

# Epilepsy and attention-deficit hyperactivity disorder: links, risks, and challenges

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**Abstract:** Attention-deficit hyperactivity disorder (ADHD) has a prevalence rate of 7%–9% in the general population of children. However, in children with epilepsy, ADHD has been found to be present in 20%–50% of patients. This paper provides a review of ADHD prevalence in pediatric epilepsy populations and reviews data on specific symptom presentation and attention deficits in patients with epilepsy. This paper also reviews evidence-based treatments for ADHD and specifically the treatment of ADHD as a comorbid condition in children with epilepsy.

**Keywords:** ADHD, epilepsy, seizure disorder, children

## Introduction

Children with epilepsy (CWE) experience not only seizures but also multiple cognitive, behavioral, and emotional problems. One of the most common difficulties is impaired attention or attention-deficit hyperactivity disorder (ADHD). For this review, we have assessed recent reports for information on the prevalence of ADHD, potential risk factors for ADHD, and possible treatments for ADHD in CWE. The articles were identified by a search on Ovid Medline using the terms attention, hyperactivity, or ADHD, and epilepsy. We also scanned the references in the review articles on ADHD and epilepsy to find additional reports.

## Attention-deficit hyperactivity disorder

ADHD is described in the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5)*,<sup>1</sup> as a neurodevelopmental disorder associated with at least six symptoms of inattention and/or at least six symptoms of hyperactivity and impulsivity. Symptoms must be severe enough to interfere with functioning, must occur in at least two settings (ie, school and home), and must have an age of onset before 12 years of age. Diagnoses can be specified as a predominantly inattentive, predominantly hyperactive/impulsive, or combined presentation. ADHD has a prevalence rate of ~7%–9% of children and 2.5%–4% of adults,<sup>2–5</sup> with twice as many boys as girls with an ADHD diagnosis. There is a strong genetic component to ADHD with an elevated risk in first-degree relatives of a person with an ADHD diagnosis. Although environmental and social factors can impact symptom presentation and outcomes in ADHD, the role of these factors is much less significant than the contribution of genetics.<sup>6</sup> Of note, in addition to some other modifiers, epilepsy is cited by the *DSM-5* as a potentially influencing ADHD symptom.

Comorbid mental health diagnoses are common in children with ADHD, with disruptive behavior disorders (oppositional defiant disorder and conduct disorder) present in about half of the children with ADHD combined presentation.<sup>1</sup> Specific learning disorders are another common comorbid condition. Anxiety disorders,

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depressive disorders, and, in adults, substance-use disorders are present at a higher rate in persons with ADHD than in the general population.

A leading theory for ADHD proposes core deficits in executive functioning abilities such as working memory, self-regulation abilities (affect, motivation, and arousal), internalization of speech, and analysis/synthesis of information.<sup>6,7</sup> A 2005 meta-analysis looking at executive functioning tasks in children with ADHD found significant impairments in these abilities in children with ADHD compared to peers, with the greatest group differences in response inhibition, vigilance, working memory, and planning.<sup>7</sup> These data support the important role of executive function deficits in ADHD; however, there is some evidence that this theory may not provide a comprehensive explanation of causality in ADHD (moderate effect sizes and lack of consistent deficits across all executive functions within individuals with ADHD).<sup>7</sup> Executive functions may represent one of several neuropsychological skill deficits that may contribute to ADHD. Another theory has proposed that deficits in cognitive control operations (involving executive control processes and motivation or regulation processes) contribute to ADHD.<sup>8</sup>

Abnormalities in frontostriatal circuits have frequently been implicated in ADHD, and imaging studies have supported the presence of abnormalities in these circuits in persons with ADHD.<sup>9,10</sup> However, it is likely that more widespread neurological abnormalities are involved in ADHD.<sup>9</sup> For example, in addition to the dorsolateral prefrontal cortex (PFC) and caudate, research supports decreased volumes of the pallidum, corpus callosum, and cerebellum as consistent findings in ADHD.<sup>9</sup> In addition to the findings of neurological abnormalities in persons with ADHD compared to controls, there is an evidence that the treatment of ADHD with stimulant medications can reduce or normalize these differences.<sup>11</sup>

## ADHD in epilepsy

Analysis of data from the 2007 National Survey of Children's Health found a lifetime prevalence of epilepsy/seizure disorder in 1% (0.06% prevalence of current epilepsy) of the US population of children between birth and 17 years of age.<sup>12</sup> CWE were more likely to have academic and social difficulties compared to peers without a seizure disorder.<sup>12</sup>

A recent population-based study of children with active epilepsy found that neurobehavioral comorbidities were present in most (80%) of the CWE.<sup>13</sup> In addition to ADHD that was present in 33% of patients and will be discussed in detail later, 40% had an intellectual disability and 21% had

an autism spectrum diagnosis. Another study found that CWE are more likely than healthy peers to have been diagnosed with depression, anxiety, conduct problems, developmental delay, and autism spectrum disorders.<sup>12</sup>

Most studies assessing the prevalence of ADHD in patients with epilepsy have found two to three times higher rates of ADHD in the epilepsy population compared to controls. Several population-based studies have found ADHD prevalence rates between 23% and 40% in patients with epilepsy<sup>12-14</sup> compared to a prevalence of 6%–12% in controls. This finding of increased prevalence in population-based studies suggests that referral bias (CWE possibly more likely to be referred for ADHD assessment) is unlikely to explain the increased rates of ADHD in epilepsy populations. In contrast to the higher prevalence of ADHD in boys compared to girls in the general population, several recent studies have found statistically equivalent rates of ADHD in boys and girls with epilepsy.<sup>15-18</sup>

There is evidence to suggest that predominantly inattentive presentation of ADHD is more prevalent than combined presentation in patients with epilepsy (24%–52% vs 3%–11%, respectively<sup>15,19,20</sup>), which is different from the rates in the general population that indicate a greater frequency of combined presentation. This is consistent with the parents' report of the children's ADHD symptoms in a recent study in which parents of children with ADHD alone reported more predominant symptoms of hyperactivity and impulsivity compared to parents of children with ADHD and epilepsy who reported more problems with attention.<sup>21</sup> However, Gonzalez-Heydrich et al<sup>18</sup> found the rates of ADHD subtypes in an epilepsy group to be similar to the distributions in the general population (ie, combined presentation > inattentive presentation). When participants with a low intelligence quotient (IQ) (<80) were excluded from the analyses, ADHD inattentive and combined presentations were equal in prevalence. Sherman et al<sup>20</sup> found that in a group of children with severe epilepsy, those with ADHD combined presentation were more likely to have generalized epilepsy, an earlier age of onset, and lower functioning. Thus, further research is needed to fully understand the potential differences in ADHD subtypes in epilepsy.

ADHD symptoms are frequently present at the time of, or before, first seizure onset, suggesting that ADHD is a comorbid condition and not a condition caused solely by the seizure disorder or treatments. Hesdorffer et al<sup>17</sup> found that children with new-onset seizures were 2.5 times more likely to have ADHD inattentive presentation (but not combined presentation) than were seizure-free controls. Austin et al<sup>22</sup>

found a similar increased prevalence of ADHD in children with new-onset seizures and even higher rates in children with a new diagnosis but with previously unrecognized seizures.

Similar to children with ADHD and no epilepsy, the children with ADHD and epilepsy are at risk for additional emotional, behavioral, and cognitive problems. Few studies have assessed the rates of psychiatric comorbidities in patients with epilepsy and ADHD. Gonzalez-Heydrich et al<sup>18</sup> found oppositional defiant disorder and anxiety disorders to be common in CWE and ADHD but noted that the rates of comorbidities were similar to that seen in children with ADHD without epilepsy. In contrast, Reilly et al<sup>23</sup> noted that oppositional defiant disorder and developmental coordination disorder were more common in CWE and ADHD than in those with epilepsy alone. ADHD in CWE has been associated with learning difficulties.<sup>24</sup> Hermann et al<sup>25</sup> showed that children with new-onset seizures and ADHD had significantly more learning difficulties at baseline and 2-year follow-up than children with seizures and no evidence of ADHD. Reilly et al<sup>26</sup> found that low achievement was associated with ADHD, but after controlling for IQ, ADHD was no longer predictive of learning difficulties in CWE.

## Dissecting attention difficulties in epilepsy

Neuropsychological studies suggest that sustained attention is more often impaired than divided or selective attention and complex attention more affected than simple attention in CWE.<sup>27–29</sup> A review of neuropsychological studies of attention problems in epilepsy found evidence for deficits in sustained attention in children with complex partial seizures (CPSs) and benign childhood epilepsy with centrotemporal spikes.<sup>30</sup> On neuropsychological measures of sustained attention, children with CPS and ADHD performed worse than children with ADHD without epilepsy.<sup>30</sup> Children with CPS without a diagnosis of ADHD had performance similar to those with ADHD without epilepsy on measures of sustained attention.<sup>30</sup> Sustained attention has been shown to be impaired when interictal right hemisphere epileptiform activity is present compared to those with left hemisphere discharges.<sup>30</sup> Difficulty with sustained attention has been found to be more impaired in children with generalized compared to focal seizures.<sup>31</sup> Children with benign childhood epilepsy with centrotemporal spikes who have epileptiform discharges during sleep also have deficits in selective and divided attention; further, these deficits show significant improvement with remission of epileptiform activity during sleep.<sup>30</sup> More impaired complex attention and relatively normal

simple attention have been found in children with new-onset epilepsy not receiving antiepileptic drugs (AEDs)<sup>28</sup> and in children with seizures and hippocampal abnormalities.<sup>29</sup> A population-based study of cognitive abilities in CWE found significant difficulties in working memory and processing speed compared to controls, with over half of the patients displaying a relative weakness in at least one of the four working memory subtests administered.<sup>32</sup>

Berl et al<sup>33</sup> assessed attention with the Test of Everyday Attention for Children (TEA-Ch) in 75 children/teens (aged 6–15 years) with localization-related epilepsy compared to age-matched controls. CWE and IQ <70 were excluded. Over 90% were on AEDs. They found that CWE performed similar to controls on measures of simple auditory and visual attention; however, the CWE had slower motor speed compared to controls on a simple visual attention task (ie, similar accuracy but slower speed). Earlier age of seizure onset was associated with slower motor speed. Further, CWE performed significantly worse than controls on tasks of complex attention with over half of the epilepsy group scoring at least one standard deviation below the mean of the normative sample for these tasks.

Bechtel and Weber<sup>21</sup> found that children with ADHD and epilepsy are likely to have a similar developmental course of their ADHD symptoms as children with ADHD alone. In this study, children with ADHD and epilepsy and ADHD alone were assessed at ~11 and 16 years of age, and both groups of children had a similar and significant decline in ADHD symptoms at follow-up. They also showed similar changes on functional magnetic resonance imaging in CWE compared to children with ADHD. Although, a couple of studies have observed increased problems with attention<sup>34</sup> and executive functioning<sup>35</sup> in children with frontal lobe seizures, most studies have not found significant differences in attention and executive functioning based on seizure type or location.<sup>15,19,36,37</sup>

## Risk factors

Animal models of epilepsy suggest an association between ADHD-type symptoms and epilepsy. When epilepsy was experimentally induced in rats, half of the rats also had evidence of inattention and impulsivity.<sup>38</sup> These impairments were associated with suppressed noradrenergic transmission in the locus coeruleus. Another study found that frequent interictal spikes in rats were associated with significant inattentiveness.<sup>39</sup> Imaging studies have suggested that CWE and ADHD have disruptions in gray and white matter in a frontostriatal-cerebellar distribution, suggesting

similar neurological areas to those implicated in ADHD without epilepsy.<sup>27</sup>

Children with complicated epilepsy have been found to be at higher risk for ADHD compared to those with uncomplicated epilepsy.<sup>40</sup> Seizure frequency is positively associated with a diagnosis of ADHD,<sup>41</sup> and symptoms of hyperactivity are associated with intractable epilepsy. ADHD combined presentation has also been associated with more severe seizure disorders.<sup>20</sup> Earlier age of seizure onset has also been found to be associated with greater cognitive deficits,<sup>42</sup> including attention.<sup>33</sup> This could be the result of neuronal damage resulting from frequent seizures or seizures in an immature brain, the effects of AEDs,<sup>42</sup> or an underlying pathology, or genetic defect, contributing to etiology for both seizures and cognitive/attention deficits.

There is some evidence that AEDs can contribute to symptoms of ADHD,<sup>42–44</sup> with polytherapy likely resulting in more cognitive deficits compared to monotherapy.<sup>45,46</sup> Of the AEDs, phenobarbital is particularly implicated for causing cognitive symptoms, including problems with attention and hyperactivity.<sup>42</sup> Phenytoin, carbamazepine, and valproic acid can also cause some problems with attention and hyperactivity but to a lesser extent than those seen with barbiturates.<sup>42</sup> Topiramate has also been found to cause significant attention problems similar to those seen with valproic acid.<sup>42</sup> Available data at this time suggest that gabapentin, tiagabine, vigabatrin, and lamotrigine have few cognitive side effects and are thus not likely contributing significantly to ADHD symptoms.

Psychosocial factors have also been found to play a role in the manifestation of ADHD symptoms in CWE but are not thought to play a unique role in the etiology of ADHD in CWE (versus in healthy children with ADHD). Family and behavioral variables have been found to be more strongly associated with attention problems than seizure variables.<sup>47</sup>

In summary, CWE have two to three times higher rates of ADHD (and more frequent occurrence of predominantly inattentive subtypes) than their healthy peers, with neuropsychological testing showing impairments in sustained and complex attention tasks.

## Treatment of ADHD in epilepsy

### General considerations for treating children with ADHD and no history of seizures

When children with symptoms of ADHD require medication, current guidelines recommend starting with a trial of a stimulant (methylphenidate [MPH] or amphetamine

[AMP]).<sup>48–50</sup> Should the first stimulant not be effective, the alternative stimulant is used next. If stimulants are not effective or cause intolerable adverse effects, nonstimulants, including atomoxetine, alpha-2 agonists, and antidepressants, are employed.

## Psychostimulants

Stimulants are Food and Drug Administration (FDA) approved in the treatment of ADHD, including MPH and the AMPs dextroamphetamine and mixed salt AMPs.<sup>48</sup> Both MPH and AMP work through blockade of dopamine and noradrenaline reuptake into the neurons.<sup>51,52</sup> Furthermore, AMP causes release of catecholamines.<sup>51,53</sup> Both stimulant groups have been found useful in the ADHD treatment. Stimulants have been demonstrated to be highly efficacious in double-blind, placebo-controlled trials with 65%–75% of healthy adult and child subjects responding to stimulants compared to 4%–30% on placebo.<sup>48</sup> MPH and AMPs are equally efficacious with a combined response rate of 85% when tried sequentially.<sup>34</sup> Generally, this allows the provider to choose either one as first line and should this fail trialing the other.

Details on medication treatment for ADHD are available in standard references.<sup>48</sup> Generally, patients should be started on a long-acting formulation to promote greater adherence to treatment.<sup>48,54</sup> However, short-acting stimulants and lower doses are often used in children at the age of 5 years or younger due to higher rates of emotional adverse events and slower metabolism of MPH in this age range.<sup>48,55,56</sup> Parent, teacher, and child ADHD scales can be used to follow effectiveness of the medication formulation and dosage. Monitoring of side effects before and during treatment includes insomnia, headache, appetite, weight loss/growth, irritability, and tics. Although there are reports suggesting very minimal increased risk of sudden death associated with stimulant use, most authorities recommend against additional cardiac evaluation in healthy individuals.<sup>48</sup>

## Nonstimulants

Generally, it is recommended that stimulants be first line in treatment. The nonstimulants have a lower effect size than stimulants. However, there may be other concerns making stimulants unfavorable, such as tics, concerns for growth, substance issues, intolerability to stimulants, or health contraindications. Nonstimulants have less effect on appetite, growth, and sleep and may be beneficial in children with comorbid emotional conditions such as anxiety disorder or Tourette syndrome.

## Atomoxetine

Atomoxetine is a nonstimulant FDA-approved medication for ADHD that works by noradrenergic reuptake inhibition. In a study by Michelson et al,<sup>57</sup> the effect size of atomoxetine in ADHD was determined to be 0.7 with the greatest effects starting at 6 weeks of treatment. A meta-analysis further looked at the efficacy of atomoxetine versus stimulants showing an effect size of 0.62 compared to 0.95 for long-acting stimulants.<sup>48,58</sup> In another large study, using the ADHD Rating Scale IV (ADHD-RS-IV), 45% of patients treated with atomoxetine demonstrated a 40% decrease in core ADHD symptoms.<sup>59</sup> In addition, in children with ADHD with comorbid anxiety, atomoxetine has been shown to be effective in treating the symptoms of both ADHD and anxiety<sup>48,60</sup> and may be used as a first-line treatment.

The most common adverse effects of atomoxetine are decreased appetite, gastrointestinal issues, and sedation. Much less common are reports of irritability, suicidal ideation, and hepatic disease.

## Alpha-2 agonists

In addition to stimulants and atomoxetine, alpha-adrenergic agonists – clonidine and guanfacine – are used to treat ADHD. In particular, the alpha-adrenergic agonists, guanfacine extended release (Intuniv) and clonidine extended release (Kapvay), have been approved by the US FDA for the treatment of childhood ADHD as monotherapy or as an adjunctive treatment to stimulants. The alpha-2 adrenergic agonists are thought to act in ADHD through postsynaptic alpha-2 adrenoreceptors in the PFC.<sup>61</sup> Similar to atomoxetine, the alpha-adrenergic agonists are considered less effective than stimulants for the treatment of ADHD; however, they should be considered an alternative treatment option when insufficient efficacy or intolerable side effects are present during stimulant treatment. Ruggiero et al<sup>62</sup> performed a systematic review and meta-analysis of ADHD treatment with guanfacine versus placebo. Using seven included studies and 1,752 participants, they found 59% of patients benefiting from treatment compared to 33.3% on placebo, and the most prominent side effects were noted as somnolence, headache, and fatigue. With regard to the side effects, guanfacine has selectivity for alpha-2 adrenoreceptors in the PFC and has shown less central nervous system depressant and hypotensive effects than clonidine.<sup>62</sup> Of additional interest, a multicenter, double-blind, placebo-controlled dose-optimization study of guanfacine extended release used as an adjunct to stimulant treatment in children with ADHD and comorbid oppositional symptoms demonstrated

significant improvement in oppositional symptoms when compared to the combination of stimulant and placebo.<sup>63</sup>

Alternative nonstimulant medications for the child with ADHD and no evidence of epilepsy include the tricyclic antidepressants and bupropion. The effect size is low, and there are concerns about cardiac toxicity of tricyclic antidepressants and the lowering of seizure threshold with bupropion.

## Prescribing ADHD medications for CWE

In CWE and ADHD, there are several questions. Are the standard medications for ADHD effective in CWE, and if so, which medications are most likely to be effective. Second, are the standard medications for ADHD safe in CWE. Finally, are there additional concerns about potential adverse effects of ADHD medications that should be considered in CWE.

Because there are multiple causes for impaired attention in the child with epilepsy, including current seizures, effects of chronic seizures on cognitive functioning, AED side effects, and medication interactions, the provider should review the patient's seizure frequency and AEDs to determine if improvements in seizure frequency could be made, the medication regimen is contributing to behavioral and attention symptoms, and/or the regimen can be simplified to limit drug interactions.

As seen in children with ADHD and no seizures, stimulant medication appears to be effective for treatment of ADHD in CWE.<sup>51,64-68</sup> The use of MPH in children with ADHD appears to show a 70%–80% response rate.<sup>64</sup> In contrast to the robust data for the use of stimulants in the child with ADHD alone, the data for the treatment of ADHD in CWE are much weaker. There are two double-blind, placebo-controlled trials. Feldman et al<sup>66</sup> assessed ten children with multiple seizure types, no seizures in the past 3 months, and cognitive function ranging from disabled to normal in a 4-week trial of MPH, given twice daily at 0.3 mg/kg/dose and found that 70% improved. Gonzalez-Heydrich et al<sup>69</sup> studied 33 children and adolescents who had been seizure free for 1 month. Patients received osmotic release oral system MPH 18, 36, or 54 mg, or placebo for 1 week. There was a significant improvement in ADHD symptoms during the time on MPH compared to the time on placebo. Three open-label studies using MPH found a response rate of 70%–77%.<sup>69-71</sup> There is much less data on response of ADHD symptoms to AMPs in CWE. In one retrospective study, 12 out of 19 patients had a favorable response to MPH compared to four of 17 who received AMP. Two open-label studies have looked at the treatment of ADHD in children and adolescents

with active and refractory seizure disorders. Santos et al<sup>72</sup> evaluated the impact of low-dose MPH (up to 1 mg/kg) on ADHD symptoms in 22 children with severe epilepsy and found that after 3 months of treatment, 73% had entered remission with subthreshold scores on an ADHD symptom questionnaire. Fosi et al treated 18 patients with refractory epilepsy and intellectual disability with MPH 0.3–1 mg/kg/d and found reduction of ADHD symptoms in 63%.<sup>73</sup> Of note, the impact of MPH on ADHD symptoms does not appear to be affected by IQ or learning disability.<sup>72,73</sup> In addition to ADHD symptom improvement, another study of MPH in children with difficult-to-treat epilepsy suggested a positive impact on quality-of-life scores related more to behavioral improvement than simply AED adjustment and improvement in seizures.<sup>74</sup>

A persistent concern with the use of stimulant medication in CWE is the risk of increase in seizure frequency. In the two controlled trials, there were no seizures during the 4-week treatment trial reported by Feldman et al,<sup>66</sup> but there was a trend for more seizures during the week on the highest dose of osmotic release oral system MPH in the study of Gonzalez-Heydrich et al.<sup>69</sup>

In the open-label trial reported by Gross-Tsur et al,<sup>64</sup> none of the 25 children who had any seizures in the 2 months prior to MPH treatment had additional seizures, but three of five children with seizures during the lead-in period had an increase in seizure number. Gucuyener et al<sup>70</sup> found no increase in mean seizure frequency but noted increase in seizure number in five of 57 patients who had seizures prior to starting MPH. Koneski and Casella<sup>71</sup> found that during a 6-month open-label treatment with MPH, 91.6% had no increase in seizures; however, increased numbers were seen in 8.3%. In the retrospective study of Gonzalez-Heydrich et al,<sup>69</sup> none of the 17 patients who were seizure free at the beginning of stimulant treatment had additional seizures, but three of 19 patients with seizures had an increase in seizure frequency. In the two studies of patients with refractory epilepsy, one noted no deterioration in seizure control and the second found increased seizure frequency in four out of 22 patients.

In the literature, there is less information on efficacy and tolerability of AMP, atomoxetine, and alpha-2 adrenergic agonists in CWE. In one study, a retrospective medical records review allowed a comparison of MPH and AMP in a population of 36 CWE and ADHD treated with stimulants. A higher response rate in the treatment of ADHD was seen in the MPH group (12/19, 63%) versus the AMP group (4/17, 21%). Within the group before treatment with stimulant, 47% were considered seizure free and 53% had

active seizures, and there were no significant differences in the number of patients in each group prescribed MPH versus AMP. During the trial, one patient on MPH and two patients on AMP had increased seizure frequency that returned to baseline with discontinuation of stimulants.<sup>16</sup> In a review of the clinical trials, database and postmarketing reported spontaneous adverse events, 12 out of 5,082 patients (0.2%) on atomoxetine had a seizure, at the same rate as placebo, suggesting that children taking atomoxetine for ADHD are not at increased risk of seizures.<sup>75</sup> In another study by Torres et al,<sup>76</sup> tolerability of atomoxetine in CWE and ADHD with previous treatment failure was reviewed and found that 63% of 27 patients discontinued treatment with the majority due to poor response or worsening behavior. There is a lack of studies reviewing alpha-2 adrenergic agonists, both in their impact on ADHD treatment in CWE and on their effect on seizures. However, there have been reports of seizures following clonidine ingestions (1, 126–130).<sup>77–80</sup>

There are additional considerations for using ADHD medications in CWE. Tricyclic antidepressants and bupropion have been used in children with ADHD but can lower seizure threshold and should be avoided in patients with epilepsy. Drug interactions between medications for ADHD and AEDs are minimal. MPH may increase phenytoin serum levels, and carbamazepine may reduce MPH levels. There are no reports of interaction between atomoxetine or alpha adrenergics and AEDs. Because of the sedative effects of alpha adrenergics, they should be used cautiously in patients receiving sedating AEDs. Sudden unexpected death in patients with epilepsy is a concern, but there are no data to suggest that stimulant medications may increase the risk of sudden death associated with seizures.

Any statement about efficacy and safety of medical treatment of ADHD in patients with epilepsy must acknowledge the major limitation in data. There are only two double-blind placebo-controlled trials, and one has only ten participants and the other limited treatment to 1 week. There are more open-label trials, but the number of participants in each study is small. Only the report by Gucuyener et al<sup>70</sup> had >50 patients with epilepsy. Most studies used samples with both intellectual disability and normal intelligence and with multiple seizure types. The samples are too small to comment on the effect of cognitive function or seizure type on the efficacy of medication for ADHD. Only the trials of MPH have sufficient numbers for reasonable suggestions on efficacy and adverse effects. The reports on AMP and atomoxetine are open label and have small numbers of participants, and there are no reports on alpha adrenergics in CWE.

From this review of the literature, we conclude that MPH is effective in the treatment of symptoms of ADHD in children and adolescents with seizures though the effect size is possibly lower than that seen in children with ADHD without epilepsy. AMPs and atomoxetine may be effective but with lower effect size and very limited data. The risk of increase in seizure frequency appears to be minimal with MPH, atomoxetine, and the alpha adrenergics, but patients should be warned of a low risk of seizures and should be monitored closely.

## Treatment of ADHD with behavioral therapies

While psychopharmacology is the primary treatment modality for ADHD, behavioral treatment may be recommended for use in combination with medication treatment or in children with minimal impairment or when medication is not an option due to contraindications or parental objections. Behavioral therapies would not be expected to differ significantly in implementation or efficacy in children with ADHD with and without epilepsy. However, in CWE, compared to otherwise healthy children with ADHD, there may be a higher likelihood for medical contraindications or parental objections (eg, a desire to minimize the number of overall medications) to medication treatment of ADHD, and thus, behavioral therapies may present an important avenue for treatment. There is some evidence that behavioral therapies can be effective adjuncts to medication treatment or as stand-alone treatments for ADHD. A large randomized controlled trial assessing treatment efficacy (behavioral treatment, medication treatment, both medication and behavioral treatment, and community treatment) over a 14-month period found that ADHD symptoms improved in all groups with the greatest improvements for those in the medication only and combined intervention groups.<sup>81</sup> Participants receiving both medication and behavioral treatment received lower doses of medications compared to those in medication management alone and had more improvement in non-ADHD symptoms (eg, oppositional behaviors, internalizing) compared to medication management alone. However, there were no significant differences in ADHD symptoms in participants receiving combination treatment versus medication alone. Behavioral treatments for ADHD are often modeled off of the work by Barkley<sup>82</sup> and typically include parent behavior training to improve the use of effective contingency management, reinforcement, and routines to target challenges associated with ADHD. Similar interventions are also implemented in the school setting. There is very limited research assessing behavioral therapies for ADHD in children with comorbid epilepsy. Triplett et al<sup>83</sup>

conducted a functional magnetic resonance imaging study in CWE and demonstrated improvements in inhibitory control following reward trials. Thus, there is evidence that cognitive rehabilitation may be effective at targeting ADHD symptoms in CWE; however, further research is needed.

## Conclusion

Research indicates that ADHD is more prevalent in CWE compared to healthy peers, with some evidence indicating that the inattentive presentation (as opposed to combined presentation) is more common in this population. Some aspects of the seizure disorder and its treatment could contribute to ADHD symptoms. For example, children with complicated epilepsy may be at greater risk for ADHD, and some antiepileptic medications can contribute to ADHD symptoms. However, the seizure disorder and its treatment are not likely the sole cause of increased prevalence of ADHD in this population, as evidenced by the increased presence of ADHD symptoms even before diagnosis of a seizure disorder. Research should continue to investigate the nature of the comorbidity of these two conditions. Many studies have demonstrated the importance of ADHD medication treatment both in healthy children and in CWE. The importance of consideration for ADHD treatment was recently highlighted again by a large population-based study by Sayal et al.<sup>84</sup> In the study, with each one-point increase in inattention symptoms at 7 years old, an associated worse academic outcome was seen at 16 years old, demonstrating a long-term academic risk. While there may be some individual risk of increase in seizures in treated patients, the benefit of treatment appears to outweigh the risk. There are limitations in the current research of treatment for ADHD in CWE with the lack of larger patient studies, controlled trials, and long-term outcome data showing that treatment improves cognitive outcome. Further research testing of efficacy and seizure effects of psychotropic medications should continue, particularly with regard to AMPs and the alpha-2 adrenergic agonists.

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