Antimanic Efficacy of Topiramate in 11 Patients in an Open Trial With an On-Off-On Design

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Background: A series of open studies suggests that topiramate has efficacy in bipolar disorder. To further investigate the potential value of topiramate as an antimanic agent, we conducted an open trial in 11 manic patients.

Method: Eleven patients with bipolar I disorder with an acute manic episode (DSM-IV) were treated with a mood stabilizer and/or antipsychotics in sufficient and fixed doses. All had a Young Mania Rating Scale (YMRS) score of at least 24 (mean ± SD = 33.5 ± 8.1). Topiramate was added after stable plasma levels of concomitant mood stabilizers had been reached and was titrated within 1 week to a final dose in the range of 25 to 200 mg/day, depending on clinical efficacy and tolerability. Topiramate was discontinued after 10 days, while concomitant medication remained unchanged. After 5 days, topiramate was reintroduced at similar or increased dosages for another 7 days. Patients were assessed with the YMRS; the Clinical Global Impressions scale version for bipolar patients; and the 21-item Hamilton Rating Scale for Depression.

Results: Seven of the 11 patients initially showed a good antimanic response with > 50% reduction in YMRS score. One patient showed psychotic features following rapid increase in topiramate dosage and dropped out on day 10. After discontinuation of topiramate, 7 of the remaining 10 patients worsened (increase of ≥ 25% in YMRS score), 2 remained stable, and 1 discontinued follow-up after good recovery. After reintroducing topiramate, all patients improved again within a week, with 8 of 9 meeting the responder criterion of ≥ 50% YMRS score reduction when comparing baseline values with those of day 22. With the exception of the patient who developed psychosis, topiramate was well tolerated. Concomitant medication did not interfere with plasma levels of drug, except for carbamazepine level in 1 patient.

Conclusion: The antimanic response among patients in this study appears reproducibly linked to the addition of topiramate.

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Topiramate is a structurally unique anticonvulsant insofar as it belongs to a sulfamate-substituted *d*-fructose substance group. However, many of the known mechanisms of action of topiramate are similar to those of established antiepileptic drugs, especially the putative mood stabilizers carbamazepine, valproate, and lamotrigine. Topiramate modulates sodium conductance, inhibits L-type calcium channels (at 10 μmol/L, but may also cause a transient increase in current through other voltage-activated calcium channels at 50 μmol/L), potentiates GABAergic inhibition, decreases α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/kainate receptor–mediated currents, and is a weak inhibitor of carbonic anhydrase. It is difficult to explain this broad spectrum of action by a single synaptic mechanism. However, a potential common denominator may be intracellular inhibition of protein kinase A and C,[1] which are critically involved in second messenger pathways.[2] Inhibition of protein kinase A and C, a mechanism already demonstrated with carbamazepine[3] and valproate,[4] is an effective method of down-regulating neuronal excitability.

The advantageous pharmacokinetic profile of topiramate also makes the drug attractive for the treatment of bipolar disorder. Topiramate is completely absorbed and passes the blood-brain barrier (*c* [cerebrospinal fluid] ≈ 40% of *c* [plasma]). The pharmacokinetics of topiramate are characterized by a linear decay with minimal plasma protein binding. Only a very small fraction of drug is metabolized by the liver. This means that there are no clinically significant plasma drug level interactions with other mood stabilizers (valproate, lamotrigine), antipsychotics, antidepressants, digoxin, or oral contraceptives. Only when given as comedication with a strong enzyme-inducing agent such as carbamazepine is topiramate metabolism

enhanced, leading to a reduction (approximately 40%) in plasma concentration. Due to its excretion by the kidneys, special care should be taken when topiramate is administered in patients with renal failure. Otherwise, its elimination half-life is approximately 21 hours; thus, topiramate can be administered twice daily—an advantage in manic patients unwilling to take medication.

Another point in favor of topiramate use, particularly for maintenance therapy, is its lack of propensity to cause weight gain. Unlike other mood stabilizers, such as lithium and valproate, and atypical antipsychotics, topiramate has been associated with lack of weight gain, and, in many overweight patients, even weight loss.[5] The incidence of other adverse events associated with topiramate treatment is also reasonably low, as studies in epilepsy have previously demonstrated.[6,7] The more common central nervous system (CNS) side effects, such as ataxia, nervousness, psychomotor slowing, and speech disturbances, are more likely to occur when topiramate is coadministered with other antiepileptic drugs.

The efficacy of topiramate in bipolar disorder has been suggested by several open studies.[8–11] However, the results can be difficult to interpret, since they are confounded by open designs with changing comedications in most (in the study by Chengappa et al.,[10] patients were kept on constant treatment with comedication throughout the trial). On the other hand, it is almost impossible for a single investigator to conduct a large-scale controlled trial of a nonapproved drug. Therefore, we utilized a design already in use in the early 1980s in preliminary studies of valproate, carbamazepine, and oxcarbazepine in bipolar disorder,[12] comprising an on-off-on period for the study medication. After using this design incidentally in 1 patient who clearly demonstrated a response to topiramate,[13] we decided to conduct the trial described here in a larger number of patients.

METHOD

Subjects were recruited from the inpatients of the departments of psychiatry at the University of Munich and the University of Freiburg, Germany. Eleven consecutively admitted acutely manic patients participated after being extensively informed about the trial and giving written informed consent. Their ability to give informed consent was confirmed by a certified psychiatrist not participating in the study. The patient group consisted of 6 men and 5 women, all white, with a mean ± SD age of 39.1 ± 9.8 years (range, 24–64 years). Patients remained hospitalized throughout the trial. The inclusion criterion was a bipolar I diagnosis with an acute manic episode (Young Mania Rating Scale [YMRS] score ≥ 20) according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV).[14] Exclusion criteria were another DSM-IV Axis I disorder, inability to give informed consent, and suicidality. Eight patients were diagnosed with euphoric mania, and 3 patients with dysphoric mania. At the time of inclusion, all patients had been receiving treatment with a mood stabilizer or antipsychotic for at least 2 weeks without response. Comedications included lithium, valproic acid, carbamazepine, clozapine, haloperidol, and perazine. At baseline, blood levels of the concomitant medication were determined, and the individual drugs were continued at an unchanged dosage throughout the trial. At baseline, 5 of the 6 patients receiving valproic acid had a plasma level > 65 mg/L, and the other patient had a valproic acid level of 56.8 mg/L. Of those patients receiving lithium, 3 had a plasma level < 0.75 mmol/L, and 1 was in the low therapeutic range (0.62 mmol/L). The 1 patient receiving carbamazepine had a blood drug level of 8.24 mg/L at baseline. Regular checks were performed throughout the trial to ensure stability of these blood levels and compliance. The only additional treatment allowed during the study period was oxazepam, at a maximum dosage of 20 mg/day for the first 7 days.

The psychometric scales administered at baseline (day 1) and at days 4, 10, 13, 16, and 22 included the YMRS,[15] the 21-item Hamilton Rating Scale for Depression (HAM-D-21),[16] and the Clinical Global Impressions scale version for bipolar patients (CGI-BP).[17] Neither raters nor patients were blinded to topiramate administration. However, raters were not informed about the "off" period. Blood samples were drawn on the days when ratings were taken at 8:00 a.m. (12 hours after the previous dose of medication), to check the plasma levels of topiramate and any concomitant medication. Blood levels of topiramate were determined at the Neurochemistry Laboratory at the German Epilepsy Center at Kehl; thus, it usually took several days between drawing the samples and receiving the results. Plasma levels of concomitant antipsychotics and mood stabilizers were determined in the in-house laboratory, enabling any changes in plasma levels of drug to be addressed on the same day.

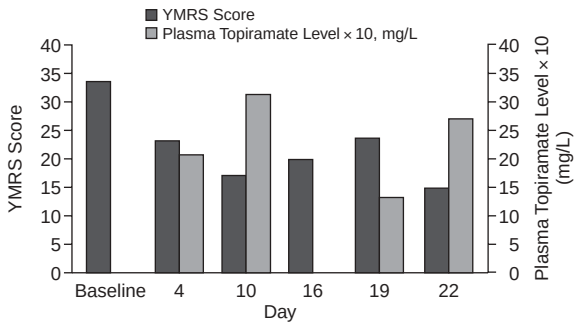
Topiramate was administered according to an on-off-on design. All patients initially received 25 mg of topiramate on day 1, following the baseline ratings and blood sampling. Topiramate was titrated on an individual basis dependent on clinical impression and tolerability rather than blood levels of drug. Starting from a 50-mg daily dosage, topiramate was administered twice daily in identical doses. On day 10, topiramate was discontinued without a tapering phase and was reintroduced on day 16 after the final rating of the off period, starting with 25 mg/day and increasing dose on an individualized basis for another 6 days until day 22 (end of the trial). During this second "on" period, topiramate was titrated more rapidly in those patients who showed good tolerability during the first on period and who were still severely manic.

Table 1. Topiramate Dosage, Comedication, and Outcome (YMRS score)[a]

Source	Gender	Comedication	Maximum Topiramate Dose (mg/d)	YMRS Score Baseline	Day 4	Day 10	Day 16	Day 19	Day 22
Patient									
1[b]	M	Valproic acid, haloperidol, lorazepam	50	41	…	17	33	33	20
2	F	Valproic acid, haloperidol, lorazepam	100	29	20	14	12	17	13
3	M	Valproic acid, haloperidol, lorazepam	150	32	23	13	15	19	13
4	F	Valproic acid, haloperidol, lorazepam	150	28	21	6	11	22	14
5	F	Valproic acid, haloperidol, lorazepam	200	39	22	12	19	25	15
6	M	Carbamazepine, perazine, lorazepam	50	24	1	1	9	6	0
7	M	Lithium, valproic acid	200	29	24	17	11	11	8
8	F	Olanzapine, lorazepam	400	37	34	28	32	35	28
9[c]	M	Lithium, haloperidol, lorazepam	100	35	13	13	…	…	…
10	F	Clozapine, lamotrigine, lithium	400	51	49	33	37	44	24
11[d]	M	Lithium	100	24	24	32	…	…	…
YMRS score									
Mean				33.5	23.1	16.9	19.9	23.5	15.0
SD				8.1	12.5	10.2	11.0	12.1	8.3
Significance of YMRS change compared with baseline[e]				…	.0039*	.0020*	.0039*	.0039*	.0039*
Significance of YMRS change compared with prior timepoint[e]				…	.0039*	.00469*	.00781	.00469*	.0039*
Plasma topiramate level, mg/L									
Mean					2.1	3.2		1.3	2.7
SD					1.3	1.2		0.4	1.0

[a]Abbreviation: YMRS = Young Mania Rating Scale.
[b]YMRS data missing for day 4.
[c]Dropout on patient's request after reasonable recovery.
[d]Dropout due to adverse events (psychotic features).
[e]Wilcoxon signed rank test; * = statistically significant.

Figure 1. Treatment Response (mean YMRS score) and Mean Plasma Topiramate Concentrations[a]



[a]Abbreviation: YMRS = Young Mania Rating Scale.

RESULTS

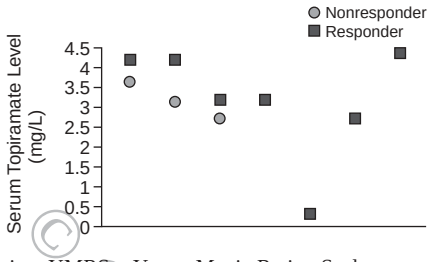
Psychometric Rating Scales

At baseline, the mean ± SD YMRS score of all patients was 33.5 ± 8.1, with a range of 24 to 51. Five patients had a score ≥ 35. The mean score for the CGI-BP was 5.6 (range, 5–7) and for the HAM-D-21, 8.2 ± 6.1. On day 10, before discontinuing topiramate, the mean YMRS score had declined to 16.9 ± 10.2 (range, 1–33), the mean CGI-BP score to 4.2, and the mean HAM-D-21 score to 6.3 ± 3.1. At this stage, 2 patients dropped out, 1 due to adverse events, the other to withdrawal of consent after a virtually full recovery. Their respective last ratings were carried on for last-observation-carried-forward analysis. At day 10, seven of the 11 patients who participated in the study initially showed a good antimanic response with > 50% reduction in YMRS score. Three other patients showed a less pronounced response. One patient worsened, developing psychotic features, and dropped out. During and shortly after the "off" period, the YMRS and CGI-BP scores increased, with a peak on day 19, three days after reintroducing topiramate. The mean YMRS score at this timepoint was 23.5 ± 12.1 (range, 6–44); the mean CGI-BP score, 5.1; and the mean HAM-D-21 score, 6.5 ± 4.2. Of the 9 patients remaining in the trial, 7 worsened again (increase of ≥ 25% in YMRS score) and 2 remained stable. Finally, at day 22, the mean scores declined again: YMRS, 15.0 ± 8.3 (range, 0–32); CGI-BP, 4; HAM-D-21, 5.1 ± 4.2. All patients improved again within a week or remained improved, with 8 of 9 meeting the responder criterion of ≥ 50% YMRS score reduction compared with their baseline scores. Table 1 lists the individual YMRS scores for all patients throughout the trial. Figure 1 shows the course of the mean YMRS ratings in relation to the plasma topiramate levels.

Dosing and Plasma Levels of Topiramate

Topiramate was introduced at a starting dose of 25 mg/day and titrated within 1 week to a final dose in the

Figure 2. Distribution of Plasma Topiramate Concentrations at Day 10 in Responders (reduction in YMRS score > 50%) and Nonresponders[a]



[a]Abbreviation: YMRS = Young Mania Rating Scale.

range of 25 to 200 mg/day, depending on clinical efficacy and tolerability. The mean dosage of topiramate at day 10 was 127 ± 56 mg/day. Plasma levels of drug were determined in 10 of 11 patients. One patient refused regular blood draws. At day 10, the mean plasma topiramate level in these 10 patients was 3.2 ± 1.2 mg/L (range, 0.3–4.4). The patient with a plasma topiramate level of only 0.3 had the lowest YMRS score (24) at baseline and remained on treatment with 50 mg/day topiramate, which was sufficient to improve his moderate manic syndrome. Excluding this patient, there appeared to be a tendency toward higher plasma topiramate levels in responders compared with nonresponders at day 10 (Figure 2). Responders (excluding the patient with a plasma topiramate level of 0.3 mg/L) had a mean plasma topiramate level of 3.65 ± 0.70 mg/L. The 3 nonresponders had a mean plasma topiramate level of 3.13 ± 0.45 mg/L. In view of the small number of patients who participated in this study, this is clearly not statistically significant, but may be a finding worthy of further investigation.

Topiramate was abruptly discontinued after 10 days, while concomitant medication remained unchanged. On day 16, topiramate was reintroduced at 25 mg/day, followed by a rapid dosage increase for another 6 days. In the 2 patients with severe mania, dosage was increased to 400 mg/day. In the 9 patients remaining in the study, the mean dosage of topiramate on day 19 was 139 ± 108 mg/day (plasma drug level = 1.3 ± 0.4 mg/L). On day 22, the mean dosage was 172 ± 137 mg/day (range, 50–400 mg) with a mean plasma topiramate level of 2.7 ± 1.0 mg/L.

Adverse Events

Topiramate was generally well tolerated, even when administered according to a more aggressive dosing schedule usually applied in epileptology. Abrupt discontinuation of topiramate had no withdrawal effects (except for worsening of manic symptoms). As a minor adverse event, 2 patients complained of sedation with 50 mg/day. One was receiving comedication with carbamazepine and experienced a transient plasma carbamazepine level increase (from 8.24 to 10.40 mg/L) before readjusting the carbamazepine dose. The other patient was receiving concomitant valproic acid with no change in plasma levels. An increased frequency of CNS side effects has been observed in epileptology when topiramate is administered as adjunctive therapy with other anticonvulsant agents, even without any change in plasma drug levels.[18]

One patient dropped out on day 10 after developing paranoid and questionable delusional symptoms. His plasma topiramate level was 2.7 mg/L and thus within the range of the other patients. His concomitant lithium level was 0.59 mmol/L and was well tolerated. He had no other concomitant medication at that time. He also had no history of psychotic symptoms. After discontinuing topiramate, psychotic features reversed within a week following treatment with haloperidol. Ethical considerations did not allow a reexposure to topiramate to clarify the causality. However, it appears likely that topiramate at least triggered the psychosis, an adverse event observed with several antiepileptic drugs following rapid dosage increase.[19]

Interestingly, manic patients appear to tolerate higher dosages and more rapid titration of anticonvulsants than nonmanic individuals. Paresthesia in particular was not reported in our sample. The incidence of sedation was comparable to that previously observed in patients with epilepsy. However, the latter effect may, at least in some patients, be considered desirable.

DISCUSSION

This open trial supports previous observations of possible antimanic efficacy of topiramate. The on-off-on design with the rater blinded to the off period provides, in our opinion, even stronger evidence of efficacy than other open trials conducted to date. While the small sample size limits the conclusions that can be drawn from these data, the individual courses and scores and the correlation between antimanic effects and the on and off periods of topiramate appear strong.

Considering the potency of topiramate, it is worth mentioning that 2 patients had a pronounced response at a dosage of 50 mg/day. The study participants cannot be characterized as nonresponders to standard treatments, since they had been receiving their treatment regimen for only 2 to 3 weeks at baseline. However, neither can they be categorized as rapid responders to antimanic drugs.

The mean peak YMRS score after discontinuation was not reached on day 16 (end of the off period), but on day 19, when patients had been taking the drug again for 3 days. This may be explained by the relatively long half-life of topiramate, which probably accounted for activity for some time into the off period, and by the fact that plasma drug levels were still low at day 19 after reintroduction of topiramate. By day 22, when plasma drug levels increased, patients who had previously worsened became responders again.

In retrospect, the strategy of increasing topiramate to high levels in nonresponders may be considered controversial. Although raising the dose seemed to have at least a small effect in 1 patient whose YMRS score declined from 44 to 24, it did not translate into a clinical breakthrough for either of the 2 patients whose doses were increased to 400 mg/day. In vitro work also suggests that the calcium antagonistic effect of topiramate, which may be one of the drug's decisive antimanic mechanisms of action, is most pronounced in a concentration window of approximately 10 μmol/L. Increasing the topiramate dosage to 50 μmol/L can lead to a transient increase in high voltage–gated calcium influx.[21] Thus, it could be hypothesized that increasing topiramate doses to very high levels may, in some patients, worsen the symptoms of mania. However, the effects on calcium fluxes are still discussed controversially, as other groups found no significant effects of topiramate on voltage-gated calcium channels.[22]

With the exception of the patient who developed psychosis and the 2 patients who experienced sedation, topiramate was, both objectively and in the patients' opinions, well tolerated. Drug level interference was not observed with valproic acid, lithium, haloperidol, or perazine. Thus, no dosage corrections of these medications were required during the trial. The plasma clozapine level varied extensively in 1 patient without any change in medication; the reason remains unclear. It does not necessarily suggest a compliance problem, as intraindividual variations have previously been reported to occur spontaneously with clozapine.[23] The patient receiving carbamazepine experienced a transient increase in blood carbamazepine levels (approximately 20%) on day 10 that reversed after adjusting the carbamazepine dosage. This is a characteristic interaction of these drugs, previously documented in patients with epilepsy.

The overall incidence of adverse events appeared low in this sample of manic patients compared with those in previous controlled trials in epileptology. Common events (incidence > 15%) observed in a controlled trial of topiramate monotherapy in recently diagnosed partial epilepsy during rapid titration up to 200 to 500 mg/day included paresthesia (35%), headache (19%), fatigue (18%), somnolence (17%), and weight loss (15%).[20]

Limitations of this trial are clearly its open design, the potential confound of carryover effects, and the relatively small sample size. However, the on-off-on design reduces the risk of confusing the effects of topiramate with those of other medication or with spontaneous remission.

In summary, this trial supports previous observations suggesting antimanic efficacy of topiramate, which appears to be reproducibly linked to the addition of the drug.

Drug names: carbamazepine (Tegretol and others), clozapine (Clozaril and others), digoxin (Lanoxin and others), haloperidol (Haldol and others), lamotrigine (Lamictal), lorazepam (Ativan and others), olanzapine (Zyprexa), oxazepam (Serax and others), oxcarbazepine (Trileptal), topiramate (Topamax), valproic acid (Depakene and others).

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