic agents (one antipsychotic agent, and/or one anxiolytic or hypnotic drug) were also permitted. Patients had already been receiving lithium or valproate or both for several weeks to months prior to the study; none were initiated on either of these mood stabilizers for purposes of study entry. Patients who had unstable medical illnesses, those receiving carbonic anhydrase inhibitors, and those with a history of renal stones or glaucoma were excluded, as were patients with a history of non-response or allergy to previous topiramate treatment. Women of childbearing potential who were not taking adequate contraceptive measures were excluded, as were those who were pregnant or lactating. Subjects with alcohol or marijuana abuse were permitted to enter the study, but not with dependence. Subjects with any other substance abuse or dependence (except nicotine and/or caffeine) were excluded.

Treatment

During the initial 8-week, double-blind study, topiramate was dispensed using a titration schedule: 25 mg b.i.d. on day 1, increasing to 100 mg b.i.d. by day 7. Further titration occurred in increments of 100 mg/week up to a maximum of 400 mg/day by the end of 4 weeks. At each weekly visit, if patients were found *not* to show a ≥20% improvement in PANSS total scores (from baseline), further titration was carried out to that week's daily dosage. The dosage remained constant until completion of the initial 8 weeks, either at the tolerated dosage (100–400 mg/day) or at the maximum dosage (400 mg/day) or at the dosage where a ≥20% total PANSS score decrease (from baseline) was noted. Placebo was given as identical tablets and matched on dosage strengths. Concomitant medication changes of mood stabilizers (lithium or valproate) were not permitted. In the case of antipsychotic drugs, changes or switching of an antipsychotic agent led to termination from the trial.

Evaluations

The PANSS, Young Mania Rating Scale (YMRS), Montgomery–Asberg Depression Rating Scale (MADRS), and CGI-S were used to assess psychopathology (7, 10–12). The Drug Attitude Inventory (DAI) was used to assess patient attitudes toward study drug (13). The Abnormal Involuntary Movements Scale (AIMS), Barnes Akathisia Rating Scale (BAS), and Simpson–Angus Scale were used to assess movement disorders (14–16).

Safety and tolerability as well as spontaneously reported or observed adverse events were recorded, probed clinically, and evaluated for possible association to the study drug. Laboratory assessments included urine drug tests, complete blood count and blood chemistry, including hepatic, renal, and thyroid function tests at baseline, 8 weeks, and end of study. A 12-lead electrocardiogram (ECG) was performed at baseline and at study completion.

Statistical analyses

Efficacy analyses were performed in the intent-to-treat population of patients who received at least one dose of study medicine, and who had pre-randomization efficacy assessments and also at least one post-randomization assessment at study termination. The primary efficacy endpoint was the change in PANSS total score from baseline to the final visit at 8 weeks, which was compared between treatment groups. An endpoint analysis of treatment on the final PANSS total score covarying for baseline PANSS total score was run using analyses of covariance. Missing efficacy data at 8 weeks were imputed with the last observation carried forward. Secondary outcomes between treatments evaluated subscales of the PANSS, including positive, negative and aggression subscale scores, YMRS total scores, MADRS total scores, CGI-S, DAI dysphoric and non-dysphoric subscale scores. Other secondary analyses included evaluating 16-week data with endpoint analyses between the treatment groups covarying for baseline scores. On all secondary outcomes, the Bonferroni correction was applied for testing multiple variables. Response was defined as a ≥20% improvement in the baseline PANSS total or positive symptom scores at 8 weeks and was compared between treatment groups using a chi-square test. The Cohen's h effect size, used for differences between independent proportions, was calculated by taking the absolute difference between the nonlinear arcsine transformation of the proportions (17). Proportions of patients completing the 8-week and 16-week double-blind study were compared between treatment groups using a chi-square test. Proportions of patients in each treatment group who experienced increases in MADRS total scores from ≥10 at baseline to ≥18 at two consecutive visits (or at the final visit) were evaluated using a chi-square test, as were proportions of patients experiencing a ≥10% worsening of PANSS total scores in each treatment group.

Adverse events reported by ≥10% of patients in each treatment group were compared using a chi-square test. Laboratory values, vital signs and physical examinations were compared from baseline and in reference to normal ranges, and reported as normal or abnormal. Changes in body weight (lb), body mass index (BMI; kg/m^2) and waist size (inches) at last visit in the 16-week dataset were compared as mean changes between treatment groups using *t*-tests.

Results

Patients

Of 55 patients who provided consent and were screened for randomization (Fig. 1), 48 were randomized (topiramate, n = 32; placebo, n = 16). Twenty subjects were recruited from Mayview State Hospital and 28 subjects were recruited as outpatients at Western Psychiatric Institute and Clinic. The baseline PANSS total scores did not

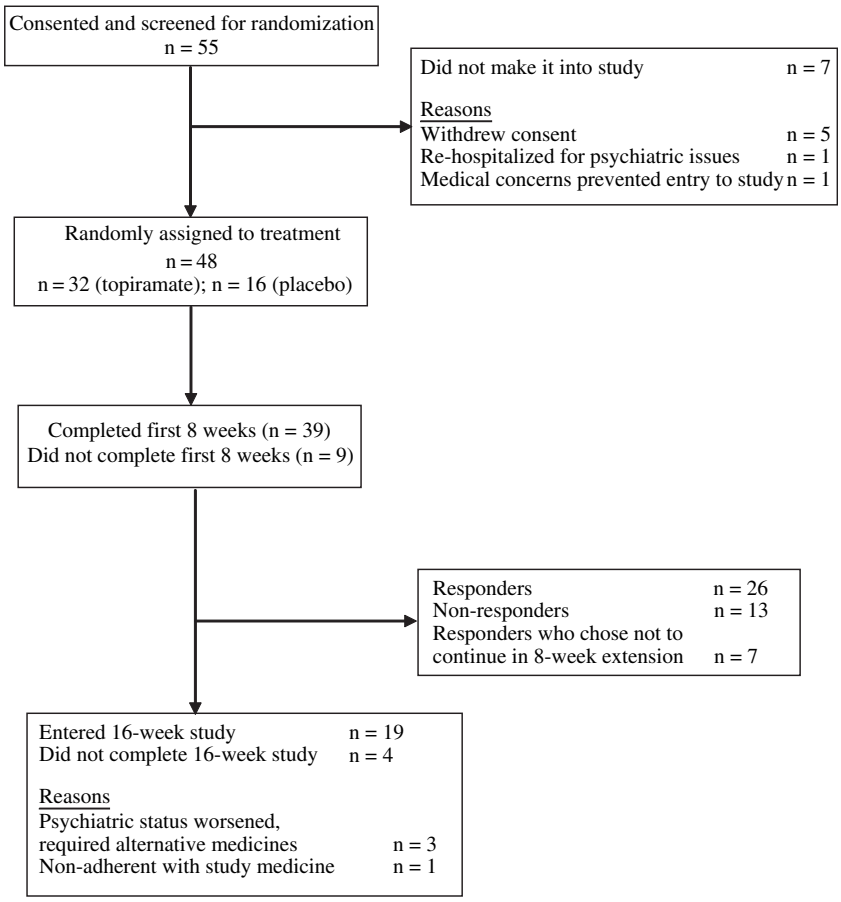

Fig. 1. Disposition details of topiramate study participants.

significantly differ between these two patient groups (data not shown). A total of 39 patients completed 8 weeks of the double-blind study (Fig. 1, Table 1), with no statistically significant differences between the treatment groups in completion rates. Of the 26 responders at 8 weeks, 19 chose to enter the 8-week double-blind extension phase, and 15 of those patients completed the entire 16 weeks (Fig. 1, Table 1).

Baseline demographic characteristics and scores on the various psychopathology scales were not significantly different between treatment groups (Tables 2 and 3). The proportions of patients in each group receiving either lithium or valproate, or both, were not significantly different; and neither were there any significant differences in proportions of patients receiving first- or second-generation antipsychotic agents (Table 2). The median time for the duration of mood stabilizer treatment (i.e., either lithium or valproate, or both) prior to the study was 7.1 weeks for both groups combined, 6.2 weeks for the placebo group, and 8.3 weeks for the topiramate group (Mann–Whitney U-test = 0.89). Visual inspection of the mean blood levels of lithium or valproate at three time-points did not show any significant differences between the two treatment groups, and pooled results indicated mean valproate levels of 69.4 ± 15 mg/mL for the placebo group and 61 ± 7 mg/mL for the topiramate-treated group. Similarly, the pooled mean lithium levels were 0.69 ± 0.13 mEq/L for the placebo group and 0.70 ± 0.15 mEq/L for the topiramate-treated group.

Following titration, the topiramate group received a mean dose of 276 ± 108 mg/day throughout the study. Twenty-five patients reached a target dose of 200 mg/day, of whom 10 subjects reached 400 mg/day, and 7 received < 200 mg/day.

Efficacy and secondary outcome measures

Similar reductions in PANSS total scores were observed in each treatment group (Fig. 2, Table 3) by 8 weeks, with no statistically significant differences between the two treatments. The results were very similar for all the PANSS subscale scores, and for scores on the YMRS, CGI-S and the DAI subscales (Table 3). There was a greater reduction

Table 1. Disposition details of study participants

	Topiramate (n = 32)	Placebo (n = 16)	χ^2	df	p
Completed double-blind, first 8 weeks	28/32 (88%)	11/16 (69%)	2.46	1	0.12
Response in intent-to-treat population (≥20% in PANSS total or positive symptom scale scores), first 8 weeks	19/32 (59%)	7/16 (44%)	1.05	1	0.30
Completed double-blind extension, 16 weeks	12/13 (92%)	3/6 (50%)	4.42	1	0.04
Discontinued during double-blind, 8 weeks	4	5			
Reasons:					
Adverse experience	1	1			
Unsatisfactory response	2	0			
Failure to follow-up	0	2			
Therapy refusal	0	1			
Other	1	1			
Discontinued in double-blind extension	1	3			
Reasons:					
Required other antipsychotic medicine	0	3			
Other	1	0			

PANSS = Positive and Negative Syndrome Scale.

Table 2. Baseline demographic comparison of subjects assigned to either topiramate or placebo

	Topiramate (n = 32)	Placebo (n = 16)
Age, years, mean ± SD	42.6 (8.9)	42.8 (6.7)
Men (%)	14 (44)	8 (50)
White (%)	20 (63)	7 (44)
African-American (%)	12 (37)	8 (50)
Other (%)	0 (0)	1 (6)
Education, years, mean ± SD	13.2 (2.4)	13.1 (2.4)
Married (%)	1 (3)	2 (13)
Never married (%)	13 (41)	9 (56)
Separated/divorced (%)	18 (56)	5 (31)
Currently unemployed (%)	24 (75)	11 (69)
Valproate	20	10
Lithium	9	5
Receiving both lithium and valproate	3	1
First-generation antipsychotic agents	8	6
Second-generation antipsychotic agents	22	9

SD = standard deviation.

in mean MADRS total scores in the adjunctive placebo group, but after Bonferroni correction, this result was not statistically significant. The Cohen's h effect size, used for differences between independent proportions, was calculated to be 0.30 (small effect) on the response of ≥20% on the PANSS total or positive symptoms subscale at 8 weeks. Treatment differences at 16 weeks for PANSS and other psychopathology scale scores did not significantly differ between the two treatment groups; however, only 3 patients receiving placebo and 12 patients receiving topiramate completed the entire study (data not shown).

None of the patients in either treatment group worsened by ≥10% on PANSS total scores after randomization. One of 13 (7.7%) patients randomized to placebo had an increase in MADRS total scores to ≥18 from a baseline of ≤10 and one of 25 (4.0%) patients receiving topiramate had a similar result (Fisher's exact test, p = 1.0, not significant).

Safety and tolerability

Treatment discontinuations were not significantly different between treatment groups at 8 weeks, but in the 8-week extension phase significantly more placebo-treated patients (3 of 6 patients) discontinued treatment compared with those who received topiramate (1 of 13 patients; Table 1).

Concomitant medications

Three subjects in the adjunctive placebo arm of the 8-week, double-blind extension phase required a switch in their antipsychotic medication and were terminated from further participation.

Treatment-emergent adverse events

There were no serious adverse events in the study. Furthermore, there were no clinically significant changes in vital signs, laboratory values, or ECGs. Certain adverse events, mostly reported as 'mild', were noted more frequently in the topiramate

Table 3. Psychopathology measures in topiramate study: 8-week outcome – LOCF data

	Topiramate (n = 32)	Placebo (n = 16)	Treatment effect in endpoint analyses
PANSS total, mean (SD)			NS
Baseline	74.8 (8.4)	76.3 (10.3)	
Endpoint	61.8 (13.6)	60.6 (15.7)	
Mean difference	−13.0 (11.9)	−15.1 (12.9)	
% Difference	−17.3 (15.1)	−20.0 (15.9)	
PANSS positive, mean (SD)			NS
Baseline	21.9 (3.5)	23.1 (4.3)	
Endpoint	16.8 (4.4)	17.9 (4.9)	
Mean difference	−5.1 (4.4)	−5.0 (4.0)	
% Difference	−22.5 (18.0)	−21.7 (15.7)	
PANSS negative, mean (SD)			NS
Baseline	16.0 (3.3)	14.7 (4.0)	
Endpoint	14.1 (4.0)	12.5 (4.1)	
Mean difference	−1.9 (3.4)	−1.7 (3.0)	
% Difference	−11.0 (21.5)	−11.4 (20.3)	
PANSS aggression, mean (SD)			NS
Baseline	7.4 (2.0)	9.1 (2.7)	
Endpoint	5.8 (2.5)	6.7 (2.8)	
Mean difference	−1.6 (2.4)	−2.5 (2.6)	
% Difference	−20.2 (29.4)	−25.7 (25.5)	
MADRS, mean (SD)			NS
Baseline	7.9 (6.4)	8.8 (5.1)	
Endpoint	7.0 (6.2)	3.7 (2.3)	
Mean difference	−0.9 (6.2)	−4.1 (2.9)	
% Difference	−10.4 (96.9)	−48.3 (30.7)	
YMRS, mean (SD)			NS
Baseline	17.7 (7.1)	20.4 (7.4)	
Endpoint	12.6 (6.9)	12.9 (7.6)	
Mean difference	−4.8 (5.8)	−8.0 (5.1)	
% Difference	−21.0 (42.1)	−39.7 (22.8)	
DAI dysphoric, mean (SD)			NS
Baseline	1.5 (1.2)	1.5 (0.9)	
Endpoint	1.5 (1.5)	0.7 (0.7)	
Mean difference	−0.1 (1.4)	−0.7 (1.0)	
% Difference	−2.3 (114.9)	−41.7 (46.6)	
DAI non-dysphoric, mean (SD)			NS
Baseline	5.1 (1.2)	5.1 (0.8)	
Endpoint	4.9 (1.4)	4.8 (1.5)	
Mean difference	−0.1 (1.3)	−0.1 (1.4)	
% Difference	−1.0 (41.2)	−1.1 (29.1)	
CGI-Severity, mean (SD)			NS
Baseline	4.3 (0.6)	4.4 (0.5)	
Endpoint	3.6 (0.8)	3.5 (0.8)	
Mean difference	−0.8 (0.7)	−0.8 (0.9)	
% Difference	−17.2 (15.0)	−17.7 (20.2)	

PANSS = Positive and Negative Syndrome Scale; MADRS = Montgomery–Asberg Depression Rating Scale; YMRS = Young Mania Rating Scale; DAI = Drug Attitude Inventory; CGI = Clinical Global Impression; NS = not statistically significant; SD = standard deviation.

group: paresthesia, sedation, word-finding difficulty, sleepiness, and forgetfulness; however, the difference was not statistically significant (Table 4). Constipation was reported more frequently in those receiving placebo. Eight subjects (four in the placebo treatment arm and four in the topiramate group) tested positive for either alcohol or marijuana during the urine drug screens conducted throughout the study. They were sent for a dual diagnosis clinical consultation, but none of the subjects dropped out of this study due to either substance or alcohol abuse/dependence.

Movement disorders were reported infrequently. One patient in the placebo group receiving fluphenazine and valproate met criteria for akathisia, and one patient in the topiramate group, who received haloperidol and lithium, met criteria for mild extrapyramidal symptoms. Two patients, one receiving topiramate and the other receiving placebo, met pre-existing tardive

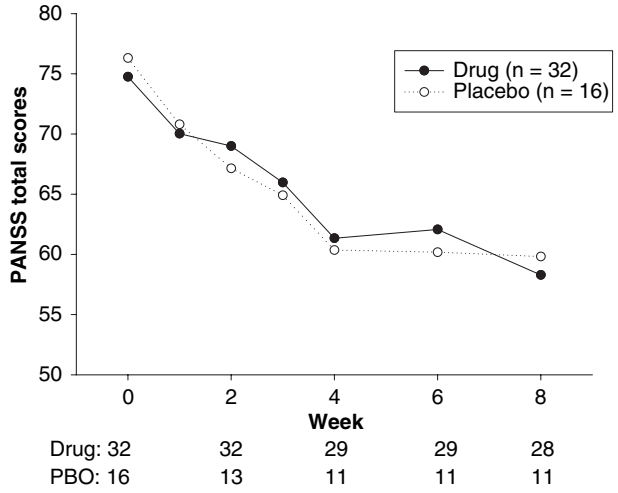

Fig. 2. Averaged observed Positive and Negative Syndrome Scale (PANSS) total score across 8 weeks of study by treatment group.
PBO = placebo.

Table 4. Treatment emergent adverse events occurring at ≥10% in each treatment arm, n (%)

Event	Topiramate (n = 32)	Placebo (n = 16)	χ^2	df	p
Paresthesia	10 (31.3)	3 (18.8)	0.84	1	0.36
Sedation	8 (25.0)	1 (6.3)	2.46	1	0.12
Urinary frequency	4 (12.5)	2 (12.5)	0.0	1	1.0
Diarrhea	4 (12.5)	2 (12.5)	0.0	1	1.0
Word-finding difficulty	5 (15.6)	1 (6.3)	0.86	1	0.35
Sleepiness	5 (15.6)	1 (6.3)	0.86	1	0.35
Headache	2 (6.3)	3 (18.8)	1.79	1	0.18
Forgetfulness	4 (12.5)	1 (6.3)	0.45	1	0.50
Constipation	0	2 (12.5)	4.17	1	0.04

dyskinesia criteria at study initiation (18), and these symptoms persisted throughout the study but did not worsen. Mean scores on the BAS, Simpson–Angus Scale and AIMS tended to be low at baseline, and there were no significant differences between the treatment groups in the study (data not shown).

Compliance

Compliance was assessed by pill counts at each visit; we found ≥95% compliance using this method. Only one patient was unable to comply with study medication in the 8-week, double-blind extension, and he discontinued in that phase of the study.

Body weight, body mass index and waist size

The topiramate-treated patients lost nearly 3.3 ± 8.5 lb on average, whereas the lithium- or valproate-treated group (i.e., adjunctive placebo) gained 6.6 ± 14.2 lb, a statistically significant difference [$F(1,43) = 6.46$, $p < 0.02$] (Table 5). Similarly, patients randomized to topiramate augmentation of lithium or valproate experienced a significantly greater reduction in BMI than those receiving lithium or valproate and placebo [$F(1,43) = 6.50$, $p < 0.02$] (Table 5). Even though the topiramate group lost, on average, a little more than 0.5 ± 2.18 inches at the waistline, and those receiving lithium or valproate gained, on average, a little over 0.75 ± 3.11 inches, the difference was not statistically significant [$F(1,38) = 0.96$, $p = 0.33$] (Table 5).

Discussion

This pilot study did not show clinical efficacy for adjunctive topiramate in patients with a diagnosis of SAD-BT. What may be the reasons? Is it

Table 5. Changes in body weight, body mass index (BMI) and waist size

	Topiramate (n = 32)	Placebo (n = 14)	Treatment effect in endpoint analyses (p-value)
Body weight, lbs, mean ± SD			0.02
Baseline	214.5 (51.7)	195.4 (19.2)	
Endpoint	211.2 (50.6)	201.4 (24.6)	
Mean difference	−3.3 (8.5)	6.0 (14.2)	
% Difference	−1.4 (3.8)	3.0 (7.1)	
BMI, kg/m^2, mean ± SD			0.02
Baseline	33.8 (7.7)	30.8 (3.9)	
Endpoint	33.3 (7.4)	31.7 (4.7)	
Mean difference	−0.5 (1.3)	1.0 (2.2)	
Waist, inches, mean ± SD	(n = 29)	(n = 12)	0.33
Baseline	44.2 (7.2)	40.0 (3.2)	
Endpoint	43.7 (6.7)	40.8 (4.3)	
Mean difference	−0.6 (2.2)	0.8 (3.1)	

SD = standard deviation; BMI = body mass index.

possible this study was statistically underpowered? Even if this were the case, there were no significant treatment effects for any of the psychopathology scale scores favoring topiramate. Furthermore, the calculated size of the treatment effect for topiramate was small (Cohen's $h = 0.30$). Were these patients treatment-refractory, thus making it difficult to see any benefits of topiramate? This possibility is less likely given that the inclusion criteria permitted less ill patients (PANSS total scores ≥60) to enter the study, and so there was room for improvement. As these patients were already receiving active psychotropic agents, is it possible that 'time on drug' effects would eventually show that adjunctive placebo (i.e., time on lithium or valproate) was as good as initiating topiramate? The results of this study are consistent with this possibility. A report of four large, controlled trials of topiramate also confirmed no efficacy advantage for topiramate over placebo in acute mania (19).

Why then were the open adjunctive studies of topiramate in bipolar and schizoaffective disorders positive? (2, 20, 21) Open studies are often confounded by patient and clinician expectations and bias toward favorable outcomes. This expectation bias may result in assigning favorable scores on clinical rating scales by both patients and clinicians for newer treatments that randomized, double-blind studies typically avoid. Finally, several psychiatric disorders are episodic in nature, and results in open-label studies may be confounded by spontaneous improvements being incorrectly attributed to the newer open-label treatment. Double-blind, random-assignment studies are also affected by spontaneous improvements, but it is hoped that the random assignment to an active drug or placebo results in the inclusion of nearly equal numbers of spontaneously recovering patients in each treatment arm.

Not unexpectedly, adjunctive topiramate was associated with weight loss and a reduction in BMI. These weight loss and BMI results have been reported in several studies involving topiramate (22). A combination of factors including, but not limited to, obesity, a higher prevalence of the metabolic syndrome, a sedentary lifestyle, and very high rates of smoking conspire to increase medical morbidity and mortality in people with bipolar or schizoaffective disorder or schizophrenia (23, 24). Reduction of body weight and BMI is likely to be beneficial for such patients. Topiramate has shown benefits in controlled trials for obese patients in terms of significant weight loss accompanied by significant improvements in blood pressure and glucose tolerance (25). Overall, the tolerability of topiramate was good in this study and the profile of adverse events reported with topiramate was consistent with that reported in the literature.

How does the present study compare with recent studies that have added either anticonvulsants or placebo to either lithium or valproate in patients with bipolar disorder? Adjunctive gabapentin did not separate from adjunctive placebo when added to either lithium or valproate for patients with bipolar disorder type I experiencing a hypomanic, manic or mixed episode (26). A small, inpatient mania study found similar efficacy for combining lithium and carbamazepine versus combining lithium with low-dose haloperidol (27), with differences in adverse event profiles between the combination treatments. However, that combination study (27) was not an add-on study such as the gabapentin study (26) or the present topiramate study, but rather involved combining the drugs from the start in an acute hospital setting, which limits the ability to compare these studies. In contrast, combination or add-on studies that have used olanzapine, quetiapine or risperidone with either lithium or valproate for manic or mixed bipolar episodes have resulted in positive outcomes (28–30).

In summary, this pilot study did not show efficacy for adjunctive topiramate on the primary efficacy or secondary outcome measures. Topiramate was relatively well tolerated, and topiramate-treated patients lost significant body weight and reduced their BMI.

Acknowledgements

The authors gratefully acknowledge the following individuals for their various roles in facilitating and completing the study: Dr Mukesh Sah, Dr James Baird, Dr Holly Swartz, Deborah Stapf, Dr Anthony Vagnucci, Dr Norman R Rosenthal, Lesley Schwartzman, Julie Capece, Naomi Sinclair, Rebecca Atzert, and Betty C Stocksdale.

References

1. Chengappa KNR, Rathore D, Levine J et al. Topiramate as add-on treatment for patients with bipolar mania. Bipolar Disord 1999; 1: 42–53.
2. McElroy SL, Suppes T, Keck PE et al. Open-label adjunctive topiramate in the treatment of bipolar disorders. Biol Psychiatry 2000; 47: 1025–1033.
3. Casey DE, Daniel DG, Wassef AA, Tracy KA, Wozniak P, Sommerville KW. Effect of divalproex combined with olanzapine or risperidone in patients with an acute exacerbation of schizophrenia. Neuropsychopharmacology 2003; 38: 182–192.
4. Tiihonen J, Hallikainen T, Ryynanen OP et al. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. Biol Psychiatry 2003; 54: 1241–1248.

5. White HS. Mechanism of action of newer anticonvulsants. J Clin Psychiatry 2003; 64: 5–8.
6. Post RM, Weiss SR, Clark M, Chuang D-M, Hough C, Li H. Lithium, carbamazepine, and valproate in affective illness: biochemical and neurobiological mechanisms. In: Manji HK, Bowden CL, Belmaker RH eds. Bipolar Medications: Mechanisms of Action. Washington DC: American Psychiatric Press, Inc., 2000: 219–248.
7. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13: 261–276.
8. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. Washington, DC: American Psychiatric Association, 2000.
9. First MB, Spitzer RL, Gibbon M, Williams JBW, eds. Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition (SCID-I/P, Version 2.0). New York, NY: New York State Psychiatric Institute, 1995.
10. Young RC, Briggs JT, Ziegler VE, Meyer P. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978; 133: 429–435.
11. Montgomery SA, Asberg M. A new depression scale designed to be sensitive of change. Br J Psychiatry 1979; 134: 382–389.
12. Guy W, ed. Clinical Global Impressions. Rockville, MD: National Institutes of Mental Health, 1976.
13. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol Med 1983; 13: 177–183.
14. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989; 154: 672–676.
15. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970; 212: 11–19.
16. Guy W, ed. Abnormal Involuntary Movement Scale. Rockville, MD: National Institute of Mental Health, 1976.
17. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988.
18. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry 1982; 39: 486–487.
19. Kushner SF, Khan A, Lane R, Olson WH. Topiramate monotherapy in the management of acute mania: results of four double-blind placebo-controlled trials. Bipolar Disord 2006; 8: 15–27.
20. Vieta E, Torrent C, Garcia-Ribas G et al. Use of topiramate in treatment-resistant bipolar spectrum disorders. J Clin Psychopharmacol 2002; 22: 431–435.
21. Marcotte D. Use of topiramate, a new antiepileptic, as a mood stabilizer. J Affect Disord 1998; 50: 245–251.
22. Chengappa KNR, Gershon S, Levine J. The evolving role of topiramate among other mood stabilizers in the management of bipolar disorder. Bipolar Disord 2001; 3: 215–232.
23. Basu R, Brar JS, Chengappa KNR et al. The prevalence of the metabolic syndrome in patients with schizoaffective disorder – bipolar subtype. Bipolar Disord 2004; 6: 314–318.
24. Fagiolini A, Frank E, Scott JA, Turkin S, Kupfer DJ. Metabolic syndrome in bipolar disorder: findings from the Bipolar Disorder Center for Pennsylvanians. Bipolar Disord 2005; 7: 424–430.
25. Wilding J, Van Gaal L, Rissanen A, Vercruysse F, Fitchet M, OBES-002 Study Group. A randomized double-blind placebo-controlled study of the long-term efficacy and safety of topiramate in the treatment of obese subjects. Int J Obes Relat Metab Disord 2004; 28: 1399–1410.
26. Pande AC, Crockatt JG, Janey CA, Werth JL, Tsaroucha G. Gabapentin in bipolar disorder: a placebo-controlled trial of adjunctive therapy. Gabapentin Bipolar Disorder Study Group. Bipolar Disord 2000; 2: 249–255.
27. Small JG, Klapper MH, Marhenke JD, Milstein V, Woodham GC, Kellams JJ. Lithium combined with carbemazepine or haloperidol in the treatment of mania. Psychopharmacol Bull 1995; 31: 265–272.
28. Tohen M, Chengappa KNR, Suppes T et al. Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially non-responsive to valproate or lithium monotherapy. Arch Gen Psychiatry 2002; 59: 62–69.
29. Sachs G, Chengappa KNR, Suppes T et al. Quetiapine with lithium or divalproex for the treatment of bipolar mania: a randomized, double-blind, placebo-controlled study. Bipolar Disord 2004; 6: 213–223.
30. Sachs GS, Grossman F, Ghaemi SN, Okamoto A, Bowden CL. Combination of a mood stabilizer with risperidone or haloperidol for treatment of acute mania: a double-blind, placebo-controlled comparison of efficacy and safety. Am J Psychiatry 2002; 159: 1146–1154.