The impact of methylphenidate on seizure frequency and severity in children with attention-deficit–hyperactivity disorder and difficult-to-treat epilepsies

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ABBREVIATIONS

AED	Antiepileptic drug
CBCL	Child Behavior Checklist
HASS	Hague Seizure Severity Scale
SNAP-IV	Swanson, Nolan, and Pelham Questionnaire, version IV

AIM Difficult-to-treat epilepsies and attention-deficit–hyperactivity disorder (ADHD) often co-occur. Because of concerns about the use of stimulants in children with this comorbidity, the impact of ADHD treatment on seizure frequency and severity is not known. This pilot study evaluated the safety and efficacy of methylphenidate in this population.

METHOD After a 3 month period in which antiepileptic drugs were adjusted, 22 patients recruited from a specialist outpatient clinic for severe epilepsy (16 males, six females; mean age 11y 2mo, SD 3y 2mo) received methylphenidate for 3 months in an open label, non-controlled trial; four with generalized or multifocal (symptomatic/cryptogenic) epilepsy, one with generalized (idiopathic) epilepsy, 17 with partial (symptomatic/cryptogenic) epilepsy; five with partial seizures only, 17 with primarily or secondarily generalized seizures). Epilepsy, ADHD symptoms, and side effects were assessed using the Swanson, Nolan, and Pelham Questionnaire, the Child Behavior Checklist, the Hague Seizure Severity Scale, and the Side Effects Rating Scale.

RESULTS Methylphenidate significantly improved ADHD. After 3 months of treatment, 73% of patients no longer had clinically significant symptoms. Methylphenidate also reduced seizure severity (9-point median decrease on the Hague Seizure Severity Scale). Seizure frequency increased in four out of 22 patients, but only one patient withdrew from the study for this reason. Most patients experienced no major side effects.

INTERPRETATION These data are among the first showing that low doses of methylphenidate are safe and effective to treat ADHD symptoms in patients with difficult-to-treat epilepsies. Randomized controlled trials are needed to replicate the findings.

Psychosocial outcomes are considered to be increasingly important in epilepsy.[1,2] Around 60% of patients have behavioural problems,[2] often even more disabling than the seizures. However, in only a minority of patients are behavioural problems identified and treated,[3] further limiting integration in society.[4] Structural and electrical abnormalities probably interact with adverse social and genetic factors, particularly in patients with more severe epilepsies, increasing the risk of comorbid psychiatric disorders.[5]

Attention-deficit–hyperactivity disorder (ADHD) is one of the most common psychiatric comorbidities in children with epilepsy, affecting 12% of patients.[2] Greater prevalence of ADHD comorbidity is particularly present in patients with refractory seizures, who are commonly treated in tertiary epilepsy centers.[6,7] Treating ADHD in children with epilepsy may be difficult because of the long-held view that stimulants decrease the seizure threshold.[8] Although this perspective received some support from a study showing an increased risk of seizures with high doses of osmotic-controlled release oral delivery system (OROS) methylphenidate,[9] it has been challenged by many other studies using lower doses, suggesting that methylphenidate is both safe and effective in patients with epilepsy[10–12] (see Table SI, online supporting information). However, these studies usually included patients with well-controlled seizures. Only one open-label study has shown the safety and efficacy of pharmacological treatment of ADHD symptoms in children with uncontrolled epilepsy.[13] Studying the risk of worsening seizures or improvement of ADHD symptoms with stimulants in children with difficult-to-control or refractory

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seizures is important, as these patients have the highest risk of comorbid ADHD.[6] Because this clinical profile is often seen in the epilepsy clinic, the aim of this study was to investigate whether methylphenidate is safe and effective to treat ADHD in children and adolescents with difficult-to-control or refractory seizures. We also assessed seizure frequency and severity before and after methylphenidate in this population.

METHOD

Participants

Patients were recruited at the Severe Epilepsies Outpatient Clinic of the Neurology Service, Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil, between March 2008 and December 2009. This is a specialized outpatient clinic for treatment of severe epilepsies in a tertiary center. Most patients had been referred from the community but had already been followed at the clinic for several years before enrolment in the study (Table I). The hospital serves a large referral region and patients come from a broad range of socioeconomic backgrounds. Inclusion criteria were (1) meeting DSM-IV criteria for ADHD,[14] (2) having active epilepsy manifested by at least one seizure in the 3 months preceding inclusion on adequate doses of at least one antiepileptic drug (AED) judged appropriate for the epilepsy syndrome, and (3) consent of the parents to participation in the study. The presence of behavioural difficulties at school was not an inclusion criterion; however, based on clinical observations, most children and adolescents with severe epilepsies followed at the clinic did have behavioural or school difficulties.

Seventy-five children and adolescents with epilepsy (aged 6–16 y) were consecutively screened for ADHD symptoms with the Swanson, Nolan, and Pelham Questionnaire, version IV (SNAP-IV).[15] Patients with a SNAP-IV score of at least 1.5 underwent a clinical interview by two certified neurologists to establish the ADHD diagnosis. Trained raters applied the Schedule for Affective Disorders and Schizophrenia for School-Age[16] and the Child Behavior Checklist (CBCL).[17] The Wechsler Intelligence Scale for Children, 3rd edition (WISC III)[18] was used to estimate IQ. Epilepsy diagnosis was verified by a complete epileptological evaluation including seizure history, electroencephalography (EEG), and magnetic resonance imaging.

Of the 75 patients who were screened, 53 were excluded. Reasons for exclusion were not meeting DSM-IV ADHD criteria (n=27), not meeting the criteria for active epilepsy at the time of study enrollment (n=19), the presence of a progressive neurological disorder (n=4), being in the process of epilepsy surgery (n=2), and parents' refusal to participate in the study (n=1). Clinical features of the 22 enrolled patients are shown in Table I. Although four patients had multifocal or generalized symptomatic epilepsies, none had Lennox–Gastaut or other syndromes involving re-entrant absence seizures or myoclonic status epilepticus.

Table I: Demographic and clinical characteristics of patients

Characteristic	n=22
Mean age (SD), y:mo	11:2 (3:16)
Median age at onset of seizures (IR), y	2.5 (0.5–6.3)
Median epilepsy duration (IR), y	7.0 (5–12)
Median follow-up in a tertiary center (IR), mo	28 (16.8–69.0)
Sex, *n*	
Male	16
Female	6
Epilepsy type, *n*	
Generalized or multifocal (symptomatic/cryptogenic)	4
Generalized (idiopathic)	1
Partial (symptomatic/cryptogenic)	17
Seizure types, *n*	
Partial only	5
Primarily or secondarily generalized	17
Attention-deficit–hyperactivity disorder subtype, *n*	
Hyperactive	1
Inattentive	8
Combined	13
IQ (WISC), mean (SD; range)	74.3 (25.5; 34–106)

IR, interquartile range: difference between 25th and 75th centiles; WISC, Wechsler Intelligence Scale for Children.

What this paper adds

- Low-dose methylphenidate improves symptoms of ADHD and seizure severity in patients with difficult-to-treat epilepsies.
- Low-dose methylphenydate is a safe treatment for symptoms of ADHD in patients with difficult-to-treat epilepsies.

Outcome measures

Seizure frequency was assessed through diaries filled in by the parents and returned at each visit. At inclusion, parents were instructed to describe each recurrent seizure in the diary. Seizure severity was based in these entries and quantified with the Hague Seizure Severity Scale (HASS),[19] an inventory of 13 ictal and postictal manifestations in children with epilepsy, considered reliable in terms of test–retest stability and internal consistency. The HASS, scored at each visit, captures aspects related to impairment of consciousness, motor symptoms, injury from seizures, and incontinence, with scores ranging from 13 (no seizures) to 52 (maximum seizure severity). The Side Effects Rating Scale[20] assesses 17 symptoms and scores each from 0 (absent) to 9 (severe); it measures side effects due to stimulant medication. Only those symptoms reaching a score between 7 and 9 were considered for statistical analysis. The SNAP-IV and the CBCL were used to measure change in ADHD and other behavioural symptoms throughout the course of the study.

Procedures

A schematic overview of the study is shown in Figure SI (online supporting information). During the initial 3 months (baseline period) of study participation, AED treatment was adjusted to optimize seizure control and to verify the impact of these adjustments on ADHD symptoms.

Overall, 14 of the 22 patients had AED adjustments during this period, involving increments in dosage and/or the addition of another AED (Table SII, online supporting information). Specifically, 12 patients used valproate, an enzyme-inhibitor AED. Serum levels of AED were not measured during the study because all patients had had monitoring of AED levels over the years at the clinic and the dosages being used had previously been shown to be within therapeutic levels. After the first 3 months of study participation, other changes in AED treatment were not performed.

After 3 months, methylphenidate was then added and slowly titrated at a rate of 2.5mg/week (when weight was $\leq$30kg) or at 5mg/week (when weight >30kg), until the minimum dosage with efficacy or the maximum dosage of 1.0mg/kg was reached. Dosages were not increased further when significant side effects ensued. Efficacy and safety of methylphenidate in seizure control and behavior were assessed monthly by clinical interviews and completion of the HASS, the SNAP-IV, and the Side Effects Rating Scale.[20] The CBCL (parent ratings) was applied at baseline and 3 months after onset of methylphenidate.

Parents were informed about the objectives and risks of the study, particularly about the risk of more frequent and severe seizures, which should be balanced against the potential benefits of treating ADHD symptoms. Patient inclusion occurred only after formal parental agreement, according to the rules of the 196/96 resolution of the National Health Council of the Ministry of Health of Brazil. The study was approved by the ethics committee of the Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul. Additional safety measures included providing the researchers' mobile telephone numbers to parents, neurology residents, and emergency room staff. Parents were instructed to call or present to the emergency room should generalized seizures or any other serious side effects occur.

Statistical analysis

Seizure frequency and the scores of the HASS, SNAP-IV, and the Side Effects Rating Scales were not normally distributed, as shown by a Kolmogorov–Smirnov test. Therefore, the effects of methylphenydate were analyzed using the Friedman and Wilcoxon's signed-ranks test adjusted by Finner to control for type I error and by the Cochran's Q and McNemar test. Associations between the outcome measures were tested with Spearman's correlation, whereas Mann–Whitney *U* and Kruskal–Wallis tests were used to compare group medians. Analysis of variance for repeated measures was used to compare CBCL data before and after methylphenidate. Data were analyzed using SPSS software, version 17, (SPSS Inc., Chicago, IL, USA).

RESULTS

Three months after the start of methylphenidate treatment, 18 of the 22 patients were still using methylphenidate. Of the four who discontinued two had severe side effects (alopecia and headache). A third patient discontinued because of significant agitation and the fourth was the only patient who stopped using methylphenidate because of significant worsening in seizure frequency. This patient was a 16-year-old male with complex partial seizures and normal magnetic resonance imaging, who had an average of five seizures per week during baseline, despite a combination of 1400mg/day carbamazepine and 20mg/day clobazam. In the first week of methylphenidate titration, seizure frequency doubled. No secondary generalization occurred, however, and upon discontinuation of methylphenidate seizure frequency returned to baseline. These four patients were included in the intention-to-treat analysis as last observation carried forward.

ADHD symptoms

ADHD scores did not differ between the two baseline measures. Notably, improvement was already observed after the first month of methylphenidate treatment; by the end of the study, 16 out of 22 of the patients had entered into remission with sub-threshold SNAP-IV scores. Mean methylphenidate doses at months 1 and 3 were, respectively, 0.35 and 0.36mg/kg/day (Table II; range at month 3, 0.14–0.67mg/kg/d). Effective dosages of methylphenidate did not significantly differ between patients with and without valproate treatment (mean [SD] 0.36 [0.22]mg/kg/d vs 0.34 [0.11]mg/kg/d; p=0.635). Pre- and posttreatment mean (SD) CBCL total scores (parent ratings) were respectively 71.5 (5.9) and 60 (7.9) (p<0.001), whereas mean CBCL attentional problems subscale scores were 74.2 (9.6) at baseline and 59 (6.6) in the third month after methylphenidate onset (p<0.01).

Side effects

Thirteen out of 22 of the patients had side effects, most commonly reduction of appetite. Type and frequency of side effects did not differ between the first and third month on methylphenidate (Table SIII, online supporting information).

Seizure frequency

Adjustments in AED treatment during baseline led to seizure control in 10 patients, whereas the other 12 patients continued to have seizures. An increase in seizure frequency occurred in four patients, but only one patient had to discontinue methylphenidate because a significant deterioration occurred in the first week of treatment. In the other three patients, a few seizures recurred after onset of methylphenidate, after achieving transient control with AED adjustments at month 3. However, the frequency of recurrent attacks was similar or still reduced compared with that before enrolment in the study: one patient had 10 seizures per month in the beginning and three per month after methylphenidate; another patient had one seizure per month in the beginning and one per month during methylphenidate; and the third patient had

Table II: Attention-deficit–hyperactivity disorder (ADHD) symptoms and threshold for diagnosis

	−3mo	−1mo	+1mo	+3mo	*p*
Methylphenidate dose (mg/kg)[a]	NA	NA	0.35 (0.17)	0.36 (0.20)	0.866
Total methylphenidate dose (mg)[a]	NA	NA	14.20 (5.68)	15.36 (7.56)	0.202
Symptoms[b]					
Hyperactivity[c]	14 (63.6)[f]	14 (63.6)[f]	2 (9.1)[g]	1 (4.5)[g]	<0.001
Inattention[c]	21 (95.5)[f]	21 (95.5)[f]	9 (40.9)[g]	6 (27.3)[g]	<0.001
ADHD diagnosis[c,e]	22 (100)[f]	22 (100)[f]	9 (40.9)[f]	6 (27.3)[g]	<0.001
Hyperactivity[d]	1.70 (1.01–2.05)[f]	1.70 (1.01–2.21)[f]	0.16 (0.66–1.20)[g]	0.11 (0.67–1.05)[g]	<0.001
Inattention[d]	1.60 (1.88–2.31)[f]	1.60 (1.88–2.25)[f]	0.55 (1.00–1.60)[g]	0.62 (0900–1.53)[g]	<0.001

Values are presented as mean (SD or range). [a]Means of referred doses, compared by paired *t* test. [b]Score of ADHD symptoms as assessed by the Swanson, Nolan, and Pelham Questionnaire, version IV (SNAP-IV). [c]Cochran's test. Rows show the absolute number; percentages are in parentheses. [d]Kruskal–Wallis procedures followed by Wilcoxon's signed-ranks test adjusted by Finner to control for type I errors. Rows show the median and the interquartile range. [e]Participants were screened consecutively for ADHD symptoms with the SNAP-IV. Patients with a score $\geq$1.5 underwent a clinical interview to establish the diagnosis of ADHD and its subtype according to DSM-IV criteria. A trained rater then applied the Schedule for Affective Disorders and Schizophrenia for School Age and the patients who fulfilled DSM-IV-TR ADHD criteria.[15] [f,g]Values indicated by the same letter do not differ after Finner corrections at 5% (p<0.05). NA, not applicable.

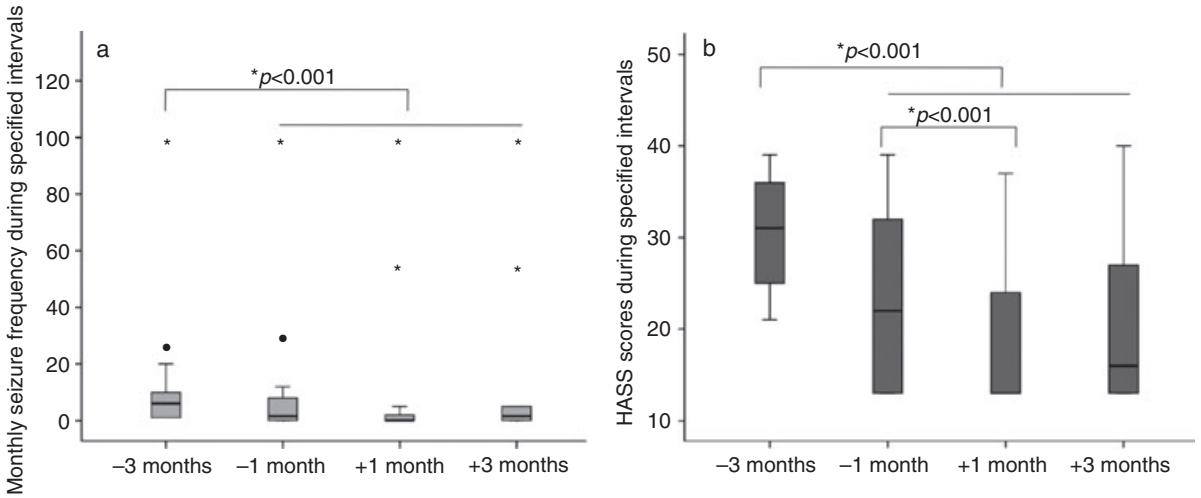

Figure 1: Seizure frequency and severity before (−3, −1mo) and after (+1, +3mo) methylphenidate onset at specified time points. (a) Seizure frequency decreased after antiepileptic drug adjustment (p<0.001). Upon the start of methylphenidate treatment, there were no differences in the frequency of seizures at the time points +1 and +3. (b) The attention-deficit–hyperactivity disorder symptoms assessed by the Hague Seizure Severity Scale (HASS) improved after 1 month of methylphenidate (p<0.001), and these improvements were more accentuated after 2 months of treatment (p<0.001, −1mo vs +1mo). There were no differences between the +1 month and +3 months of treatment. Mean methylphenidate doses at months 1 and 3 were respectively 0.35 and 0.36mg/kg/day. Bold lines, median scores. Boundaries of the boxes are the 75th and 25th centiles of the data set. Vertical lines, median (1.5) times interquartile ranges. Circles and stars are individual patients who are outliers for the median seizure frequency at specified time points. Quantitative data obtained before and after intervention with methylphenidate were compared with Friedman and Wilcoxons signed-ranks test adjusted by Finner to control for type I errors. Kruskal–Wallis tests were used in all analyses.

increased frequency from two per month before to three per month after methylphenidate. Therefore, although they lost their transient seizure-free status, parents judged that seizure frequency after stimulant institution should not interfere with maintenance of treatment. Overall, seizure frequency decreased during the adjustment of AED regimens and this effect remained for the 3 months after methylphenidate onset (Fig. 1a, Table III).

Seizure severity

No patient had significant worsening of seizure severity compared with baseline. Instead, HASS scores showed a significant reduction in seizure severity in the first month after treatment with methylphenidate compared with baseline (p < 0.001; Fig. 1b, Table III).

IQ, ADHD symptoms, and seizure severity

No significant correlations were found between IQ, ADHD symptoms, seizure severity, or frequency at any of the investigated time points.

DISCUSSION

It is clinically relevant to treat ADHD in children and adolescents with difficult-to-treat epilepsy, because behavioural

Table III: Seizure frequency and severity throughout the study

Seizures (n=22)	−3mo Median (IR)	−1mo Median (IR)	+1mo Median (IR)	+3mo Median (IR)	p[a]
Frequency	6 (1–10)[b]	1.5 (0–9)[c]	0 (0–2)[c]	1.5 (0–5)[c]	<0.001
Severity	31 (25–36)[d]	22 (13–32)[b]	13 (13–25)[c]	16 (13–27)[b,c]	<0.001

[a]Friedman test. [b,c,d]Same letter does not differ by the Wilcoxon test adjusted by Finner at 5% ($p < 0.05$). Seizure severity was quantified with the Hague Seizure Severity Scale.[19] IR, interquartile range: difference between 25th and 75th centiles.

and cognitive problems worsen health-related quality of life.[4] However, from a clinical point of view, there is some resistance to using psychotropic drugs in patients whose seizures are not under control, and the common view that methylphenidate may decrease the seizure threshold creates a particularly important clinical dilemma.

The aim of this pilot study was to test whether a low dosage of methylphenidate could be used safely in children and adolescents with epilepsy at higher risk of seizures, i.e. those with difficult-to-treat or refractory seizures. We showed that methylphenidate with dosages averaging 0.35mg/kg/day and reaching 0.8mg/kg/day did not lead to loss of seizure control in most patients with difficult-to-control seizures, nor did it lead to worsening in those with refractory seizures. The only patient who had a clinically significant increase in seizure frequency did not have a worsening in severity. Three others had seizure recurrence after full control with AEDs, but with low frequency, comparable to that before enrolment in the study. None of the others had any worsening of seizures.

Furthermore, we showed that methylphenidate was well tolerated. Side effects, occurring in 60% of patients, were primarily limited to reduced appetite. Although the discontinuation rate of 18% is higher than the 4–8% in clinical trials using full dosages,[20] it is lower than in community samples, which reached 33% in 3 months.[21] Severe side effects leading to discontinuation were uncommon, occurred early, and were independent of dosage, suggesting individual susceptibility. As we found no association between IQ and therapeutic response, the results are independent of the presence or severity of cognitive disability. Notwithstanding the limitation of a small sample and thus the possibility of a type II error, the latter confirms previous findings in patients with ADHD and intellectual disability.[22]

We chose a slow methylphenydate titration rate because there were no previous data on the use of this medication for patients with ADHD with active, difficult-to-treat epilepsies. Thus, we did not know whether slow increases in dosage were important in this context.

We found no evidence that AED adjustments alone improved ADHD symptoms. This was not unexpected, because all adjustments involved an increase in AED dosages that could, theoretically, worsen inattention. The need to adjust and often increase AED dosages is an integral part of the management of patients with difficult-to-treat epilepsies. We did not measure AED serum levels or count pills between visits. However, all patients had AED levels monitored over the years at the clinic and the dosages used had been previously shown to be within therapeutic levels. Adherence was indirectly confirmed by the improvement in seizure frequency and severity during the first 3 months of the study. It remains unclear whether such improvement in seizure frequency and severity was accompanied by changes in EEG. Available data do not support the use of EEG as predictors of seizure occurrence with methylphenidate in patients with epilepsy.[12] Thus, we decided not to base any decision upon EEG.

Because mean effective methylphenidate dosages were lower than those commonly used and recommended in practice (the MTA Cooperative Group), i.e. 0.35mg/kg/day, the favorable impact upon ADHD symptoms is somewhat intriguing[23] but may be related to the cognitive impairment seen in many of our patients. In this specific population, dosages between 0.3 and 0.6mg/kg/day have been found effective.[22] Thus, it is possible that lower dosages of methylphenidate are required in patients with severe epilepsies or more diffuse neurological dysfunction, for putative pharmacodynamic mechanisms involving cathecolaminergic systems. Another possibility we entertained for these findings was that serum levels of methylphenidate were increased by concomitant use of valproate. Because both drugs share a common cytochrome P450 metabolic pathway,[24] valproate may inhibit methylphenidate metabolism. This hypothesis, however, was not supported by the comparison of the level of improvement in the 12 patients who were using and the 10 who were not using valproate concomitant with methylphenidate. Therefore, the pharmacodynamics of low dosages of methylphenidate should be tested in future studies.

Though preliminary, it is of interest that a low dosage of methylphenidate was not only associated with a low risk of worsening seizures but, in fact, had a positive therapeutic impact in seizure severity. The level of vigilance in patients with severe epilepsies may be adversely affected by epileptic discharges, AED polytherapy, and sleep inefficiency.[25] In the past, methylphenidate was used to improve vigilance in patients with epilepsy,[26] because it modulates catecholaminergic tonus through an increase in synaptic dopamine and stimulation of noradrenergic receptors. Improvement in seizure frequency and severity with methylphenidate may thus relate to heightened vigilance.

Because the present study involves an open label, noncontrolled trial in which outcome measures postintervention had very large standard deviations, we cannot rule out

additional factors affecting our findings. For instance, a placebo effect on rating scales cannot be excluded, as ratings for ADHD symptoms, seizure frequency, and severity were completed by individuals who knew the intent and design of the study. Moreover, it could be argued that seizure frequency and severity in patients with difficult-to-treat or refractory epilepsies may have led to better compliance with AED treatment schedules and, as a corollary, better seizure control. We cannot also disregard the possibility that seizure control or ADHD symptoms would have improved with AED adjustments alone, or that better seizure control could have had an independent impact on ADHD symptoms. The latter is unlikely, however, because these patients had been followed at the clinic for several years with irregular and difficult seizure control and significant behavioural abnormalities, irrespective of repeated AED adjustments. Furthermore, parent-rated CBCL scores could be seen as confirming the behavioural results. This notwithstanding, the importance of this issue for the daily management and quality of life of these children dictates that the data presented here should be viewed with caution and considered as preliminary findings.

Despite the study limitations, results suggest that a low dose of methylphenidate can be safely used in children and adolescents with ADHD and difficult-to-treat epilepsies. It is noteworthy that the rate of improvement in ADHD symptoms observed in the present study is very similar to the improvement rate observed in a recent study in a sample of children and adolescents with uncontrolled epilepsy (73 vs 70.8%).[13] Interestingly, a comparison between the patients in the two studies suggests that our sample had a more severe form of epilepsy. Hence, the present study extends the previous findings to a more difficult-to-treat sample and shows that methylphenidate may also have a beneficial effect on seizure severity and frequency.

The findings presented here highlight the need to investigate further the efficacy and safety of low to medium doses of methylphenidate in children and adolescents with ADHD and difficult-to-treat or refractory seizures. That dosage may be an issue has been suggested by a study showing an increase in seizure risk with high doses of methylphenidate.[9] Randomized, placebo-controlled, double-blind trials in longitudinally followed samples and studies focusing on the interactions between methylphenidate and AEDs with variable pharmacokinetic profiles should prove useful.

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SUPPORTING INFORMATION

The following additional material may be found online:

Table SI: Summary of trials with methylphenidate to treat ADHD in children and adolescents with epilepsy

Table SII: Individual antiepileptic drugs and respective dosages

Table SIII: Side effects before and after methylphenidate

Figure S1: Overview of the study.

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