An Open Trial of Topiramate in the Treatment of Generalized Social Phobia

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Background: Selective serotonin reuptake inhibitors (SSRIs) are the current gold standard in the pharmacologic treatment of generalized social phobia. SSRIs are only effective in approximately 50% of individuals with generalized social phobia and can be associated with significant side effects. Based on the successful use of the anticonvulsants gabapentin and pregabalin in treating generalized social phobia, we conducted an open trial examining the efficacy of the glutamatergic and GABAergic anticonvulsant topiramate in the treatment of generalized social phobia.

Method: Twenty-three adult outpatients with DSM-IV social phobia, generalized type, were entered into a 16-week open trial of topiramate, starting at 25 mg/day, and gradually titrated up to a maximum dose of 400 mg/day.

Results: Twelve of 23 patients completed the trial. In the intent-to-treat (ITT) analysis, 11 (47.8%) of 23 were responders by a Clinical Global Impressions Improvement (CGI-I) scale rating of "much" or "very much" improved. The mean drop in the Liebowitz Social Anxiety Scale (LSAS) score for the ITT group was 29.4%. The change in LSAS score from baseline to endpoint was significant for the ITT group ($F = 3.44$, $df = 4,110$; $p = .01$). In the completers group, 9 (75.0%) of 12 were responders by CGI-I at 16 weeks, with a mean drop in LSAS score of 45.1%. The rate of remission in the ITT sample, using a definition of an LSAS score of ≤ 30, gave a remission rate of 26.1% (6/23).

Conclusion: This study suggests that topiramate may be effective in the treatment of generalized social phobia. These results also suggest the possibility that the neurotransmitters glutamate and GABA may be involved in the neurobiology of generalized social phobia.

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Pharmacologic treatments for generalized social phobia have been evolving rapidly. A variety of drug groups have been shown to be effective in the treatment of generalized social phobia, including monoamine oxidase inhibitors (MAOIs),[1–3] reversible MAOIs,[4–7] benzodiazepines,[8,9] selective serotonin reuptake inhibitors (SSRIs),[10–18] and, most recently, the anticonvulsants gabapentin[19] and pregabalin.[20] SSRIs are the current gold standard in the pharmacologic treatment of generalized social phobia. Despite such widespread use, SSRIs are only effective in approximately 50% of individuals with generalized social phobia and can be associated with significant side effects including sexual dysfunction, weight gain, insomnia, and psychomotor agitation.[10–18] There is clearly a clinical need for other pharmacologic agents for individuals with generalized social phobia who are nonresponsive to or who cannot tolerate SSRIs.

Topiramate is an anticonvulsant that has a chemically novel structure.[21] It has been used off-label, in clinical practice as an augmenting agent, and as an alternative mood stabilizer in treating bipolar disorder, refractory depression, and, recently, binge-eating disorder.[22–24] Topiramate appears to have several mechanisms of action. It

has been shown to enhance the activity of γ-aminobutyric acid (GABA-A) at nonbenzodiazepine sites and inhibit glutamate via alpha AMP/kainite subreceptors, and it appears to block voltage-gated sodium channels.[21,22,25] Topiramate is also a weak inhibitor of the carbonic anhydrase isoenzymes CAII and CAIV.[21,22,25] Based on the effectiveness of anticonvulsants in treating generalized social phobia, coupled with the use of topiramate in other psychiatric conditions, an open trial of topiramate was conducted to investigate its efficacy in the treatment of generalized social phobia.

METHOD

Twenty-three patients meeting DSM-IV criteria for social phobia, generalized type, entered an open-label trial of topiramate in the treatment of social phobia. Patients had been referred for treatment to a university-affiliated Anxiety Disorders Clinic in Hamilton, Canada, or were recruited through community advertisements over a 16-month period. All patients were evaluated using the Structured Clinical Interview for DSM-IV–Patient Edition[26] to determine Axis I diagnoses (with the exception of attention-deficit/hyperactivity disorder, which was made by clinical diagnosis). All patients gave informed consent. This study was approved by the Hamilton Health Sciences/McMaster University Research Ethics Board, and data were collected between September 2001 and October 2003.

Patients aged 18 to 65 years entered the trial if they had a primary diagnosis of social phobia, generalized type; that is, social phobia was causing the most disability to the patient. In addition, patients with generalized social phobia could be included in this study if they had comorbid anxiety disorders, major depressive disorder, and attention-deficit/hyperactivity disorder. Individuals with comorbid major depressive disorder were allowed into the study providing that they had a Montgomery-Asberg Depression Rating Scale (MADRS)[27] score of ≤ 19 and that the onset of their generalized social phobia predated the onset of depression by 5 or more years. Patients were free of antidepressant medications for at least 2 weeks prior to starting the trial and were excluded from the trial if they were taking any medications felt to be effective in the treatment of social phobia (any psychotropic agent including anticonvulsants) or were involved in any form of psychotherapy.

Topiramate was initially started at 25 mg/day. The dose was increased by 25 mg after the first week, then increased by 50-mg increments for the following week, up to 100 mg/day at the end of week 3. The dose was titrated upward until a clinical response was achieved. At the end of week 5, the topiramate dose could be further increased by 100 mg/day each week up to a maximum dose of 400 mg/day (given in 2 divided doses) at week 9.

All patients completed self-report measures at baseline and weeks 4, 8, 12, and 16, including the Beck Depression Inventory (BDI),[28] the Beck Anxiety Inventory (BAI),[29] the Social Phobia Inventory,[30] the Social Phobia Scale,[31] the Social Interaction Anxiety Scale,[31] and the Sheehan Disability Scale.[32] At each study visit, adverse events were elicited through the use of open-ended questions. Patients were also screened at baseline for severity of depressive symptoms with the MADRS. To measure change in depressive symptoms over the course of the study baseline and endpoint, MADRS measures were compared.

Primary efficacy measures were defined as the number of responders with a Clinical Global Impressions-Improvement (CGI-I)[33] scale score of 1 or 2 (very much or much improved) at week 16 and the change from baseline to endpoint in the Liebowitz Social Anxiety Scale (LSAS).[34] Remission was also assessed using 2 definitions, endpoint LSAS score of ≤ 30 and a CGI-I score of 1.

All patients who took at least 1 dose of study treatment were included in the endpoint analysis. All analyses were based on an intent-to-treat (ITT) sample, using the last-observation-carried-forward (LOCF) method. Repeated measures of analysis of variance (ANOVA) were used to compare baseline measures with outcome measures at weeks 4, 8, 12, and 16, except for the MADRS. This latter outcome measure was assessed only at baseline and week 16, and thus a t test was used.

RESULTS

The sample included 12 men and 11 women who had a mean ± SD age of 37.1 ± 10.9 years, a mean age at onset of 11.4 ± 4.6 years, and a mean duration of illness of 24.9 ± 13.0 years. Patient demographics are listed in Table 1. Nine of the 23 patients had previous treatment for generalized social phobia. Of those 9 patients who had previous treatments, 5 discontinued them due to lack of efficacy and 4 due to intolerable side effects. At baseline, the mean CGI-Severity of Illness (CGI-S) scale score was 5.3 ± 0.6 and the mean LSAS score was 82.2 ± 18.7, suggesting that most patients were "markedly ill." Concurrent diagnoses are shown in Table 2.

Twelve (52.2%) of 23 patients who entered the 16-week trial completed the trial, with 11 discontinuations; 5 due to adverse events, 2 due to lack of efficacy, 1 due to the patient's scheduling conflicts, 1 lost to follow-up, and 2 due to the reoccurrence of depressive symptoms. In the ITT analysis, 11(47.8%) of 23 were responders by CGI-I. In a post hoc analysis using a more rigorous response criteria of an LSAS score drop of ≥ 50%, 26.1% (6/23) would be considered responders. Of the patients who discontinued the study, 2 were considered responders with a CGI-I score of 2 at weeks 10 and 14, respectively. Three (27.3%) of the 11 patients with comorbidity (2 with

Table 1. Patient Demographics and Baseline Clinical Characteristics (N = 23)

Characteristic	Mean	SD (range)
Age, y	37.1	10.9 (21–58)
Age at onset, y	11.4	4.6 (6–22)
Duration of social phobia, y	24.9	13.0 (8–50)
	N	%
Gender		
Male	12	52.2
Female	11	47.8
Marital status		
Married/common law	10	43.5
Single (never married)	11	47.8
Divorced/separated	2	8.7
Employment status		
Work full-time	18	78.3
Student full-time	4	17.4
Unemployed	1	4.3

Table 2. Concurrent Diagnoses in 23 Patients With DSM-IV Social Phobia, Generalized Type[a]

Diagnosis	N	%
Major depressive disorder	1	4.3
Dysthymia	2	8.7
Bipolar disorder	1	4.3
Panic disorder with agoraphobia	3	13.0
Generalized anxiety disorder	3	13.0
Obsessive-compulsive disorder	4	17.4
Specific phobia	2	8.7
Alcohol abuse/dependence	0	0
Substance abuse/dependence	0	0
Impulse control disorder NOS	3	13.0
Attention-deficit/hyperactivity disorder	1	4.3

[a]Eleven patients had at least 1 comorbid diagnosis.
Abbreviation: NOS = not otherwise specified.

comorbid obsessive-compulsive disorder [OCD] and 1 with comorbid specific phobia) were considered responders based on the CGI-I response criteria, compared with 8 (66.7%) of 12 patients without comorbidity ($\chi^2 = 3.57$, $p = .059$). The mean percent drop in LSAS score for the ITT group was 29.4% (mean LSAS score drop of 23.8 ± 28.6 points). A significant difference was found between the mean LSAS score from baseline to endpoint in the ITT analysis ($F = 3.44$, $df = 4,110$; $p = .01$).

Of the completers, 9 (75.0%) of 12 were considered responders with a CGI-I score of 1 or 2 at 16 weeks and a mean percent drop in LSAS score of 45.1% (mean LSAS score drop of 38.8 ± 27.6 points).

The rate of remission for the ITT sample, using a definition of CGI-I equal to 1, was 34.8% (8/23). Defining remission using a score on the LSAS of ≤ 30 gave a remission rate of 26.1% (6/23). Repeated measures of ANOVA revealed a significant difference for a self-report measure of social anxiety, the Social Phobia Inventory, but not for the Social Phobia Scale, the Social Interaction Scale, or measures of generalized anxiety and depressive symptoms (Table 3). The mean time for responders to achieve a CGI-I score of 1 or 2 was 8.6 ± 2.9 weeks. The mean dose of topiramate at endpoint was 222.8 ± 141.8 mg/day, with a dose range of 25 to 400 mg/day.

All 23 patients in this trial experienced adverse events; however, only 5 individuals withdrew from the study because of them (2 due to cognitive impairment, 2 due to recurrence of depressive episode, and 1 due to paresthesia). Of the 11 patients with a comorbid psychiatric condition, 6 (54.5%) did not complete the trial, while 5 (41.7%) of the 12 patients without comorbidity did not complete the trial ($\chi^2 = 0.381$, $p = .537$).

Most commonly reported adverse events reported in greater than 10% of patients (Table 4) included weight loss (100%), paresthesias (73.9%), headache (52.2%), cognitive impairment (43.5%), anorexia (43.5%), gastrointestinal upset (39.1%), tiredness (34.8%), lightheadedness (21.7%), agitation (21.7%), and metallic taste (21.7%). Of those who completed the study, the mean weight loss was 3.9 ± 2.9 kg, with a range from 0.9 to 10.2 kg.

DISCUSSION

This study adds further support to the use of anticonvulsants in social phobia. Previous data have shown that both gabapentin[20] and pregabalin[21] have demonstrated efficacy in treating social phobia in placebo-controlled trials, while there is also some preliminary evidence for the use of valproate[35] in the treatment of generalized social phobia.

This open-trial sample had a rate of comorbidity of 47.8%. Although this high rate of comorbidity is not typically found in published clinical trials, it does represent typical treatment-seeking individuals[36] and is consistent with rates of comorbidity found in epidemiologic samples of individuals with social phobia.[37,38] However, after comparing response rates based on comorbidity status, we found a trend toward significantly more responders in the noncomorbid social phobic group. Furthermore, the measures of depression by BDI and generalized anxiety by BAI did not show a significant change. In spite of our inclusion of comorbidity in the sample, there is a suggestion that the potential effect of topiramate may be specific to social anxiety symptoms.

Although some of the study participants were unable to continue with treatment due to adverse events or lack of efficacy, a moderate rate of response was found in the ITT analysis. In a post hoc analysis using a criterion for remission of an LSAS score of ≤ 30, we found 26.1% of the ITT sample met this definition. This compares with other rates of remission found in recently published controlled trials of venlafaxine[39] and paroxetine[40] in generalized social phobia. In our current study, a broad range of responses to topiramate in generalized social phobia

Table 3. Mean Scores in ITT Group for Clinical and Psychometric Measures in 23 Patients With Social Phobia During Topiramate Treatment

	Week 0		Week 4		Week 8		Week 12		Week 16				
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p Value
Liebowitz Social Anxiety Scale	82.2	18.7	77.5	23.4	68.4	27.4	59.8	30.3	58.6	33.3	3.44	4,110	.01*
Social Phobia Inventory	58.8	11.1	53.6	11.5	50.2	12.9	47.7	13.9	47.4	14.9	3.10	4,110	.02*
Social Phobia Scale	33.6	14.7	27.6	15.5	25.9	15.4	22.0	15.1	22.5	15.3	2.17	4,110	.08
Social Interaction Anxiety Scale	43.7	11.9	40.8	14.3	37.1	14.3	34.8	14.5	33.6	14.8	2.05	4,110	.09
Beck Anxiety Inventory	34.0	6.9	31.7	7.6	29.0	5.9	30.4	8.6	30.9	8.8	1.36	4,110	.25
Beck Depression Inventory	10.3	5.9	8.1	7.3	7.9	7.0	8.3	8.9	7.5	9.4	0.44	4,110	.77
Montgomery-Asberg Depression Rating Scale	7.8	5.9	…	…	…	…	…	…	6.1	6.0	2.07[a]	22	.21
Sheehan Disability Scale													
Work	4.1	3.1	4.4	2.3	3.7	2.9	4.0	3.0	3.5	2.8	0.37	4,110	.83
Social	6.5	3.0	6.0	2.3	5.4	2.6	5.3	2.5	4.7	3.1	1.43	4,110	.22
Family	3.4	2.8	3.0	2.6	2.9	2.1	2.9	2.6	2.6	2.8	0.24	4,110	.91
Clinical Global Impressions scale													
Severity of Illness	5.3	0.6	5.3	0.1	4.7	1.0	4.3	1.4	4.1	1.5	4.64	9,220	< .001*
Improvement	…	…	3.7	0.4	3.0	1.0	2.7	1.3	2.5	1.3	5.11	7,176	< .001*

[a]t Test.
*Statistically significant based on $p < .05$.
Abbreviation: ITT = intent-to-treat. Symbol: … = scale not administered.

Table 4. Adverse Events Reported in ≥ 10% of Patients During Topiramate Treatment

Reported Adverse Event	N	%
Weight loss	23	100.0
Paresthesias	17	73.9
Headache	12	52.2
Cognitive impairment	10	43.5
Anorexia	10	43.5
Gastrointestinal upset	9	39.1
Tiredness	8	34.8
Light-headedness	5	21.7
Agitation	5	21.7
Metallic taste	5	21.7

was found; however, there seems to be a subgroup of individuals who can have a substantial response to the point of remission. This may then suggest that topiramate could be a useful treatment alternative for those who do not respond to or who cannot tolerate an SSRI. More likely, given these preliminary results, topiramate may be best utilized as an augmentation agent in treatment-resistant populations, which should be an area for future investigation.

A potential drawback to using topiramate may be related to the high rate of adverse events reported by individuals in this study. All study participants reported at least 1 adverse event; however, only 21.7% (5/23) discontinued treatment because of them. Furthermore, many patients found the adverse events tolerable or even beneficial, such as in the case of weight loss experienced by all study participants.

The design of this study has several intrinsic limitations. First, its open-label design allows for potential rater bias. Second, the lack of a control group allows for the influence of placebo response, which has been noted to occur in controlled studies of social phobia. Third, we allowed individuals with comorbidity to enter the study. The potential improvement seen in social phobic patients may have been at least partly accounted for by improvements in the comorbid conditions.

The results of this study fuel speculation about the mechanism of action of topiramate and its therapeutic response in generalized social phobia. The glutamatergic properties of topiramate may be particularly interesting in social phobia, given the finding of potential glutamatergic involvement in other anxiety disorders. Recent neuroimaging and animal research suggests that glutamatergic abnormalities may have some etiologic significance in anxiety disorders. Rosenberg and colleagues[41] found significantly higher concentrations of glutamate in the caudate of pediatric OCD patients compared with a control group. Results from that study[41] also indicate that improvement of OCD symptoms with pharmacotherapy was associated with a decrease in these caudate glutamatergic concentrations. It has been hypothesized that a glutamatergic abnormality in social anxiety may be a key component in the dysfunctional neurocircuitry. Increased levels of glucocorticoids in response to stress are thought to stimulate the release of hippocampal glutamate. This action may inhibit neurogenesis. Furthermore, a treatment that modifies glutamatergic neurotransmission might prevent the inhibition of neurogenesis.[42] A recently developed glutamatergic agent has demonstrated anxiolytic properties in animal models, and future research in human pathological anxiety with similar agents may further elucidate the role of glutamate in anxiety disorders.[43,44]

This open-trial of topiramate in generalized social phobia may be the first evidence that the manipulation of glutamatergic neurotransmission can lead to reductions in social anxiety, targeting the above-mentioned neurobiological mechanism. Further validation with a placebo-

controlled trial of topiramate in generalized social phobia is warranted to substantiate these preliminary findings.

Drug names: gabapentin (Neurontin and others), paroxetine (Paxil and others), topiramate (Topamax), venlafaxine (Effexor).

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