Open-Label Adjunctive Topiramate in the Treatment of Bipolar Disorders

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Background: To preliminarily explore the spectrum of effectiveness and tolerability of the new antiepileptic drug topiramate in bipolar disorder, we evaluated the response of 56 bipolar outpatients in the Stanley Foundation Bipolar Outcome Network (SFBN) who had been treated with adjunctive topiramate in an open-label, naturalistic fashion.

Methods: In this case series, response to topiramate was assessed every 2 weeks for the first 3 months according to standard ratings in the SFBN, and monthly thereafter while patients remained on topiramate. Patients' weights, body mass indices (BMIs), and side effects were also assessed.

Results: Of the 54 patients who completed at least 2 weeks of open-label, add-on topiramate treatment, 30 had manic, mixed, or cycling symptoms, 11 had depressed symptoms, and 13 were relatively euthymic at the time topiramate was begun. Patients who had been initially treated for manic symptoms displayed significant reductions in standard ratings scores after 4 weeks, after 10 weeks, and at the last evaluation. Those patients who were initially depressed or treated while euthymic showed no significant changes. Patients as a group displayed significant decreases in weight and BMI from topiramate initiation to week 4, to week 10, and to the last evaluation. The most common adverse side effects were neurologic and gastrointestinal.

Conclusions: These preliminary open observations of adjunctive topiramate treatment suggest that it may have antimanic or anticycling effects in some patients with bipolar disorder, and may be associated with appetite suppression and weight loss that is often viewed as

beneficial by the patient and clinician. Controlled studies of topiramate's acute and long-term efficacy and side effects in bipolar disorder appear warranted. *Biol Psychiatry* 2000;47:1025–1033 © 2000 Society of Biological Psychiatry

Key Words: Topiramate, bipolar disorders, mania, cycling, weight

Introduction

Topiramate is a structurally and pharmacologically novel antiepileptic drug (AED; a sulfamate-substituted monosaccharide) with proven anticonvulsant efficacy when used adjunctively (Ben-Menachem 1995; Ben-Menachem et al 1996; Faught et al 1996; Privitera et al 1996; Sharief et al 1996; Tassinari et al 1996) and as monotherapy (Sachdeo et al 1997) in refractory partial epilepsy. Mechanisms hypothesized to account for topiramate's antiepileptic properties include blockade of voltage-gated sodium channels, antagonism of the kainate/ α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subtype of glutamate receptor, enhancement of γ -aminobutyric acid (GABA) activity at the GABA_A receptor via interaction with a nonbenzodiazepine receptor site, and carbonic anhydrase inhibition (Ben-Menachem 1995; Meldrum 1996).

Several lines of evidence suggest that topiramate might be a useful treatment for bipolar disorder. First, several other AEDs are effective in the treatment of bipolar disorder, including in patients inadequately responsive to or intolerant of lithium (Calabrese et al 1995, 1999; Keck and McElroy 1998; Post et al 1998). Second, as noted above, topiramate affects GABAergic neurotransmission via the GABA_A receptor, and valproate's antimanic efficacy has been hypothesized to be mediated in part via its GABAergic effects (Petty et al 1996). Third, topiramate's antiglutamatergic effects may be relevant. Mounting preclinical data suggest that lithium and valproate decrease glutamatergic function at the *N*-methyl-D-aspartate

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Table 1. Demographic and Clinical Features of 56 Outpatients with Various Bipolar Disorders Receiving Topiramate

	Manic ^a (<i>n</i> = 32)	Depressed (<i>n</i> = 11)	Euthymic (<i>n</i> = 13)	All (<i>n</i> = 56)
Mood symptoms before treatment				
Bipolar diagnosis, <i>n</i> (%)				
Bipolar I	27 (84) ^b	6 (54)	10 (77)	43 (77)
Bipolar II	4 (12)	4 (36)	3 (23)	11 (19)
Schizoaffective	1 (3)	1 (9)	—	2 (4)
Females, <i>n</i> (%)	21 (66)	8 (73)	10 (77)	39 (70)
Caucasians, <i>n</i> (%)	32 (100)	11 (100)	12 (92)	55 (98)
Age at entry (years), mean (SD)	42.1 (8.5)	43.2 (8)	38.5 (9.4)	41.7 (8.6)
CGI-BP (mania) before treatment, mean (SD)	3.5 (1.0)	1.3 (0.5)	1.4 (0.5)	2.6 (1.4)
Range	1–6	1–2	1–2	1–6
YMRS before treatment, mean (SD)	10.2 (7.4) ^c	6.1 (3.8)	2.9 (2.9)	7.7 (6.7)
Range	0–34	0–14	0–8	0–34
CGI-BP (depression) before treatment, mean (SD)	3.5 (1.1)	3.6 (0.8)	1.6 (0.5)	3.1 (1.3)
Range	1–6	3–5	1–2	1–6
IDS-C before treatment, mean (SD)	27.1 (12.3)	25.4 (11.8)	10.2 (6.0)	22.8 (13.0)
Range	7–58	3–39	2–25	2–58
DSM-IV rapid cycling ^d	23 (74)	4 (50)	8 (61)	35 (67)
Alcohol/drug abuse ^e	19 (61)	6 (75)	5 (42)	30 (59)
Hospitalization ^f	15 (60)	5 (71)	8 (73)	28 (63)
Attempted suicide ^g	11 (44)	4 (57)	3 (27)	18 (41)
Days of treatment, mean (SD)	226.4 (181.4)	177.3 (180.8)	187.6 (133)	214.2 (169.6)
Weight (kg) before treatment, mean (SD)	91.4 (26.9)	79.9 (19.7)	98.4 (29.3)	92.2 (26.3)
BM ^h before treatment, mean (SD)	32.0 (9.9)	31.2 (8.1)	34.0 (10)	32.3 (9.6)

CGI-BP, Clinical Global Impressions Scale modified for Bipolar Illness; YMRS, Young Mania Rating Scale; IDS-C, Inventory of Depressive Symptoms.

^aIncludes patients with manic (3), mixed (11), and cycling (18) mood symptoms.^b22 BPI patients were hypomanic, three were manic, and two had no manic symptoms by CGI-BP.^cMean (SD), range, YMRS scores for manic = 12.0 (3.5), 10–16; mixed = 10.6 (6.5), 0–21; and cycling = 9.6 (8.6), 0–34; mood symptoms (no significant differences in YMRS scores).^dData missing for DSM-IV rapid cycling in four patients.^eData missing for alcohol/drug abuse in five patients.^fData missing for hospitalization in 12 patients.^gData missing for suicide attempts in 12 patients.^hWeight in kg/height in m².

(NMDA) receptor (Hough et al 1996; Nonaka et al 1998): though they stimulate glutamate release acutely, they decrease it chronically (Dixon and Hokin 1997, 1998). Moreover, blockade of AMPA receptors may suppress pathological components of learned or overlearned responses, because AMPA receptors are thought to mediate fully developed long-term potentiation (LTP) as opposed to its initial development (which is related to NMDA receptors; Muller et al 1988; Tocco et al 1992). Fourth, topiramate has a favorable pharmacokinetic profile: It is minimally bound to plasma proteins and has few clinically relevant pharmacokinetic interactions with other AEDs (Ben-Menachem 1995; Johannessen 1996; Langtry et al 1997). Fifth, topiramate has a high therapeutic index, is associated with anorexia and weight loss in patients with epilepsy (rather than the appetite stimulation and weight gain of many psychotropic drugs), is not associated with hematologic or hepatic abnormalities, and does not require routine serum concentration or blood monitoring (Ben-Menachem 1995; Johannessen 1996; Langtry et al 1997; Norton et al 1997; Rosenfeld et al 1997). These properties could make topiramate an attractive medication for patients with bipolar disorder who require an agent with an

alternative mechanism of action, who are receiving multiple psychotropics, who are experiencing appetite stimulation or weight gain from their medication regimens, who have hematologic or hepatic abnormalities, or who find the required blood monitoring of standard mood stabilizers onerous.

Although available clinical data regarding the efficacy of topiramate in the treatment of bipolar disorder are limited, preliminary open studies suggest it may have mood-stabilizing properties. In a 28-day, open-label trial of topiramate monotherapy titrated to a mean (range) dose of 614 mg/day (50–1300 mg/day) in 11 hospitalized bipolar patients with severe treatment-resistant acute mania, 3 (27%) patients displayed an apparent response to the drug, defined as $\geq 50\%$ decrease in the baseline Young Mania Rating Scale (YMRS) total score (Young et al 1978) at termination (Calabrese et al 1998). Two other subjects showed 25%–49% improvement on the YMRS. In another open-label trial of topiramate given as monotherapy or adjunctive therapy in 44 patients with rapid-cycling bipolar disorder, 52% were described as displaying moderate or marked improvement after a mean duration of treatment of 16 weeks with a mean (range)

Table 2. Psychotropic Drug History in 54 Patients Treated with Topiramate

Medication/medication class	Manic (<i>n</i> = 32) <i>n</i> (%)	Depressed (<i>n</i> = 9) ^a <i>n</i> (%)	Euthymic (<i>n</i> = 13) <i>n</i> (%)	All (<i>n</i> = 54) <i>n</i> (%)
Lithium	20 (62)	5 (56)	10 (77)	35 (65)
Valproate	21 (66)	6 (67)	7 (54)	34 (63)
Carbamazepine	7 (22)	1 (11)	5 (38)	13 (24)
Lamotrigine	4 (12)	—	—	4 (7)
Antidepressants	25 (78)	6 (67)	10 (77)	41 (76)
Typical antipsychotics	7 (22)	1 (11)	5 (38)	13 (24)
Atypical antipsychotics	4 (12)	1 (11)	1 (8)	6 (11)

^aMedication history not available for two depressed patients.

dosage of 200 (25–400) mg/day (Marcotte 1998). In a third open-label study, topiramate was added to existing medication regimens in 19 female outpatients with rapid-cycling bipolar disorder and psychotropic-induced weight gain (Kusumakar et al 1999). Ten patients displayed significant improvement in mood and five experienced a weight loss of more than 5%. In a fourth open-label study, 20 patients with bipolar (*n* = 18) or schizoaffective (*n* = 2) disorder with manic, hypomanic, mixed, or rapid-cycling symptoms received adjunctive topiramate from 100 to 300 mg/day (Chengappa et al 1999). By 5 weeks, 12 patients (60%) were responders, defined as $\geq 50\%$ reduction in YMRS score and a Clinical Global Impression rating (CGI; Spearing et al 1997) of much or very much improved. In addition, all patients lost weight, losing a mean of 9.4 pounds in 5 weeks. Body mass index (BMI) was also significantly reduced. In a letter describing two

patients with mood disorders and weight gain switched from valproate to topiramate, the patient with bipolar disorder displayed improved mood stability, but the patient with recurrent major depression relapsed (Gordon and Price 1999). Both patients, however, lost significant amounts of weight with topiramate.

To further preliminarily explore the potential spectrum of clinical effectiveness and tolerability of topiramate in bipolar disorder, we gathered data on 56 outpatients with bipolar illness who had been treated clinically with adjunctive topiramate in an open-label, naturalistic fashion because they were either inadequately responsive to or poorly tolerant of standard psychotropic regimens. In light of topiramate's association in epileptic patients with anorexia and weight loss, we also assessed patients' weights and BMIs, which had been routinely monitored while patients were taking topiramate.

Methods and Materials

Patients with various bipolar disorders who were either inadequately responsive to or poorly tolerant of at least one standard mood stabilizer (i.e., lithium, valproate, or carbamazepine) were offered naturalistic, open-label treatment with topiramate if they 1) were participating in the Stanley Foundation Bipolar Outcome Network (SFBN; Leverich et al, in press; Suppes et al, in press); 2) were 18 years of age or older; and 3) had a DSM-IV (American Psychiatric Association 1994) diagnosis of either bipolar I, II, NOS or schizoaffective disorder, bipolar type (as determined by Structured Clinical Interview for DSM-IV [SCID-P; First et al 1996]). Patients' index mood symptoms and

Table 3. Changes in Rating Scales in 54 Bipolar Outpatients Receiving Topiramate (at Weeks 4 and 10 and Last Evaluation) According to Initial Mood Symptoms^{a,b}

Initial Mood Symptoms	Baseline Mean (SD)	4 Weeks Mean (SD)	Change Mean (SD)	<i>p</i> value	10 Weeks Mean (SD)	Change Mean (SD)	<i>p</i> value	Last Evaluation Mean (SD)	Change Mean (SD)	<i>p</i> value
Manic^c (<i>n</i> = 30)										
CGI (Mania)	3.5 (1.1)	2.7 (1.5)	−0.8 (1.4)	.006	2.4 (1.4)	−1.2 (1.5)	.0002	2.4 (1.5)	−1.2 (1.6)	.0003
YMRS	9.9 (7.7)	6.9 (8.2)	−3.1 (6.5)	.021	5.3 (7.3)	−4.8 (7.1)	.001	6.3 (7.8)	−3.9 (6.9)	.004
CGI (Depression)	3.4 (1.2)	3.1 (1.5)	−0.4 (1.2)	.115	3.2 (1.6)	−0.3 (1.7)	.326	3.3 (1.4)	−0.2 (1.7)	.600
IDS	27.6 (12.5)	20.9 (13.9)	−6.7 (10.0)	.002	20.5 (14.1)	−6.4 (14.5)	.022	21.7 (13.8)	−5.2 (1.7)	.099
Depressed^d (<i>n</i> = 11)										
CGI (Mania)	1.3 (0.5)	1.4 (0.5)	+0.1 (0.3)	.343	1.3 (0.6)	0.0 (0.8)	1.000	1.1 (0.3)	−0.2 (0.6)	.341
YMRS	6.1 (3.8)	4.2 (3.6)	−2.0 (3.8)	.130	5.4 (5.0)	−0.7 (4.7)	.617	4.6 (3.7)	−1.4 (3.3)	.171
CGI (Depression)	3.6 (0.8)	2.7 (1.4)	−0.8 (1.4)	.104	3.4 (1.5)	−0.2 (1.3)	.659	3.6 (1.0)	0	1.000
IDS	25.4 (11.8)	17.2 (8.2)	−6.9 (11.3)	.087	22.2 (14.3)	−3.3 (14.8)	.481	24.5 (12.4)	0.9 (9.2)	.751
Euthymic^e (<i>n</i> = 13)										
CGI (Mania)	1.4 (0.5)	1.5 (0.7)	+0.1 (0.5)	.586	1.2 (0.4)	−0.1 (0.7)	.436	1.5 (1.1)	+0.1 (0.9)	.549
YMRS	3.2 (2.8)	1.8 (2.2)	−1.3 (3.9)	.258	1.6 (1.9)	−1.6 (3.1)	.103	3.6 (4.8)	+0.7 (4.5)	0.588
CGI (Depression)	1.6 (0.5)	2.0 (0.7)	+0.3 (0.6)	.104	1.7 (0.9)	+0.1 (0.9)	.776	2.2 (1.1)	+0.6 (0.9)	.025
IDS	10.9 (5.7)	12.8 (8.1)	+1.9 (10.2)	.527	10.2 (7.6)	−0.7 (9.5)	.79	12.1 (9.8)	+1.9 (7.3)	.361

CGI, Clinical Global Impressions Scale; YMRS, Young Mania Rating Scale; IDS, Inventory of Depressive Symptoms.

^aLast-observation-carried-forward for patients who completed at least 2 weeks of topiramate therapy.^bMean (SD) duration of topiramate treatment for all 54 patients = 214.2 (169.6) days; patients received drug for at least 2 weeks.^cMean (SD) duration of topiramate treatment for all 30 patients with manic symptoms = 239.2 (180.2) days.^dMean (SD) duration of topiramate treatment for all 11 patients with depressive symptoms = 177.3 (180.8) days.^eMean (SD) duration of topiramate treatment for all 13 euthymic patients = 187.6 (133.0) days.

Table 4. CGI-BP Response at 4 and 10 Weeks in 54 Bipolar Outpatients Receiving Topiramate^a

	Much or very much improved ^b		Minimal or no change ^b		Much or very much worsened ^b	
	4 Weeks <i>n</i> (%)	10 Weeks <i>n</i> (%)	4 Weeks <i>n</i> (%)	10 Weeks <i>n</i> (%)	4 Weeks <i>n</i> (%)	10 Weeks <i>n</i> (%)
Initial symptoms						
Manic ^c (<i>n</i> = 30)						
Mania	9 (34.6)	19 (63.3)	13 (50.0)	7 (23.3)	4 (15.4)	4 (13.3)
Overall	5 (18.5)	11 (36.7)	18 (66.7)	15 (50.0)	4 (14.8)	4 (13.3)
Depressed ^d (<i>n</i> = 11)						
Depression	3 (33.3)	3 (27.3)	6 (66.7)	6 (54.5)	0	2 (18.2)
Overall	3 (33.3)	3 (27.3)	6 (66.7)	6 (54.5)	0	2 (18.2)
Euthymic (<i>n</i> = 13)						
Mania	NA	NA	13 (100)	13 (100)	0	0
Depression	NA	NA	13 (100)	13 (100)	0	0
Overall	NA	NA	13 (100)	13 (100)	0	0

CGI-BP, Clinical Global Impressions Scale modified for Bipolar Illness.

^aFor patients who completed at least 2 weeks of topiramate therapy.^bCGI change from phase (symptoms) at the beginning of treatment.^cMissing CGI mania scores for four manic patients and depression and overall scores for three patients at 4 weeks.^dMissing CGI mania, depression, and overall scores for two depressed patients at 4 weeks.

overall clinical state were determined by clinical evaluation and the National Institute of Mental Health-Life Chart Methodology (NIMH-LCM; Leverich and Post 1998). All patients had provided written informed consent to participate in the SFBN and to have their course of illness and response to treatment prospectively evaluated with regular visits and serial rating instruments on an ongoing basis. The potential risks and benefits of topiramate treatment based on the available literature in neurological and psychiatric patients, which included controlled trials in the former and open case series in the latter, were also discussed with each patient. All patients were thus informed that the potential use of this drug was “off-label” (i.e., not FDA approved for psychiatric indications).

Topiramate was openly added to pre-existing psychotropic regimens, and was generally begun at 25–50 mg/day, given either all at night or b.i.d. Topiramate doses were subsequently typically increased by 25–50 mg/day every 3–14 days according to patient response and side effects to the maximum dose utilized in this case series (1200 mg/day). Of note, when the first patient was treated with topiramate, 222 patients were enrolled in the

SFBN. When the last patient in this series was treated, 364 patients were enrolled, indicating that only a small portion of the total SFBN population was treated with this agent.

Patients were generally seen every 2 weeks for the first 10 weeks of topiramate treatment and monthly thereafter to assess response, weight, and side effects. Response to topiramate add-on was evaluated at each visit using the standard cross-sectional ratings of the naturalistic follow-up phase of the SFBN (Leverich et al, in press). These ratings included the Clinical Global Impressions Scale modified for Bipolar Illness (CGI-BP; Spearing et al 1997) to rate degree of improvement in index mood symptoms and overall severity of illness, the YMRS to rate manic symptoms, and the Inventory of Depressive Symptoms (IDS; Rush et al 1985) to rate depressive symptoms. The CGI-BP assessed patients' symptoms over the past 2–4 weeks (depending on the time of a patient's last rating); the YMRS assessed symptoms over the past 48 hours; and the IDS assessed symptoms over the past week. Thus, ultrarapid or ultradian cycling patients may have had affective symptoms rated on the CGI-BP but not on the YMRS or IDS, owing to these differing time frames. Patients' progress was further monitored clinically by assessment of their NIMH-LCMs.

Assessment of response to topiramate was retrospectively divided into two phases for purposes of analysis: 1) acute, defined as the first 10 weeks of treatment (when patients were typically assessed every 2 weeks); and 2) maintenance, defined as treatment that extended beyond the first 10 weeks (when patients were more typically assessed every 4 weeks). Termination of topiramate add-on evaluation was defined as discontinuation of the drug or SFBN participation for any reason, or addition of another psychotropic drug to further control affective symptoms (e.g., addition of a mood stabilizer or an antipsychotic to relieve residual, increased, or recurrent manic symptoms).

Statistical analyses were performed using the Statistical Products for Service Solutions (SPSS), version 8.0. Frequencies were utilized for analysis of the demographic and clinical features of the patient population. Means were calculated using the descrip-

Figure 1. Mean Clinical Global Impressions Scale modified for Bipolar Illness (CGI) Mania scores (1, normal, not ill; 2, minimally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; 7, very severely ill) for manic patients during acute treatment (*n* = 30). **p* < .05; ***p* < .01; ****p* < .001.

Figure 2. Mean Young Mania Rating Scale (YMRS, —■—) and Inventory of Depressive Symptoms (IDS, —▲—) scores for manic patients during acute treatment ($n = 30$). * $p < .05$; ** $p < .01$.

tives function for continuous demographics and clinical variables at baseline. Mean change scores over the course of treatment with topiramate were examined using the paired-sample t test.

Results

In collecting this open case series, 56 outpatients with bipolar I ($n = 43$), bipolar II ($n = 11$), or schizoaffective, bipolar type ($n = 2$) disorders were found to have received at least one dose of open-label topiramate. The clinical characteristics and psychotropic drug histories of these patients are summarized in Tables 1 and 2. Specifically, 32 patients had manic, mixed, or extremely rapid (i.e., ultra-rapid or ultradian cycling) mood symptoms, 11 were depressed, and 13 were relatively euthymic at the time topiramate was begun. Ultra-rapid cycling has been defined as four or more hypomanic, manic and/or depressive episodes occurring within one month; and ultradian cycling as mood shifts occurring within a day on 4 or more days a week (Leverich and Post 1998). Of note, for purposes of analysis, the cycling patients were combined with patients with manic or mixed symptoms, because their baseline mean (SD) YMRS score as a group did not differ significantly from that of the manic or mixed groups (see Table 1). The combined group will hence be referred to as the manic group.

The mean (SD) number of psychotropic medications per patient at the time of topiramate addition was 1.4 ± 1.1 . The most common concomitant medications were valproate ($n = 25$), antidepressants ($n = 20$), antipsychotics ($n = 12$), benzodiazepines ($n = 12$), thyroxine and/or tri-iodothyronine ($n = 11$), lithium ($n = 10$), gabapentin ($n = 8$), and lamotrigine ($n = 5$). The 43 patients with manic or depressive symptoms receiving topiramate chose to do so because they were inadequately responsive to their current pharmacologic regimens. All 13 euthymic patients received the drug to see if its putative anorexic and weight loss effects would reverse psychotropic drug-

induced hyperphagia or weight gain and/or suppress binge eating.

Fifty-four of the 56 patients had received topiramate for at least 2 weeks. The acute response of these patients to topiramate is summarized in Tables 3 and 4. The two patients who did not receive topiramate for 2 weeks (both of whom had manic symptoms at topiramate initiation) had discontinued the drug after 1 and 5 days of treatment due to side effects (dizziness and hallucinations, respectively) before ratings had been repeated.

As shown in Table 3, patients with manic symptoms at initiation of topiramate treatment displayed significant decreases in CGI-BP-Mania and YMRS scores after both 4 weeks and 10 weeks of treatment and at their last evaluation. They also showed significant decreases in IDS (but not CGI-BP-Depression) scores at weeks 4 and 10. By contrast, patients who were initially depressed and those who were initially euthymic showed no significant changes in these ratings at most time points. Figures 1 and 2 show that initially manic patients also achieved significant decreases in some measures of manic symptoms at weeks 6 and 8 of treatment, but not by week 2. Table 4 shows that of the 30 patients who were treated for manic symptoms at 10 weeks, 19 (63.3%) showed much or very much improvement in their manic symptoms on the CGI-BP. Of the initially depressed patients, however, only 3 of 11 (27.3%) at 10 weeks showed much or very much improvement in their depressive symptoms.

Because the mean (SD) baseline YMRS of 10.2 (7.4) in patients with manic symptoms reflected only mild manic symptomatology, we analyzed antimanic response to topiramate in three subsets of manic patients with increasingly severe symptoms—reflecting, respectively, definite hypomania, mild mania, and mild-to-moderate mania (Young et al 1978). As shown in Table 5, patients with baseline mean (SD) YMRS scores ≥ 12 and those with scores ≥ 15 both displayed significant decreases at 10 weeks and at

Table 5. Changes in YMRS Scores in Patients with ≥ 12 , ≥ 15 , and ≥ 20 on Baseline YMRS

	YMRS ≥ 12 (<i>n</i> = 11)		YMRS ≥ 15 (<i>n</i> = 7)		YMRS ≥ 20 (<i>n</i> = 4)	
	Mean YMRS (SD)	Mean Change (SD)	Mean YMRS (SD)	Mean Change (SD)	Mean YMRS (SD)	Mean Change (SD)
Baseline	18.3 (6.2)	NA	21.1 (6.1)	NA	24.2 (6.5)	NA
4 weeks	12.4 (11.6)	−5.9 (8.5)	15 (13.2)	−6.0 (9.9)	18.5 (17.0)	−6.5 (10.3)
10 weeks	9.4 (10.5)	−0.1 (8.3) ^a	9.2 (13.7)	−12.8 (8.3) ^b	12.2 (16.5)	−12.0 (10.6)
Last evaluation	9.9 (10.6)	−8.4 (8.0) ^a	10.8 (13.4)	−10.3 (9.3) ^b	15.0 (17.1)	−9.2 (12.4)

YMRS, Young Mania Rating Scale.

^a*p* < .01.^b*p* < .05.

their last evaluation. The decreases in mean (SD) YMRS scores displayed by the four patients with baseline mean (SD) YMRS scores ≥ 20 were of a similar magnitude but were not significant.

Thirty-seven patients continued open maintenance treatment with topiramate for a mean $\pm$ SD of 294.6 ± 145.3 days, (i.e., more than 7 months). Of the 22 patients who had manic mood symptoms at topiramate initiation, 12 (55%) were rated as much or very much improved at their last evaluation after a mean $\pm$ SD of 312.5 ± 154.0 days of treatment. Eleven of the 12 acute phase responders remained well throughout the maintenance phase. Of the 10 patients rated as minimally or not changed, five remained on topiramate because of weight loss, whereas four others stayed on the drug because of some minimal improvement in manic mood symptoms throughout topiramate treatment. The tenth patient displayed minimal worsening at his last evaluation after showing much or very much improvement through 8 months of continuation treatment. Five of the 11 initially depressed patients continued topiramate treatment; one was much or very much improved, whereas four displayed minimal or no change at their last visit after a mean $\pm$ SD of 345.2 ± 129.7 days. Of the 10 initially euthymic patients who entered maintenance treatment, nine continued to display minimal or no change, but one worsened with the development of mixed symptoms after a mean $\pm$ SD of 229.9 ± 121.5 days of treatment.

Table 6 shows that the daily dose of topiramate was increased gradually over the course of treatment, in both the acute and maintenance phases. Topiramate doses in responders did not differ from those in nonresponders. Topiramate treatment was associated with a substantial rate of drug discontinuation. In total, 29 (52 %) patients discontinued the drug—19 during the first 10 weeks of treatment and 10 during the maintenance phase. Reasons for topiramate discontinuation during acute treatment were increase in depressive symptoms (*n* = 7), side effects (*n* = 6), increase in manic symptoms (*n* = 4), discontinuation of all medications (*n* = 1), and failure to prevent olanza-

pine-induced weight gain (*n* = 1). Reasons for stopping topiramate during maintenance treatment were side effects (*n* = 4), lack of efficacy or worsening symptoms (*n* = 4), and discontinuation of SFBN participation (*n* = 2). Side effects leading to topiramate discontinuation were cognitive impairment (*n* = 2), poor appetite and weight loss (*n* = 2), sedation (*n* = 1), parathesia (*n* = 1), psychosis (*n* = 1), anxiety (*n* = 1), altered taste (*n* = 1), tremors (*n* = 1), nausea (*n* = 1), and rash (*n* = 1). Of note, serial ratings were either subsequently not analyzed or discontinued in seven patients who continued topiramate therapy: four patients had another psychotropic drug added to topiramate to treat breakthrough or increased mood symptoms (two valproate, one olanzapine, and one quetiapine) and three patients decided to discontinue SFBN participation altogether and were referred to other treatment settings.

Although 10 (18%) patients discontinued topiramate because of side effects, many patients tolerated topiramate well. The most common side effects (which often did not result in drug discontinuation) were neurological and gastrointestinal, and included reduced appetite (*n* = 11), cognitive impairment (*n* = 10), fatigue (*n* = 5), and sedation (*n* = 5). Indeed, reduced appetite was usually viewed as beneficial. These effects often occurred when topiramate was initiated or increased in dose, and fre-

Table 6. Mean (SD) Topiramate Dose at Each Acute Visit, 6 Months, 1 Year, and Each Patient's Last Evaluation

Time of evaluation	<i>n</i>	Dose (mg/day)	Range (mg/day)
Baseline	56	37.0 (34.4)	25–200
2 weeks	46	83.7 (57.8)	25–300
4 weeks	44	121.9 (79.3)	25–350
6 weeks	40	156.2 (99.2)	50–400
8 weeks	38	169.7 (109.8)	50–500
10 weeks	37	193.2 (122.0)	25–500
6 months	27	290.7 (185.9)	50–800
1 year	7	425.0 (352.1)	100–1000
Last evaluation ^a	54	244.7 (241.7)	25–1200

^aMean (SD) duration of topiramate treatment = 214 (169.6) days.

Table 7. Change in Weight (kg) in Patients Receiving Topiramate

Time of evaluation	<i>n</i>	Weight Mean (SD)	Range	Weight loss (kg) Mean (SD)	% Change
Study entry ^a	53	92.2 (26.3)	54–171	NA	NA
4 weeks ^{a,b}	50	91.1 (27.0)	53–171	−0.7 (1.9) ^c	−0.1%
10 weeks ^{a,b}	50	91.1 (27.0)	51–165	−1.6 (2.9) ^d	−1.7%
6 months ^b	37	94.4 (26.9)	53–162	−4.7 (5.9) ^d	−4.8%
1 year ^b	37	93.0 (26.5)	49–156	−6.2 (7.5) ^d	−6.2%
Last evaluation ^{a,b,e}	53	87.7 (25.1)	51–156	−4.5 (6.7) ^d	−4.9%

^aWeight missing for 1 patient at pretreatment, 4 patients at 4 weeks, 4 patients at 10 weeks, and 1 patient at last evaluation.^bLast-observation-carried-forward.^c*p* < .05.^d*p* < .001.^eMean (SD) of 214.2 (169.6) days.

quently resolved or lessened with time and/or dosage reduction. Other side effects reported by more than one patient were dry mouth (*n* = 4), unwanted weight loss (*n* = 4), increased thirst (*n* = 4), parathesia (*n* = 4), altered taste (*n* = 4), dyspepsia (*n* = 4), ataxia (*n* = 4), dizziness (*n* = 4), itching (*n* = 4), slurred speech (*n* = 2), decreased libido (*n* = 2), increased libido (*n* = 2), headaches (*n* = 2), blurred vision (*n* = 2), increased salivation (*n* = 2), insomnia (*n* = 2), and psychosis (*n* = 2).

Tables 7 and 8 show that topiramate treatment was associated with significant decreases in both weight and body mass index (BMI) at 4 weeks of treatment, 10 weeks of treatment, and at the last evaluation for patients as a group. Neither baseline weight nor BMI prior to treatment was associated with degree of decrease in weight or BMI. For example, patients with BMIs ≥ 27 lost as much weight as patients with BMIs < 27. Although most patients found this weight loss beneficial, two patients who lost substantial amounts of weight with topiramate (and who initially described the weight loss as favorable) eventually stopped the drug because of persistently suppressed appetite and the fear that they would continue to lose weight. Both patients experienced weight gain after topiramate discontinuation, prompting one patient to re-

sume the drug at a lower dose. By contrast, two other patients who discontinued topiramate for cognitive impairment and lack of efficacy, respectively, each resumed the drug because it had helped them lose weight.

Discussion

Fifty-six outpatients with various bipolar disorders who were either inadequately responsive to or poorly tolerant of standard mood-stabilizer regimens and who received naturalistic, open-label, adjunctive treatment with topiramate were evaluated. Patients with manic, mixed, or cycling symptoms at topiramate initiation displayed significant decreases in ratings of manic symptoms at 4 weeks, 10 weeks, and at their last evaluation. IDS (but not CGI-BP-Depression) ratings in these patients also displayed significant improvement at some time points. By contrast, patients who began topiramate treatment for depressive symptoms or during relative euthymia did not display notable changes in ratings at most time points. Adverse effects of topiramate were usually neurological or gastrointestinal, often mild and transient, but sometimes led to drug discontinuation. Topiramate treatment was associated with reduced appetite and a consistent decrease

Table 8. Change in Body Mass Index (BMI; Weight in kg/Height in m²) in Patients Receiving Topiramate

Time of evaluation	<i>n</i>	BMI Mean (SD)	Range	Change in BMI Mean (SD)	% Change
Study entry ^a	52	32.3 (9.6)	20–61	NA	NA
4 weeks ^{a,b}	49	31.3 (8.8)	19–56	−0.9 (4.7)	−2.9%
10 weeks ^{a,b}	49	32.1 (9.7)	19–59	−0.6 (1.0) ^c	−1.7%
6 months ^b	37	33.3 (9.9)	19–58	−1.6 (1.9) ^c	−4.7%
1 year ^b	37	32.7 (9.8)	19–56	−2.2 (2.5) ^c	−6.3%
Last evaluation ^{a,b,d}	52	30.7 (9.2)	19–56	−1.6 (2.3) ^c	−5.0%

^aBody mass index missing for 2 patients at pretreatment, 5 patients at 4 weeks, 5 patients at 10 weeks, and 2 patients at last evaluation.^bLast-observation-carried-forward.^c*p* < .001.^dMean (SD) of 214.2 (169.6) days.

in weight and BMI which most patients described as favorable.

The interpretations of these findings are limited by several methodologic shortcomings. Most importantly, this is a naturalistic, nonrandomized, open-label case series. Thus, the possibility that the observed favorable response to topiramate therapy was instead due to clinician or patient bias, a placebo response, or spontaneous improvement cannot be excluded.

Although the increasing rate of antimanic response from 4 to 10 weeks and the persistence of that response at the last evaluation argues against a placebo response, it also suggests topiramate may have a relatively slow onset of response (perhaps owing in part to it having been begun at a low dose and increased gradually). Another clear limitation is that topiramate was added to other medications, which were inadequately effective. It is therefore unknown whether the apparent antimanic response after topiramate addition was due to topiramate alone or to a combination with concurrently administered mood stabilizers. Moreover, the manic patients' mean (SD) baseline YMRS score of only 9.9 (7.7) reflects a mild level of manic symptomatology, and effectiveness in more severe manic pathology remains uncertain. In other words, if topiramate is ultimately shown to have antimanic properties, it might be efficacious in mild mania and very rapid cycling patterns but not in more severe mania.

In summary, this open-label, clinical case series preliminarily suggests that adjunctive topiramate may have positive acute and long-term effects in a subgroup of manic, mixed, or cycling patients with bipolar disorder inadequately responsive to standard mood stabilizers. Acute antidepressant effects were not evident. Moreover, topiramate may be associated with the favorable side effects of anorexia and weight loss for patients with psychotropic-induced weight gain. Thus, formal controlled studies of topiramate in bipolar disorder appear warranted, especially in light of its novel combined GABAergic and antilutamatergic properties. If shown to have therapeutic properties in controlled trials, topiramate's relatively favorable pharmacokinetic and side-effect profile and lack of need for regular serum concentration and blood monitoring could prove to be of further benefit.

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