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Topiramate in Treatment of Tourette Syndrome

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Abstract

Objectives: To describe the efficacy and safety of topiramate in the treatment of Tourette syndrome (TS).

Methods: Charts of subjects whose conditions were diagnosed as tic disorders seen at our clinic from 2003 to 2007 were retrospectively reviewed. Patients who met diagnostic criteria for TS and were started on topiramate at our clinic with at least 1 follow-up visit after beginning topiramate were included. The efficacy of topiramate on a subjective scale, the global impression of response (0 = no response/worse, 1 = mild improvement, 2 = moderate improvement, 3 = marked improvement), and adverse effects were recorded for analysis.

Results: Of 453 subjects, 367 met diagnostic criteria for TS and 41 (11.1%; 34 males) were treated with topiramate for tics for 9.43 ± 7.03 months (range, 1–27 months). Mean age at onset of tics was 6.93 ± 2.78 years (range, 2–14 years) and at start of topiramate treatment was 14.83 ± 5.63 years (range, 9–27 years). The average efficacy on tics was 2.15 ± 1.11, and 75.6% (n = 31) of subjects had moderate to marked improvement and adverse effects included cognitive/language problems (24.4%, n = 10) and aggression or mood swings (9.8%, n = 4).

Conclusions: This retrospective chart review suggests that topiramate can be used for tics in TS with at least moderate efficacy and typical adverse effects. Randomized controlled trials are needed.

Keywords

topiramate; Tourette syndrome; tics

Tourette syndrome (TS) is a neurodevelopmental disorder defined by motor and phonic tics and frequent association with psychiatric comorbidities.[1,2] Tics usually start in childhood and have a waxing and waning course. They may cause varying degrees of difficulty with academic or psychosocial functioning but often improve significantly or resolve by adulthood.[2] Dopamine receptor blocking drugs (DRBDs) remain the mainstay of tic therapy

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but have potentially treatment-limiting adverse effects such as dystonic reactions, sedation, weight gain, and tardive dyskinesia.[3] Non-DRBD medications often offer insufficient control of symptoms, such that additional and safer therapies are needed, especially for adults in whom the risk for tardive dyskinesia is greatest. Case reports have described positive effects of the antiepileptic medication topiramate on tics in TS,[4] and we have since treated TS patients in an open-label fashion with this medication. Here, we describe our open-label experience with 41 TS patients treated with topiramate and postulate on the possible mechanisms of benefit.

MATERIALS AND METHODS

A retrospective chart review of patients whose conditions were diagnosed as tic disorders at an academic Movement Disorders Clinic from 2003 to 2007 was conducted. Subjects were included for analysis if they met diagnostic criteria for TS,[5] were started on topiramate for their tics at our clinic, and had at least 1 follow-up visit. The basic demographic characteristics of subjects treated and not treated with topiramate (age of tic onset, sex, weight before and at last visit on treatment, comorbidities, and family histories) were recorded and compared. The reasons for topiramate treatment were categorized into groups: prior therapeutic failure, intolerable adverse effects from prior medications, or first time treatment of tics. Previous medications used for tics and concurrent medications used for TS or comorbidities were documented. Response to topiramate treatment was assigned according to a global impression of response scaled from 0 to 3, where 0 = no response or worsening of tics, 1 = mild improvement of tics, 2 = moderate improve-mentof tics, and 3 = marked improvement of tics. Each score was a composite assessment derived from patient, parent, and caregiver input and physician documentation through all clinic follow-up visits on this medication. We made the best attempt to determine the response specifically to topiramate. Adverse effects of topiramate treatment were recorded and classified according to whether a dose reduction or discontinuation was required. All data were deidentified before entry into a database for analysis. Between-group comparisons were made using Student *t* test with significance based on $\alpha < 0.05$.

RESULTS

Of 453 charts reviewed, 367 patients met criteria for TS, and 41 total patients (34 males) met all inclusion criteria. The average age at onset of tics was 6.93 ± 2.78 years (range, 2–14 years). Basic demographic characteristics between groups treated with and without topiramate showed no statistically significant differences on several measures (Table 1).

The treatment effects of topiramate are described in Table 2. Mean age at onset of treatment was 14.83 ± 5.63 years (range, 9–27 years) during a mean follow-up period of 9.44 ± 7.03 months (range, 1–27 months). Indications for topiramate treatment included prior therapeutic failure (n = 28, 68.3%) or adverse effects (n = 8, 19.5%) or de novo tics (n = 10, 24.4%). Topiramate was used as a monotherapy in 51.2% of patients (n = 21) or was added to DRBDs in 26.8% of patients (n = 11), clonidine or guanfacine in 14.6% of patients (n = 6), tetra-benazine in 7.3% of patients (n = 3), or botulinum toxin in 7.3% of patients (n = 3). All adverse effects resolved with dosage reduction or discontinuation of topiramate. The

mean dose in those with and without adverse effects was similar (123.75 ± 86.02 and 167.86 ± 133.50 mg/d, respectively, $P = 0.21$). Mean body weight before and at last visit on treatment did not change (138.55 + 66.67 and 139.03 + 66.21 lb, respectively, $P = 0.97$).

DISCUSSION

This study suggests that topiramate can be an effective alternate tic treatment. Common first-line therapies include α_2-adrenergic agonists such as clonidine or guanfacine, but patients with multiple, frequent, and/or complex tics are best treated with DRBDs. Haloperidol and pimozide are approved in the United States for TS; however, haloperidol is poorly tolerated with high rates of treatment-limiting adverse effects and discontinuation.[3,6] Pimozide can cause QT prolongation necessitating electrocardiogram monitoring. Other DRBDs including fluphenazine, olanzapine, risperidone, and aripiprazole have been reported useful in TS but have potential adverse effects of weight gain, dystonic reactions, tardive dyskinesia, and neuroleptic malignant syndrome.[3] Tetrabenazine, a dopamine-depleting agent, is reported to be effective but is also associated with drug induced parkinsonism and depression.[7] Botulinum toxin and deep-brain stimulation are used in severe cases.[8,9] Alternative safe and effective medications are therefore needed for the treatment of tics.

Tourette syndrome is postulated to be a neurodevelopmental disorder involving multiple neurotransmitter systems within cortical–basal ganglia–thalamocortical loops.[2,10,11] Striatal medium spiny neurons receive glutamatergic input from the cerebral cortex and dopaminergic input from the substantia nigra, whereas their output is mainly through GABAergic inhibition to the thalamus in either direct or indirect pathways.[11] Tics likely result from reduced inhibition of thalamocortical circuits, which could be a function of aberrant activation of striatal matrisomes[10] or aberrant motor patterns in the globus pallidus interna.[12] Dopamine receptor blocking drugs generally suppress the direct pathway leading to greater inhibition of thalamic outflow, whereas topiramate may normalize firing patterns within the striatum, globus pallidus interna, or other basal ganglia structures by balancing GABAergic and glutama-tergic transmission.[13] Topiramate has previously been used safely and effectively in the pediatric population.[14,15]

In our open-label experience, topiramate was felt to be at least moderately effective in treating tics in three-fourths of patients. Adverse effects occurred in about half, but most were tolerable and/or reversible, in keeping with other topiramate studies.[14,15] Of note, weight loss was not seen in our patients despite relatively higher dosages used.[15]

This study is limited by its retrospective, open-label design and use of subjective ratings. However, it provides preliminary evidence that topiramate can be a safe and potentially effective medication to treat tics in TS as either monotherapy or adjunct therapy. Randomized, blinded, placebo-controlled trials of topiramate in TS are warranted to confirm its use as an alternate, DRBD-sparing therapy for tics.

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TABLE 1.

Basic Demographics Characteristics of Patients With or Without Topiramate Therapy

	Topiramate Therapy	No Topiramate Therapy	*P*
n	41	313	
Male sex	82.9%	79.5%	0.59
Age at onset of tics, yr	6.93 ± 2.78	6.96 ± 3.49	0.94
ADHD	58.5%	63.4%	0.55
OCB	65.9%	55.1%	0.19
Mood disorders	9.8%	6.7%	0.54
Family history of tics	34.2%	42.2%	0.32

ADHD indicates attention-deficit/hyperactivity disorder; OCB, obsessive-compulsive behaviors.

TABLE 2.

Treatment Effects of Topiramate in 41 Patients With TS

	n	Percentage/Value
Mean stable dose of therapy	41	146.34 ± 113.68 mg/d (range, 50–600 mg/d)
Mean GIR	41	2.15 ± 1.11
Patients with moderate to marked tic improvement (GIR, 2–3) Adverse effects of topiramate	31	75.6%
Adverse effects of topiramate		
Cognitive and language problems	10	24.4%
Aggression or mood swings	4	9.8%
Paresthesia	3	7.3%
Nausea	2	4.9%
Sweating problems	2	4.9%
Decreased appetite	1	2.4%
Discontinuation of topiramate therapy	10	
Lack of clinical response	3	7.3%
Intolerable adverse effects	7	17.1%
Cognitive or language problems	5	12.2%

GIR indicates global impression of response.