Six-week Open-label Trial of Topiramate to Treat Disruptive Behaviors in Children and Adolescents with or without Mental Retardation

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Abstract

Objective: Anticonvulsants are known to be effective to manage affective instability and aggressive behavior by reducing neuronal excitability. This study examined the efficacy and safety of topiramate, a novel anticonvulsant, on disruptive behavioral problems in children and adolescents, with or without mental retardation (MR), and the differences of short-term efficacy and safety according to the IQ levels. **Methods and Materials:** Fifty-four children and adolescents with disruptive behavioral problems were enrolled in a 6-week, open-label study. All subjects were divided into 3 groups (subjects without MR, Non-MR; subjects with mild MR, Mild MR; and subjects with moderate to severe MR, Mod-Severe MR) based on their intellectual ability, and treated with topiramate. Outcome measures included the Aberrant Behavior Checklist Hyperactivity (ABC-H) and Irritability (ABC-I) subscales and the Clinical Global Impression Severity (CGI-S) scale. **Results:** Significant reduction of CGI-S, ABC-H, and ABC-I scores were noted in all three groups in the following order: Non-MR, Mild MR, and Mod-Severe MR. Parethesia, anorexia, somnolence, nocturnal enuresis, and urinary frequency were relatively common adverse event. However, no serious adverse events were reported. **Conclusions:** Topiramate was effective and well tolerated for managing disruptive behavioral problems and emotional instability in children and adolescents.

Key words: Topiramate, Youth, Disruptive behavior, Mental retardation.

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Introduction

Mental retardation (MR) is associated with a higher prevalence of psychopathology than in the general population, for both children and adolescents, as well as adults. The disruptive behaviors such as aggressive behavior toward self (self-injurious behavior including biting, self-hitting, head banging, etc.), aggressive behavior toward others (hitting, biting, kicking, etc.), and generally aggressive behaviors (breaking or overturning furniture, breaking windows, screaming, run-

ning, etc.) are some of the most common forms of psychopathology in children and adolescents with MR. Rutter et al. reported that the rate of behavioral problems in children with MR was several times higher than in normal IQ children and that it is negatively correlated with IQ.[1,2]

Anticonvulsants have been used to treat affective instability and aggressive behaviors in a variety of neuropsychiatric disorders. The possible mechanisms for the antiaggressive and mood stabilizing effect of anticonvulsants fall into three major categories: (1) blockade of voltage-gated sodium channels, (2) direct or indirect enhancement of inhibitory GABAergic neurotransmission, and (3) inhibition of excitatory glutamatergic neurotransmission. Anticonvulsants were effective in the amygdale-kindled rat model.[3,4] In this context, it seems that anticonvulsants can be effective to manage affective instability and aggressive behavior by reducing neuronal excitability. Most clinical trials using carbamazepine and valproate in children and adolescents demonstrated a decrease in aggressive behavior, irritability and affective instability.[5-9]

Topiramate is a novel antiepileptic drug with a proven efficacy for treating seizure disorders.[10] Its mechanisms of action include inhibition of sodium channels blocking activity, enhancement of GABA inhibitory neurotransmission, attenuation of excitatory glutamatergic neurotransmission, inhibition of calcium channels, and inhibition of carbonic anhydrase.

Topiramate has been primarily evaluated for its potential efficacy in neurological conditions such as migraine, neuropathic pain, essential tremor and seizure disorder. Investigations have also begun to evaluate the therapeutic effects of topiramate in psychiatric disorders such as post-traumatic stress disorder,[11] bulimia,[12] obesity,[13] bipolar disorder,[14] and schizoaffective disorder.[15] A major advantage of topiramate compared to other antiepileptic drugs is its adverse events profile. Because it is free of serious hepatotoxicity, routine blood monitoring is not necessary.[10] Topiramate has the advantage of often being associated with a lack of weight gain and/or with weight loss.[16] Also, it offers the advantage of having relatively few, drug-drug interactions.[17,18]

Therefore, topiramate may be potentially beneficial in the treatment of individuals with behavioral problem, especially accompanied with MR. Janowsky et al. conducted a retrospective study into the effects of topiramate on aggressive, self-injurious, and disruptive/destructive behaviors in the intellectually disabled.[19] The results suggested that topiramate might have a role in the treatment of challenging/maladaptive behaviors in intellectually disabled individuals. However, these individuals were adults having a mood disorder. In children and adolescents with pervasive developmental disorder (PDD), an open-label, retrospective study was conducted to assess the efficacy on associated symptoms of PDD and the tolerability of topiramate.[20] However, it remains unknown whether topiramate is beneficial in the treatment of disruptive behaviors in child and adolescent patients with MR. We conducted an open-label study to evaluate the efficacy and safety of topiramate on disruptive/destructive behaviors in children and adolescents with or without MR.

Methods and Materials

The subjects in the study were 54 child and adolescent psychiatric outpatients (41 boys and 13 girls) who had disruptive behavioral problems such as aggressive-impulsive behaviors, self-injurious behaviors, irritability and hyperactivity. Subjects were diagnosed based on Diagnostic and Statistical Manual of Mental Disorders, Fourth edition (DSM-IV)[21] criteria by two child and adolescent psychiatrists at baseline. The DSM-IV diagnoses of the subjects were Attention Deficit/ Hyperactivity Disorder (38.9%), PDD (46.3%), Tourette Disorder (11.1%), Anxiety Disorders (7.4%), Bipolar Disorders (7.4%), etc. All subjects were divided into 3 groups (16 subjects without MR, Non-MR; 10 subjects with mild MR, Mild

MR; and 28 subjects with moderate to severe MR, Mod-Severe MR) based on their intellectual ability as measured on the Wechsler Intelligence Scale. There were no significant differences in the frequencies of disruptive behavioral problems among the three groups except self-injurious behavior (0.0% in Non-MR, 30.0% in Mild MR, 67.9% in Mod-Severe MR; p=.000) (Table 1). Among the three groups, there were no significant differences in the frequencies of aggressive behavior (75.0% in Non-MR, 70.0% in Mild MR, 46.4% in Mod-Severe MR; p=.133) and irritability (56.3% in Non-MR, 40.0% in Mild MR, 67.9% in Mod-Severe MR; p=.293)

The subjects took a tablet form of topiramate (25mg/tablet) for the treatment of aggressive-impulsive behaviors, self-injurious behaviors, irritability and hyperactivity. Topiramate was given at an initial daily dose of 25mg, and was increased weekly in 25mg/day increments to a tolerable dose using b.i.d. or t.i.d. regimen.

This prospective, open-label study was carried out during 6 weeks of observation and treatment.

. The Aberrant Behavior Checklist Irritability (ABC-I) and Hyperactivity (ABC-H) subscales and the Clinical Global Impression Severity (CGI-S) scale were administered at baseline and at the end of the post-treatment 6th week. CGI-S is rated on a scale from 1 to 7 (1=normal, 7=extremely ill). We also investigated the adverse events following topiramate administration in the subjects.

Statistical analysis

We analyzed the data at baseline using ANOVA and chi-square test. Repeated measures ANCOVA (analysis of co-variance) were performed to compare the CGI-S and ABC subscales' scores by groups and assessment periods (pre-treatment versus post-treatment 6th week), because the mean scores of CGI-S and ABC subscales were significantly different (Table 2). For analysis of

TABLE 1. Comparative clinical data of the subjects

	Total (N=54)	Non-MR (N=16)	Mild MR (N=10)	Mod-Severe MR (N=28)	P
Age Mean (±SD)	14.0 (±7.8)	14.9 (±6.2)	10.5 (±5.6)	13.8 (±6.5)	N.S.
Male: Female ratio	41:13	12:4	6:4	23:5	N.S.
IQ Mean (±SD)	63.7 (±30.2)	98.4 (±17.9)	58.7 (±8.4)	37.0 (±9.8)	< .001
DSM-IV Dx: N (%)					
ADHD	21 (38.9%)	7 (43.7%)	3 (30.0%)	11 (39.3%)	N.S.
PDD	25 (46.3%)	1 (6.3%)	5 (50.0%)	19 (67.9%)	.000
Anxiety D/O	4 (7.4%)	2 (12.5%)	0 (0.0%)	2 (7.1%)	N.S.
Bipolar D/O	4 (7.4%)	4 (25%)	0 (0.0%)	0 (0.0%)	.001
Tourette D/O	6 (11.1%)	6 (37.5%)	0 (0.0%)	0 (0.0%)	< .001
OBS	3 (5.5%)	1 (6.3%)	2 (20.0%)	0 (0.0%)	N.S.

Non-MR: subjects without mental retardation; Mild MR: subjects with mild mental retardation; Mod-Severe MR: subjects with moderate to severe mental retardation

N.S.: not significant statistically by chi-square test

DSM-IV Dx: diagnoses using Diagnostic and Statistical Manual of Mental Disorders, Fourth edition

ADHD: attention-deficit/hyperactivity disorder

PDD: pervasive developmental disorder

D/O: disorder

OBS: organic brain syndrome.

TABLE 2. The mean maintenance dosage of topiramate

	Non-MR	Mild MR	Mod-Severe MR	F	P
Mean ± SD (mg/day)	105.0 ± 91.7	82.5 ± 67.7	100.4 ± 87.1	.226	.798
Range (mg/day)	25 - 400	25 - 200	12.5 - 400		
Dosage/BWt ± SD (mg/kg)	2.2 ± 2.4	2.4 ± 1.3	2.4 ± 1.3	.085	.919
Range (mg/kg)	0.67 - 10.53	1.14 - 5.00	0.42 - 4.88		

Non-MR: subjects without mental retardation; Mild MR: subjects with mild mental retardation; Mod-Severe MR: subjects with moderate to severe mental retardation; BWt: body weight

the temporal changes of CGI-S scores and reduction on ABC subscales, we assigned the pre-treatment scores as the covariate variable, the assessment time as the within-subject variable, and the groups as the between-subject variable.

Results

There were no significant differences of mean (± SD) maintenance dosage of topiramate among the three groups (Table 2). There were significant differences of mean (±SD) body weight among the three groups: 55.7 (±18.8) kg in Non-MR, 31.8 (±17.1) kg in Mild MR, and 40.0 (±18.0) kg in Mod-Severe MR (F=6.009, p=.005). However, the mean maintenance dosages per body weight showed no significant differences (Table 2).

CGI-S scores were significantly changed after the medication in all three groups (Table 3). CGI-S scores were significantly reduced with significant interaction

TABLE 3. Mean changes of CGI-S, ABC-H, and ABC-I scores

		Non-MR	Mild MR	Mod-Severe MR	F	P
CGI-S	pretreatment	4.56	5.50	6.18	54.19	< .001
	pretreatment (EMM)	5.57	5.57	5.57		
	6th week (EMM)	3.58	4.26	4.97		
ABC-H	Pretreatment	23.81	28.80	32.93	113.16	< .001
	Pretreatment(EMM)	29.46	29.46	29.46		
	6^{th} week (EMM)	21.53	24.98	26.24		
ABC-I	pretreatment	9.75	19.10	26.04	199.14	< .001
	Pretreatment (EMM)	19.93	19.93	19.93		
	6^{th} week (EMM)	12.73	15.63	18.83		

EMM: estimated marginal mean; CGI-S: Clinical Global Impression - severity scale (1=normal, 7=extremely ill); ABC-H: Aberrant Behavior Checklist Hyperactivity subscale; ABC-I: Aberrant Behavior Checklist Irritability subscale; Non-MR: subjects without mental retardation; Mild MR: subjects with mild mental retardation; Mod-Severe MR: subjects with moderate to severe mental retardation

Note: CGI-S changes in Non-MR vs. Mild MR, p<.05 by repeated measure ANCOVA;

CGI-S changes in Mild MR vs. Mod-Severe MR, p<.01 by repeated measure ANCOVA;

ABC-H changes in Non-MR vs. Mod-Severe MR, not significant by repeated measure ANCOVA;

ABC-H changes in Mild MR vs. Mod-Severe MR, p<.05 by repeated measure ANCOVA;

ABC-I changes in Non-MR vs. Mild MR, p<.01 by repeated measure ANCOVA;

ABC-I changes in Mild MR vs. Mod-Severe MR, p<.05 by repeated measure ANCOVA.

group by assessment period (F=4.70, p<.01). Through the test of within-group assessment period effect, interaction *group by assessment period* was also significant (F=6.71, p<.001). Comparing assessment periods, there was a significant difference between pre- and post-treatment 6th week results (F=7.48, p<.01). CGI-S scores were significantly reduced in all three groups in the following order: Non-MR, Mild MR, and Mod-Severe MR (Non-MR vs. Mild MR, p<.05; Mild MR vs. Mod-severe MR, p<.01).

There was a significant reduction of ABC-H with significant interaction *group by assessment period* (F=2.97, p<.05). In the test of within-group assessment period effect, interaction *group by assessment period* was also significant (F=4.29, p<.01). Comparing assessment periods, there was a significant difference between pre-treatment and post-treatment 6th week (F=3.26, p<.05). ABC-H scores were significantly reduced in all three groups in the following order (table 3): Non-MR, Mild MR, and Mod-Severe MR (Non-MR vs. Mild-MR, p<.05; Non-MR vs. Mod-severe MR, p<.05; Mild MR vs. Mod-Severe MR, p=.255).

ABC-I was also significantly reduced with significant interaction *group by assessment period* (F=3.04, p<.05). In the test of the within-group assessment period effect, interaction *group by assessment period* was also significant (F=4.07, p<.01). Comparing assessment periods, there was a significant difference between pre-treatment and post-treatment 6th week (F=5.74, p<.01). ABC-I scores were significantly reduced in all three groups in the following order (Table 3): Non-MR, Mild MR, and Mod-Severe MR (Non-MR vs. Mild-MR, p<.01; Mild MR vs. Mod-severe MR, p<.05).

Table 4 shows the frequencies of topiramate-induced adverse events. Paresthesia, anorexia, somnolence, nocturnal enuresis, and urinary frequency were relatively common in this study, but there were no significant frequency differences among the groups except for paresthesia. All subjects tolerated the administration of topiramate during the study period. All adverse events were tolerable and not serious.

Discussion

The U.S. Food and Drug Administration has approved topiramate for use as an adjunctive therapy for partial onset and primary generalized tonic-clonic seizures. The recommended dosage for children with epilepsy, aged 4-17 years, is 5-9mg/kg/day. A relatively lower dosage of topiramate may be recommended to manage the neuropsychiatric problems compared with epilepsy. Hardan et al.[20] reported that a mean topiramate dosage of 3.36mg/kg/day (235mg/day) was required to treat the behavioral symptoms in children and adolescents with

TABLE 4. Adverse reaction frequencies

Adverse reaction	Total (N=54) N (%)	Non-MR (N=16) N (%)	Mild MR (N=10) N (%)	Mod-Severe MR (N=28) N (%)	P
Paresthesia	7 (13.0%)	6 (37.5%)	0 (0.0%)	1 (3.6%)	002
Anorexia	6 (11.1%)	2 (12.5%)	1 (10.0%)	3 (10.7%)	N.S.
Somnolence	3 (5.6%)	1 (6.3%)	1 (10.0%)	1 (3.6%)	N.S.
Urinary symptoms	6 (11.1%)	2 (12.5%)	1 (10.0%)	3 (10.7%)	N.S
: Nocturnal enuresis	3 (5.6%)	1 (6.3%)	0 (0.0%)	2 (7.1%)	N.S.
: Urinary frequency	3 (5.6%)	1 (6.3%)	1 (10.0%)	1 (3.6%)	N.S.
Poor concentration	2 (3.7%)	1 (6.3%)	1 (3.6%)	0 (0.0%)	N.S.

Non-MR: subjects without mental retardation; Mild MR: subjects with mild mental retardation; Mod-Severe MR: subjects with moderate to severe mental retardation:

N.S.: not significant statistically by chi-square test

PDD. In a few previous clinical studies, much lower dosages of topiramate were administered to manage migraine (mean dosage of 1.4mg/kg/day, 8.4mg/day) or bipolar disorder (104mg/day) in children and adolescents.[22,23] In this study, lower dosages (2.2 to 2.4mg/kg/day, 82.5 to 105.0mg/day) of topiramate were sufficient to improve the behavioral problems in the subjects. Our results suggest that lower dosages of topiramate might be helpful to treat neuropsychiatric symptoms, compared to those required for epilepsy, in children and adolescents.

As shown in table 3, topiramate was effective to improve aggressive-impulsive behaviors, self-injurious behaviors, irritability, and hyperactivity, as indicated in the reduced CGI-S, ABC-H, and ABC-I scores in all groups. Topiramate has been suggested to be as effective as carbamazepine and valproate in managing disruptive behaviors, and affective instability in children and adolescents. In a pilot study[8] of 10 youths with conduct disorder, carbamazepine reduced aggressive and explosive behaviors. However, a subsequent double-blind study[5] of carbamazepine use in 22 youths with conduct disorder failed to show the superiority of carbamazepine over a placebo in reducing aggressive behavior. A brief report of a double-blind, placebo-controlled, crossover study[6] of valproate demonstrated a decrease in explosive temper and mood lability in children and adolescents with oppositional defiant disorder and conduct disorder. Valproate has been reported to be also effective in controlling disruptive behaviors in children and adolescents with MR or autism spectrum disorder. In two open trials,[7,9] valproate showed efficacy of 71-78% in reducing affective instability, impulsivity, aggressive behavior, irritability, and self-injurious behavior.

In the Expert Consensus Survey,[24] anticonvulsants were generally recommended for managing self-injurious behavior, physical aggression, agitation, hyperactivity, anxiety, and suicidal ideation/behavior in subjects with MR. Anticonvulsants were highly recommended for treating severe and persistent hyperactivity in MR patients, whose symptom severity of hyperactivity did not meet the full criteria of ADHD.

Topiramate is known to be effective in treating affective instability, irritability, and aggressive behavior, at least as an adjunctive mood stabilizer. Only in Non-MR of our study (see table 1), four of sixteen subjects were comorbid with bipolar disorder, which may have influenced the topiramate effect on affective instability, irritability, and aggressive behavior as a confounding factor. We performed repeated measure ANCOVA for all groups, excluding the four subjects with bipolar disorder from Non-MR. Nevertheless, the comorbidity of bipolar disorder did not influence the ANCOVA results in terms of the significant reduction of CGI-S and ABC scores in the group by assessment period, comparison between pre-treatment and post-treatment 6th week, and comparisons of treatment periods in Non-MR vs. Mild MR and Mild MR vs. Mod-Severe MR.

Compared to the pre-treatment period, CGI-S and ABC scores improved significantly at post-treatment 6th week period in all three groups. The treatment efficacy of topiramate on disruptive/destructive behavior was noted at post-treatment 3 months and 25 ($\pm$16) weeks in two retrospective studies[19,20] in adults with MR, and children and adolescents with PDD. Our prospective design revealed the short-term effects (6 weeks) of topiramate in decreasing the severity of disruptive behaviors in children and adolescents with or without MR. We defined 'responder' as cases with 'very much improved' and 'much improved'. The overall responder rate was 53.7%, but the rate declined from 93.8% in Non-MR, to 60% in Mild MR, and 28.8% in Mod-Severe MR. This suggests that topiramate showed more favorable efficacy on disruptive behaviors in patients with higher cognitive functions.

It has been reported that the most common adverse events of topiramate are central nervous system (CNS)-related adverse events and paresthesia. In CNS-related adverse events of our study, anorexia (11.1%) and somnolence (5.6%) were relatively common, followed by poor concentration (3.7%). There

were no reports of other CNS adverse events such as dizziness, fatigue, confusion, and abnormal vision. This study showed lower frequencies of CNS adverse events than previous reports of topiramate tolerability, such as 12.9~16.8% for anorexia, 16.1~21.1% for somnolence, and 12.6~19.4% for impaired concentration as reported by Biton et al.[17] This discrepancy of the frequencies could be related with topiramate dosage. The mean doses of our study were lower (range 82.5-105.0mg/day) than the 346 to 353mg/day in Biton et al.'s report.[17] It has been generally accepted that CNS adverse events are minimized by lowering doses followed by slow titration.[18,25]

The most common adverse event in our study was paresthesia, which is known to be related to the inhibition of carbonic anhydrase activity by topiramate.[26] The prevalence of paresthesia was relatively lower in the two MR groups (Mild MR and Mod-Severe MR) than in Non-MR. In MR subjects, the limited ability to express the subjective sense may lower the reports of paresthesic sensation. Antonio et al. reported only observable adverse events in their study, although paresthesia was one of the common adverse events in other previous studies.[20]

In our results, urinary adverse events such as nocturnal enuresis and urinary frequencies were also common, being reported by 11.1% (6 of 54) of the subjects. Urinary symptoms have only been rarely reported in previous studies for topiramate. It is unclear whether the urinary symptoms observed in the present study were associated with topiramate administration.

This study had two potential limitations. First, the trial was open label without a placebo-control. The second limitation was the presence of comorbid psychiatric disorder and different rates of comorbidities between the groups.

Conclusions

Topiramate was effective and well tolerated in the management of disruptive/destructive behaviors and affective instability in child and adolescent patients. In future research, systematically designed clinical studies will be required to evaluate the efficacies on stabilizing behavior and mood problems, and the safety of topiramate in children and adolescents with mental disorders.

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