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Comparing stimulant effects in youth with ADHD symptoms and epilepsy

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ABSTRACT

To retrospectively examine response to stimulant treatment in patients with epilepsy and ADHD symptoms as predicted by seizure freedom for six months, use of methylphenidate (MPH) versus amphetamine (AMP) preparations, cognitive level, and medical records were searched for patients under the age of 18 with epilepsy and ADHD symptoms treated with MPH or AMP (n = 36, age = 10.4 ± 3.5; male = 67%). "Responders" had a CGI-improvement score of ≤2 and did not stop medication because of adverse effects. "Worsened" patients discontinued medication because of agitation/emotional lability. Seizure freedom did not predict treatment response. Lower cognitive level was associated with increased rate of worsening ($p = 0.048$). No patients who were seizure-free at the start of the medication trial experienced an increase in seizures. Of the patients having seizures at the start of trial, one patient on MPH and two patients on AMP had increased seizures during the trial. Seizures returned to baseline frequency or less after stimulant discontinuation or anticonvulsant adjustment. Methylphenidate was associated with a higher response rate, with 12 of 19 given MPH (0.62 ± 0.28 mg/kg/day) compared with 4 of 17 given AMP (0.37 ± 0.26 mg/kg/day) responding ($p = 0.03$). Methylphenidate treatment and higher cognitive level were associated with improved treatment outcome, while seizure freedom had no clear effect. Confidence in these findings is limited by the study's small, open-label, and uncontrolled design.

1. Introduction

There are relatively few studies of stimulant treatment in youth with cooccurring epilepsy and attention deficit hyperactivity disorder (ADHD) [1,2]. This has led clinicians to prescribe standard ADHD medications to these children despite the meager evidence base. This retrospective chart review study examines the treatment outcomes of children with epilepsy who were prescribed either methylphenidate (MPH) or amphetamine (AMP) preparations for symptoms of ADHD.

Compared with the estimated 2–16% of school-age children in the general population with ADHD [3,4], rates of ADHD in children with epilepsy range from 30 to 40%, making ADHD the most common behavioral problem that is associated with pediatric epilepsy [2]. Attention deficit hyperactivity disorder symptoms have deleterious effects on youth with and without epilepsy. In patients with ADHD without epilepsy, studies have found robust and approximately equal response rates to MPH and AMP preparations [5,6]. However, there are concerns about potential seizure-related adverse effects. For example, the Physician's Desk Reference [7] contains warnings not to use methylphenidate in patients with seizures. While these warnings have little empirical support, chart reviews have shown an initial reluctance to diagnose and initiate ADHD treatment in children with epilepsy [8].

There have been few prospective studies on the use of MPH for the treatment of comorbid epilepsy and ADHD. In a double-blind placebo crossover MPH trial involving 10 children with ADHD and well-controlled epilepsy on one antiepileptic drug [9], Feldman and colleagues found that on a 0.3 mg/kg/dose of MPH twice per day, 70% of the participants had improved, and none experienced seizures during

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the trial. Gross-Tsur and colleagues [10] studied 30 children with ADHD and epilepsy in an open-label study with a single-day double-blind crossover portion. After a two-month observation period, a single morning 0.3-mg/kg/day MPH dose was given for 8 weeks. According to parent report, 70% of the children had an improvement in ADHD symptoms. None of the children who had been seizure-free during the observation period experienced seizures during MPH treatment. Five patients with an average of 1.8 seizures/week during the observation period experienced an average of 3 seizures/week during MPH treatment (p = NS). Following 57 children with epilepsy on open-label MPH for one year, Gucuyener and colleagues found that the average seizure frequency during the year of treatment did not increase [11].

In contrast, Hemmer and colleagues [12] studied 205 children with ADHD who did not have epilepsy but underwent EEG examination prior to starting MPH. Thirty-six patients exhibited epileptiform activity. Three out of these 36 patients had new-onset seizures compared with one of the 169 with a normal EEG. A randomized, controlled crossover study of 33 children with ADHD and epilepsy demonstrated good efficacy for an extended release-MPH preparation (OROS-MPH) but found some evidence of increased seizure risk with higher MPH doses [13]. Yoo and colleagues assessed tolerability and effectiveness of MPH with respect to quality-of-life improvements for patients with ADHD and epilepsy. While quality of life improved, there were two seizures among the 25 patients in this trial, though this study was not designed to address the question of MPH effect on seizure risk. Collectively, these studies suggest that MPH can improve ADHD symptoms in children with epilepsy, though none had enough statistical power to determine conclusively whether MPH is associated with an increase in risk of seizures [14].

Even less research exists to guide treatment with AMP products. There is only one study of AMP preparations used to treat ADHD symptoms in children with epilepsy. Ounsted found that only 10% of the patients with epilepsy and impulsive/hyperactive symptoms responded well to dextroamphetamine [15]. There is also a case report of possible seizures in a 9-year-old girl after taking mixed AMP salts [16].

While the above studies provide valuable data on the effect of stimulants in patients with epilepsy, they are difficult to generalize to actual clinical practice where children with epilepsy are often taking multiple antiepileptic drugs, have other comorbid medical conditions, and may require higher doses of stimulant preparations. They also do not address cognitive impairment, which commonly accompanies epilepsy and ADHD. Studies have found a positive but reduced response to stimulant treatment in children with cognitive impairments [17,18]. Furthermore, they do not address the significant clinical question as whether to prescribe stimulants in the face of ongoing seizures.

These studies also do not compare the effects of MPH and AMP on patients with epilepsy. Both MPH and AMP competitively bind to the dopamine and the norepinephrine transporters, thus blocking the reuptake of dopamine and norepinephrine from the synapse [19]. However, AMP also causes release of catecholamines from intracellular vesicles [20]. In theory, this additional effect of AMP might decrease the ability of presynaptic autoreceptors and other homeostatic mechanisms to dampen the increase in dopamine and norepinephrine at the synapse, thereby reducing its tolerability [20].

This study examined the response to and tolerability of stimulants in youth with cooccurring epilepsy and ADHD symptoms seen in an outpatient clinical program. Seizure status (seizure-free for at least six months versus not), the type of stimulant medication (an MPH versus an AMP preparation), and patient cognitive level were hypothesized to predict differential response to stimulant medication.

2. Methods

2.1. Participants

Between 11/1998 and 11/2002, the electronic medical record system (EMRS) of the Boston Children's Hospital's Psychopharmacology Clinic [21] was searched for patients <18 years with a diagnosis of epilepsy who had past or current treatment with MPH or AMP preparations. Most patients were referred from the clinician treating their epilepsy to the outpatient psychopharmacology clinic specifically for treatment of their ADHD symptoms. Epilepsy was defined using the International League Against Epilepsy (ILAE) criteria [22] as a history of repeated, afebrile, unprovoked seizures or a single seizure that lasted longer than 15 min before starting antiepileptic treatment or the presence of electroencephalographic (EEG) findings clearly implicating an epilepsy diagnosis [23]. Patients with febrile seizures, seizures occurring only during an acute illness with known metabolic dysfunction, or isolated seizures were excluded. This study was approved by the Hospital's Committee on Clinical Investigation and conducted in accordance with institutional guidelines.

2.2. Procedures

During patient visits, the treating child psychiatrist or nurse practitioner entered information prospectively into the EMRS which includes entries for all the axes of the DSM-IV, Clinical Global Impression (CGI) [24] scores and narrative fields for psychiatric history, medical history, laboratory evaluations, psychiatric history, and demographic information [21]. Information was based on treating clinicians' interviews with the patient and family during the visits. Missing data and some neurological information were abstracted from the patients' medical charts at the hospital.

2.3. Patient characteristics

The following information from the EMRS and medical charts was obtained: demographic information, psychological information such as clinical psychiatric diagnoses, and neurological information such as seizure types, description of earlier EEGs, and characterization of abnormal EEG localization. As this was a retrospective chart review, the clinical psychiatric diagnoses recorded were those given by the treating clinician and were not based on structured interviews. For patients given a clinical diagnosis of ADHD, information in the medical record was insufficient to reliably categorize the ADHD into its subtypes.

Patients had all begun stimulant treatment in the clinic. “Baseline visit” was defined as the last visit for which patient data were available before beginning stimulant medication. “Last visit” was the last visit during which the patient was still taking stimulant medication or, if the patient discontinued the stimulant between visits, the visit immediately after discontinuation. The last visit was examined for the effects of the stimulant and the length of treatment, as well as dosages of stimulants and concurrent medications.

2.3.1. Seizure frequency

Seizure frequency for the 6 months before beginning stimulant treatment, during the trial, and at its end was determined by patient and/or parent reports on the number of seizures experienced during a given period of time. Despite limitations [25,26], use of a seizure count was considered appropriate in this population because patients with pediatric epilepsy and their parents have considerable experience in recognizing seizures, increasing the likelihood that their reports would be accurate [27].

2.3.2. Seizure status

Patients were considered “seizure-free” if they had been seizure-free for at least six months prior to starting the stimulant, while patients were categorized as “not-seizure-free” if they had had at least one seizure in the six months prior to starting the stimulant. The six-month time frame was deemed more reliable than a shorter time frame given the frequency of patient visits noted in the medical records.