Adjunctive Topiramate Therapy in Patients Receiving a Mood Stabilizer for Bipolar I Disorder: A Randomized, Placebo-Controlled Trial

K. N. Roy Chengappa, M.D.; Lesley K. Schwarzman, M.B.A.; Joseph F. Hulihan, M.D.; Jim Xiang, Ph.D.; and Norman R. Rosenthal, M.D., for the Clinical Affairs Product Support Study-168 Investigators

Objective: To investigate the efficacy and safety of topiramate versus placebo as adjunctive therapy for the outpatient management of bipolar I disorder.

Method: In this 12-week, randomized, double-blind, placebo-controlled trial, adults with bipolar I disorder (DSM-IV criteria) experiencing a manic or mixed episode with a Young Mania Rating Scale (YMRS) score of ≥ 18 while taking therapeutic levels of valproate or lithium received adjunctive topiramate or placebo. Topiramate was titrated from 25 to 400 mg/day over 8 weeks and was continued for 4 additional weeks. The study was conducted from October 2001 through October 2003. The primary outcome measure was the change in YMRS score from baseline to last study visit during the double-blind phase.

Results: The mean ± SD change in YMRS score from baseline was –10.1 ± 8.7 (–40.1%) in the topiramate group (N = 143) and –9.6 ± 8.2 (–40.2%) in the placebo group (N = 144, p = .797). Greater than 50% reduction in YMRS was achieved by 39% of the topiramate group and 38% of the placebo group (p = .914). No significant treatment differences were observed for secondary efficacy measures. Compared with adjunctive placebo, adjunctive topiramate did not worsen mania or induce depression. Paresthesia, diarrhea, and anorexia were more common in the topiramate group. The topiramate group achieved greater reductions than the placebo group in body weight (–2.5 vs. 0.2 kg, p < .001) and body mass index (–0.84 vs. 0.07 kg/m^2, p < .001).

Conclusion: In patients treated with lithium or valproate, there was no difference in the reduction of YMRS score in the topiramate and placebo groups. Both groups showed declines of 40%. Topiramate reduced body weight significantly relative to placebo without worsening depressive or manic symptoms.

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Received Oct. 24, 2005; accepted April 10, 2006. *From the Department of Psychiatry, University of Pittsburgh Medical Center and Mayview State Hospital, Pittsburgh, Pa. (Dr. Chengappa); the Department of Medical Affairs, Ortho-McNeil Neurologics, Inc., Titusville, N.J. (Ms. Schwarzman and Dr. Hulihan); the Department of Quantitative Methodology, Ortho-McNeil Janssen Scientific Affairs, LLC, Raritan, N.J. (Dr. Xiang); and the Department of Medical Affairs, PriCara, Unit of Ortho-McNeil Pharmaceutical, Inc., Raritan, N.J. (Dr. Rosenthal).*

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Participating investigators are listed at the end of this article.

Corresponding author and reprints: K. N. Roy Chengappa, M.D., Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213-2593 (e-mail: chengappakn@upmc.edu).

The pharmacologic management of acute manic or mixed episodes of bipolar disorders includes the use of a mood stabilizer (lithium, valproate, or carbamazepine) or one of the second-generation antipsychotic agents (risperidone, olanzapine, quetiapine, aripiprazole, or ziprasidone).[1,2] Antipsychotic agents may be used as monotherapy to treat symptoms in patients with severe episodes, but patients with bipolar I disorder often need a mood stabilizer to avoid frequent cycling or relapses. Lithium or valproate, each of which has proven antimanic properties, is used in combination with one of the second-generation antipsychotic agents to treat more severe manic or mixed episodes. Other clinical scenarios in which combination treatment may be appropriate include situations in which patients either do not respond to a single agent or experience a breakthrough episode while receiving lithium, valproate, or lamotrigine.

There is inconclusive evidence regarding the efficacy and safety of combining lithium and an anticonvulsant or combining 2 anticonvulsants in the management of bipolar disorder.[3–6]

Second-generation antipsychotic agents, in spite of short-term efficacy gains when used adjunctively in patients with bipolar disorder receiving lithium or valproate, can induce significant weight gain and metabolic issues

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that are of clinical concern.[7–10] Consequently, there remains an unmet need for adjunctive agents that effectively treat manic or mixed episodes while being free of metabolic adverse events.

The neurostabilizer topiramate has the following properties that may contribute to therapeutic effects in bipolar disorder: augmentation of neuronal response to the inhibitory neurotransmitter γ-aminobutyric acid (GABA) through potentiation of GABA receptor activity and an increase in GABA levels, inhibition of the excitatory neurotransmitter glutamate through α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid/kainate receptor blockade, blockade of voltage-sensitive sodium and calcium channels, and carbonic anhydrase inhibition.[11] Topiramate was investigated for use as monotherapy or adjunctive therapy in numerous smaller trials, but all were open-label studies or case reports.[12–29] Therefore, a comprehensive program of randomized, controlled clinical trials was undertaken to evaluate the safety and efficacy of topiramate monotherapy and adjunctive therapy in bipolar disorder. Pooled results of 4 controlled monotherapy trials of topiramate in adults with acute bipolar I mania were reported elsewhere.[30] The objective of this trial was to investigate the efficacy and safety of topiramate versus placebo as adjunctive therapy for manic or mixed episodes of bipolar I disorder in an ambulatory setting among adults already receiving a therapeutic dose of either lithium or valproate.

METHOD

Study Design

This 12-week, random-assignment, double-blind, placebo-controlled, parallel-group, multicenter trial was conducted from October 2001 through October 2003. Study visits occurred weekly during an 8-week titration period and then biweekly for the remaining 4 weeks. Adults between 18 and 70 years of age were eligible for the study if they were outpatients and they had bipolar I disorder, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV) criteria and supported by the Structured Clinical Interview for DSM-IV Axis I Disorders,[31] and a Young Mania Rating Scale (YMRS)[32] score of ≥ 18. Subjects were required to have received either lithium or valproate for 6 weeks or more, including a stable dose during the 2 weeks before the screening visit. Serum levels of mood stabilizers at the screening visit were required to be between 0.5 and 1.2 mEq/L for lithium or between 45 and 100 mg/L for valproate when drawn 8 to 12 hours after the last dose.

Exclusion criteria included substance abuse or dependence (except alcohol or marijuana) in the previous 3 months; mania requiring hospitalization; an organic mental disorder; mental retardation or a developmental disability; treatment-emergent mania due to antidepressant use; use of an antidepressant or stimulant within the previous 2 weeks (4 weeks for fluoxetine), unless the antidepressant was given at a subtherapeutic dose; use of carbamazepine within the previous 2 weeks or another anticonvulsant within the previous 3 weeks; initiation of nutriceutical treatment (e.g., St. John's wort) within the previous 4 weeks; long-acting antipsychotic medication or oral antipsychotic medicine that was given above the maximum recommended dose or was not given at a stable dose during the previous 4 weeks; use of opiates or barbiturates within the previous 3 months; any clinically unstable comorbid disease; liver disease; untreated hypothyroidism; history of nephrolithiasis, seizures, or any contraindication or precaution that would preclude use of topiramate; and pregnancy, lactation, or inadequate contraception in women.

Informed written consent was obtained for all subjects at screening. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the appropriate institutional review board for each study site.

Treatment

Subjects were randomly assigned to receive either topiramate or placebo. A computer-generated randomization schedule was prepared before the study and was balanced using randomly permuted blocks. Study medication was packaged by the sponsor according to the randomization schedule and provided to the study sites with identification numbers to maintain the double-blind status. Subjects were assigned to the randomization schedule for each site sequentially.

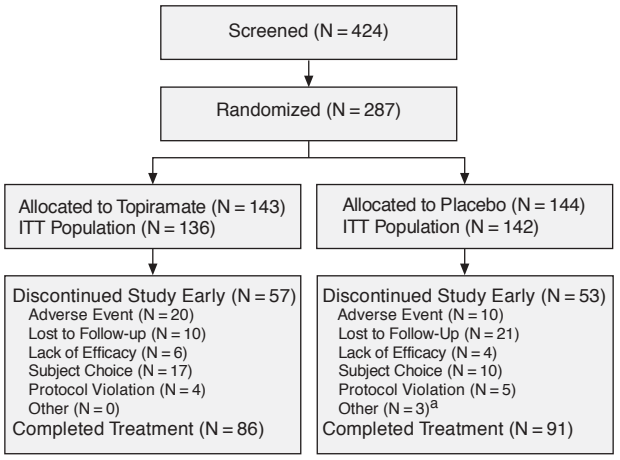
The initial dose of topiramate was 25 mg once daily. The total daily dose was then titrated at weekly study visits, using the following sequence and a twice-daily dosing schedule: 50, 75, 100, 150, 200, 300, and 400 mg. The investigator could stop titrating study medication because of adverse events, but the minimum allowed dose after the first week was 50 mg daily. After the 8-week titration period, the same dose was continued for the remaining 4 weeks. At the end of treatment, the dose of topiramate was tapered by approximately 30% every 3 days.

In addition to study medication and a stable dose of lithium or divalproex sodium, subjects were permitted to continue taking a stable dose of an oral antipsychotic agent. The use of a short-acting benzodiazepine (lorazepam) for sleep or agitation was permitted only during the first 4 weeks of the titration period using the following tapering schedule: 5 to 6 times weekly during week 1; 3 to 4 times weekly during week 2; and 1 to 2 times weekly during weeks 3 and 4.

Outcomes Measured

The primary efficacy assessment was the change of the YMRS score from baseline to last study visit during the

Figure 1. Subject Disposition[a]



[a]Other reasons in the placebo group included 2 subjects who moved and 1 subject who was lost to follow-up and returned after missing required evaluations.
Abbreviation: ITT = intent-to-treat.

double-blind phase.[32] YMRS ratings were assessed during screening and then at every visit during the double-blind phase. Secondary efficacy assessments that were measured at screening and baseline (day 1) and then biweekly included the Clinical Global Impressions-Severity of Illness scale (CGI-S),[33] the Brief Psychiatric Rating Scale (BPRS),[34] the Montgomery-Asberg Depression Rating Scale (MADRS),[35] and the Global Assessment Scale (GAS).[36] Safety assessments included the following: reports of adverse events and vital signs at every visit; clinical laboratory tests and serum pregnancy tests every 4 weeks and at the end of treatment; and serum levels of lithium, valproate, and topiramate at baseline, the end of dose titration, and the end of the study.

Statistical Analysis

SAS Version 9.1 (SAS Institute, Cary, N.C.) was used for statistical analyses. Efficacy analyses were performed in the intent-to-treat (ITT) population of subjects who received at least 1 dose of study medication and completed at least 1 postbaseline efficacy assessment. Missing efficacy data were imputed with the last postbaseline observation carried forward.

The primary efficacy endpoint was the change from baseline to final visit for total YMRS score, which was compared between groups with an analysis of covariance (ANCOVA) with treatment and center as independent factors and baseline score as covariate. Response rate was summarized according to the proportion of subjects in each treatment group with a reduction in total YMRS score from baseline of > 50% and was analyzed with a logistic regression including treatment, center, and baseline YMRS score in the model. Mean YMRS scores observed at each visit were plotted against time.

Secondary analyses of the change from baseline to final visit for CGI-S, BPRS, MADRS, and GAS used ANCOVA, with treatment and center as independent factors and baseline value as covariate. Worsening of mania was analyzed with 2 definitions: first as a ≥ 10% increase in YMRS score and then as a ≥ 20% increase from baseline. Treatment-emergent depression was defined as a MADRS score of ≥ 18 with an increase of ≥ 4 points from baseline at any 2 consecutive assessments or at the last observation.[35]

The safety population included all subjects who took at least 1 dose of study medication and provided postrandomization safety information. Serious treatment-related adverse events included those events that were fatal, were life-threatening, or required hospitalization and that the investigator considered to have a possible, probable, or very likely relationship to study medication. Laboratory values, vital signs, and physical examination results were summarized by change from baseline to final value, and individual values were compared with normal ranges. Analyses of body weight included the mean change in body weight and body mass index from baseline to final visit, compared between groups using ANCOVA, with treatment and center as factors and baseline value as covariate. Shift tables were constructed for body mass index using the following categories: underweight < 18.5 kg/m^2; normal weight = 18.5 to 24.9 kg/m^2; overweight = 25.0 to 29.9 kg/m^2; moderately obese = 30.0 to 39.9 kg/m^2; and severely obese ≥ 40 kg/m^2.

The study was powered to detect a mean reduction from baseline of 10 points in the total YMRS score for the topiramate treatment group and a mean reduction of 7.5 points in the placebo group. Assuming a standard deviation of 5.0 for both groups, a sample size of 172 subjects (or 86 in each treatment group) would have 90% power to detect this treatment difference of 2.5 points between the groups at a 2-sided significance level of .05. Therefore, the original randomization had 200 subjects total, based on an assumed attrition rate of 15%. When it became apparent during the study that the attrition rate would exceed this estimate, the sample size was amended to randomly assign 260 subjects, based on an assumed attrition rate of 33%.

RESULTS

Study Participants

Of the 424 subjects who were screened for eligibility by investigators at 36 sites, 287 subjects were enrolled and randomly assigned to treatment with adjunctive topiramate (N = 143) or adjunctive placebo (N = 144; Figure 1). Forty-nine subjects (26 topiramate treated and 23 placebo treated) were included in the ITT population for

Table 1. Baseline Characteristics of 287 Adults With Bipolar I Disorder

Characteristic	Topiramate (N = 143)	Placebo (N = 144)
Age, mean ± SD, y	41.0 ± 12.2	39.0 ± 11.9
Sex, N (%)		
Male	58 (40.6)	67 (46.5)
Female	85 (59.4)	77 (53.5)
Race, N (%)		
White	119 (83.2)	122 (84.7)
Black	14 (9.8)	14 (9.7)
Hispanic	5 (3.5)	6 (4.2)
Asian	2 (1.4)	1 (0.7)
Other	3 (2.1)	1 (0.7)
Body mass index, mean ± SD, kg/m^2	31.0 ± 7.8	30.4 ± 7.3

Table 2. Psychiatric History of 287 Adults With Bipolar I Disorder

Variable	Topiramate (N = 143)	Placebo (N = 144)
Rapid cycling, N (%)	39 (27.3)	43 (29.9)
Current episode, N (%)		
Mania	105 (73.4)	102 (70.8)
Mixed	30 (21.0)	35 (24.3)
Missing	0 (0.0)	7 (4.9)
No. of hospitalizations during lifetime, mean ± SD	2.7 ± 5.8	3.3 ± 13.1
History of psychotic episodes, N (%)	42 (29.4)	36 (25.0)
No. of psychotic episodes, mean ± SD	7.3 ± 20.0	7.8 ± 17.1

efficacy analyses despite violating the study protocol by starting lithium or valproate fewer than 6 weeks before the study.

Fifty-seven subjects (39.9%) in the topiramate group and 53 subjects (36.8%) in the placebo group discontinued treatment early. The leading reasons for early discontinuation in the topiramate group were adverse event (14.0%), subject choice (11.9%), and loss to follow-up (7.0%); in the placebo group, the leading reasons were loss to follow-up (14.6%), adverse event (6.9%), and subject choice (6.9%). The mean ± SD duration of double-blind treatment was 70.8 ± 31.6 days in the topiramate group and 74.7 ± 30.0 days in the placebo group, out of a possible 91 days.

Baseline characteristics (Table 1) and psychiatric history (Table 2) were generally similar between treatment groups. Rapid cycling was present in 39 subjects (27.3%) in the topiramate group and 43 subjects (29.9%) in the placebo group. Approximately one quarter of subjects in each group had a prior history of psychotic episodes, with a mean of more than 7 episodes among these subjects.

Medication Use

The mean daily dose of topiramate after dose titration was 254.7 mg, and 60 subjects in the topiramate group (42.0%) received a mean dose > 200 mg/day. Mean ± SD serum levels of topiramate were 6.2 ± 3.1 μg/mL on day 42 and 7.8 ± 4.5 μg/mL on day 84. Valproate tended to be used more commonly than lithium in the topiramate group (66.9% vs. 33.1%) and the placebo group (54.9% vs. 43.0%; Table 3), but these values were not statistically different between the 2 treatment groups. Mean ± SD serum concentrations of lithium were as follows: 0.7 ± 0.2 and 0.7 ± 0.3 mEq/L in the topiramate and placebo groups, respectively, at baseline; 0.7 ± 0.2 and 0.7 ± 0.3 mEq/L on day 42; and 0.8 ± 0.3 and 0.8 ± 0.1 mEq/L on day 84. Mean ± SD serum concentrations of valproate were as follows: 69.8 ± 22.9 and 71.0 ± 20.7 μg/mL in the topiramate and placebo groups, respectively, at baseline; 58.5 ± 18.8 and 60.0 ± 24.1 μg/mL on day 42; and 51.7 ± 17.8 and 53.4 ± 28.7 μg/mL on day 84.

Table 3. Central Nervous System Medications Taken by > 1 Subject in Either Group, at Baseline or During the Study

	Topiramate (N = 136)		Placebo (N = 142)	
Medication Class	N	%	N	%
Mood stabilizer				
Valproate	91	66.9	78	54.9
Lithium	45	33.1	61	43.0
Antianxiety				
Lorazepam	15	11.0	23	16.2
Alprazolam	2	1.5	2	1.4
Clonazepam	2	1.5	0	0.0
Antidepressant[a]				
Escitalopram	2	1.5	0	0.0
Sertraline	2	1.5	1	0.7
Bupropion	1	0.7	3	2.1
Paroxetine	1	0.7	2	1.4
Antipsychotic				
Quetiapine	9	6.6	7	4.9
Olanzapine	6	4.4	5	3.5
Risperidone	6	4.4	5	3.5
Aripiprazole	3	2.2	0	0.0
Ziprasidone	2	1.5	1	0.7

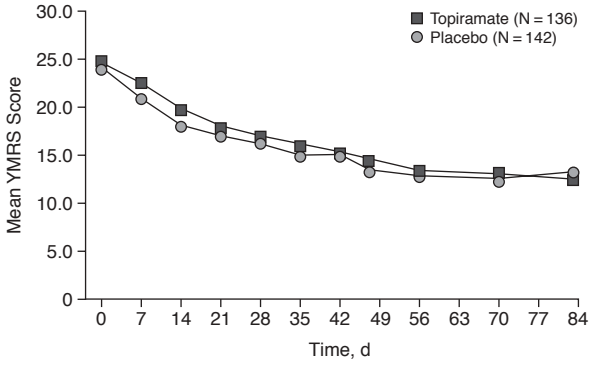
[a]Therapeutic doses of antidepressants were not permitted, but subjects could receive a subtherapeutic dose of an antidepressant.

In accordance with the study protocol, several subjects in the topiramate group (11.0%) and the placebo group (16.2%) used lorazepam during the dose-titration phase (Table 3). Use of other central nervous system medications at baseline or during the study was uncommon with the exception of the antipsychotic medications quetiapine, olanzapine, and risperidone, which were used by 5 or more subjects in each treatment group, also in accordance with the study protocol.

Efficacy

Similar reductions in YMRS scores from baseline were observed in each treatment group at every follow-up visit (Figure 2). The primary efficacy endpoint, mean ± SD change in total YMRS score from baseline to final visit, was not significantly different between the topiramate group (–10.1 ± 8.7; –40.1% from baseline) and the placebo group (–9.6 ± 8.2; –40.2% from baseline; Table 4). Response rate was not significantly different between

Figure 2. Mean YMRS Score by Study Visit[a]



[a]p Value not significant between treatment groups at any visit.
Abbreviation: YMRS = Young Mania Rating Scale.

groups, as measured by the proportion of subjects with a > 50% reduction in YMRS (39.0% vs. 38.0%, p = .914). Based on suggestions emerging during the peer review of this article, post hoc analyses were conducted on the differences in scores between treatment groups on individual items of the YMRS scale, focusing on irritability and disruptive-aggressive behavior and on the 2 other double-weighted items in this scale, speech and content. These additional analyses did not reveal any significant differences between treatment groups for any individual YMRS item score. There were no significant differences in the treatment response of patients receiving concomitant antipsychotics versus those who did not, nor was there a statistical difference in the treatment response of the patients who received valproate versus those who received lithium. Scores for most secondary efficacy endpoints—CGI-S, BPRS, MADRS, and GAS—improved from baseline in both groups, and no significant treatment differences were observed at the final visit (Table 4).

Adjunctive treatment with topiramate was determined not to be associated with worsening of mania or induction of depression. Similar proportions of subjects in the topiramate and placebo groups experienced a 10% or greater increase in YMRS score from baseline (8.8% vs. 8.5%, p = 1.000), a 20% or greater increase in YMRS score from baseline (4.4% vs. 5.6%, p = .786), or a MADRS score ≥ 18 and an increase from baseline in MADRS score ≥ 4 points on 2 consecutive visits or at the final visit (24.1% vs. 20.9%, p = .563).

Safety

Most subjects (85.3% in the topiramate group and 83.9% in the placebo group) had at least 1 adverse event. Of the most commonly reported adverse events (Table 5), paresthesia (23.1% vs. 3.5%), diarrhea (16.8% vs. 8.4%), and anorexia (13.3% vs. 5.6%) occurred significantly more frequently in the topiramate group than in the placebo group. Abnormal vision was reported by fewer than 10% of subjects (8.4% topiramate treated vs. 4.9% placebo treated, p > .05), and there were no reports of glaucoma. Two subjects in the placebo group had suicidal ideation considered unrelated to treatment, and 1 subject in the topiramate group was suicidal, which was considered possibly related to study treatment. No other serious adverse events were considered related to either study treatment, and no deaths occurred during the study.

Mean values for clinical laboratory tests and vital signs were within the normal range at baseline and final visit in both treatment groups. Similar proportions of subjects in each group had markedly abnormal laboratory values, and mean values for laboratory tests did not demonstrate clinically significant changes overall in either treatment group. Subjects in the topiramate group had a mean decrease in body weight of –2.5 ± 3.4 kg and a mean decrease in body mass index of –0.84 ± 1.2 kg/m^2 from baseline to final visit, compared with mean increases of 0.2 ± 3.0 kg (p < .001 vs. topiramate) and 0.07 ± 1.1 kg/m^2 (p < .001 vs. topiramate) in the placebo group. Subjects in the topiramate group tended to be more likely than subjects in the placebo group to move from a higher weight class to a lower one (Figure 3).

DISCUSSION

It was hypothesized before this study that the addition of topiramate to ongoing therapy with lithium or valproate would improve control of manic symptoms. This hypothesis was based on the mechanisms of action of topiramate and the theoretical similarities in the pathophysiology of bipolar disorder and epilepsy,[11] as well as the findings of a number of single-arm, open-label studies and case reports in which mania response rates to topiramate often were greater than 50%.[12–29] This multicenter, placebo-controlled study showed a responder rate of approximately 40% for both treatment groups but no efficacy advantage for topiramate relative to placebo. In previously published reports, open-label topiramate monotherapy reduced mania symptoms among patients with bipolar disorder, but a pooled analysis[30] of 4 randomized, controlled trials found no evidence that topiramate monotherapy was superior to placebo for the management of acute bipolar mania, which corresponds to the findings of this trial.

What might account for discrepant results between the nonrandomized and randomized trials? Nonrandomized studies are confounded by several factors, including but not limited to patient and clinician bias toward favorable reporting of outcomes, as well as patient, family, and clinician expectations of improvement; consequently, nonrandomized studies are more likely than randomized studies to demonstrate a treatment effect.[37]

It is well documented that lithium and valproate are effective in the reduction of acute manic symptoms.[1,2] In

Table 4. Efficacy Endpoints and Change From Baseline in the Intent-to-Treat Population

	Topiramate				Placebo				
Measure	N	Baseline	Final	Change	N	Baseline	Final	Change	p Value[a]
YMRS	136	24.9 ± 5.0	14.8 ± 8.5	–10.1 ± 8.7[b]	142	24.0 ± 4.3	14.4 ± 8.4	–9.6 ± 8.2[b]	.797
CGI-S	133	4.3 ± 0.6	3.4 ± 1.1	–0.9 ± 1.1[b]	139	4.2 ± 0.6	3.4 ± 1.0	–0.9 ± 1.1[b]	.698
BPRS	133	18.7 ± 10.8	15.4 ± 11.5	–3.3 ± 9.6[b]	139	18.0 ± 9.2	13.1 ± 10.3	–4.8 ± 9.0[b]	.052
MADRS	133	13.0 ± 8.6	13.6 ± 9.1	0.6 ± 8.8[c]	139	12.5 ± 7.9	11.4 ± 9.7	–1.1 ± 9.0[b]	.057
GAS	133	51.6 ± 8.2	58.8 ± 11.2	7.2 ± 9.9[c]	139	52.5 ± 8.9	59.6 ± 12.2	7.1 ± 11.5[c]	.838

[a]p Value between treatment groups for change from baseline.
[b]Negative change represents improvement.
[c]Positive change represents improvement.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAS = Global Assessment Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

Table 5. Adverse Events Reported by > 10% of Subjects in Either Group

	Topiramate (N = 143)		Placebo (N = 143)	
Adverse Event	N	%	N	%
Headache	34	23.8	37	25.9
Paresthesia*	33	23.1	5	3.5
Upper respiratory tract infection	25	17.5	16	11.2
Diarrhea*	24	16.8	12	8.4
Nausea	22	15.4	17	11.9
Somnolence	22	15.4	23	16.1
Anorexia*	19	13.3	8	5.6
Insomnia	17	11.9	16	11.2
Difficulty with memory	16	11.2	10	7.0
Dizziness	15	10.5	15	10.5

*p < .05 between treatment groups.

order to be able to show a treatment effect of topiramate, it was essential to exclude patients from the trial if they might still experience a lithium- or valproate-induced reduction of the YMRS score. Thus, the trial was designed to include only patients receiving a stable dose of these mood stabilizers in order to avoid a possible treatment bias, but 26 subjects (19%) in the topiramate group and 23 subjects (16%) in the placebo group did not meet these inclusion criteria and had received lithium or valproate for fewer than 30 days before randomization. However, exploratory analyses of the efficacy endpoints excluding these subjects did not reveal any significant treatment differences (data not shown).

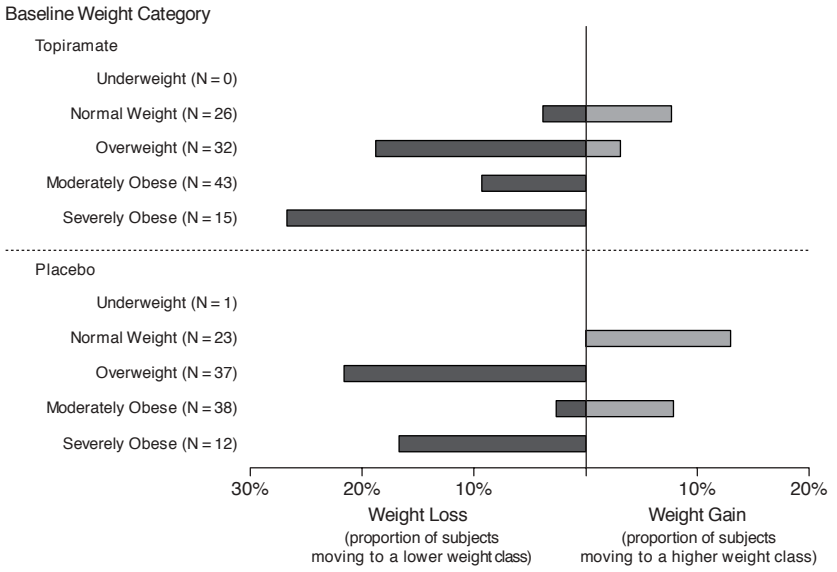
Also, the absence or presence of concomitant treatment with antipsychotic medications could have influenced the ability to show an antimanic effect of topiramate because these substances have been proven to reduce acute manic symptoms.[1,2] In an exploratory analysis, we therefore excluded data from subjects taking concomitant antipsychotics, but we were not able to detect a significant difference in the reduction of the YMRS scores in topiramate-treated versus placebo-treated subjects in this subpopulation (data not shown).

It is also possible that the dose of topiramate was suboptimal. A phase II trial comparing placebo with topiramate 256 or 512 mg/day in 97 patients with bipolar I disorder demonstrated significant reductions in YMRS favoring the higher-dose group when subjects with antidepressant-induced mania were excluded from the analyses.[38] In the present trial, only 44% of all subjects received a mean maintenance dose of topiramate > 200 mg/day, and the mean dose of topiramate after titration (255 mg/day) was approximately equal to the lower dose studied previously. Therefore, additional controlled trials of higher doses of adjunct therapy with topiramate may answer this question.

Other anticonvulsants have also been evaluated for bipolar mania. Like topiramate, the anticonvulsants gabapentin and lamotrigine were effective for the treatment of mania symptoms in patients with bipolar disorder in open-label studies of adjunctive therapy.[4–6] However, adjunctive therapy with gabapentin was no different from adjunctive placebo in a 10-week, placebo-controlled trial; in fact, the placebo group had a better response than the gabapentin group in that trial.[3] Even though it is nearly impossible to compare data from different clinical trials with differences in methodology, it is interesting to note that the adjunctive placebo group (i.e., subjects receiving lithium or valproate monotherapy) of that trial achieved nearly a 9-point reduction in mean YMRS score from baseline, which was similar to the observed improvement in both groups of this study, whereas adjunctive gabapentin achieved only a 6-point reduction. To our knowledge, no published placebo-controlled, randomized clinical trial supports the superiority of adjunctive lamotrigine over placebo as an adjunct to another mood stabilizer for the treatment of mania.

In contrast, randomized, placebo-controlled trials support the efficacy of combination treatment with an antipsychotic agent and a mood stabilizer for the management of manic or mixed episodes. The combination of olanzapine plus a mood stabilizer resulted in a 13.1-point YMRS score decline in 6 weeks, compared with a 9.1-point YMRS score decrease in the lithium or valproate monotherapy group.[8] Similar results were obtained in a shorter 3-week comparison of quetiapine plus a mood stabilizer

Figure 3. Change in Body Mass Index From Baseline to Final Visit[a]



[a]Weight categories were defined by body mass index as follows: underweight < 18.5 kg/m^2, normal weight = 18.5–24.9 kg/m^2, overweight = 25.0–29.9 kg/m^2, moderately obese = 30.0–39.9 kg/m^2, severely obese ≥ 40 kg/m^2.

(13.8-point YMRS score reduction) versus lithium or valproate monotherapy (9.9-point YMRS score reduction).[10] Differences in methodology notwithstanding, those trials achieved significant separation between adjunctive antipsychotic therapy and adjunctive placebo despite placebo responses that were comparable in magnitude to the placebo response in this study.

A potential limitation of this study was the inclusion of subjects with a baseline YMRS score of 18 or greater, rather than just those with more severe disease. Exploratory analyses were performed to determine if subjects with more severe mania or mixed episodes were more likely to respond to adjunctive topiramate than adjunctive placebo, using cutoff values for YMRS of 20, 22, and 26, but these analyses did not reveal a significant response to adjunctive topiramate compared with continued lithium or valproate monotherapy among subjects with more severe disease (data not shown). It is important to note that the small sample sizes of these subgroups may have precluded the detection of significant differences due to insufficient statistical power.

Adjunctive topiramate was generally safe and well-tolerated. The most commonly reported adverse events were consistent with those reported during topiramate therapy in patients with epilepsy or bipolar disorder[38] and included paresthesia, gastrointestinal adverse events, cognitive effects, and anorexia. Common adverse events associated with antipsychotics, such as weight gain, extrapyramidal symptoms, dyslipidemia, type 2 diabetes, and hyperprolactinemia,[39] were not observed. In fact, during this 12-week study, body weight decreased by 2.5 kg, and body mass index decreased by 0.84 kg/m^2 in the topiramate group, compared with slight increases in the placebo group, and subjects were significantly more likely to lose weight during topiramate therapy. Similar data on weight loss have been reported in controlled trials of topiramate for the management of epilepsy,[40] painful conditions,[41,42] and psychiatric disorders.[43]

In summary, adding topiramate at a mean dose of approximately 250 mg/day to ongoing therapy with either lithium or valproate in patients with bipolar I disorder with manic or mixed episodes did not produce significant improvement in YMRS scores or other efficacy endpoints when compared with placebo over a period of 3 months. Adjunctive topiramate therapy was relatively well-tolerated and did not worsen manic symptoms or induce depression compared with placebo. Topiramate-treated subjects had significantly greater weight loss and reductions in body mass index than subjects in the placebo group. Although this study demonstrated the tolerability and weight benefits of topiramate in patients with bipolar I disorder, it was unable to confirm the therapeutic benefit of topiramate for manic or mixed states in adults receiving lithium or valproate for the management of bipolar disorder.

Drug names: alprazolam (Xanax, Niravam, and others), aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Equetro, Carbatrol, and others), clonazepam (Klonopin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), gabapentin (Neurontin and others), lamotrigine (Lamictal and others),

lithium (Eskalith, Lithobid, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others), topiramate (Topamax), ziprasidone (Geodon).

In addition to the authors, the following investigators participated in the Clinical Affairs Product Support Study-168: Scott Aaronson (Sheppard Pratt Health System, Baltimore, Md.); Alex Alva (Harbor Medical Associates, Fountain Valley, Calif.); Valerie Arnold (Clinical Neuroscience Solutions, Memphis, Tenn.); Scott Balogh (Southeastern Neuroscience, Inc., Augusta, Ga.); Bijan Bastani (North Coast Clinical Trials, Inc., Beachwood, Ohio); Louise Beckett (IPS Research Company, Oklahoma City, Okla.); Gary Booker (Lagniappe Hospital, Shreveport, La.); Richard Brown (Hartford Research Group, Cincinnati, Ohio); Edward P. Burdick (Segal Institute for Clinical Research, North Miami, Fla.); Harry Croft (Croft Group Research Center, San Antonio, Tex.); Andrew Cutler (CORE Research, Inc., Winter Park, Fla.); Bernadette D'Souza (Midwest Clinical Research Center, Dayton, Ohio); Prakash Ettigi (private practice, Richmond, Va.); Joseph Fanelli (Midwest Center for Neurobehavioral Medicine, Oakbrook Terrace, Ill.); Mildred V. Farmer (Meridien Research, St. Petersburg, Fla.); Ronald Fieve (Fieve Clinical Research Center, New York, N.Y.); Gordon L. Gibson (Clinical Study Centers, LLC, Little Rock, Ark.); Mahlon Hale (New Britain General Hospital Behavioral Health Services, New Britain, Conn.); Linda Harper (Clinical Neuroscience Solutions, Orlando, Fla.); Howard Hassman (Comprehensive Clinical Research–CNS, Clementon, N.J.); Shivkumar Hatti (Suburban Psychiatric Associates, Media, Pa.); Scott Hoopes (private practice, Boise, Idaho); Debra Kelsh (Vince & Associates Clinical Research, Overland Park, Kan.); Arifulla Khan (Northwest Clinical Research Center, Bellevue, Wash.); Steve Lynn (private practice, Atlanta, Ga.); Janice Miller (Clinical Neuroscience Solutions, Orlando, Fla.); Hemant Patel (Psychiatry & Anxiety Disorders Research Clinic, Oklahoma City, Okla.); Pauline Powers (University of South Florida, Tampa, Fla.); William J. Privitera (Future Search Trials, Austin, Tex.); Sohail Punjwani (Segal Institute for Clinical Research, North Miami, Fla.); Murray Rosenthal (BMR Healthquest, San Diego, Calif.); Mary Shemo (Psychiatric Alliance of the Blue Ridge Clinical Research Center, Charlottesville, Va.); Rajinder Shiwach (Terrell State Hospital Research Center, Terrell, Tex.); David P. Walling (CNS Network, Garden Grove, Calif.); Kashinath Yadalam (Lake Charles Clinical Trials, Lake Charles, La.); Jill Zweig (Meadowbrook Research, Inc., Scottsdale, Ariz.).

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