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Treatment of Children and Adolescents with Epilepsy with Atomoxetine

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Objective The objective of this study was to assess the effectiveness and safety of atomoxetine in Korean children and adolescents with epilepsy.

Methods We retrospectively reviewed the electronic medical records of 105 children and adolescents with epilepsy treated with atomoxetine. Effectiveness was measured with the Clinical Global Impressions-Severity (CGI-S) and/or Clinical Global Impressions-Improvement (CGI-I) scales at baseline, and after 4 and 12 weeks. We defined response to atomoxetine as a CGI-I score less than three at week 12. Safety was evaluated at each visit, based on clinical assessment by a child and adolescent psychiatrist and reports from participants or their caregivers.

Results In total participants (n=105), 33 (31.4%) showed a response to treatment: a significant decrease in CGI-S scale score was observed over 12 weeks of atomoxetine treatment. The most common adverse event (AE) was decreased appetite (n=16, 15.2%), and life-threatening AEs were not observed. Seizure aggravation due to atomoxetine was observed in 7.6% (n=8) of total participants, and one of them discontinued atomoxetine.

Conclusion Our results provide preliminary evidence of the effectiveness and safety of atomoxetine in children and adolescents with epilepsy.
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Key Words Atomoxetine, Effectiveness, Epilepsy, Safety.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders affecting children, with a reported worldwide prevalence in childhood of 5%.[1] Inattention, hyperactivity, and impulsivity constitute its core symptoms,[2,3] and children and adolescents with ADHD commonly experience behavioral problems and impaired academic and occupational achievements.[2]

Nearly 80% of children with epilepsy have attention problems, and one-third of children with epilepsy have a diagnosis of ADHD.[4] Among children with epilepsy, the prevalence of ADHD was reported as 17−40%.[4,5] Youth with epilepsy and comorbid ADHD are more likely to experience academic underachievement and impaired executive function.[6] Thus, identifying and managing ADHD in children with epilepsy is very important. Pharmacologic treatment has been considered as the first-line intervention for ADHD.[7] Medications which are approved for ADHD, and which could be used for the treatment of youth with epilepsy and comorbid ADHD, include atomoxetine, clonidine, and methylphenidate.[8] Methylphenidate has been reported to well tolerate and effective in improving ADHD symptoms in children whose epilepsy is well controlled.[9,10] However, because of possible aggravation of epilepsy,[11] controversy exists about the use of methylphenidate.[12] There has been limited research with other medications used to treat ADHD in childhood epilepsy. Although Torres and colleagues reported that atomoxetine did not increase seizure risk in children with ADHD and epilepsy, their study was conducted with a small population of less than thirty.[13]

To our knowledge, only a few studies have been performed with atomoxetine in populations with epilepsy. Therefore, we aimed to investigate the effectiveness and safety of atomoxetine in Korean children and adolescents with epilepsy.

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METHODS

Participants

We retrospectively reviewed electronic medical records from 105 patients diagnosed with epilepsy at the Department of Pediatric Neurology at Asan Medical Center, referred to the Department of Child and Adolescent Psychiatry, and then prescribed atomoxetine between June 2007 and June 2018. Participants met the following inclusion criteria: age 5–18 years; confirmed epilepsy diagnosis according to the International League Against Epilepsy Classification of Epileptic Seizures;[14,15] completion of electroencephalography before atomoxetine administration; prescribed atomoxetine for longer than one week; and underwent at least one assessment for effectiveness and safety. Participants were excluded if they met one or more of the following criteria: a report by youths or their caregivers that percent of the prescribed medication taken during the study period was below 70%; or a clinician-confirmed diagnosis of a major psychiatric disorder, such as schizophrenia, other psychotic disorders, or bipolar disorder. The study was approved by the Institutional Review Board of Asan Medical Center (IRB No. 2018-0984).

Assessment and measures

One pediatric neurologist and one child and adolescent psychiatrist retrospectively reviewed data from each participant. Diagnoses of ADHD and other psychiatric disorders were assessed based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition.[1]

Atomoxetine effectiveness was retrospectively measured with the Clinical Global Impressions-Severity (CGI-S)[16] and/or Clinical Global Impressions-Improvement (CGI-I) scale[16] at baseline, and after 4 and 12 weeks. Safety was evaluated at each visit based on clinical assessment by the child and adolescent psychiatrist and on reports from youths and caregivers. We defined response to atomoxetine as a CGI-I score less than three at week 12.

Statistical analyses

The chi-squared test or Fisher's exact test was used for categoric variables and the independent t-test for continuous variables. We used repeated measures analysis of variance (ANOVA) to analyze the time effect of atomoxetine treatment and mixed between-within ANOVA to compare responders and non-responders regarding atomoxetine effects on CGI-S score. Missing data were imputed by last observation carried forward. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS version 22.0; IBM Corp., Armonk, NY, USA), and statistical significance was defined as a p-value of less than 0.05. All comparisons were two-tailed.

RESULTS

Participant characteristics

One hundred and five children and adolescents (age 9.7±3.0 years, range 5–18; 67 boys, 63.8%) were included in the study. The mean duration and dose of entire atomoxetine treatment period were 541.6±574.3 days (range 14–3,825) and 35.9±15.5 mg/day (range 10–96), respectively. The mean daily dose of atomoxetine for up to 12 weeks' treatment was 0.79±0.24 mg/kg/day (range 0.19–1.39). Atomoxetine was discontinued in 16 patients before week 12 due to: loss to follow-up (n=8); adverse events (AEs; n=6); or inadequate treatment response (n=2).

Overall, CGI-S scores for ADHD symptoms were significantly decreased during 12 weeks' atomoxetine treatment [$F(2,103)=40.025$, $p<0.001$, partial $\eta^2=0.437$] (Figure 1). The mean CGI-S score was decreased to 4.2±0.4, 3.9±0.6, and 3.7±0.7 at baseline, 4 week, and 12 week, respectively. For treatment responders (n=33) versus non-responders (n=72), significant between-group differences were evident in the main effects for time [$F(2,101)=11,634$, $p<0.001$, partial $\eta^2=0.187$), group [$F(1,102)=50.880$, $p<0.001$, partial $\eta^2=0.333$], and time-by-group interaction [$F(2,101)=63.680$, $p<0.001$, partial $\eta^2=0.558$). The mean CGI-S score was 4.1±0.3 at baseline, 3.5±0.6 at 4 week, and 3.0±0.3 at 12 week in treatment responders and that of non-responders was 4.2±0.5 at baseline, 4.1±0.4 at 4 week, and 4.0±0.5 at 12 week. Similar results were also observed in the 89 participants who completed 12 weeks' atomoxetine treatment.

In total participants (n=105), 33 (31.4%) were showed a treatment response. Treatment responders were significantly younger than non-responders (t=2.551, p=0.013). There were no significant differences between treatment responders and non-responders in all other demographic and clinical characteristics (Table 1). Among the 89 participants who completed 12 weeks' atomoxetine treatment, responses to atomoxetine, and differences between treatment responders and non-re-

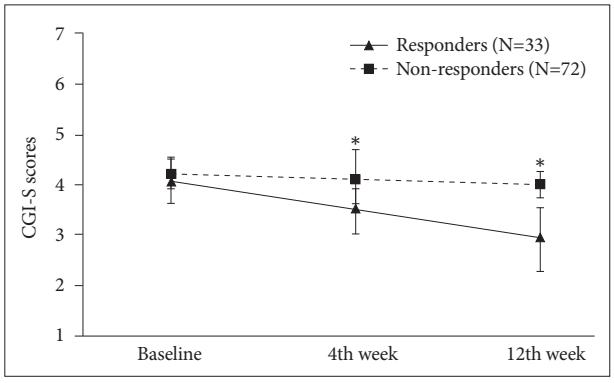

Figure 1. Comparison of mean values and standard deviations of the Clinical Global Impressions-Severity (CGI-S) scores between responders and non-responders to atomoxetine. *p<0.001.

sponders in demographic and clinical characteristics, were similar to those in the overall study population.

AEs of the study participants are shown in Table 2. Fifty-one youths (48.6%) experienced AEs. The most common AE was decreased appetite (n=16, 15.2%), followed by nausea/vomiting (n=14, 13.3%), seizure aggravation (n=8, 7.6%), irritability (n=7, 6.7%), insomnia (n=6, 5.7%), somnolence (n=5, 4.8%), abdominal pain (n=4, 3.8%), dizziness (n=1, 1.0%), headache

Table 1. Comparison of demographic and clinical characteristics between responders and non-responders to atomoxetine

	Responders (N=33)	Non-responders (N=72)	t or χ^2	p
Age, years, mean (SD)	8.8 (2.3)	10.1 (3.2)	-2.551	0.013
Gender, boys, N (%)	21 (63.6)	46 (63.9)	0.001	0.980
FSIQ, mean (SD)	83.5 (20.2)	79.9 (20.5)	0.821	0.413
ADHD subtype, N (%)			3.680	0.298
Inattentive	19 (57.6)	33 (45.8)		
Hyperactive-impulsive	2 (6.1)	1 (1.4)		
Combined	11 (33.3)	34 (47.2)		
NOS	1 (3.0)	4 (5.6)		
Comorbid diagnosis, N (%)				
Mental retardation	10 (30.3)	24 (33.3)	0.095	0.758
Mood disorder	3 (9.1)	2 (2.8)		0.177*
ODD	0 (0.0)	4 (5.6)		0.306*
Anxiety disorder	0 (0.0)	5 (6.9)		0.322*
ASD	0 (0.0)	2 (2.8)		1.000*
Tic disorder	0 (0.0)	2 (2.8)		1.000*
Trichotillomania	0 (0.0)	1 (1.4)		1.000*
Epilepsy diagnosis, N (%)			2.754	0.431
Focal epilepsy	23 (69.7)	40 (55.6)		
Generalized epilepsy	7 (21.2)	21 (292.2)		
Combined epilepsy	0 (0.0)	3 (4.2)		
Unknown epilepsy	3 (9.1)	8 (11.1)		
Etiology of epilepsy, N (%)			5.333	0.255
Structural etiology	6 (18.2)	11 (15.3)		
Genetic etiology	5 (15.2)	17 (23.6)		
Infectious etiology	3 (9.1)	1 (1.4)		
Metabolic etiology	0 (0.0)	2 (2.8)		
Unknown etiology	19 (57.6)	41 (56.9)		
Number of AEDs at baseline, N (%)			1.439	0.487
None	5 (15.2)	9 (12.5)		
Monotherapy	22 (66.7)	42 (58.3)		
Polypharmacy	6 (18.2)	21 (29.2)		
Uncontrolled seizure at baseline, N (%)	0 (0.0)	3 (4.2)		0.550*
Seizure aggravation due to atomoxetine, N (%)	3 (9.1)	5 (6.9)		0.704*
Previous ADHD medication, N (%)	3 (9.1)	17 (23.6)	3.094	0.079
Mean daily dose of atomoxetine for up to 12 week (mg/kg/day) (SD)	0.81 (0.26)	0.78 (0.24)	<0.001	0.993
Atomoxetine adverse event, N (%)	14 (42.4)	37 (51.4)	0.728	0.394

Definition of response to atomoxetine was determined as less than three in CGI-I score at post-treatment. *using Fisher's exact test. ADHD: attention-deficit/hyperactivity disorder, AED: antiepileptic drug, ASD: autism spectrum disorder, FSIQ: full-scale intelligence quotient, NOS: not otherwise specified, ODD: oppositional defiant disorder, SD: standard deviation

Table 2. Comparison of treatment emergent adverse events between responders and non-responders to atomoxetine

	Responders (N=33)	Non-responders (N=72)	χ^2	p
Decreased appetite	5	11	<0.001	0.987
Nausea/vomiting	2	12		0.217*
Seizure aggravation	3	5		0.704*
Irritability	4	3		0.202*
Insomnia	3	3		0.376*
Somnolence	1	4		1.000*
Abdominal pain	0	4		0.306*
Dizziness	0	1		1.000*
Headache	0	1		1.000*
Stuttering	0	1		1.000*
Tremor	0	1		1.000*
Chest discomfort	0	1		1.000*
Encephalopathy	0	1		1.000*

Definition of response to atomoxetine was determined as less than three in CGI-I score at post-treatment. *using Fisher's exact test. CGI-I: Clinical Global Impressions–Improvement

(n=1, 1.0%), stuttering (n=1, 1.0%), tremor (n=1, 1.0%), chest discomfort (n=1, 1.0%) and encephalopathy (n=1, 1.0%). Among these participants who experienced AEs, six discontinued treatment before 12 week, because of AEs: gastrointestinal-related AEs (abdominal pain, nausea, and decreased appetite) in three cases, seizure aggravation in one case, irritability in one case and encephalopathy in one case.

DISCUSSION

In this study, we found that atomoxetine was effective and generally well tolerated in children and adolescents with epilepsy and comorbid ADHD. To our knowledge, this is the only study to evaluate the effectiveness and safety of atomoxetine in Korean children and adolescents with epilepsy. The response rate of atomoxetine was 31.4% in children and adolescents with epilepsy and ADHD. The most common adverse event was decreased appetite, and life-threatening AEs were not observed. Seizure aggravation due to atomoxetine was observed in about 8% of total participants, and one of them discontinued atomoxetine.

The response rates of atomoxetine have been reported as 70–85% with methylphenidate[17] and 47–50% with atomoxetine[18,19] in youth with ADHD only. In a study of methylphenidate, the response rate was almost 60% in Korean children and adolescents with epilepsy and comorbid ADHD.[9] However, to the best of our knowledge, response rates to atomoxetine in youths with epilepsy and comorbid ADHD have not yet been published. The response rate of atomoxetine was 31.4% in youths with epilepsy and comorbid ADHD in the present study. As in the case of methylphenidate, the response rate of atomoxetine was lower in youths with epilepsy and comorbid ADHD than in that of children with ADHD only. The inclusion of participants with different forms of epilepsy,[13] multiple antiepileptic drugs,[13] and relatively short durations of treatment might have affected the lower response rate. Further prospective studies with large samples are needed.

The most common AE profiles for atomoxetine in this trial was consistent with a previous study in Korean ADHD children without epilepsy.[20] The most frequently observed AEs in both trials were gastrointestinal-related AEs, including decreased appetite, nausea and vomiting. A previous study reported the incidence rates of seizure adverse events with atomoxetine between 0.1% and 0.2%, and these rates were not significantly different from placebo in ADHD youth without epilepsy.[21] Those results suggest that atomoxetine did not significantly affect seizure occurrence in children with ADHD only. In our study, about 8% of participants experienced seizure aggravation related to atomoxetine, and one of them discontinued atomoxetine. In a previous study for children with both epilepsy and comorbid ADHD, about 6% of participants had an increased number of seizures[22] and 4% of participants had a discontinuation of atomoxetine due to exacerbation of seizure.[13] The rate of seizure aggravation in our study has consistent results to a few previous studies.[13,22] Seizure aggravation rates related to methylphenidate were reported as up to 20% in previous studies,[9,23] and these rates are much higher than in those of atomoxetine. Our results with relatively large sample provide more reliable reference for the safety of atomoxetine and suggest that atomoxetine may be a safer treatment of ADHD than methylphenidate in children with epilepsy.

There were several limitations to our analyses. First, this study was designed as a retrospective chart review. Second, we did not compare the effectiveness and safety of atomoxetine between our participants and children without epilepsy. Third, we could not adjust for the effects of concomitant medication, including antiepileptic drugs. Fourth, we did not conduct structured interviews for the diagnosis of psychiatric disorders. Fifth, AEs may have been under-reported, as we relied on self-reporting of such events by youths or their parents/caregivers.

Despite these caveats, our results provide preliminary evidence of the effectiveness and safety of atomoxetine in Korean children and adolescents with epilepsy. Prospective studies with larger samples are needed to support these findings.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Hyo-Won Kim, Tae-Sung Ko, Mi-Sun Yum. Data curation: Kee Jeong Park, Hyunji Ahn. Formal analysis: Kee Jeong Park. Investigation: Hyo-Won Kim. Methodology: Hyo-Won Kim, Tae-Sung Ko, Mi-Sun Yum. Project administration: Hyo-Won Kim. Resources: Hyo-Won Kim. Software: Hyo-Won Kim. Supervision: Hyo-Won Kim. Validation: Hyo-Won Kim. Visualization: Kee Jeong Park. Writing—original draft: Kee Jeong Park. Writing—review & editing: Hyo-Won Kim, Tae-Sung Ko, Mi-Sun Yum, Hyunji Ahn.

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