Topiramate Treatment of Aggression in Female Borderline Personality Disorder Patients: A Double-Blind, Placebo-Controlled Study

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Objective: The goal of this study was to compare the efficacy and safety of topiramate versus placebo in the treatment of aggression in women who meet the criteria for borderline personality disorder.

Method: We conducted a double-blind, placebo-controlled study of topiramate in 29 female subjects (response rate 93.5%) meeting SCID (Structured Clinical Interview for DSM-IV) criteria for borderline personality disorder. The subjects were randomly assigned in a 2:1 ratio to topiramate (N = 21, analysis based on N = 19) or placebo (N = 10). Treatment lasted 8 weeks (November 2003–January 2004). Primary outcome measures were self-reported changes on the anger subscales of the State-Trait Anger Expression Inventory (STAXI).

Results: Significant improvements on 4 subscales of the STAXI (state-anger, trait-anger, anger-out, anger-control) were observed in the topiramate-treated subjects after 8 weeks, in comparison with the placebo group. The difference in improvement in score between the 2 groups for state-anger, trait-anger, and anger-out ranged from 21% to 24%, and the difference for anger-control was –13%. As an exception, a difference of only 8.5% ($p < .2$) was found on the anger-in subscale. Significantly greater weight loss was observed in the topiramate-treated group than in those treated with placebo (difference in weight loss between the 2 groups: 2.3 kg [5.1 lb] [3.2%]; 95% CI = 1.3% to 4.4%, $p < .01$). All patients tolerated topiramate well.

Conclusions: Topiramate appears to be a safe and effective agent in the treatment of anger in women with borderline personality disorder as defined by SCID criteria. Additionally, significant weight loss can be expected.

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Diverse psychiatric disorders, such as borderline personality disorder, are associated with subjective anger and aggressive behavior.[1] About 2% of the adult American population meets the criteria for borderline personality disorder.[2] This is a serious psychiatric disorder that makes extensive demands on mental health resources.[3] Establishing a good, trusting physician-patient relationship with a borderline patient is made more difficult by characteristic interaction disorders[4] and emotional instability, which are in turn superimposed on aggressive and paranoid characteristics.[5,6] The likelihood of aggression is increased by environmental overstimulation, stress, or the presence of problems related to impulsiveness. Treatment for aggression is based on the underlying causes and should generally combine pharmacologic with environmental or psychotherapeutic measures.[7,8]

Most controlled studies of standard psychopharmacologic agents in the treatment of borderline personality disorder have shown that these agents have a broad spectrum of effects that significantly alleviate several symptoms of borderline personality disorder.[6,9–12]

The efficacy of anticonvulsant medications in the treatment of pathologic aggression, with the exception of perhaps valproate and carbamazepine, remains to be established.[11,13–18] Effective topiramate interventions in aggressive patients are also reported.[19,20] Topiramate is an anticonvulsant known to block 1-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate-gated ion channels and sodium channels and positively modulate γ-aminobutyric acid (GABA) receptors.[21] Most published data are derived from case reports, retrospective studies, or reviews.[19,20,22] Our goal was to assess the efficacy and safety of topiramate monotherapy in a placebo-controlled trial for treatment of aggression among female patients with borderline personality disorder.

METHOD

Recruitment of women between the ages of 20 and 35 years who were disturbed by moodiness, distrustfulness,

impulsivity, and painful and difficult relationships was accomplished primarily through advertisements by general practitioners.

Seventy-four women agreed to take part in the study. They were screened over the telephone to assess whether they met DSM-IV criteria for borderline personality disorder. A general medical history was also taken at the time of the first telephone contact.

The women included in the study were those who subjectively perceived that the excessive burdens caused by their life situations had produced feelings of constantly increasing anger. Grounds for exclusion were schizophrenia, major depression, or bipolar disorder, the current use of topiramate or other psychotropic medication, or psychotherapy. Potential subjects were also excluded if they were pregnant (or planning to be or were not using contraception), somatically ill, actively suicidal, or abusing alcohol or drugs.

Subjects were next invited to participate in face-to-face interviews. The possible side effects were fully explained. Written informed consent was obtained. The Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I)[23] and personality disorders (SCID-II)[24] were then carried out for each subject. Subjects were included if they met criteria for borderline personality disorder. They then underwent a physical and laboratory examination.

The study was performed using the German version of the State-Trait Anger Expression Inventory (STAXI)[25] as the primary outcome measure. This is a procedure for measuring anger and the expression of anger (Cronbach alpha for women = 0.75; retest correlation for women 8 weeks later = 0.70–0.76) consisting of 44 items that form 5 subscales:

1. State-anger (S-A): subjective state of anger at time of measurement
2. Trait-anger (T-A): readiness to react with anger (mean score in normal subjects = 18.1, SD = 5.34)
3. Anger-in (AI): tendency to repress anger (mean score in normal subjects = 16.0, SD = 4.04)
4. Anger-out (AO): tendency to direct anger outward (mean score in normal subjects = 13.0, SD = 4.02)
5. Anger-control (AC): tendency to keep anger under control (mean score in normal subjects = 22.4, SD = 5.29)

The scores for S-A and T-A range from 10 to 40, and scores for the other subscales range from 8 to 32.[25]

Thirty-one subjects were eligible to take part in the study on the basis of the above-mentioned criteria. According to a power analysis, 21 patients were required for a topiramate trial.[26] The randomization was carried out confidentially by the clinic administration and arranged so that twice as many test subjects would be treated with the active drug (N = 21) as with a placebo (N = 10). We opted for a 2:1, rather than 1:1, randomization ratio in order to treat as many patients with the active drug as possible.

Subjects received blinded medication daily, which, in the beginning, constituted either 50 mg of topiramate or a matching placebo. Topiramate was titrated to a dose of 250 mg/day in the sixth week and then stayed constant. Tablets were supplied in numbered boxes. Both subjects and clinicians were blinded regarding topiramate/placebo assignment.

The study duration was 8 weeks, from November 2003 to January 2004. Subjects were seen and tested with the STAXI every week. In addition, the presence of side effects was assessed weekly using a nonstructured questionnaire (available from the authors by request). During the course of the trial, the intermediate results were not analyzed. After the eighth week, both groups were tested for the last time and physically examined. Two subjects, who failed to appear 2 to 3 times for the weekly evaluations, dropped out of the study, and their data were not further analyzed. Finally, data from 29 women (response rate 93.5%) were evaluated. The STAXI questionnaire was filled out by the patients both independently and anonymously. Our staff checked the data for completeness. The focus of the study was first revealed after acquisition of all final data for all subjects. The data were twice fed independently into the computer and automatically checked for deviations. One percent of the entries were identified as erroneous and adjusted. The study was concluded according to plan.

Data Analysis

We used the statistical program SPSS, Version 11 (SPSS Inc., Chicago, Ill.). Since the data were arbitrarily distributed, the Mann-Whitney U test was performed for comparison of continuous variables. We employed standard deviations, difference with its 95% confidence intervals (95% CI), and probability (p) for reporting the treatment results.[26]

Source of Funding and Ethical Considerations

The study was planned and conducted in accordance with the Declaration of Helsinki and ethical laws pertaining to the medical professions, and its design was approved by the clinic's "Ethikkomision" (the German equivalent of the Committee on Human Subjects). The study was conducted independently of any institutional influence and was not externally funded.

RESULTS

The women's sociodemographic data at the time of randomization are found in Table 1. Table 2 shows the initial STAXI test results. As can be seen, no essential topiramate versus placebo differences were found. At the beginning of the study, both groups had distinctly increased

Table 1. Basic Sociodemographic Data for Women With Borderline Personality Disorder Being Treated for Aggression

Variable	Topiramate (N = 19)	Placebo (N = 10)
Age, mean, y	25.5	26.6
Weight, mean, kg	71.3	73.4
Living with a partner, N (%)	7 (36.8)	4 (40.0)
Occupation, N (%)		
Laborer	6 (31.6)	3 (30.0)
Professional	8 (42.1)	4 (40.0)
Homemaker	5 (26.3)	3 (30.0)
Treatment history, N (%)		
Psychotherapy	11 (57.9)	6 (60.0)
Pharmacotherapy	13 (68.4)	7 (70.0)
Hospitalized for psychiatric reasons	2 (10.5)	1 (10.0)

Table 2. Mean STAXI Scores at Initial Evaluation for Women With Borderline Personality Disorder Being Treated for Aggression

	Topiramate (N = 19)		Placebo (N = 10)	
Subscale	Mean	SD	Mean	SD
State-anger	31.4	2.5	31.3	2.2
Trait-anger	30.9	2.4	29.0	1.6
Anger-in	23.7	1.3	24.3	1.6
Anger-out	24.2	1.5	23.8	1.8
Anger-control	19.1	1.4	18.7	0.9

Abbreviation: STAXI = State-Trait Anger Expression Inventory.

STAXI scores, indicating the presence of anger-related symptoms.

Table 3 summarizes topiramate versus placebo rates of improvement over the course of the entire study. The topiramate group experienced a significantly greater rate of improvement than the placebo group on all of the STAXI subscales except the AI subscale.

Figures 1 through 5 show the change over time on the STAXI subscales for the topiramate and placebo groups. Topiramate was associated with an initially (first to approximately fourth week of treatment) gradual but later (from approximately the fifth week) a relatively rapid improvement in the following categories: self-reported anger sensation (S-A and T-A, Figures 1–2), 1 type of anger processing (AO, Figure 4), and anger control (AC, Figure 5). Only the change on the AI scale (another type of anger processing) remained continuously moderate (Figure 3).

Additionally, after 8 weeks of treatment, significantly greater weight loss was observed in the topiramate group compared with the placebo group. The mean starting weight for the topiramate group was 71.3 kg (158.4 lb) (SD = 11.6 kg [25.8 lb]), and the mean final weight was 68.7 kg (152.7 lb) (SD = 9.9 kg [22.0 lb]). The mean starting weight for the placebo group was 73.4 kg (163.1 lb) (SD = 10.5 kg [23.3 lb]), and the mean final weight was 73.1 kg (162.4 lb) (SD = 9.7 kg [21.6 lb]). The mean difference in weight loss between the groups was 2.3 kg (5.1 lb) (3.2%; $p < .01$, 95% CI = 1.3% to 4.4%).

Of note, no psychotic symptoms or other serious side effects were observed, nor did subjects in either treatment group engage in self-mutilation or suicidal acts during the study. In isolated cases, fatigue, dizziness, headache, and paresthesia were reported.

DISCUSSION

Both groups were comparable in light of their sociodemographic data. Topiramate treatment resulted in a significantly greater rate of improvement than did placebo on 4 STAXI subscales. Specifically, topiramate was more effective than placebo in treating the aggression component of borderline psychopathology.

Persons with high S-A scores experience relatively intense feelings of anger, and those with high T-A scores experience anger relatively frequently. Whether they suppress their anger or direct it inward can be assessed through the AI, AO, and AC subscales. Because AI and AO are independent of each other, subjects can have high scores on both subscales.[25] Persons with high AC scores expend a lot of energy on directing and controlling their emotions in situations that provoke anger.[25]

Among our patients, topiramate appeared to influence the intensity of their subjective state of anger (S-A) (Table 3, Figure 1) as well as their readiness to react with anger (T-A) (Table 3, Figure 2). Furthermore, the tendency to direct anger outward (AO) (Table 3, Figure 4, cf. also reference 27) decreased significantly. This decrease is important because the socially desirable tendency to control anger (AC) was strengthened (Table 3, Figure 5).

The most common side effects of topiramate are dizziness, fatigue, somnolence, cognitive impairment, paresthesia, reduced appetite, and weight loss.[22] These symptoms are mild to moderate and often occur when topiramate is initiated or the dose is increased.[22]

Our patients tolerated topiramate well or very well. Unincisive, objectionable symptoms were reported only in isolated cases. It is possible that higher starting doses of topiramate or increasing the dosages might have caused broader, more dramatic side effects.[20] Reduced appetite and weight loss were observed and usually seen as beneficial. In the literature, both weight loss and mood stabilization have been attributed to topiramate[19,20,22]; however, the change in weight during this trial was less than that in most other trials.[19,22]

The results of this trial are consistent with those of earlier studies finding that anticonvulsant medications are effective in the treatment of pathologic aggression.[13–18] Teter et al.[19] and Janowsky et al.[20] reported significantly decreased symptoms of aggression with topiramate therapy. The patients' behavior improved dramatically: over the course of 6 weeks of topiramate therapy, with a

Table 3. Mean STAXI Scores for Women With Borderline Personality Disorder After 8 Weeks of Treatment for Aggression (final evaluation)

	Topiramate (N = 19)		Placebo (N = 10)		Change From Baseline				
Subscale	Mean	SD	Mean	SD	Topiramate	Placebo	Difference, %[a]	95% CI	p Value[b]
State-anger	22.5	1.8	29.0	1.6	8.9	2.3	21.0	9.0% to 33.0%	.01
Trait-anger	22.0	2.0	27.6	1.8	8.9	1.4	24.0	0.9% to 8.3%	.05
Anger-in	20.7	4.9	23.3	2.3	3.0	1.0	8.5	–8.0% to 25.0%	.2
Anger-out	17.6	1.8	22.6	1.6	6.6	1.2	23.0	3.0% to 43.0%	.01
Anger-control	20.6	1.0	17.7	0.9	–1.5	1.0	–13.0	–24.0% to –2.0%	.01

[a]Percentage difference between the 2 groups in reduction in score from initial evaluation.
[b]Mann-Whitney U test.
Abbreviation: STAXI = State-Trait Anger Expression Inventory.

Figure 1. State-Trait Anger Expression Inventory: Mean State-Anger Subscale Scores for Women With Borderline Personality Disorder Treated for Aggression

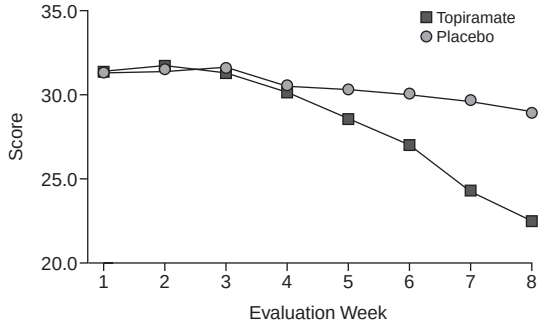


Figure 2. State-Trait Anger Expression Inventory: Mean Trait-Anger Subscale Scores for Women With Borderline Personality Disorder Treated for Aggression

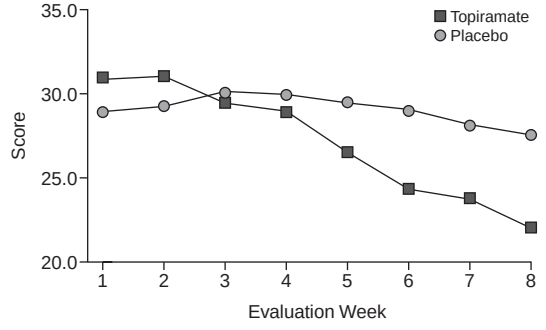


Figure 3. State-Trait Anger Expression Inventory: Mean Anger-In Subscale Scores for Women With Borderline Personality Disorder Treated for Aggression

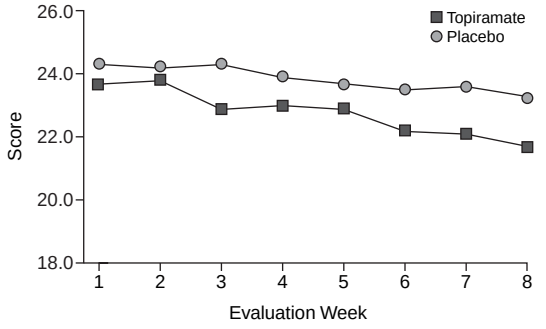
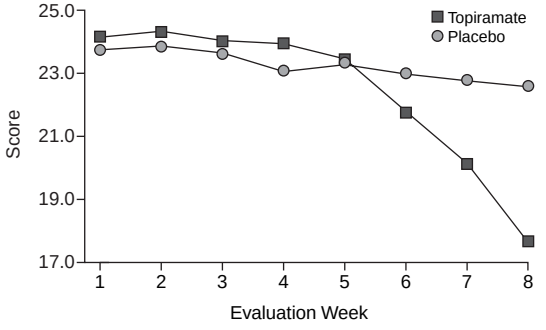


Figure 4. State-Trait Anger Expression Inventory: Mean Anger-Out Subscale Scores for Women With Borderline Personality Disorder Treated for Aggression

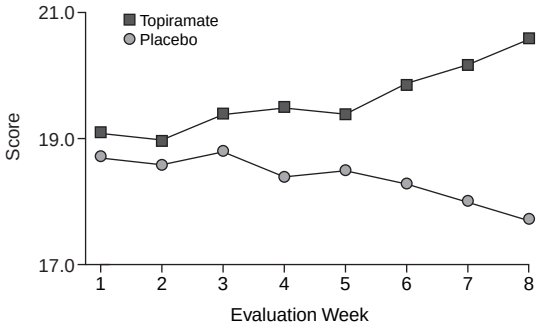


dosage of at least 200 mg/day, there were no aggressive outbursts.[19] This outcome is consistent with our experiences. However, the results of our study have broader implications than the Teter et al. and Janowsky et al. findings because we tested topiramate against a placebo. Altogether, the results from our trial suggest that topiramate may be efficacious in reducing aggression in borderline patients. This concurs with the conclusions from other studies.[19,20,22,28,29]

Methodological Limitations and Directions for Further Research

This study had several methodological limitations. First, the sample size was (in spite of a valid power analysis) relatively small. Second, the sample consisted only of women with borderline personality disorder. Whether these results could also be replicated with men meeting the criteria for borderline personality disorder is unknown. Third, the sample was composed of moderately ill

Figure 5. State-Trait Anger Expression Inventory: Mean Anger-Control Subscale Scores for Women With Borderline Personality Disorder Treated for Aggression



outpatients who were not suffering from a concurrent major depressive episode and were not abusing substances or taking concurrent medications. Fourth, the length of this trial was only 2 months, which reduced the dropout rate (cf. also reference 30), particularly in the placebo group. In a 6-month study with olanzapine, Zanarini and Frankenburg[6] had a distinctly higher dropout rate.

Additional research is needed to see if these results can be replicated and how long-lasting the benefits are. Studies that contain male borderline personality disorder patients and borderline personality disorder patients with more severe morbidity and/or comorbid psychiatric disorders are also needed.

Conclusions

Topiramate appears to be a safe and effective agent in the treatment of anger and aggressive behavior in women with borderline personality disorder. As a side effect, weight loss can be expected.

Drug names: carbamazepine (Carbatrol, Tegretol, and others), olanzapine (Zyprexa), topiramate (Topamax).

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