Received: 6 June 2018 | Revised: 28 July 2018 | Accepted: 31 July 2018

DOI: 10.1111/epi.14549

SPECIAL REPORT

Epilepsia®

Systematic review of the screening, diagnosis, and management of ADHD in children with epilepsy. Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission

Stéphane Auvin[1] | Elaine Wirrell[2] | Kirsten A. Donald[3] | Madison Berl[4] | Hans Hartmann[5] | Kette D. Valente[6] | Patrick Van Bogaert[7] | J. Helen Cross[8] | Makiko Osawa[9] | Hideaki Kanemura[10] | Masao Aihara[11] | Marilisa M. Guerreiro[12] | Pauline Samia[13] | Kollencheri Puthenveettil Vinayan[14] | Mary Lou Smith[15] | Lionel Carmant[16] | Michael Kerr[17] | Bruce Hermann[18] | David Dunn[19] | Jo M. Wilmshurst[20]

[1]Department of Pediatric Neurology, Robert-Debré University Hospital, APHP, Paris, France

[2]Divisions of Child and Adolescent Neurology and Epilepsy, Mayo Clinic, Rochester, Minnesota

[3]Division of Developmental Paediatrics, Department of Paediatrics and Child Health, Neurosciences Institute, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa

[4]Division of Pediatric Neuropsychology, Children's National Medical Center, Washington, District of Columbia

[5]Clinic for Pediatric Kidney, Liver and Metabolic Disorders, Hannover Medical School, Hannover, Germany

[6]Division of Clinical Neurophysiology, Institute and Department of Psychiatry, Clinics Hospital (HCFMUSP), Faculty of Medicine, University of São Paulo, São Paulo, Brazil

[7]Department of Pediatric Neurology and Neurosurgery, University Hospital of Angers, Angers, France

[8]Developmental Neurosciences Programme, UCl Great Ormond Street Institute of Child Health, London & Young Epilepsy, Lingfield, UK

[9]Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan

[10]Department of Pediatrics, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

[11]Graduate Faculty of Interdisciplinary Research, Graduate School, University of Amanashi, Yamanashi, Japan

[12]Department of Neurology, University of Campinas (Unicamp), Campinas, Brazil

[13]Department of Paediatrics and Child Health, Aga Khan University, Nairobi, Kenya

[14]Division of Pediatric Neurology, Department of Neurology, Amrita Institute of Medical Sciences, Cochin, India

[15]Department of Psychology, The Hospital for Sick Children, University of Toronto Mississauga, Toronto, Canada

[16]Department of Neurosciences and Pediatrics, CHU Sainte-Justine, University of Montreal, Montreal, Canada

[17]Division of Psychological Medicine and Clinical Neuroscience, Cardiff University, Cardiff Wales, UK

[18]Department of Neurology, School of Medicine and Public Health, University of Wisconsin, Madison, Wisconsin

[19]Section of Child and Adolescent Psychiatry, Departments of Psychiatry and Neurology, Indiana University School of Medicine, Indianapolis, Indiana

[20]Division of Paediatric Neurology, Neuroscience Institute, Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa

Correspondence
Stéphane Auvin, Service de Neurologie Pédiatrique, Centre de Référence Epilepsies Rares, CHU Robert-Debré, 48 Boulevard Serurier, 75019 Paris, France.
Email: stephane.auvin@aphp.fr

Summary

Attention-deficit/hyperactivity disorder (ADHD) is a common and challenging comorbidity affecting many children with epilepsy. A working group under the International League Against Epilepsy (ILAE) Pediatric Commission identified key questions on the

Stéphane Auvin and Elaine Wirrell are the joint first authors.

identification and management of ADHD in children with epilepsy. Systematic reviews of the evidence to support approaches to these questions were collated and graded using criteria from the American Academy of Neurology Practice Parameter. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) requirements were followed, with PROSPERO registration (CRD42018094617). No increased risk of ADHD in boys with epilepsy compared to girls with epilepsy was found (Level A). Valproate use in pregnancy is associated with inattentiveness and hyperactivity in offspring (1 class I study), and children with intellectual and developmental disabilities are at increased risk of ADHD (Level A). Impact of early seizure onset on development of ADHD was unclear (Level U), but more evident with poor seizure control (Level B). ADHD screening should be performed from 6 years of age, or at diagnosis, and repeated annually (Level U) and reevaluated after change of antiepileptic drug (AED) (Level U). Diagnosis should involve health practitioners with expert training in ADHD (Level U). Use of the Strength and Difficulties Questionnaire screening tool is supported (Level B). Formal cognitive testing is strongly recommended in children with epilepsy who are struggling at school (Level U). Behavioral problems are more likely with polytherapy than monotherapy (Level C). Valproate can exacerbate attentional issues in children with childhood absence epilepsy (Level A). Methylphenidate is tolerated and effective in children with epilepsy (Level B). Limited evidence supports that atomoxetine is tolerated (Level C). Multidisciplinary involvement in transition and adult ADHD clinics is essential (Level U). In conclusion, although recommendations could be proposed for some of the study questions, this systematic review highlighted the need for more comprehensive and targeted large-population prospective studies.

KEYWORDS

antiepileptic drug, attention-deficit/hyperactivity disorder, children, epilepsy, methylphenidate, screening tools

1 | INTRODUCTION

Epilepsy is a "spectrum" disorder, with associated cognitive and psychiatric impairment in approximately half of the patients. Attention-deficit/hyperactivity disorder (ADHD), defined by Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria as a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, is the most common comorbidity in children with epilepsy.[1,2] Prevalence of ADHD in children with epilepsy is reported as 30%-40% in targeted studies[3-5] and 12.5%-15% in a nontargeted, population registry study,[6] overall a rate 2.5 to 5.5 times higher than in otherwise healthy children without seizures. Attention problems often predate onset of seizures.[6,7] The predominantly inattentive type of ADHD is more prevalent in patients with epilepsy.[5,9,10] A large, population-based cohort study has suggested that both genetic and environmental factors contribute to this comorbidity.[7]

Key points

- Risk factors for ADHD in children with epilepsy include comorbid developmental disabilities, as well as poor seizure control
- Data support the ability of the Strengths and Difficulties Questionnaire to predict ADHD diagnosis in children with epilepsy
- Polytherapy is more associated with behavioral problems than monotherapy
- Valproate can exacerbate attentional issues in children with Childhood Absence Epilepsy
- Methylphenidate is tolerated and effective in children with epilepsy and comorbid ADHD

The impact of comorbid ADHD in people with epilepsy is significant, often associated with academic and vocational underachievement, depression, and anxiety.[8,9]

Furthermore, ADHD is underdiagnosed in children with epilepsy,[10] as difficulties with attention and behavior are attributed to the epilepsy itself, or to the effects of antiepileptic drugs (AEDs). Even if recognized, ADHD is frequently untreated[10] compounded by the myth that stimulants may lower seizure threshold.[11]

The purpose of this consensus paper developed by the International League Against Epilepsy (ILAE) Pediatric Commission was to provide evidence-based guidance to inform clinical practice regarding screening, diagnosis, and management of ADHD in patients with pediatric epilepsy.

2 | METHODS

A Task Force on Pediatric Comorbidities was recruited by the Pediatric Commission of the International League Against Epilepsy (ILAE). The working group identified 5 specific questions that were highly relevant to clinical care (Table 1), and for each, a group of 3-4 members reviewed the existing literature.

The systematic review was completed for each study question using a National Library of Medicine and Embase search with focused search terms (Table S1). The process followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) requirements (Table S2) and was registered on PROSPERO (registration number CRD42018094617) (Table S3). The literature search was performed with a date-range spanning January 1990 to January 2018. Only papers in English were considered. Table S1 provides more detail on the specific study question–related search terms and the number of studies identified. Where possible, recommendations were graded according to level of the evidence-based data according to the American Academy of Neurology Practice Parameter (Table S4).[12] Where there were single studies that related to the study question, the class (I, II, III, IV) of the study rather than a grade (A,B,C,U) was documented. Where consistent evidence was lacking but a recommendation remained useful, Level U category was implemented, and the working group acknowledged that this was their expert opinion. Formal workshops to synthetize the literature search, and to discuss grading of evidence and "expert opinion," were organized by the ILAE pediatric commission during the International Epilepsy Congress in Turkey 2015 and the American Epilepsy Society meeting in 2016, in addition to regular informal communications among each subquestion working group.

TABLE 1 List of clinical practice–oriented questions about ADHD in Children and Teens with Epilepsy identified by the ILAE Pediatric Commission

1. What are the risk factors for ADHD in children and teens with epilepsy and when should screening begin?
2. What screening tools should be used, and how should ADHD be diagnosed in children and adolescents with epilepsy?
3. What criteria can be used to distinguish ADHD from other conditions such as absence seizures, learning disorders, and other conditions that mimic ADHD?
4. What is the recommended management of ADHD in children and adolescents with epilepsy?
5. What is the recommended follow-up and transition of children and adolescents with ADHD and epilepsy?

3 | RESULTS

An executive summary is presented in Table 2. The full document reports the available data and the group agreement question by question.

3.1 | What are the risk factors for ADHD in children and adolescents with epilepsy and when should screening begin?

3.1.1 | What are the risk factors of ADHD in children with epilepsy?

There is a bidirectional association between epilepsy and ADHD, with ADHD occurring 2.54 times more commonly in children with epilepsy than in control children without epilepsy and epilepsy occurring 3.94 times more in children with ADHD than in control children without ADHD.[5]

Discussion of Findings (Table S1).

Sex (Level A)

In the general population, ADHD is 3- to 7-fold more common in boys than girls.[13] However, most studies document equal sex distributions of ADHD in children with epilepsy.[14] Two studies evaluating children with new-onset epilepsy found that male sex was not predictive of higher rates of ADHD.[14,15] Similar findings were noted in studies of children with preexisting epilepsy.[4,16] In contrast, a single cross-sectional study investigating the risk of ADHD in patients aged 10-19 years with focal or generalized epilepsy found a strong trend between the presence of ADHD and male sex ($P = 0.06$).[17] In conclusion, most studies found no increased risk in boys with epilepsy compared to girls with epilepsy.

Prenatal insults

A single, class I, prospective observational study of children born to mothers on monotherapy AEDs during pregnancy found that a higher level of inattentiveness and hyperactivity in children at 3 years of age with prenatal exposure to valproate, compared to carbamazepine, lamotrigine, or phenytoin.[18]

TABLE 2 Summary of recommendations with regard to screening, diagnosis, and management of ADHD in children with epilepsy

Study question	Recommendation	Level of recommendation	Comment
(1) What are the risk factors for ADHD in children and teens with epilepsy and when should screening begin?			
What are the risk factors of ADHD in children with epilepsy?	There is no increased risk of ADHD in boys with epilepsy compared to girls with epilepsy	A	
	Valproate use in pregnancy is associated with inattentiveness and hyperactivity in offspring	Class I	Single class I study
	Children with epilepsy with comorbid intellectual and developmental disabilities are at increased risk of ADHD	A	
	Evidence is conflicted for the impact of early seizure onset on the development of ADHD in children with epilepsy	U	Need large prospective studies
	Specific seizure types are not predictive of higher rates of ADHD	U	
	Poor seizure control is associated with increased risk of ADHD	B	
When to screen the children with epilepsy for ADHD	Screening for ADHD should be performed from 6 years or at the time of diagnosis and repeated annually	U	Expert opinion
	Reevaluation of attention function after any change of AED	U	Expert opinion
	Screening should not be performed within 48 h of seizure event associate with a postictal state	U	Expert opinion
(2) What screening tools should be used, and how should ADHD be diagnosed in children and adolescents with epilepsy?			
	The diagnosis of ADHD should involve health practitioners who have undergone expert training in the recognition of ADHD	U	Expert opinion
	Data support the ability of the SDQ to predict ADHD diagnosis in children with epilepsy	B	Expert opinion — research on other screening tools is needed
	It is more important to over identify (false positive) on screening rather than miss children (false-negative) who are at risk	U	Expert opinion
(3) What criteria can be used to distinguish ADHD from other conditions such as absence seizures, learning disorders, and other conditions that mimic ADHD?			
	A distinction between ADHD and CAE should be based on history and an EEG with hyperventilation	U	Expert opinion
	Formal cognitive testing is strongly recommended in children with epilepsy who are struggling at school	U	Expert opinion
	Careful screening for anxiety and depression, and queries regarding sleep should be undertaken routinely in children with epilepsy, particularly if inattention and academic concerns are present	U	Expert opinion
(4) What is the recommended management of ADHD in children and adolescents with epilepsy?			
Are there precautions to consider with certain AEDs with regards to ADHD?	Polytherapy is more likely to be associated with behavioral problems than monotherapy	C	
	Valproate can exacerbate attentional issues in children with CAE	A	
Does methylphenidate exacerbate seizures?	Methylphenidate is tolerated in children with epilepsy (both controlled and refractory)	B	
	Limited evidence supports that atomoxetine is tolerated in children with epilepsy and ADHD	C	
	Tolerability for amphetamine in children with epilepsy is not defined	U	

(*Continues*)

TABLE 2 (Continued)

Study question	Recommendation	Level of recommendation	Comment
Is there any evidence-based treatment to the management of ADHD in children and adolescent with epilepsy?	Evidence supports efficacy of methylphenidate in children with epilepsy and comorbid ADHD	B	
	Limited evidence exists for the efficacy of atomoxetine and amphetamines in children with epilepsy and ADHD	U	
5. What is the recommended follow-up and transition of children and adolescents with ADHD and epilepsy?			
	Multidisciplinary involvement in transition and adult ADHD clinics is essential as many patients experience challenges with housing, employment, relationships and psychosocial well-being	U	Expert opinion

Intellectual and developmental disabilities (Level A)

Class I and II studies consistently note a higher prevalence of ADHD in children with associated intellectual and developmental disabilities. A cross-sectional survey of British children noted a higher rate of comorbid ADHD in those with complicated epilepsy, inclusive of severe learning disorders, speech, or language problems.[19] In children with newly diagnosed epilepsy, significantly higher rates of school-based remedial services and neuropsychological deficits in executive function occurred in children with the additional comorbidity of ADHD.[14] A study of 85 children with epilepsy found that ADHD was present in only 20% of patients with normal cognitive function, versus 59% of those children with cognitive delays.[20] A prospective, community-based study of children with epilepsy found that children with intellectual disability had a higher mean level of symptoms than those without intellectual disability on both the Parent and Teacher versions of the ADHD-Rating Scale IV.[21] In addition, Reilly and colleagues found that developmental coordination disorder was significantly predictive of a higher risk of ADHD.[22] In conclusion, children with epilepsy as well as intellectual and developmental disabilities are at increased risk of ADHD.

Family history of ADHD

It is generally accepted that genetic factors play a significant role in predisposition to ADHD.[23] Only one small class III study has evaluated this association in children with epilepsy and comorbid ADHD. Sixteen mothers of children with ADHD plus epilepsy were evaluated using the ADHD-Rating Scale IV, and half met criteria for ADHD.[24]

Age at epilepsy onset (Level U)

Although some studies show a higher prevalence of ADHD among those with earlier age of epilepsy onset, the literature is conflicted on this topic. Alfstad and colleagues demonstrated that early onset of epilepsy increased the risk of developing psychiatric disorders overall, although the study did not specifically address ADHD alone (class II).[17] Similarly, a study of adolescents with epilepsy attending mainstream schools noted higher rates of ADHD in those with younger age at seizure onset (class II).[25] A small study on children with childhood epilepsy with centrotemporal spikes (CECTS) found that children who were younger at epilepsy onset had a higher prevalence of attention deficit (class II).[26]

In contrast, Hermann and colleagues found no significant correlation between younger age at seizure onset and higher rates of ADHD (class II) in a cohort of children with newly diagnosed epilepsy.[14] Similarly, Kral et al[27] found no association between earlier age at epilepsy onset and ADHD in a retrospective cohort study of children with epilepsy (class III).

Seizure and epilepsy type (Level U)

Several well-designed studies provide evidence that children with childhood absence epilepsy (CAE) have high rates of ADHD; however, these studies did not compare CAE to other epilepsy types.[28-30] Four studies have assessed whether specific seizure types correlate with greater risk of ADHD and found no correlation.[4,14,15,27] In contrast, one study comparing 23 children with temporal lobe epilepsy to 20 children with idiopathic generalized epilepsy found that those with temporal lobe epilepsy performed worse on tests of attentional control (class III).[31] Another study comparing 51 children with focal seizures with altered awareness to 31 with CAE found similar prevalence of executive dysfunction in both cohorts (class II).[32]

EEG variables (Level U)

Several studies on small cohorts of children with CECTS noted a correlation between higher spike index and poorer

function on measures of attention.[26,33] In contrast, a small pilot study did not find any correlation between spike index during sleep and severity of ADHD symptoms in children with various types of epilepsy.[34] A prospective study of children evaluated at seizure onset and compared to healthy siblings found that interictal spikes were an independent risk factor of processing speed but not of attention/executive/construction impairment.[35] In conclusion, there is no convincing evidence for a relationship between interictal EEG changes and the severity of attention deficits.

Seizure frequency and control (Level B)

Most studies support a link between poor seizure control and higher risk of ADHD. In a prospective observational class III study of 40 children with "idiopathic or cryptogenic epilepsy," both higher seizure frequency and polypharmacy correlated with a greater risk of developing ADHD.[36] In a survey of children with drug-resistant epilepsy attending a regional epilepsy center, higher seizure frequency was correlated with a greater risk of attention and hyperactivity subscale scores on the Child Behavior Checklist (CBCL) (class III).[37] In a class III study of 75 children with focal epilepsy, those with seizures occurring at least weekly were rated by their parents to have more symptoms of hyperactivity than those having less frequent seizures.[38] A study of adolescents with epilepsy, found a significant correlation between a greater number of AEDs used and lower scores on an inattentive subscale (class III).[25]

A single class III study reported a prevalence of ADHD of over 60% in a cohort of children with refractory epilepsy.[16] Although this study suggests that intractability is highly correlated with ADHD, a comparison group with less severe epilepsy was lacking. Conversely, a single population-based, case-control study found no significant correlation between seizure frequency at initial diagnosis in children with newly diagnosed epilepsy (class II).[15]

Based on combined study findings, but balanced by the limitation of most data being from class III studies, there is evidence to support an association between poor seizure control and increased risk of ADHD. Future studies need to examine the interaction effect of polypharmacy and seizure frequency and control to determine if the increased risk for ADHD is related to seizure frequency and control or the adverse effects of polypharmacy.

3.1.2 | When to screen children with epilepsy for ADHD (Level U; expert opinion)

There are no studies that evaluate when to screen children with epilepsy for ADHD. Based on reports that children with epilepsy are at elevated risk of ADHD at the time of presentation with their first seizure[39] or when epilepsy is first diagnosed,[14] screening for ADHD should be performed in every child with epilepsy starting at the age of 6 years, or at the time of diagnosis if older than 6 years, and should be repeated annually. Attention should also be reevaluated after any change of AED. Screening should not be performed within 48 hours of a seizure associated with a postictal state.

3.2 | What screening tools should be used and how should ADHD be diagnosed in children and adolescents with epilepsy?

Although guidelines and consensus statements for assessment of Attention-Deficit/ Hyperactivity Disorder (ADHD) exist,[40,414243] the ideal assessment method and how to differentiate among subtypes is not defined. The diagnosis of ADHD should involve health practitioners with expertise in ADHD, such as psychologists, child psychiatrists, child neurologists, and developmental pediatricians (Level U: expert opinion). Diagnosis of ADHD requires the following: (1) validated ADHD-rating scales from parents and teachers based on the Diagnostic and Statistical Manual of Mental Disorders—4th or 5th editions (DSM-IV and 5); (2) rating scale information through parent interview; and (3) exclusion of other causes. Rating scales permit screening to assess ADHD symptoms but no formal recommendations state using one tool over the other (Table S5). Measures differ in terms of normative populations, availability in languages other than English, cost, whether they assess impairment in various areas (school, home, work), screening for symptoms other than ADHD, and time required to complete.[44]

Six studies met the inclusion criteria with a total of 608 participants with childhood-onset epilepsy. Three were ranked as class I,[21,22,45] 2 as class II,[17,46] and one as class III.[47] Four of the studies[21,22,45,46] included diagnostic efficiency statistics (e.g., sensitivity, specificity), and one study reported the concordance between the screener identification of problematic behavior and a psychiatric diagnosis.[17] A summary of study findings is provided in Table 3.

Three of the studies used the Strengths and Difficulties Questionnaire (SDQ),[48] with 2 of them reporting data on the Hyperactivity subscale—among other SDQ scores,[22,46] and one using the Total score only.[17] All studies combined both Borderline and Abnormal cutoffs on the SDQ as a positive screen for ADHD. More children screened positive on parental reporting of the Hyperactivity scale than actually had the diagnosis, compared to teachers who underidentified children who ultimately received a diagnosis of ADHD.[22] Another study of similar sample size and with similar ADHD rate found the sensitivity and specificity of parental report on the SDQ hyperactivity subscale to be stronger than the Reilly et al[22] UK study at 86.4% and

TABLE 3 Summary of the studies with data to assess which screening tools should be used in the diagnosis ADHD in children and adolescents with epilepsy

Study	Country	Sample	Measure	Seizure characteristics	DSM diagnosis
Reilly et al 2014[22]	UK-South	New-onset epilepsy in the community; IQ > 34; n = 69; ages 5-15	SDQ Abnormal/Borderline Parent Rating on the Hyperactivity scale had 50%/75% sensitivity	1/3 had weekly seizures; 2/3 had no or less often	Consensus of psychologist, pediatrician, psychiatrist based on case notes, standardized screening and cognitive measures, and school observations. N = 28 ADHD (19 ADHD-C; 9 ADHD-I)
Reilly et al 2017[21]	UK-South	Active epilepsy in the community: IQ>34, n = 69, ages 5-15	ADHD-RS IV Abnormal parent total score had 86% sensitivity and 51% specificity Abnormal teacher total score had 63% sensitivity and 90% specificity	1/3 had weekly seizures; 2/3 had no or less often	Consensus of psychologist, pediatrician, psychiatrist based on case notes, standardized screening and cognitive measures, and school observations. N = 28 ADHD (19 ADHD-C; 9 ADHD-I)
Tanabe et al 2014[46]	Japan	Primary clinic; severely mentally or physically handicapped excluded; n = 68; ages 4-17	SDQ Abnormal/Borderline Hyperactivity Parent had 86.4% sensitivity; 3 children missed and 2 of them had ADHD-I ADHD-RS was significantly correlated with SDQ Hyperactivity scale but not compared with diagnosis	76% had no seizures; 74% on 1 AED; 77% LRE; 23% generalized	Structured interview with parents and teachers, mental evaluation, and behavioral observation. N = 22 (32.4%) dx with ADHD (14 ADHD-C; 8 ADHD-I)
Alfstad et al 2016[17]	Norway but used UK norms	Consecutive patients with a hospital stay at a tertiary center; IQ < 70 excluded; n = 101; ages 10-19	SDQ Abnormal/Borderline Parent or Self Total Score	Range of epilepsy types (52% focal/48% generalized) and etiologies; but occipital/parietal focal epilepsy excluded; 53% on 1 AED/55% had no GTC in last 6 months	Kiddie-SADS-PL; neuropsychological testing; n = 32 (31.7%) had ADHD
Loutfi et al 2011[47]	Brazil	Routine neurology clinic visit; n = 30; ages 6-13 y	CBCL Attention Problems; 82% sensitivity; 85% specificity SNAP-IV cutoff; 93% sensitivity; 81% specificity	Idiopathic epilepsy, well controlled	Clinical Interview; n = 16 (53.3% had ADHD (7 ADHD-C; 6 ADHD-HI; 3 ADHD-I)
Hesdorffer et al 2014[45]	U.S.A.-Connecticut	Longitudinal study of community-based cohort of epilepsy cases over 4 y: baseline, 9 y follow-up; n = 163	CBCL-DSM oriented ADHD score; 0% sensitivity; 96% specificity	Median age of onset 6.8 y	Diagnostic Interview Schedule for DSM-IV (DIS-IV); n = 13 (5.4%) had ADHD

95%, respectively.[46] Borderline or abnormal SDQ total scores are highly correlated with the presence of a validated psychiatric diagnosis (93.6%), of which ADHD is the most common (31.7%).[17] Overall, the SDQ had better sensitivity than specificity, suggesting that it can be used as a screener, but that more detailed psychiatric diagnosis should follow for those identified at risk.

Two of the studies[45,47] used the parent (CBCL) version of the Achenbach System of Empirically Based Assessment.[49] Using 3 rating scales found specificity for the scores above the clinical cutoffs for ADHD, namely the CBCL (85%), the teacher version of the Achenbach measure (TRF) (64%), and the Swanson, Nolan, and Pelham-IV Questionnaire (SNAP-IV) (81%).[50] There was low concordance between the information obtained from parents compared to the teachers, because the TRF results were normal for a large proportion of patients diagnosed with ADHD by the psychiatric evaluation. Hesdorffer and colleagues also used the parent version of the Achenbach System (CBCL) in their longitudinal study of cases of a community cohort of childhood onset epilepsy.[45,51] Sensitivity for the CBCL at the 9-year assessment was 0%, while specificity was 97%.[45] The sensitivity and specificity of the CBCL were adequate in a small sample of patients with idiopathic epilepsy and comparable to the SNAP-IV, but the CBCL was a poor screener when compared against an ADHD diagnosis based on a structured interview at a 9-year follow-up.

A study using the ADHD-Rating Scale IV found significantly higher scores on parent versus teacher ratings on all 3 subscales (total score, inattentive score, and hyperactive-impulsive score).[21] Using the 80th percentile cutoff, sensitivity and negative predictive values were higher for parent reports but specificity and positive predictive values were higher for teacher responses.

Given the limited number of studies that met criteria, additional research is needed. Nonetheless, one class I and 2 class II studies support the ability of the SDQ to predict ADHD diagnosis in children with epilepsy (Level B). These 3 studies had relatively larger sample sizes (>65), included a wide age range, represented diverse epilepsy types, and were from different countries. The SDQ is available at no cost in multiple (>80) languages and has ability to screen for other problems. Potential drawbacks of the SDQ include lower sensitivity for the inattentive presentation of ADHD,[52,53] which is often more prevalent in epilepsy populations.[14,16,54] However, this weakness was not reflected in the studies reviewed here where the combined subtype was more prevalent, and thus may be contributing to the strong ability of the SDQ to perform well. The low specificity of the SDQ could be a limitation; but, as a *screening* tool, that limitation can be remedied by appropriate follow-up with a diagnostic interview by a qualified clinician. It is more important to overidentify (false-positive) on screening rather than miss children (false negative) who are at risk (Level U; expert opinion). Other limitations of the SDQ, as well as other measures, may be its utility in different subpopulations who have epilepsy including children with intellectual disability[55,56] or of different racial and ethnic backgrounds.[57] Overall very few measures evaluating children for a diagnosis of ADHD are validated (nor do they have generated scoring or cutoff norms) for populations from different ethnic or cultural backgrounds or those with intellectual disability.

Results are limited to questionnaires. There is also good rationale for using a multitrait, multimethod approach which includes a short computerized evaluation.[58] Continuous Performance Tasks (CPTs) have high positive predictive value but poor negative predictive value, meaning that a child who performs poorly is likely to have ADHD but a child who "passes" may also still have ADHD; thus, computerized tests do not reliably differentiate children with ADHD from those without.[59,60] CPTs that rely on reaction time may also be a challenge, as children with epilepsy have slow processing speed which may interfere with performance rather than a primary attention problem.[38] Access to free cognitive functioning tools in children with epilepsy is available, but these need to be assessed for sensitivity and specificity.[61] One such tool is EpiTrack Junior, a screening tool to assess attention and executive function validated in German and Austrian cohorts.[61] The tool has not yet been tested for its reliability in predicting ADHD.

3.3 | What criteria can be used to distinguish ADHD from other conditions such as absence seizures, learning disorders, and other conditions that mimic ADHD?

ADHD may be misdiagnosed in children with absence epilepsy and vice versa.[62] Furthermore, ADHD is a common comorbidity in children with absence seizures, occurring in 30-60% of affected cohorts.[28]

Studies reporting the clinical aspects to make the distinction between ADHD and absence epilepsy were scarce. Three features were more suggestive of nonepileptic staring than absence seizures: (1) lack of interruption of play; (2) more commonly noted by a professional rather than a parent; and (3) interruptible by external stimuli, such as touch.[63] Furthermore, hyperventilation induces an absence seizure in most children with untreated childhood absence epilepsy.[64] Comparing 17 children with CAE to 27 with ADHD, 2 items, "does not complete homework" and "does not remain on task," were found, which had a 79% sensitivity and 92% specificity for ADHD.[62] Lee and colleagues found that commission errors (number of responses to nontargets) and response time variability were increased in

children with ADHD and CAE, compared to those with CAE alone.[29] Differing study methodologies limited comparison. In conclusion, a distinction between ADHD and CAE should be based on history and an EEG with hyperventilation (Level U, expert opinion).

Approximately, 21%-33% of children with epilepsy have comorbid intellectual disability.[65-67] Furthermore, even in children with normal IQ, learning disabilities are common.[68] It has already been documented that intellectual disability is correlated with higher risk of ADHD (see Intellectual and developmental disabilities, above). Similarly, sleep disorders are more prevalent among children with epilepsy and comorbid ADHD compared to those with epilepsy alone.[69] Both learning and sleep disorders may present as staring and inattention. Formal cognitive testing should be strongly considered in children with epilepsy who are struggling at school (Level U: expert opinion). Careful screening for anxiety and depression, as well as bipolar disorder and early onset schizophrenia, and queries regarding sleep should be undertaken routinely in children with epilepsy, particularly if inattention and academic concerns are present (Level U: expert opinion). Where the child neurologist is unable to exclude these disorders, psychologist or psychiatric evaluation using screening instruments should be implemented.

3.4 | What is the recommended management of ADHD in children and adolescents with epilepsy?

3.4.1 | Are there some precautions to consider with certain AEDs with regard to ADHD?

Sixteen studies were identified (Tables S1 and S6 with additional references).

There were 3 class I studies.[70-72] Study populations reviewed were CAE and focal seizures treated with various AEDs.[70,71] The 2 studies reviewing ethosuximide, lamotrigine, and valproate in CAE provided strong evidence that valproate is associated with exacerbation of attentional issues in this population.[70,71] The other study compared levetiracetam to placebo in children with focal seizures and showed marginal improvement in behavior, but not specifically attention in those treated with levetiracetam.[72]

There were 2 class II studies, one assessed focal seizures and the other children with CECTS.[73,74] The focal seizure study reported that children on monotherapy or combined therapy with carbamazepine, oxcarbazepine, or sodium valproate had no significant difference in combined processing speed and attention, as secondary outcomes, but was limited by a short study period.[73] The other study reviewed topiramate and carbamazepine in children with CECTS.[74] The topiramate group had a trend toward improvement in attention but worsened cognition, compared to those on carbamazepine; however, the lack of significance of these findings limited further conclusions.

There were 11 class III studies**.** Two studies reviewed CECTS, one focal seizures, one generalized seizures, one complex seizure disorders, and 6 all seizure types. Diverse AEDs were included with little consistency across studies limiting comparison. Polytherapy was associated with a higher rate of behavioral problems. (Level C). Several studies from both resource-poor and resource-equipped settings found no correlation between AEDs and behavior and attention problems. A Tanzanian-based study found no evidence of behavior exacerbation with AEDs, including phenobarbital, but assessments were based solely on parental feedback, and access to AEDs was limited, with only 48% of the study group receiving therapy.[75] This is supported by studies from resource-equipped settings as well. In contrast, other studies reported that patients with CECTS on AEDs were more likely to have social problems, aggressive behavior, and attention problems and be anxious/depressed.[76] The study group alluded that this finding was related to ongoing seizures rather than specifically AEDs. Another study concluded that topiramate was associated with worsening in behavior in children with epilepsy aphasia syndromes at 3 months, but this was much less marked at 6 and 12 months of intervention time.[77]

Should precautions be considered with specific AEDs with regard to ADHD? (Table S7 with additional references)

There was strong evidence (Level A) to support the finding that valproate can exacerbate attentional issues in children with CAE. Polypharmacy is more likely than monotherapy to be associated with behavioral problems (Level C). Studies are needed to elucidate whether the polytherapy itself has resulted in the behavioral problems, or the combination of polytherapy and the underlying brain problem reflects difficult-to-control epilepsy, which, in turn, has resulted in the prescription of polytherapy. As such, polytherapy has not been proven to be the cause of behavioral problems but is a marker for the complication. Data to support adverse behavioral effects from phenobarbital, while reported, are inconsistent and lacking good quality evidence due to small study sizes, lack of accepted behavioral screens, and poor consistency in study methodologies. More studies with one epileptic syndrome comparing AEDs are necessary.

3.4.2 | Do methylphenidate, atomoxetine, or amphetamines have a worsening effect in seizure frequency? (Tables S6 and S7)

Exacerbation of seizures is reported in 0%-18% of study populations on methylphenidate, but most are mild and

transient, with no more than 5% stopping medication. Because these studies were not placebo-controlled, it is not possible to determine if the changes are related to baseline fluctuations. Seizure exacerbation rates for atomoxetine were 7%-9%, but again the numbers were too small to draw conclusions, and there are no data for amphetamines. Seven studies, which included patients with refractory epilepsy, indicated that methylphenidate is probably safe. There was only one study that documented tolerability to atomoxetine in a complex population group; 7% had seizure exacerbation.[78] Data collected by the pharmaceutical manufacturer found that seizures were no more prevalent in children with ADHD treated with atomoxetine than in children with ADHD without psychostimulant intervention.[79] These data did not separate out children with comorbid epilepsy.

3.4.3 | Are there any evidence-based treatment recommendations with respect to the management of ADHD in children and adolescent with epilepsy?

Data relating to treatment of ADHD in children and adolescents with epilepsy are limited (Table S7). There are no class I studies on efficacy and only 7 class II and 8 class III studies. For tolerability, only 9 class II and 9 class III studies were identified. Most available data are on methylphenidate (n = 16), with very limited data addressing amphetamines (n = 1) or atomoxetine (n = 2). Three studies involved adult patients. Lack of consistency in study methodology limited comparison between studies. For methylphenidate, overall, there was a 65%-83% improvement in ADHD symptoms of affected patients with comorbid epilepsy, with statistical significance identified in several papers. Atomoxetine and amphetamines may be less effective, but data are too limited to draw conclusions. One adult-based class III study comparing response to methylphenidate versus amphetamines found greater efficacy in the methylphenidate group.[80] Two class III and one class IV study reviewed response to atomoxetine in a pediatric population with epilepsy and ADHD; 59% and 82% reported benefit, with the remaining study reporting that 37% continued therapy but actual efficacy was not quantified.[78,81,82]

In conclusion, Level B evidence supports efficacy of methylphenidate in children with epilepsy and comorbid ADHD. There is Level U evidence for efficacy of atomoxetine and amphetamines. For tolerability, safety of methylphenidate in children with epilepsy (both controlled and refractory) and ADHD is supported by Level B evidence; atomoxetine is Level C and amphetamine Level U.

Class I studies are needed to confirm these recommendations.

3.5 | What is the recommended follow-up and transition of children and adolescents with ADHD and epilepsy?

- When and how to discontinue pharmacologic treatment of ADHD in children and adolescents with epilepsy

There are no studies that focus specifically on the natural history of ADHD in children and teens with epilepsy. Thus, there are no data to inform decisions regarding the need for maintenance of pharmacologic treatment for ADHD in such cohorts.

However, in approximately two-thirds of cases with ADHD alone, symptoms persist into adulthood.[83] ADHD is often associated with other comorbidities including substance abuse and mood disorders, and lack of symptom management at this critical time in adolescence and young adulthood, which may have profound consequences on academic and vocational performance, social relationships, and risk-taking behavior. Furthermore, young adults with ADHD may not appreciate and therefore not seek care for their symptoms, or they may stop stimulants as they perceive they have outgrown this disorder.[83]

Thus, if pharmacologic treatment of ADHD is beneficial and appears well tolerated, it may be continued for as long as it remains effective, but it should be reviewed annually, as recommended by ADHD clinical guidelines (class IV).[42]

- What is the ideal management of transition of care to the adult services?

There were no studies devoted to transition of patients with both comorbid ADHD and epilepsy. But various guidelines for transition of care for adolescents with special needs exist[84] (Table S8).

A transition working group comprising pediatric and adult health care providers and patient representatives identified 7 steps to maximize a successful transition (Table S8) and highlighted psychiatric issues such as ADHD as a factor that may increase the risk of unsatisfactory transfer.[85] Another report from the Transition in Epilepsies symposium identified ADHD as a treatable disorder that may interfere with transition and successful adulthood.[86]

The National Institute for Health and Care Excellence (NICE) guidelines for transition of adolescents with ADHD were established in the UK in 2008[42] and accepted throughout Europe (class IV), and specific recommendations are listed in Table S6. Treatment of ADHD declines sharply from childhood through young adulthood despite persistence of functional impairment. Primary care providers are less likely than pediatricians or psychiatrists to prescribe medications for ADHD.[83]

Recommendations (Level U: expert opinion)[83,87] include multidisciplinary involvement in transition and adult ADHD clinics. This is essential as many patients experience challenges with housing, employment, relationships, and psychosocial well-being.

4 | CONCLUSION

This article addresses the common and challenging clinical aspects of managing children with epilepsy and ADHD. Key study questions on common and practical issues were identified, and the evidence in the literature was critiqued to establish the strength of evidence to support statements and where possible to put forward recommendations (Table 2).

Despite ADHD being a common comorbidity for children with epilepsy,[5] the analysis was limited by the lack of class I studies, consistency across study methodology, and directness to the study questions. Specifically there was lack of controlled, randomized double-blind studies of large sample and follow-up, lack of specific evaluation of attention, inadequate data on impact of each AED on attention, and study cohorts of broad, phenotypic heterogeneity. Few studies used a neuropsychological battery to evaluate attention. Those studies that did use appropriate batteries (eg, Masur et al[70]), in general, used one instrument. In the case of Masur and colleagues, Continuous Performance Test (CPT) was used, which is regarded as the gold standard tool for sustained attention. Some studies used the CBCL, which is based on parent report and does not replace neuropsychological testing.

Young children with suspected ADHD should be screened for psychiatric diagnoses that might mimic ADHD, in particular anxiety disorders that are comorbid with pediatric epilepsy.

Impulsivity is one of the core features of ADHD, but this symptom is not well studied in children with comorbid epilepsy. The most common form of ADHD in children with epilepsy is the inattentive form, with the result that there are limited data on impulsivity.[4]

The report was useful to identify where common management concepts were not supported by strong evidence base and where there are significant areas in need of a more structured and targeted research.

This report has been generated to provide a practical but evidence-based guide to challenging areas in the approach to the care of children with epilepsy who are at risk of, or affected by, the comorbidity ADHD. The outcome of this systematic review is to demonstrate the need for better-designed studies to address many of the important areas addressed.

ACKNOWLEDGMENT

This report was written by experts selected by the International League Against Epilepsy (ILAE) and was approved for publication by the ILAE. Opinions expressed by the authors, however, do not necessarily represent the policy or position of the ILAE.

DISCLOSURES OF CONFLICT OF INTEREST

SA has served as consultant or received honorarium for lectures from Advicenne Pharma, Biocodex, Eisai, GW Pharma, Novartis, Nutricia, Shire, UCB pharma, Ultragenyx, Zogenyx. He has been investigator for clinical trials for Advicenne Pharma, Eisai, UCB Pharma, and Zogenix. SA is an associate editor for the journal *Epilepsia*. EW has received consulting fees from Sunovion and Biomarin. KAD has nothing to disclose. MMB has nothing to declare. HH has received honorarium for lectures from Novartis, Nutricia, and Shire and been investigator for clinical trials for UCB. KDV has received consulting fees from Abbott, Novartis, and UCB. PvB has received consulting fees from Livanova, UCB Pharma, and Eisai. JHC has acted as advisory board member and/or speaker for Eisai, GW Pharma, Nutricia, Shire, UCB Pharma, Zogenix, and Takeda, for which remuneration was made to her department. She has been investigator for clinical trials for Vitaflo, Zogenix, and GW Pharma. MO has nothing to declare. HK has nothing to declare. MA has nothing to declare. MMG has nothing to declare. PS has nothing to declare. KVP has nothing to declare. MLS has nothing to declare. LC has nothing to declare. MK has nothing to declare. BH is an associate editor for *Epilepsy & Behavior* and has no financial conflicts. DD has nothing to declare. JMW is an associate editor for the journal *Epilepsia*. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

AUTHOR CONTRIBUTIONS

The following authors conducted the literature review, classified the evidence, and wrote the narratives for their allocate questions. All authors proofread and approved the final version of the paper. VKP, PS, KAD, EW, MLS, MO, HK, and MA contributed to the question "who is at risk of ADHD in children with epilepsy." MLS, MMB, LC, and PvB contributed to the question "how to screen and how to diagnosis ADHD in children and adolescents with epilepsy." KAD, DD, PvB, MMB, and LC contributed to the question "how to differentiate absence seizures from ADHD and the differential diagnoses to consider before diagnosing ADHD." MLS, KV, SA, LC, HH, VKP, MMG, JMW, EW, and MMB

contributed to the question "how to manage children and adolescents with epilepsy and ADHD." HH, MMG, KV, EW, and MK contributed to the question on "follow-up and transition of children and adolescents with ADHD and epilepsy." SA, EW, and JMW compiled the final combined version of the paper.

ORCID

Stéphane Auvin http://orcid.org/0000-0003-3874-9749
Madison Berl http://orcid.org/0000-0002-2469-1518
Hideaki Kanemura http://orcid.org/0000-0002-6216-0275
Jo M. Wilmshurst http://orcid.org/0000-0001-7328-1796

REFERENCES

1. Dunn DW, Austin JK. Differential diagnosis and treatment of psychiatric disorders in children and adolescents with epilepsy. Epilepsy Behav. 2004;5(Suppl 3):S10–7.
2. Plioplys S, Dunn DW, Caplan R. 10-year research update review: psychiatric problems in children with epilepsy. J Am Acad Child Adolesc Psychiatry. 2007;46:1389–402.
3. Cohen R, Senecky Y, Shuper A, et al. Prevalence of epilepsy and attention-deficit hyperactivity (ADHD) disorder: a population-based study. J Child Neurol. 2013;28:120–3.
4. Dunn DW, Austin JK, Harezlak J, Ambrosius WT. ADHD and epilepsy in childhood. Dev Med Child Neurol. 2003;45:50–4.
5. Chou IC, Chang YT, Chin ZN, et al. Correlation between epilepsy and attention deficit hyperactivity disorder: a population-based cohort study. PLoS ONE. 2013;8:e57926.
6. Aaberg KM, Bakken IJ, Lossius MI, et al. Comorbidity and childhood epilepsy: a nationwide registry study. Pediatrics. 2016;138:pii: e20160921.
7. Brikell I, Ghirardi L, D'Onofrio BM, et al. Familial Liability to Epilepsy and Attention-Deficit/Hyperactivity Disorder: A Nationwide Cohort Study. Biol Psychiatry. 2018;83:173–80.
8. Schatz DB, Rostain AL. ADHD with comorbid anxiety: a review of the current literature. J Atten Disord. 2006;10:141–9.
9. Kwong KL, Lam D, Tsui S, et al. Self-esteem in adolescents with epilepsy: Psychosocial and seizure-related correlates. Epilepsy Behav. 2016;63:118–22.
10. Davis SM, Katusic SK, Barbaresi WJ, et al. Epilepsy in children with attention-deficit/hyperactivity disorder. Pediatr Neurol. 2010;42:325–30.
11. Salpekar JA, Mishra G. Key issues in addressing the comorbidity of attention deficit hyperactivity disorder and pediatric epilepsy. Epilepsy Behav. 2014;37:310–5.
12. Edlund W, Gronseth G, So Y, Franklin G. *Clinical practice guideline process manual*. St Paul, MN: American Academy of Neurology; 2004.
13. Barkely RA. *Attention-Deficit Hyperactivity Disorder: a handbook for diagnosis and treatment* (3rd ed.). New York, NY: Guilford; 2006.
14. Hermann B, Jones J, Dabbs K, et al. The frequency, complications and aetiology of ADHD in new onset paediatric epilepsy. Brain. 2007;130:3135–48.
15. Hesdorffer DC, Ludvigsson P, Olafsson E, Gudmundsson G, Kjartansson O, Hauser WA. ADHD as a risk factor for incident unprovoked seizures and epilepsy in children. Arch Gen Psychiatry. 2004;61:731–6.
16. 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.
17. Alfstad K, Torgersen H, Van Roy B, et al. Psychiatric comorbidity in children and youth with epilepsy: an association with executive dysfunction? Epilepsy Behav. 2016;56:88–94.
18. Cohen MJ, Meador KJ, Browning N, et al. Fetal antiepileptic drug exposure: motor, adaptive, and emotional/behavioral functioning at age 3 years. Epilepsy Behav. 2011;22:240–6.
19. Davies S, Heyman I, Goodman R. A population survey of mental health problems in children with epilepsy. Dev Med Child Neurol. 2003;45:292–5.
20. Holdsworth L, Whitmore K. A study of children with epilepsy attending ordinary schools. I: their seizure patterns, progress and behaviour in school. Dev Med Child Neurol. 1974;16:746–58.
21. Reilly C, Atkinson P, Das KB, et al. Parent- and teacher-reported symptoms of ADHD in school-aged children with active epilepsy: a population-based study. J Atten Disord. 2017;21:887–97.
22. Reilly C, Atkinson P, Das KB, et al. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. Pediatrics. 2014;133:e1586–93.
23. Wallis D, Russell HF, Muenke M. Review: genetics of attention deficit/hyperactivity disorder. J Pediatr Psychol. 2008;33:1085–99.
24. Gonzalez-Heydrich J, Hamoda HM, Luna L, et al. Elevated rates of ADHD in mothers of children with comorbid ADHD and epilepsy. Neuropsychiatry (London). 2012;2:385–91.
25. Kwong KL, Lam D, Tsui S, et al. Attention deficit hyperactivity disorder in adolescents with epilepsy. Pediatr Neurol. 2016;57:56–63.
26. Danhofer P, Pejčochová J, Dušek L, et al. The influence of EEG-detected nocturnal centrotemporal discharges on the expression of core symptoms of ADHD in children with benign childhood epilepsy with centrotemporal spikes (BCECTS): a prospective study in a tertiary referral center. Epilepsy Behav. 2017;79:75–81.
27. Kral MC, Lally MD, Boan AD. Identification of ADHD in youth with epilepsy. J Pediatr Rehabil Med. 2016;9:223–9.
28. Caplan R, Siddarth P, Stahl L, et al. Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. Epilepsia. 2008;49:1838–46.
29. Lee HJ, Kim EH, Yum MS, et al. Attention profiles in childhood absence epilepsy compared with attention-deficit/hyperactivity disorder. Brain Dev. 2018;40:94–9.
30. D'Agati E, Cerminara C, Casarelli L, et al. Attention and executive functions profile in childhood absence epilepsy. Brain Dev. 2012;34:812–7.
31. Gascoigne MB, Smith ML, Barton B, et al. Attention deficits in children with epilepsy: preliminary findings. Epilepsy Behav. 2017;67:7–12.
32. Kernan CL, Asarnow R, Siddarth P, et al. Neurocognitive profiles in children with epilepsy. Epilepsia. 2012;53:2156–63.
33. Metz-Lutz MN, Kleitz C, de Saint Martin A, et al. Cognitive development in benign focal epilepsies of childhood. Dev Neurosci. 1999;21:182–90.
34. Wannag E, Eriksson AS, Larsson PG. Attention-deficit hyperactivity disorder and nocturnal epileptiform activity in children with epilepsy admitted to a national epilepsy center. Epilepsy Behav. 2010;18:445–9.

35. Fastenau PS, Johnson CS, Perkins SM, et al. Neuropsychological status at seizure onset in children: risk factors for early cognitive deficits. Neurology. 2009;73:526–34.
36. Bennett-Back O, Keren A, Zelnik N. Attention-deficit hyperactivity disorder in children with benign epilepsy and their siblings. Pediatr Neurol. 2011;44:187–92.
37. McCusker CG, Kennedy PJ, Anderson J, et al. Adjustment in children with intractable epilepsy: importance of seizure duration and family factors. Dev Med Child Neurol. 2002;44:681–7.
38. Berl MM, Terwilliger V, Scheller A, et al. Speed and complexity characterize attention problems in children with localization-related epilepsy. Epilepsia. 2015;56:833–40.
39. Austin JK, Harezlak J, Dunn DW, et al. Behavior problems in children before first recognized seizures. Pediatrics. 2001;107:115–22.
40. Pliszka S. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:894–921.
41. Wolraich M, Brown L, Brown RT, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128:1007–22.
42. NICE. *Attention deficit hyperactivity disorder: diagnosis and management of ADHD in children, young people and adults*. London: NICE; 2008.
43. Taylor E, Döpfner M, Sergeant J, et al. European clinical guidelines for hyperkinetic disorder – first upgrade. Eur Child Adolesc Psychiatry. 2004;13(Suppl 1):I7–30.
44. Pelham WE, Fabiano GA, Massetti GM. Evidence-based assessment of attention deficit hyperactivity disorder in children and adolescents. J Clin Child Adolesc Psychol. 2005;34:449–76.
45. Hesdorffer DC, Baldin E, Caplan R, et al. How do we measure psychiatric diagnoses? Implications of the choice of instruments in epilepsy. Epilepsy Behav. 2014;31:351–5.
46. Tanabe T, Kashiwagi M, Shimakawa S, et al. Outpatient screening of Japanese children with epilepsy for attention-deficit/hyperactivity disorder (AD/HD). Brain Dev. 2014;36:301–5.
47. Loutfi KS, Carvalho AM, Lamounier JA, et al. ADHD and epilepsy: contributions from the use of behavioral rating scales to investigate psychiatric comorbidities. Epilepsy Behav. 2011;20:484–9.
48. Goodman R, Ford T, Richards H, et al. The development and well-being assessment: description and initial validation of an integrated assessment of child and adolescent psychopathology. J Child Psychol Psychiatry. 2000;41:645–55.
49. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, V.T.: University of Vermont, Research Center for Children, Youth, & Families; 2001.
50. Bussing R, Fernandez M, Harwood M, et al. Parent and teacher SNAP-IV ratings of attention deficit hyperactivity disorder symptoms: psychometric properties and normative ratings from a school district sample. Assessment. 2008;15:317–28.
51. Robins L, Cottler L, Bucholz K, et al. *Diagnostic interview schedule for DSM-IV (DIS-IV-Revision 11 Sep 1998)*. St Louis, MO: Washington University, School of Medicine, Department of Psychiatry; 1998.
52. Carballo JJ, Rodríguez-Blanco L, García-Nieto R, et al. Screening for the ADHD phenotype using the strengths and difficulties questionnaire in a clinical sample of newly referred children and adolescents. J Atten Disord. 2018;22:1032–39.
53. Ullebø AK, Posserud MB, Heiervang E, et al. Screening for the attention deficit hyperactivity disorder phenotype using the strength and difficulties questionnaire. Eur Child Adolesc Psychiatry. 2011;20:451–8.
54. Dunn DW, Kronenberger WG. Childhood epilepsy, attention problems, and ADHD: review and practical considerations. Semin Pediatr Neurol. 2005;12:222–8.
55. Deb S, Dhaliwal AJ, Roy M. The usefulness of Conners' Rating Scales-Revised in screening for attention deficit hyperactivity disorder in children with intellectual disabilities and borderline intelligence. J Intellect Disabil Res. 2008;52:950–65.
56. Freeman NC, Gray KM, Taffe JR, et al. Development of a new attention rating scale for children with intellectual disability: the scale of attention in intellectual disability (SAID). Am J Intellect Dev Disabil. 2015;120:91–109.
57. Flowers A, McDougle L. In search of an ADHD screening tool for African American children. J Natl Med Assoc. 2010;102:372–4.
58. Valo S, Tannock R. Diagnostic instability of DSM-IV ADHD subtypes: effects of informant source, instrumentation, and methods for combining symptom reports. J Clin Child Adolesc Psychol. 2010;39:749–60.
59. Grodzinsky GM, Barkley RA. Predictive power of frontal lobe tests in the diagnosis of attention deficit hyperactivity disorder. Clin Neuropsychol. 1999;13:12–21.
60. Sims DM, Lonigan CJ. Multi-method assessment of ADHD characteristics in preschool children: relations between measures. Early Child Res Q. 2012;27:329–37.
61. Helmstaedter C, Schoof K, Rossmann T, et al. Introduction and first validation of EpiTrack Junior, a screening tool for the assessment of cognitive side effects of antiepileptic medication on attention and executive functions in children and adolescents with epilepsy. Epilepsy Behav. 2010;19:55–64.
62. Williams J, Sharp GB, DelosReyes E, et al. Symptom differences in children with absence seizures versus inattention. Epilepsy Behav. 2002;3:245–8.
63. Rosenow F, Wyllie E, Kotagal P, et al. Staring spells in children: descriptive features distinguishing epileptic and nonepileptic events. J Pediatr. 1998;133:660–3.
64. Wirrell EC, Camfield PR, Gordon KE, et al. Will a critical level of hyperventilation-induced hypocapnia always induce an absence seizure? Epilepsia. 1996;37:459–62.
65. Sillanpaa M. Epilepsy in children: prevalence, disability, and handicap. Epilepsia. 1992;33:444–9.
66. Camfield C, Camfield P. Preventable and unpreventable causes of childhood-onset epilepsy plus mental retardation. Pediatrics. 2007;120:e52–5.
67. Berg AT, Langfitt JT, Testa FM, et al. Global cognitive function in children with epilepsy: a community-based study. Epilepsia. 2008;49:608–14.
68. Mitchell WG, Chavez JM, Lee H, et al. Academic underachievement in children with epilepsy. J Child Neurol. 1991;6:65–72.
69. Ekinci O, Isik U, Gunes S, et al. Understanding sleep problems in children with epilepsy: associations with quality of life, attention-deficit hyperactivity disorder and maternal emotional symptoms. Seizure. 2016;40:108–13.
70. Masur D, Shinnar S, Cnaan A, et al. Pretreatment cognitive deficits and treatment effects on attention in childhood absence epilepsy. Neurology. 2013;81:1572–80.

71. Glauser TA, Cnaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med. 2010;362:790–9.
72. Levisohn PM, Mintz M, Hunter SJ, et al. Neurocognitive effects of adjunctive levetiracetam in children with partial-onset seizures: a randomized, double-blind, placebo-controlled, noninferiority trial. Epilepsia. 2009;50:2377–89.
73. Donati F, Gobbi G, Campistol J, et al. Effects of oxcarbazepine on cognitive function in children and adolescents with partial seizures. Neurology. 2006;67:679–82.
74. Kang HC, Eun BL, Lee CW, et al. The effects on cognitive function and behavioral problems of topiramate compared to carbamazepine as monotherapy for children with benign rolandic epilepsy. Epilepsia. 2007;48:1716–23.
75. Powell K, Walker RW, Rogathe J, et al. Cognition and behavior in a prevalent cohort of children with epilepsy in rural northern Tanzania: A three-year follow-up study. Epilepsy Behav. 2015;51:117–23.
76. Samaitienė R, Norkūnienė J, Jurkevičienė G, et al. Behavioral problems in children with benign childhood epilepsy with centrotemporal spikes treated and untreated with antiepileptic drugs. Medicina (Kaunas). 2012;48:338–44.
77. Coppola G, Verrotti A, Resicato G, et al. Topiramate in children and adolescents with epilepsy and mental retardation: a prospective study on behavior and cognitive effects. Epilepsy Behav. 2008;12:253–6.
78. Torres A, Whitney J, Rao S, et al. Tolerability of atomoxetine for treatment of pediatric attention-deficit/hyperactivity disorder in the context of epilepsy. Epilepsy Behav. 2011;20:95–102.
79. Wernicke JF, Holdridge KC, Jin L, et al. Seizure risk in patients with attention-deficit-hyperactivity disorder treated with atomoxetine. Dev Med Child Neurol. 2007;49:498–502.
80. Gonzalez-Heydrich J, Hsin O, Gumlak S, et al. Comparing stimulant effects in youth with ADHD symptoms and epilepsy. Epilepsy Behav. 2014;36:102–7.
81. Mulas F, Roca P, Ros-Cervera G, et al. Pharmacological management of attention deficit hyperactivity disorder with methylphenidate and atomoxetine within a context of epilepsy. Rev Neurol. 2014;58(Suppl 1):S43–9.
82. Carreras-Saez IP-M. Atomoxetine treatment in patients with attention deficit hyperactivity disorder and epilepsy. International Child Neurology Congress. Iguacu Falls, Brazil; 2016.
83. Montano CB, Young J. Discontinuity in the transition from pediatric to adult health care for patients with attention-deficit/hyperactivity disorder. Postgrad Med. 2012;124:23–32.
84. Blum RW. Introduction. Improving transition for adolescents with special health care needs from pediatric to adult-centered health care. Pediatrics. 2002;110:1301–3.
85. Andrade DM, Bassett AS, Bercovici E, et al. Epilepsy: Transition from pediatric to adult care. Recommendations of the Ontario epilepsy implementation task force. Epilepsia. 2017;58:1502–17.
86. Nabbout R, Andrade DM, Bahi-Buisson N, et al. Outcome of childhood-onset epilepsy from adolescence to adulthood: Transition issues. Epilepsy Behav. 2017;69:161–9.
87. Reale L, Frassica S, Gollner A, et al. Transition to adult mental health services for young people with attention deficit hyperactivity disorder in Italy: parents' and clinicians' experiences. Postgrad Med. 2015;127:671–6.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Auvin S, Wirrell E, Donald KA, et al. Systematic review of the screening, diagnosis, and management of ADHD in children with epilepsy. Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission. *Epilepsia*. 2018;59:1867–1880. https://doi.org/10.1111/epi.14549