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Effect of methylphenidate on the quality of life in children with epilepsy and attention deficit hyperactivity disorder:

an open-label study using an osmotic-controlled release oral delivery system

Hanik K. Yoo[1], Subin Park[1], Hee-Ryung Wang[1], Joong Sun Lee[1], Kunwoo Kim[1], Kyoung-Won Paik[2], Mi Sun Yum[3], Tae-Sung Ko[3]

[1] Department of Psychiatry, University of Ulsan College of Medicine, Asan Medical Center
[2] Department of Psychiatry, Hanyang University Medical Center
[3] Department of Pediatrics, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

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ABSTRACT – This open study explored whether methylphenidate could be tolerated and effective in improving the quality of life (QOL) and attention deficit hyperactivity disorder (ADHD) symptoms of children with epilepsy and ADHD. Twenty-five subjects (aged 10.1 ± 3.0 years) with ADHD and epilepsy were recruited at an outpatient clinic in Seoul, Korea. We used the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE), ADHD rating scale (ARS) and clinical global impression (CGI) in this study. Osmotic-controlled release oral delivery system (OROS) methylphenidate, 1.0 ± 0.4 mg/kg/day, was administered for 55.2 ± 7.5 days. The QOL subscales including physical restriction ($p = 0.005$), self-esteem ($p = 0.002$), memory ($p < 0.001$), language ($p = 0.005$), other cognition ($p < 0.001$), social interaction ($p = 0.002$), behaviour ($p < 0.001$), general health ($p = 0.002$) and QOL ($p < 0.001$) were significantly increased and the ARS ($p < 0.001$) and CGI-Severity of illness scores ($p < 0.001$) were significantly reduced after medication. Although 60% of subjects had experienced adverse effects, most were tolerable and only two subjects withdrew from the study owing to unbearable adverse effects (anorexia and insomnia). Two subjects had seizure attacks during the study period without having to discontinue the trial drug. Despite limitations related to the small sample size and the open design of the present pilot study, our results suggest that OROS methylphenidate may be well tolerated and effective in reducing ADHD symptoms and improving QOL in this patient population.

Key words: ADHD, epilepsy, methylphenidate, quality of life, OROS

Correspondence:
H.K. Yoo, M.D., Ph.D.
Department of Psychiatry,
University of Ulsan College of Medicine,
Children's Hospital,
Asan Medical Center,
388-1 Pungnap-2dong,
Songpa-gu,
Seoul 138-736, Korea
<hiyoo@amc.seoul.kr>

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Epilepsy is one of the most prevalent paediatric neurological disorders, with a prevalence of approximately 0.5-1% (Waaler *et al.*, 2000). Children with seizure disorders have been found to suffer from more frequent and severe behavioural and emotional problems than healthy children (Carlton-Ford *et al.*, 1995; Dunn *et al.*, 2003). The causes of the psychiatric complications in epileptic children can include multiple complex etiologies such as organic lesions of the central nervous system, unexpected effects of antiepileptic drugs and negative psycho-social influences related to epilepsy (Domizio *et al.*, 1993; Carlton-Ford *et al.*, 1995). According to previous studies, the incidence of ADHD is higher in patients with epilepsy than in the general population (Carlton-Ford *et al.*, 1995). One fifth to one third of patients with epilepsy have ADHD characteristics (Sanchez-Carpintero and Neville, 2003; Tan and Appleton, 2005) and over 60% of children with severe epilepsy satisfy criteria for ADHD (Sherman *et al.*, 2007). In addition to seizure disorders, accompanying ADHD also reduces the quality of life (QOL) in children with epilepsy, indicating that ADHD symptoms have real-world adverse implications for epileptic children and their families (Sherman *et al.*, 2007).

Although psychostimulants such as methylphenidate and amphetamine are commonly used in children with ADHD to reduce inattention and hyperactivity symptoms (Stein *et al.*, 1996), methylphenidate has been prescribed reluctantly in children with ADHD and epilepsy, owing to its potential adverse effects which include lowering the seizure threshold (Tavakoli and Gleason, 2003). Feldman *et al.* (1989) reported that methylphenidate was effective in reducing ADHD symptoms in 10 children with ADHD and epilepsy without seizure recurrence. However, conflicting data were also reported for three of five children with ADHD and active seizures who experienced an increased seizure frequency during methylphenidate medication (Gross-Tsur *et al.*, 1997). In a recent study with 57 children and adolescents with ADHD and active seizures, methylphenidate was effective in reducing ADHD symptoms without changing seizure frequency from baseline (Gucuyener *et al.*, 2003). In addition, two studies have reported a low risk of seizure attacks during methylphenidate treatment in adults with ADHD plus epilepsy (Moore *et al.*, 2002; van der Feltz-Cornelis and Aldenkamp, 2006). Moreover, Moore *et al.* (2002) suggested that, without reducing the seizure threshold, methylphenidate relieved sedation and improved the QOL of adults with epilepsy. However, low baseline seizure frequencies, small numbers of samples and short observation periods limit the power of these studies to detect the effect of methylphenidate to increases in seizure frequency.

Osmotic-controlled release oral delivery system (OROS) methylphenidate has been used widely based on advantages regarding drug adherence and unique pharmacokinetic properties which are used to control the release rate and action for a duration of 12 hours (Chavez *et al.*, 2009), however, there have been no clinical studies examining whether OROS methylphenidate can improve the QOL of children with epilepsy and ADHD.

We therefore investigated whether OROS methylphenidate could be tolerated and effective in improving the QOL as well as ADHD symptoms of this population. We also tried to identify demographic-, seizure-, and ADHD-related variables that affect the change of QOL in this group with an 8-week open trial of OROS methylphenidate.

Materials and methods

Subjects

Twenty-five epileptic children and adolescents with ADHD (17 boys and 8 girls; mean age ± SD = 10.1 ± 3.0 years; mean total intelligence quotient [IQ] ± SD = 72.4 ± 18.9) were recruited at an outpatient clinic at a general hospital, Seoul, Korea, from April 2005 to March 2007 *(table 1)*. After informed consent, which included a warning of possible adverse effects such as a decreased seizure threshold, was obtained from each parent and child, subjects were screened for eligibility. The protocol was reviewed and approved by the local institutional review board. The inclusion criteria included both a DSM-IV diagnosis of ADHD according to the Korean version of the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) (Kim *et al.*, 2004) as ascertained by a child psychiatrist. Subjects with evidence of current mood disorders, anxiety disorders or psychotic symptoms were excluded according to the KSADS-PL.

The seizure type of each child with epilepsy was diagnosed by a paediatric neurologist and classified according to the International League Against Epilepsy criteria (ILAE, 1989), based on clinical descriptions and electroencephalogram (EEG) results. All subjects had been seizure-free for more than three months on a stable antiepileptic drug regimen. This was ascertained from medical records, which noted seizure frequency at each clinic visit during three months prior to enrolment, as well as parents' reports. Antiepileptic drugs taken by subjects were reviewed by a child psychiatrist to judge whether ADHD symptoms could be improved by changing antiepileptic drug regimen. Only subjects who were not amenable to changing their antiepileptic drugs or for whom this was deemed unnecessary were included. Children with central nervous system lesions, other severe medical conditions or previous exposure or known allergy to methylphenidate were excluded from the study.

Procedure

Baseline assessment involved medical history, physical and neurological examinations, symptom ratings, IQ test using the Korean version of the Wechsler Intelligence Scale for Children-Revised (Park *et al.*, 1986), routine laboratory tests, electrocardiogram (ECG), resting pulse

Table 1. Descriptive data and medication information for 25 youths with ADHD and seizure disorders.

Gender, N (%)	17 males (68%) 8 females (32%)
Age, mean ± SD	10.1 ± 3.0 (6 to 17) years-old
Total intelligence quotient, mean ± SD	72.4 ± 18.9
Paternal education, mean ± SD	13.5 ± 2.2 years
Maternal education, mean ± SD	12.3 ± 1.9 years
Socioeconomic status, N	Middle class: 11 subjects Lower middle class: 11 subjects Lower class: 3 subjects
Type of seizure disorders, N	Partial onset seizure: 13 subjects Generalized onset seizure: 12 subjects
ADHD subtypes	Combined type: 15 subjects Predominantly inattentive type: 10 subjects
Comorbidities, N	Mental retardation: 9 subjects Oppositional defiant disorder: 6 subjects
Duration of seizure disorders, mean ± SD	5.0 ± 2.8 years
Age at onset of seizure disorders, mean ± SD	5.3 ± 2.7 years
Seizure-free duration, mean ± SD (median)	26.3 ± 18.3 months (20.0 months)
Previously medicated antiepileptic drugs, mean ± SD	1.7 ± 0.9 drugs
OROS methylphenidate dose, mean ± SD	1.0 ± 0.4 (0.25 to 1.8) mg/kg/day
Duration of OROS methylphenidate treatment, mean ± SD	55.2 ± 7.5 days

ADHD: attention deficit hyperactivity disorder; SD: standard deviation; OROS: osmotic-controlled release oral delivery system.

and blood pressure, height, weight and EEG. Demographic and seizure-related clinical data were also obtained by interviews with patients and parents and through review of medical records. Initially, 18 mg/day of OROS methylphenidate was prescribed by a child psychiatrist, which was increased by 9 to 18 mg/day increments depending on the symptom severity and drug tolerability of each patient. The maximum dose of OROS methylphenidate was 54 mg/day. Patients continued on their antiepileptic drug regimen during the study period. No drugs except OROS methylphenidate and antiepileptic drugs were administered. Patients and their caretakers visited the clinic every two weeks and the final evaluation was conducted at eight weeks after medication commencement.

Measurement of quality of life and ADHD symptoms

The Korean version of the Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) was used for measurement of the primary endpoint (Sabaz *et al.*, 2000; Lim *et al.*, 2002). This parent-assessed instrument assesses five domains of life functions such as physical function, emotional well-being, cognition, social function and behaviour, and also contains two items assessing general health and QOL. A 5-point Likert scale was used to calculate each subscale score, on a scale of 0 to 100. Higher scores indicate better functioning. The QOLCE was completed at baseline and at the end of the study.

The Korean version of the ADHD Rating Scale (ARS) (DuPaul *et al.*, 1998), which is a semi-structured clinical interview, the Clinical Global Impression-Improvement scale (CGI-I) (Conners and Barkley, 1985) and the CGI-Severity of Illness scale (CGI-S) (Guy, 1976) were used to measure the secondary endpoints. The ARS was developed to assess the severity of ADHD symptoms and gives three summary scores: inattentive, hyperactive/impulsive and total scores. The ARS was used at baseline and endpoint. The CGI-I consists of seven scores indicating the level of improvement (where 1 = much improved and 7 = much worse). The CGI-S also consists of seven scores indicating the level of symptoms (where 1 = normal and 7 = severely ill). The CGI scores were measured at every visit.

Adverse effects of OROS methylphenidate were assessed using an adverse effect checklist that recorded side effects of OROS methylphenidate including increase in seizure frequency or tics and general health issues. Each patient's height and weight were also measured at every visit. Physical and neurological examinations, laboratory tests, and ECGs were completed at the end of the study.

Statistical analyses

Paired t-tests with the last-observation-carried-forward method were used to find changes in the mean scores of each subcategory of the QOLCE, the ARS and the CGI-S from baseline to study end. Multiple linear regression analyses were also used to determine associations between the QOLCE scores and various demographic-, seizure-, and ADHD-related variables. All statistical analyses were performed using the SPSS software version 12.0 with statistical significance defined at an alpha level < 0.0071 (0.05/7) (by the Bonferroni correction for five domains of life function plus two items in the QOLCE) for 2-tailed tests.

Results

Among 25 subjects, 13 (52.0%) had partial seizures and 12 (48.0%) had generalized seizure disorders. Fifteen subjects (60.0%) showed deficits in both impulse regulation and attention and 10 subjects (40.0%) showed predominantly inattentive symptoms of ADHD. Fifteen youths

(60.0%) with ADHD and epilepsy also had comorbid psychiatric disorders, the most common comorbid psychiatric condition was mental retardation (36.0%) *(table 1)*. After eight weeks of OROS methylphenidate treatment, the scores of subscales of the QOLCE such as physical restriction ($p = 0.005$), self-esteem ($p = 0.002$), memory ($p < 0.001$), language ($p = 0.005$), other cognition ($p < 0.001$), social interaction ($p = 0.002$), behaviour ($p < 0.001$), general health ($p = 0.002$) and QOL ($p < 0.001$) were significantly increased *(table 2)*. The total inattentive ($p < 0.001$) and hyperactive/impulsive scores ($p < 0.001$) in the ARS were significantly reduced by

Table 2. Effectiveness of OROS methylphenidate in 25 youths with ADHD and seizure disorders.

Characteristics	Baseline	Endpoint	t	P-value
QOLCE, mean ± SD				
Physical function				
- Physical restriction	59.2 ± 15.2	67.0 ± 11.7	- 3.1	**0.005**
- Energy/fatigue	64.5 ± 20.6	71.5 ± 23.8	- 1.9	0.065
Emotional well-being				
- Depression	79.6 ± 18.0	81.0 ± 19.8	- 0.4	0.726
- Anxiety	68.7 ± 22.0	74.7 ± 18.9	- 1.8	0.076
- Control/helplessness	57.0 ± 31.1	64.0 ± 24.6	- 1.2	0.230
- Self-esteem	55.6 ± 13.1	65.3 ± 20.6	- 3.6	**0.002**
Cognition				
- Concentration	41.0 ± 21.5	52.0 ± 19.7	- 2.9	0.009
- Memory	43.0 ± 22.3	60.5 ± 16.8	- 5.4	**< 0.001**
- Language	57.4 ± 24.3	68.7 ± 17.4	- 3.1	0.005
- Other cognition	40.5 ± 23.2	55.5 ± 20.4	- 4.4	**< 0.001**
Social function				
- Social activities	56.0 ± 21.3	68.7 ± 19.1	- 3.7	0.009
- Social interaction	42.0 ± 35.0	60.0 ± 30.4	- 3.4	**0.002**
Behaviors	56.4 ± 4.6	63.9 ± 7.5	- 4.2	**< 0.001**
General health	60.0 ± 30.6	71.0 ± 24.7	- 3.4	**0.002**
Quality of life	52.0 ± 23.8	69.0 ± 19.5	- 4.5	**< 0.001**
ARS, mean ± SD				
Total	27.7 ± 8.3	16.2 ± 7.9	10.3	**< 0.001**
Inattentive	16.5 ± 3.7	9.5 ± 4.2	10.4	**< 0.001**
Hyperactive/impulsive	11.2 ± 5.6	6.6 ± 4.2	7.0	**< 0.001**
CGI-I rating, N (%)				
Very much improved		3 (12.0)		
Much improved		13 (52.0)		
Minimally improved		7 (28.0)		
No change		2 (8.0)		
Minimally worse				
Much worse				
Very much worse				
CGI-S score, mean ± SD	5.3 ± 0.6	3.2 ± 0.7	11.9	**< 0.001**
CGI-S rating, N (%)				
Normal, not ill	0	0		
Minimally ill	0	3 (12.0)		
Mildly ill	0	16 (64.0)		
Moderately ill	1 (4.0)	5 (20.0)		
Markedly ill	15 (60.0)	1 (4.0)		
Severely ill	9 (36.0)	0		
Extremely severely ill	0	0		

OROS: osmotic-controlled release oral delivery system; ADHD: attention deficit hyperactivity disorder; QOLCE: quality of life in childhood epilepsy questionnaire; SD: standard deviation; ARS: ADHD rating scale; CGI-I: clinical global impression-improvement; CGI-S: clinical global impression-severity of illness.

41.5%, 42.4% and 41.1%, respectively. The CGI-I scores showed that 16 subjects (64.0%) had improvements rated as "much" or "very much" improved. In addition, the CGI-S score was lowered by medication with time ($p < 0.001$) *(table 2, figure 1)*.

There were no significant associations between the QOLCE scores and various demographic and seizure-related characteristics. Change of the CGI-S scores was negatively correlated with changes in self-esteem ($r = 0.57$, $p = 0.003$) *(figure 2A)* and social activity scores ($r = 0.53$, $p = 0.007$) from baseline to study end *(figure 2B)*. Changes in the ARS scores were not significantly correlated with changes in the total and subscale scores in the QOLCE after treatment.

Two patients (8.0%) did not complete the study protocol owing to intolerable adverse effects such as anorexia and insomnia. Fifteen subjects (60.0%) experienced adverse events. The most common side effects were anorexia (32.0%; n = 8) and insomnia *(table 3)*. For two subjects that did have seizures during the study, their seizure-free periods prior to study enrolment were 11 months and 20 months, respectively. Both subjects had seizures at about six weeks after taking OROS-methylphenidate, within two weeks after increasing the dose (from 18 mg to 36 mg and from 18 mg to 27 mg, respectively). There were no significant changes in body weight, height, laboratory test results or ECG findings.

Discussion

This pilot study suggests that OROS methylphenidate may improve QOL and also be efficacious in reducing ADHD symptoms in these subjects. This effect of methylphenidate on QOL appears to be similar in ADHD populations with and without epilepsy. Flapper and Schoemaker (2008) reported positive effects of methylphenidate on the QOL scores as well as physical, emotional, cognitive and social functions in children with developmental co-ordination disorder and ADHD. One study using amphetamine also showed increases in the total health-related QOL scores in children with ADHD (Wigal etMcGough, 2005).

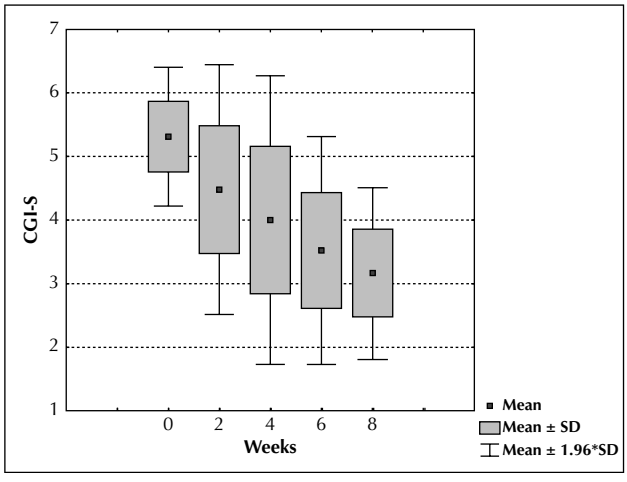

Figure 1. Mean scores for the Clinical Global Impression-Severity (CGI-S), error bars indicate standard deviation.

There were insignificant reductions in negative emotions such as depression and anxiety with stimulant treatment in this study *(table 2)*. Exclusion criteria on the observed pattern of mood or anxiety disorders might limit the effects of methylphenidate on emotional function. In general, mood symptoms such as depression and anxiety are common in patients with seizure disorders (Ettinger *et al.*, 1998; Dunn *et al.*, 1999; Alwash *et al.*, 2000), so further study involving the broader population of patients with mood or anxiety disorders is required to identify the effect of methylphenidate on mood or anxiety symptoms. Self-esteem of youths with epilepsy and ADHD increased with medication and was not quantified as just simple mood status but an overall complex perspective of the individual, composed of the individual's own preference, acceptance and respect. Although a stimulant cannot influence a mood status, other functions such as cognitive, social and behavioural functions that affect the self-esteem of patients may be altered *(table 2)*; in this study a negative correlation between self-esteem and ADHD severity was observed *(figure 2B)*.

Compared with emotional aspects, the cognitive and social functions of youths with epilepsy and ADHD were enhanced after eight weeks of OROS methylphenidate *(table 2)*. Previous studies, in which psychostimulants had improved not only inattentiveness but also various kinds of cognitive functions such as memory (O'Toole *et al.*, 1997; Bedard *et al.*, 2004), execution (Konrad *et al.*, 2005; Fallu *et al.*, 2006), reaction time (Krusch *et al.*, 1996) and language (McInnes *et al.*, 2007) in patients with ADHD, were in line with our results. The dopamine system, which has effects over the whole brain, may be strengthened by methylphenidate and enhance cognitive functions (Mehta and Riedel, 2006). However our results are insufficient to provide strong evidence which can support the improvement of cognition by OROS methylphenidate in epileptics with ADHD because the QOLCE are determined by subjective parental responses, not by objective measures of cognitive function.

The social dysfunctions of youths with epilepsy and ADHD were improved by OROS methylphenidate *(table 2)*. Epilepsy itself can affect the social competence of patients (Sturniolo and Galletti, 1994; Caplan and Austin, 2000) and comorbid ADHD symptoms could also reduce social activities and interaction (Shelton *et al.*, 1998; Bagwell *et al.*, 2001). ADHD symptoms could be more problematic because they are more apparent (Sonuga-Barke *et al.*, 1994; Gresham *et al.*, 1998) than seizure-related social problems, which are mainly introverted and make the patient appear withdrawn

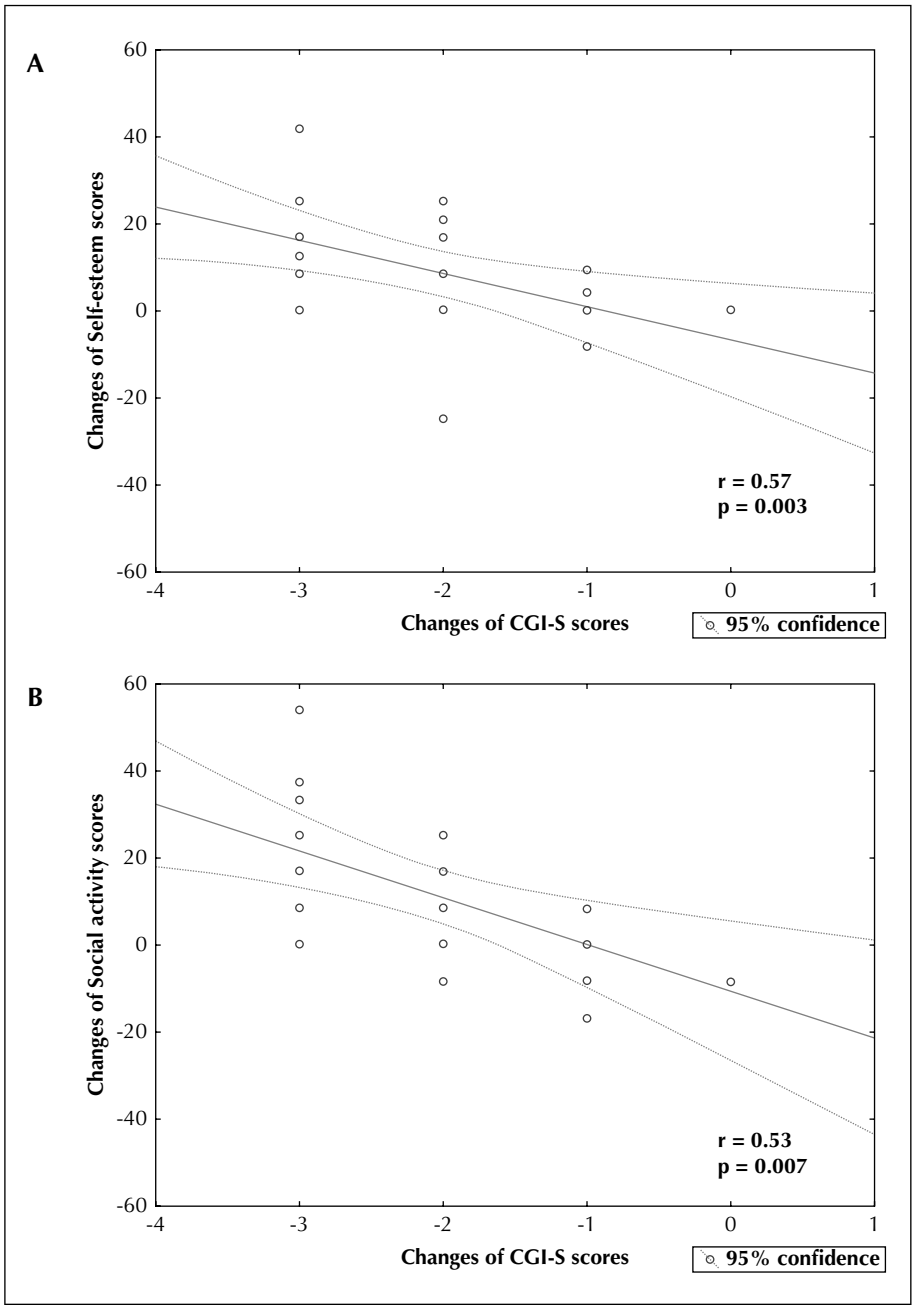

Figure 2. Correlation between Quality of Life in Childhood Epilepsy Questionnaire (QOLCE) scores and Clinical Global Impression-Severity (CGI-S) scores after eight weeks of treatment: **A**) self-esteem scores; **B**) social activity scores.

(Kim, 1991; Carlton-Ford *et al.*, 1995). Thus, stimulant medication may enhance the social ability of the patient *(figure 2B)*.

Behaviour related to the QOL of youths with epilepsy and ADHD were also altered by stimulant treatment. Several items in the behavioural subscale of the QOLCE overlapped with the clinical features of ADHD, such as hyperactivity, impulsivity and aggressiveness. Therefore improvement of ADHD symptoms by methylphenidate might affect the improvement of behavioural subscale. However, these relationships may be more complex because behavioural subscale also included variable items such as attention-seeking, phobic behaviour and independence, and there was no significant correlation between scores of the ARS and behavioural subscale of the QOLCE.

Table 3. Adverse events.

Adverse events	N (%)
Anorexia	8 (32.0%)
Insomnia	4 (16.0%)
Weight loss	2 (8.0%)
Seizure	2 (8.0%)
Dizziness	1 (4%)
Stomachache	1 (4%)

Every clinical measure including symptom severity and clinical global function level was significantly reduced after 8-week treatment. Even though OROS methylphenidate improved both ADHD symptoms and QOL, there were no significant correlations between them because QOL measure involves complex components beyond just ADHD symptoms (Jacoby, 1992; Sabaz *et al.*, 2000). For instance, improvement of ADHD symptoms by stimulants can have a positive effect on QOL, while side effects of stimulants can reduce QOL (Trimble and Cull, 1988). Therefore, global function changes, rather than symptom changes, showed correlations with changes in some QOL domains *(figure 2A, B)*. Our results suggest that OROS methylphenidate may improve the QOL of children and adolescents with epilepsy and ADHD which is independent of ADHD symptom changes. For instance, OROS methylphenidate may improve social and cognitive function by reducing sedation by antiepileptic drugs (Moore *et al.*, 2002).

In this study, short-term treatment with OROS methylphenidate seemed to be generally tolerated in children and adolescents with ADHD and seizure disorders. Sixty percent of subjects had adverse effects, but most adverse events were tolerable and only 8% of subjects discontinued medication owing to intolerable side effects. Although two patients experienced seizure episodes during stimulant treatment, and this proportion is somewhat higher than previous reports (Feldman *et al.*, 1989; Gross-Tsur *et al.*, 1997; Gucuyener *et al.*, 2003; van der Feltz-Cornelis and Aldenkamp, 2006), no patients who experienced a seizure discontinued the study drug. In such cases, a child neurologist judged these episodes as very mild and non-problematic and both patients and their parents agreed.

Limitations of this study included small sample numbers with three-month, seizure-free periods and short observation periods. An open-label design without a control group was also a limitation. To confirm our results, double-blind, controlled studies should be conducted. In addition, our subjects included a substantial proportion of intellectually disabled children and IQ could be one of the factors affecting a child's response to methylphenidate. Future studies with more detailed seizure-related information and larger sample sizes will be able to identify the factors that affect the behavioural outcome of ADHD treatment in youths with ADHD and epilepsy.

Despite these limitations, the results of this pilot study suggest that OROS methylphenidate may be tolerated and effectively reduce ADHD symptoms and improve QOL in this patient population. Therefore, OROS methylphenidate could be considered as a therapeutic option when managing children and adolescents with ADHD and epilepsy. □

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References

Alwash RH, Hussein MJ, Matloub FF. Symptoms of anxiety and depression among adolescents with seizures in Irbid, Northern Jordan. *Seizure* 2000; 9: 412-6.

Bagwell CL, Molina BS, Pelham WE, *et al.* Attention-deficit hyperactivity disorder and problems in peer relations: predictions from childhood to adolescence. *J Am Acad Child Adolesc Psychiatry* 2001; 40: 1285-92.

Bedard AC, Martinussen R, Ickowicz A, *et al.* Methylphenidate improves visual-spatial memory in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2004; 43: 260-8.

Caplan R, Austin JK. Behavioral aspects of epilepsy in children with mental retardation. *Ment Retard Dev Disabil Res Rev* 2000; 6: 293-339.

Carlton-Ford S, Miller R, Brown M, *et al.* Epilepsy and children's social and psychological adjustment. *J Health Soc Behav* 1995; 36: 285-301.

Chavez B, Sopko Jr MA, Ehret MJ, *et al.* An update on central nervous system stimulant formulations in children and adolescents with attention-deficit/hyperactivity disorder. *Ann Pharmacother* 2009; 43: 1084-95.

Conners CK, Barkley RA. Rating scales and checklists for child psychopharmacology. *Psychopharmacol Bull* 1985; 21: 809-43.

Domizio S, Verrotti A, Ramenghi LA, *et al.* Anti-epileptic therapy and behaviour disturbances in children. *Childs Nerv Syst* 1993; 9: 272-4.

Dunn D, Austin J, Huster G. Symptoms of depression in adolescents with epilepsy. *J Am Acad Child Adolesc Psychiatry* 1999; 38: 1132-8.

Dunn DW, Austin JK, Harezlak J, *et al.* ADHD and epilepsy in childhood. *Dev Med Child Neurol* 2003; 45: 50-4.

DuPaul GJ, Power TJ, Anastopoulos AD, *et al. ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretations*. New York: The Guilford Press, 1998.

Ettinger AB, Weisbrot DM, Nolan EE, *et al.* Symptoms of depression and anxiety in pediatric epilepsy patients. *Epilepsia* 1998; 39: 595-9.

Fallu A, Richard C, Prinzo R, *et al.* Does OROS-methylphenidate improve core symptoms and deficits in executive function? Results of an open-label trial in adults with attention deficit hyperactivity disorder. *Curr Med Res Opin* 2006; 22: 2557-66.

Feldman H, Crumrine P, Handen BL, *et al.* Methylphenidate in children with seizures and attention-deficit disorder. *Am J Dis Child* 1989; 143: 1081-6.

Flapper BC, Schoemaker MM. Effects of methylphenidate on quality of life in children with both developmental coordination disorder and ADHD. *Dev Med Child Neurol* 2008; 50: 294-9.

Gresham FM, MacMillan DL, Bocian KM, *et al*. Comorbidity of hyperactivity-impulsivity-inattention and conduct problems: risk factors in social, affective, and academic domains. *J Abnorm Child Psychol* 1998; 26: 393-406.

Gross-Tsur V, Manor O, van der Meere J, *et al*. Epilepsy and attention deficit hyperactivity disorder: is methylphenidate safe and effective? *J Pediatr* 1997; 130: 670-4.

Gucuyener K, Erdemoglu AK, Senol S, *et al*. Use of methylphenidate for attention-deficit hyperactivity disorder in patients with epilepsy or electroencephalographic abnormalities. *J Child Neurol* 2003; 18: 109-12.

Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Rockville, US Dept Health, Education, and Welfare publication, 1976.

ILAE. Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 1989; 30: 389-99.

Jacoby A. Epilepsy and the quality of everyday life. Findings from a study of people with well-controlled epilepsy. *Soc Sci Med* 1992; 34: 657-66.

Kim WJ. Psychiatric aspects of epileptic children and adolescents. *J Am Acad Child Adolesc Psychiatry* 1991; 30: 874-86.

Kim YS, Cheon KA, Kim BN, *et al*. The reliability and validity of Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version- Korean version (K-SADS-PL-K). *Yonsei Med J* 2004; 45: 81-9.

Konrad K, Gunther T, Heinzel-Gutenbrunner M, *et al*. Clinical evaluation of subjective and objective changes in motor activity and attention in children with attention-deficit/hyperactivity disorder in a double-blind methylphenidate trial. *J Child Adolesc Psychopharmacol* 2005; 15: 180-90.

Krusch DA, Klorman R, Brumaghim JT, *et al*. Methylphenidate slows reactions of children with attention deficit disorder during and after an error. *J Abnorm Child Psychol* 1996; 24: 633-50.

Lim KH, Kang HC, Kim HD. Validation of a Korean version of the quality of life in childhood epilepsy questionnaire (K-QOLCE). *J Korean Epilep. Soc* 2002; 6: 32-44.

McInnes A, Bedard AC, Hogg-Johnson S, *et al*. Preliminary evidence of beneficial effects of methylphenidate on listening comprehension in children with attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2007; 17: 35-49.

Mehta MA, Riedel WJ. Dopaminergic enhancement of cognitive function. *Curr Pharm Des* 2006; 12: 2487-500.

Moore JL, McAuley JW, Long L, *et al*. An Evaluation of the Effects of Methylphenidate on Outcomes in Adult Epilepsy Patients. *Epilepsy Behav* 2002; 3: 92-5.

O'Toole K, Abramowitz A, Morris R, *et al*. Effects of methylphenidate on attention and nonverbal learning in children with attention-deficit hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 1997; 36: 531-8.

Park, KS, Yoon JR, Park HJ, *et al*. *Development of the Korean Educational Development Institute Wechsler Intelligence Scale for Children-Revised (KEDI-WISC-R), individual intelligence test for Korean children*. Seoul: Korean Educational Development Institute, 1986.

Sabaz M, Cairns DR, Lawson JA, *et al*. Validation of a new quality of life measure for children with epilepsy. *Epilepsia* 2000; 41: 765-74.

Sanchez-Carpintero R, Neville BG. Attentional ability in children with epilepsy. *Epilepsia* 2003; 44: 1340-9.

Shelton TL, Barkley RA, Crosswait C, *et al*. Psychiatric and psychological morbidity as a function of adaptive disability in preschool children with aggressive and hyperactive-impulsive-inattentive behavior. *J Abnorm Child Psychol* 1998; 26: 475-94.

Sherman EM, Slick DJ, Connolly MB, *et al*. ADHD, neurological correlates and health-related quality of life in severe pediatric epilepsy. *Epilepsia* 2007; 48: 1083-91.

Sonuga-Barke EJ, Lamparelli M, Stevenson J, *et al*. Behaviour problems and pre-school intellectual attainment: the associations of hyperactivity and conduct problems. *J Child Psychol Psychiatry* 1994; 35: 949-60.

Stein MA, Blondis TA, Schnitzler ER, *et al*. Methylphenidate dosing: twice daily *versus* three times daily. *Pediatrics* 1996; 98: 748-56.

Sturniolo MG, Galletti F. Idiopathic epilepsy and school achievement. *Arch Dis Child* 1994; 70: 424-8.

Tan M, Appleton R. Attention deficit and hyperactivity disorder, methylphenidate, and epilepsy. *Arch Dis Child* 2005; 90: 57-9.

Tavakoli SA, Gleason OC. Seizures associated with venlafaxine, methylphenidate, and zolpidem. *Psychosomatics* 2003; 44: 262-4.

Trimble MR, Cull C. Children of school age: the influence of antiepileptic drugs on behavior and intellect. *Epilepsia* 1988; 29 (Suppl. 3): S15-9.

van der Feltz-Cornelis CM, Aldenkamp AP. Effectiveness and safety of methylphenidate in adult attention deficit hyperactivity disorder in patients with epilepsy: an open treatment trial. *Epilepsy Behav* 2006; 8: 659-62.

Waaler PE, Blom BH, Skeidsvoll H, *et al*. Prevalence, classification, and severity of epilepsy in children in western Norway. *Epilepsia* 2000; 41: 802-10.

Wigal SB, McGough JJ, *et al*. A laboratory school comparison of mixed amphetamine salts extended release (Adderall XR) and atomoxetine (Strattera) in school-aged children with attention deficit/hyperactivity disorder. *J Atten Disord* 2005; 9: 275-89.