Topiramate in Treatment of Tourette Syndrome

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BACKGROUND

- Tourette syndrome (TS) is a neuro-developmental disorder defined by multiple motor and phonic tics with a waxing and waning clinical course, and is often associated with psychiatric co-morbidities such as attention deficit hyperactivity disorders (ADHD), obsessive compulsive behavirs (OCB), and mood problems
- Dopamine receptor blocking drugs (DRBDs) remain the mainstay of therapy but carry the risk of significant potential side effects such as acute dystonic reactions, sedation, weight gain, and tardive dyskinesia.
- Topiramate is an anti-epileptic drug with several proposed mechanisms of action. [1]
- Case reports have described a positive effect of topiramate on tics in TS.[2]
- We have actively treated TS patients in an open-label fashion with topiramate to reduce tics.
- Here, we seek to describe our experience (via retrospective analysis) with 41 TS patients treated with topiramate as either montherapy or adjunctive therapy for tics.

METHODS

- Retrospective chart review of patients diagnosed with tic disorders at the Parkinson's Disease Center and Movement Disorders Clinic at Baylor College of Medicine from 2003 to 2007.
- Inclusion criteria:
  1) Diagnosis of TS according to the Tourette's Syndrome Study Group criteria. [3]
  2) Patients were started on topiramate for tics at our clinic
  3) At least one follow-up visit after starting topiramate.
- Basic demographics recorded and compared: age of tic onset, gender, weight (before and after treatment), cormorbidities, and family histories.
- The reasons for topiramate treatment were categorized into three groups:
  1) prior therapeutic failure
  2) intolerable side effects with prior medications for tics
  3) first time treatment for tics.
- Previous medications used for tics and concurrent medications along with topiramate for TS were documented.
- Response to topiramate treatment was assigned according to a global impression of response scaled from 0 to 3, derived from composite assessment by patients, parents, and caregivers, according to the physician's documentation
  0 = no response or worsening of tics
  1 = mild improvement of tics
  2 = moderate improvement of tics
  3 = marked improvement of tics.
- Side effects of topiramate treatment were recorded and classified according to whether a dose reduction or discontinuation was required.
- Data were entered into a database for analysis. Between-group comparisons were made using Student t-test and significance was based on $\alpha < 0.05$.

RESULTS

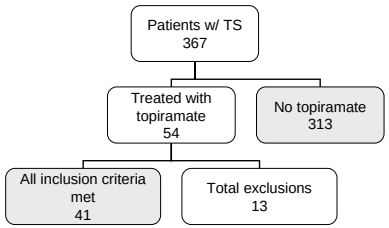

Table 1. Characteristics of patients with TS

	Topiramate therapy	*No topiramate therapy*	*P*
N	41	313	--
Male gender	82.9%	79.5%	0.59
Age @ tic onset	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 hx of tics	34.2%	42.2%	0.32

ADHD = attention deficit hyperactivity disorder; OCB = obsessive compulsive behaviors

Table 2. Treatment of tics with topiramate (N=41)

	N	Percentage/Value
Mean age at onset of treatment (years)	41	14.83±5.63 (range 9-27)
Indications for topiramate therapy		
Prior therapeutic failure	28	68.3%
Prior therapy side effects	8	19.5%
De novo tics	10	24.4%
Duration of topiramate therapy (months)		9.44±7.03 (range 1-27)
Mean stable dose of therapy (mg/day)		146.34 ± 113.68 (range 50-600)
Topiramate is used as		
Monotherapy	21	51.2%
Adjunctive to DRBD	11	26.8%
Adjunctive to clonidine or guafacine	6	14.6%
Adjunctive to tetrabenazine	3	7.3%
Adjunctive to botulinum toxin	3	7.3%
Global impression of response		
Average response		2.15 ± 1.11
Patients with GIR ≥ 2	31	75.6%

Table 3. Side effects of topiramate in TS patients

	N	Percentage/Value
Side effects of topiramate		
Cognitive/language problems	10	24.4%
Aggression and mood swing	4	9.8%
Paresthesia	3	7.3%
Nausea	2	4.9%
Sweating problems	2	4.9%
Decreased appetite	1	2.4%
Reasons for discontinuation		
Lack of clinical response	3	7.3%
Intolerable side effects	7	17.1%
Cognitive/language problems	5	12.2%
Mean body weight		
Before topiramate therapy		66.67 lbs
Last visit on topiramate		66.21 lbs

CONCLUSIONS

- Striatal medium spiny neurons receive glutamatergic input from the cerebral cortex and dopaminergic input from the substantia nigra
  - Striatal output is mainly through GABAergic inhibition to the thalamus by either direct or indirect pathways.[4]
- Tics likely result from reduced inhibition of thalamo-cortical circuits that may be due to increased inhibition of the direct pathway (striatum to globus pallidus interna (GPi)) and decreased activity of the indirect pathway (connecting striatum and subthalamic nucleus). These alterataions could be due to
  - Aberrant activation of striatal matrisomes [5]
  - Aberrant motor patterns in GPi [6]
- Topiramate increases GABAergic transmission, reduces glutamatergic transmission, and inhibits carbonic anhydrase
  - Effect on tics may be from normalizing firing patterns within striatum, GPi, or other basal ganglia structures comprising the direct and indirect pathway. [1]
- Our open-label experience suggests that topiramate is effective in the treatment of tics, with 75% of patients experiencing at least moderate benefit on a subjective scale
  - In this study, patients were treated for an average of 9 months
  - Average dose of 146mg/day (range 50-600mg)
- Topiramate may represent an alternate, or DRBD-sparing therapy for tics in TS
  - May be safely used as monotherapy or as adjunctive therapy to other, more conventional agents.
- The side effect profile of topiramate is less severe than those commonly associated with DRBDs (e.g., weight gain, tardive dyskinesia, dystonic reactions), and are reversible
  - Side effects reported in this group of patients are consistent with those seen in populations treated with topiramate for other disorders (e.g., migraine, epilepsy)
  - Treatment with topiramate for tics did not result in weight changes in this study.
- To our knowledge, this is largest reported series of patients with TS treated with topiramate for tics.
- Further randomized, controlled trials of topiramate in the treatment of TS are warranted.

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