Consensus-Based Standards for the Diagnosis and Treatment of Anxiety and Depression in Children and Adolescents with Epilepsy: A Report from the Psychiatric Pediatric Issues Task Force of the International League Against Epilepsy

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Conflict of Interest

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Abbreviations

AACAP: American Academy of Child and Adolescent Psychiatry; AAN: American Academy of Neurology; AAP: American Academy of Pediatrics; APA: American Psychological Association; ASM: anti-seizure medication; AUC: area under the curve; BASC: Behavioral Assessment System for Children; BDI: Beck Depression Inventory; CBCL: Child Behavior Checklist; CBT: Cognitive Behavioral Therapy; CDI: Children's Depression Inventory; CES-D: Center for Epidemiological Studies-Depression; CPGs: Clinical Practical Guidelines; DAWBA: Development and Well-Being Assessment; DISC: Diagnostic Interview Schedule for Children; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th Edition; False negatives; FPs: false positives; GAD: Generalized Anxiety Disorder; GRADE: Grading of Recommendations, Assessment, Development, and Evaluation system; HADS-A: Hospital Anxiety and Depression Scale-Anxiety Module ; HADS-D: Hospital Anxiety and Depression Scale-Depression Module ; HAM-D: Hamilton Depression Rating Scale; HCPs: Healthcare providers; ILAE, International League Against Epilepsy; IQ: Intelligence Quotient; K-SADS-E: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Epidemiologic Version; K-SADS-PL: Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version; MASC: Multidimensional Anxiety Scale for Children; MDD: major depressive disorder; NDDI-E: Neurological Disorders Depression Inventory-Epilepsy; NDDI-E-Y: Neurological Disorders Depression Inventory-Epilepsy for Youth; NICE: National Institute for Health and Care Excellence; NPV: Negative predictive value; NRCTs: Non-Randomized Controlled Trials; PICO: population, intervention(s), comparator(s), and outcome(s); PPV: Positive predictive value; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards; QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies, version 2; RCMAS: Revised Children's Manifest Anxiety Scale; RCTs: Randomized Controlled Trials; RoB 2: Version 2 of the Cochrane risk-of-bias tool for randomized trials; ROBINS-I: Risk of Bias In Non-randomized Studies-of Interventions; ROC: receiver operating characteristic; SCARED: Screen for Child Anxiety Related Emotional Disorders, parent and child versions; SDQ: Strengths and Difficulties Questionnaire; Se: Sensitivity; SOE: Strength of Evidence; Sp: Specificity; SSRIs: Selective serotonin reuptake inhibitors; SR: Systematic Review; STAI: State-Trait Anxiety Inventory; TCAs: Tricyclic antidepressants; TF: Task Force; TNs: true negatives; TPs: true positives; UK: United Kingdom; USA: United States of America; WHO: World Health Organization.

ABSTRACT

Objectives: In view of the limited guidance available, the Task Force on Pediatric Psychiatric Issues of the International League Against Epilepsy developed consensus-based recommendations to improve the diagnosis and treatment of anxiety and depression in pediatric epilepsy. **Methods:** The Task Force conducted a systematic review and identified two studies that validated four depression and/or anxiety screening scales against a psychiatric interview. Seven studies (six nonpharmacological [four randomized] and one pharmacological [nonrandomized and noncontrolled]) met the eligibility criteria for treatment. All had a high risk of bias and provided a very low (diagnosis) and low (treatment) strength of evidence. In view of the limited evidence, a Delphi consensus was needed generating 46 recommendations. The level of agreement to generate recommendations was ≥80% (strong) and ≥90% (very strong). The recommendations with very strong level of agreement are summarized here. **Results**: **DIAGNOSIS**: (1) Universal screening for anxiety and depression is recommended for children and adolescents with epilepsy with new-onset and annually for chronic epilepsy. Closer surveillance is recommended for adolescents after the age of 12 years, children at higher risk (e.g., suicide-related behavior), with subthreshold symptoms, and those with epilepsy experiencing seizure worsening or therapeutic modifications. (2) Multiple sources of ascertainment and a formal screening questionnaire are recommended. The instrument of choice must be translated and validated for the interviewee's language. The choice must be based on the expertise of every healthcare provider (HCP), the available resources, and the feasibility in every setting. Clinical interviews are advisable when possible. The HCP must always explain that identifying symptoms is essential to optimize treatment outcome and reduce morbidity (3) The distinction between interictal and ictal symptoms is necessary. Questioning about the relationship between symptoms of anxiety or depression with seizure worsening/control and behavioral adverse effects of antiseizure medications is recommended. **TREATMENT**: (1) General principles of treatment comprise the development of an individualized treatment plan considering psychosocial, religious, and cultural aspects. Treatment for anxiety and depression must be monitored. (2) For mild depression, active monitoring (4-6 weeks) must be considered. (3) For moderate to severe depression and anxiety, the primary physician must refer to a mental HCP and in the case of a lengthy wait time, the provider in charge must support active monitoring. Therefore, clinical care pathways must be developed. (4) Psychosocial intervention must be tailored and where available and indicated, cognitive behavioral therapy should be offered. Psychotherapy must be age-appropriate, and family involvement is relevant. (5) HCPs must monitor children and adolescents with epilepsy prescribed with antidepressants. The assessment of treatment strategy must consider symptoms and function that may not improve at the same time. (6) Education of caregivers is essential to guarantee adherence to treatment and adequate monitoring of psychiatric symptoms and adverse effects. (7) A shared-care model with the involvement of the epilepsy team is recommended in children and adolescents with epilepsy and mental health disorders. **Significance**: We identified areas in the management of depression and anxiety of children and adolescents with epilepsy that lack a solid evidence base and require more targeted research. In the meantime, we provide a consensus based guidance to address the care of children and adolescent with epilepsy, as they are a population at higher risk of developing depression and anxiety.

Key terms: Anxiety, depression, childhood, diagnosis, treatment

1. INTRODUCTION

The World Health Organization (WHO) Comprehensive Mental Health Action Plan emphasizes that "the early stages of life present a particularly important opportunity to promote mental health and prevent mental disorders, as up to 50% of mental disorders in adults begin before the age of 14 years." [1]. According to the World Health Organization (WHO), depression and anxiety are among the most common psychiatric disorders in adolescents with a high disease burden [1]. Anxiety disorders are the most prevalent in this age group (3.6% [10-14 years-old] - 4.6% [15-19 years-old]), followed by depression (1.1% [10–14 years-old] - 2.8% [15–19-years-old].

In children and adolescents with mental disorders, early diagnosis is key prompting early intervention through psychosocial and other non-pharmacological interventions based in the community, avoiding institutionalization and medicalization [1]. The comorbidity between depression and anxiety is also substantial. For youth with depression, rates of anxiety disorder range from 15 to 75%, making anxiety the most common comorbid disorder. In those with an anxiety disorder, comorbid depressive disorder occurs in 10– 15% [2]. Two epidemiological studies showed that children with epilepsy have higher rates of mental health disorders compared with the general population and children with non-neurological chronic disorders (e.g., diabetes) [3, 4]. A systematic review and meta-analysis demonstrated that the overall pooled prevalence of anxiety disorders in adolescents with epilepsy was 18.9%, and for depression, the pooled prevalence was 13.5% [5].

In children and adolescents with epilepsy, the associated impairments of depression and anxiety include disrupted relationships, school failure, increased risk for a lifelong persistent psychiatric disorder, worse quality of life, and suicide-related behavior [6-10]. The high prevalence of these disorders contrasts with the shortage of mental health care services and providers [11-16] . Notably, pediatric neurologists often have inadequate training to manage depression and anxiety but still must act as actual mental healthcare provider [17-24].

Practice guidelines and recommendations provide direction to clinicians, patients, and policymakers to enhance access to quality mental health care with improved child and youth outcomes [25, 26]. Although guidelines have been developed for specialty care settings (e.g., the American Academy of Child and Adolescent Psychiatry 22)[27], effective practice and clinician differences exist between the primary and specialty care settings, restricting the simple transfer of guidelines from one setting to another.

The Psychiatric Pediatric Issues Task Force (TF), created in 2018, represents a liaison between the Pediatric and the Psychiatry Commissions of the International League Against Epilepsy (ILAE). The TF involved experts from all ILAE world regions. The ILAE, recognizing the shortage of mental health care, entrusted the TF with developing clear, objective, and clinically meaningful recommendations for diagnosing and treating anxiety and depression to provide guidance for any healthcare provider caring for children and adolescents with epilepsy.

2. METHODS

The TF conducted a systematic review to identify the evidence for diagnosing and treating depressive and anxiety symptoms and disorders in children and adolescents with epilepsy. It was followed by a Delphi process to provide consensus-based recommendations since the evidence base was lacking. This protocol, reviewed by the ILAE Standard and Best Practice Council and endorsed by the ILAE Executive Committee, followed the Guideline development standards and adhered to the ILAE handbook and toolkit for guideline development updated in 2022 [28, 29].

2.1. Clinical practice guideline working group

Following consultation with the ILAE's Executive Committee, a working group was formed and comprised the chairs of the Psychiatry (MK) and Pediatric Commissions (SA) and nine Task Force members, including four child neurologists (KV, EW, JMW, FC), one pediatric and adolescent psychiatrist (GP), one neuropsychiatrist (MM), one psychologist (CR), one nurse (SK), and one neuropsychologist (MLS) with expertise in the field and representing all ILAE regions. In addition, one librarian with expertise in medical systematic reviews (VA), one psychiatrist with expertise in methodology and epidemiology (WP), and three methodologists (FB, NJ, and IGD) were involved at different stages. Two post-graduate students (RMC, SV) with expertise in systematic and scoping reviews were involved in the systematic review process. All members declared non-related conflicts of interest.

2.2. Evidence-Based Recommendations

2.2.1. Priority questions

The systematic review protocol, reviewed by three methodologists (WP, NJ, FB), was registered at the **International Prospective Register of Systematic Reviews (PROSPERO)** for diagnosis and treatment [CRD42020202682 ; CRD42020202702)].

Supplementary material 1 shows the eligibility criteria for studies on diagnosis and treatment.

2.2.2. Search Strategy

The search strategy (See **Supplementary material 2**) was developed by a librarian with expertise in scoping and systematic review (VA) in collaboration with study investigators with knowledge in the field (systematic reviews, scoping reviews, pediatric neurology, epilepsy, and psychiatric disorders) (GP, WP, KV, NJ). Electronic bibliographic databases (MEDLINE, Scopus, EMBASE, PsycINFO, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Epilepsy Group Specialized Register, Cochrane Systematic Review, CINAHL [Cumulative Index to Nursing and Allied Health Literature]) were searched from their respective inception dates onwards with no restrictions on date, country or language of publication. The first search was performed on August 7, 2020, repeated on September 17, 2021 and updated on November 13, 2023. The reference lists of previously published reviews and all studies included in this review were hand-searched (KV, RM) to ensure no papers were missed. Systematic reviews and meta-analyses were not included; however, their reference lists were screened to identify relevant articles. Literature that is not formally published in sources such as books or journal articles and not submitted for peer review (e.g., government reports, conference proceedings, graduate dissertations, unpublished clinical trials) was not considered for the systematic review [30].

2.2.3. Study selection

All abstracts were uploaded into RAYYAN [31], an online tool that helps streamline the systematic review screening process. A two-step process was used to select studies for inclusion in this review. First, two authors (KV, RMC) reviewed titles and abstracts to identify articles meeting the pre-determined eligibility criteria after duplicate studies were removed. Second, full-text review of all abstracts identified in the first stage was undertaken. Two reviewers conducted all steps independently, and disagreements were resolved by discussion with a third reviewer. Native speakers of the respective language screened non-English articles using the same process. When details were lacking in published papers, the authors attempted to contact

study authors. Results were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards (PRISMA) except for the abstract since the goal of this manuscript was to develop clinical practice standards rather than purely a systematic review. [32]

2.2.4. Data Extraction

For **diagnosis**, the following data were extracted: author, journal/year of publication, study region, ascertainment source (i.e., hospital or tertiary care clinic), age (range, mean, and standard deviation, when available), sex, IQ (range, mean, and standard deviation), number of participants, screening tool(s) under validation, cutpoints assessed, reference standard used for validation, the study-specific prevalence of depression and anxiety based on the reference standard, and measures of diagnostic accuracy (when reported). Sensitivity (Se) and specificity (Sp) should be available. Whenever possible, other measures of accuracy were obtained, such as: positive predictive value (PPV), negative predictive value (NPV), true positives (TPs), false positives (FPs), true negatives (TNs), false negatives (FNs), receiver operating characteristic (ROC) and area under the curve (AUC), binomial regression coefficient, Cronbach's alpha, Kappa, likelihood ratios, any effect modifiers/confounders assessed, and any recommended/optimal cut points. Our primary research objective was to establish the criterion validity of depression and anxiety screening tools in children with epilepsy. We defined criterion validity as the ability of screening tools to correctly identify depression when calibrated against a known reference standard. Criterion validity was operationalized using reported measures of diagnostic accuracy (defined below). Studies of convergent validity that indicate whether a test that is designed to measure a particular construct correlates with other tests that assess the same or similar construct were not considered for this analysis.

For treatment, the following data were extracted: authors, journal/year of publication, study type/design, study location, ascertainment source, study focus, sample size, age (range, mean and standard deviation), sex, epilepsy-related factors (type, age at onset [mean and standard deviation], duration [mean and standard deviation], number of antiseizure medications), number of participants with co-occurring anxiety and/or depression (when the information was available), controls (sample size, age, sex), assessment method for anxiety and depression, depression and anxiety management (e.g., cognitive behavioral therapy versus other measures), and assessment of psychopathology (criteria used and prevalence), time of intervention, and time of follow-up after intervention.

2.2.5. Risk of bias and evaluation of evidence

Two reviewers (KV, RM) assessed the risk of bias and rated the level of evidence independently. A methodologist (IGD) reviewed this assessment and resolved discrepancies.

2.2.5.1.Risk of Bias

Diagnosis

The risk of bias and applicability was assessed using the Quality Assessment of Diagnostic Accuracy Studies, version 2 (QUADAS-2) [33]. Overall assessment of bias was based on responses to four domains: (1) patient selection, (2) index test, (3) reference standard, and (4) flow and timing (flow of patients through the study and timing of index tests) and reference standard), for which there were multiple signaling questions to guide the assessment of each domain. If one or more of the four domains were considered as having a high or unclear risk of bias, the overall classification was rated as having a high risk of bias. The overall risk of bias was only considered low if all domains were rated as having a low risk of bias. The level of applicability (applicability concern) was also assessed using a signaling question for the first

three domains previously listed to identify if the domain of interest was consistent with the review question.

Treatment

For randomized controlled trials (RCTs), we assessed all domains of the Cochrane tool for assessing the risk of bias -RoB 2 [34]. We rated each of the following six domains as low, high, or unclear risk of bias: method of generating random sequence, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting, and other sources of bias.

Prospective non-randomized cohort studies were also considered due to scarce data on the treatment of anxiety and depression in the pediatric population with RCTs. The risk of bias for non-randomized controlled trials (NRCTs) was assessed using the ROBINS-I tool [35]. This tool considers seven domains of bias: (1) two domains of bias pre-intervention (bias due to confounding and bias in the selection of participants into the study); (2) one domain of bias at intervention (bias in the measurement of interventions); and (3) four domains of bias post-intervention (bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result).

2.2.5.2. Level of Evidence

The level or strength of evidence (SOE) was graded using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system for diagnosis and treatment [36]. In addition, we used the American Academy of Neurology (AAN) Practice Guidelines grading system (comparison studies) for treatment [37].

2.3. Consensus-Based Recommendation

2.3.1. Delphi Process

A Delphi process was followed to develop consensus-based recommendations. The expert consensus was sought to address relevant issues regarding diagnosis (e.g., time of assessment, source of information) and treatment (e.g., stage approach for treatment) not captured by the systematic review. The Task Force created a *Delphi Writing Group* to develop the initial Delphi questionnaire. Participants included the Chairs of the ILAE Psychiatry Commission (MK), Paediatric Commission (SA), Psychiatric Conditions in Pediatric Epilepsy (KV, CR), and a Delphi expert and the Chair of the ILAE Standards and Best Practice Council (NJ).

2.3.2. Delphi development and revision

The members of the Task Force of Psychiatry Conditions in Pediatric Epilepsy – *Delphi Working Group* - participated in online and on-site meetings to discuss the scope of this study that led to the elements for the survey. The *Delphi Writing Group* then generated the first Delphi questionnaire including assessment and treatment of anxiety and depression in children. The statements were based on articles obtained during this review, current guidelines for diagnosis and treatment of anxiety and depression in children and adolescents in general [18, 24, 27, 38-41] and based on the expertise of those involved in this process. The initial questionnaire was sent to all Task Force members. Revisions were made based on their feedback. They were asked to base their responses related to preferred gold standard care rather than the providers local capacity or on the resources available in their health care system. Each criterion was rated on a 5-point Likert scale. The final version was then revised by the whole group implementing additional suggestions to generate the recommendations for the Delphi process.

2.3.3. Delphi Panel

The Delphi panel of respondents was selected by the Task Force based on their expertise and credibility in the field. The panel was selected to achieve a broad representation of relevant clinical disciplines (pediatric epileptologists, child and adult neuropsychiatrists, neuropsychiatrists, child neurologists, psychologists, nurses, and neuropsychologists) and all ILAE regions.

2.3.4. Formulating Statements

The first-round Delphi survey contained 47 statements (**Supplementary Material 3)**. All statements were based on a 5-point Likert response scale [1. strongly agree, 2. agree, 3. neither agree or disagree, 4. disagree, 5. strongly disagree]. The initial survey was emailed to 104 participants. Three reminders were sent (one per month for every round). Forty-one participants responded to the initial survey. Eight of the 41 respondents provided demographic data but did not proceed to the core recommendations as they indicated that 'they were not involved in the care of children with epilepsy". The second round of the Delphi survey included 10 statements where 80% agreement still needed to be reached. Thirty-three respondents, who responded to the first round, were invited and all responded to the questionnaire. These 10 recommendations were modified based on the feedback from round 1. Again, a total of three reminders were sent. The third round of the Delphi survey comprised one modified statement about psychiatric interviews that was sent to the 33 respondents. A total of three reminders were sent and 27 responded to this questionnaire. In the first and second round, participants were encouraged to elaborate on their answers if they 'disagreed' or 'strongly disagreed' with a comment and references, whenever appropriate. Based on comments and references, statements were rephrased, modified, removed and added.

2.4. Statistical Analysis and Consensus Formulations

Results of the literature were summarized qualitatively reporting information as provided in the original included articles.

The level of agreement for consensus was set at 80% (Agree/strongly agree).

2.5. Evidence-Based Recommendations

After evaluating the quality of the evidence for diagnosis and treatment, we provided evidence-based recommendations and the level of this evidence according to the GRADE. If the evidence base for a given diagnosis or treatment was of low quality, we provided this information and complemented with consensus-based recommendations on this topic. We also emphasized the need for further research in this area and recommendations based on expert-opinion and evidence from children and adolescents without epilepsy.

2.6. Expert Recommendations

After the three rounds, the survey responses were converted into recommendations if consensus was reached, i.e., ≥80% "agree/strongly agree." We adopted the following strategy:1. A strong level of agreement (≥80% agree/strongly agree) - the recommendation was adopted and included; 2. A moderate level of agreement (<80% but ≥70% agree/strongly agree) - Recommendations were revised by members of the ILAE Task Force on Pediatric Psychiatric Issues if needed based on the feedback received in the previous round and were subjected to another round; 3. A low level of agreement (<70% agree/strongly agree) after the first round or rewording in the following rounds - Recommendation was removed. **Only recommendations that achieved a strong (≥80%) or very strong (≥90%) level of agreement were included in this document.**

3. RESULTS

3.1. Systematic Review

A total of 26,971 abstracts were identified of which 2,544 were duplicates (**Figure 1**). Of these, 407 articles were reviewed in full-text, 39 were assessed for eligibility and nine met all eligibility criteria for diagnosis and treatment [42-50]. The results were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards (PRISMA 2020)[32].

3.1.1. Diagnosis

The two studies that met the eligibility criteria for diagnosis were published in English in 2005 [42] and 2013 [43]. The study characteristics are presented in **Table 1**. The process of validation used as the gold-standard reference was the semi-structured diagnostic interview [Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime version (K-SADS-PL) [42, 43] and Epidemiologic (K-SADS-E) [42] designed to assess current and past episodes of psychopathology in children and adolescents according to DSM-IV administered in a face-to-face meeting [42] or by phone [43]. Caplan et al. [42] validated three scales: the Children's Depression Inventory (CDI), the Multidimensional Anxiety Scale for Children (MASC) and the Child Behavior Checklist (CBCL) subfactors internalizing scale and anxiety/ affective. The MASC provided the best sensitivity (0.867), and the CBCL Anxiety/Affective factor score, the best specificity (0.919) to predict mood (affective) and anxiety disorder diagnosis. The CDI had a sensitivity of 0.583 and a specificity of 0.733, CBCL Anxiety/Affective factor score had a sensitivity of 0.38. The CBCL internalizing scores presented a sensitivity of 0.627 and a specificity of 0.69.Wagner et al.(2013) [43] validated the Neurological Disorders Depression Inventory-Epilepsy for Youth (NDDI-E-Y 11) items (not the revised version) against the K-SADS PL depressive disorder module applied by phone by one interviewer and checked by one of the main authors. Eighty-seven patients responded to the K-SADS (reference standard), and five scored as having a mild or severe major depressive disorder or depressive disorder not otherwise specified. This rating scale provided a sensitivity of 0.80 and a specificity of 0.71 with a cutoff of 27.(**Table 2)**

These validation studies had an unclear risk of bias in at least one of the four **QUADAS-2** rating system categories [33] (**Figure 2**). Using the **GRADE** system [51], the strength of evidence (SOE) was very low (**Supplementary Material 4A**).
The Task Force identified two validation studies with low SOE. In a limited sample of children and adolescents [42], the CDI was tested against a gold standard measure (K-SADS) with a sensitivity of 58% and specificity of 73%. The strength of evidence for this finding was very low.

3.1.2. Treatment

The seven studies (four RCTs and three NRCTs) that met the eligibility criteria for treatment used K-SADS -PL to diagnose depression or anxiety disorder [44-50] and were published between 2006 and 2019 (**Table 3**). All studies were published in English and were conducted in tertiary care centers in the USA (02), the UK (one), Canada (one), Serbia (one), Brazil (one), and China (one). The demographics and epilepsy characteristics are shown in **Tables 4 and 5.** All studies, except for one [48], used rating scales to assess symptoms severity before and after the intervention.

Six studies assessed **non-pharmacological treatments**, including psychotherapy [44, 45, 49, 50], psychoeducational intervention [46], and physical activity [47]. The most frequent psychotherapy used in children with epilepsy was cognitive behavioral therapy (CBT) [44, 49, 50]. Considering CBT, one RCT [44], with 30 adolescents with "subthreshold depressive" symptoms, showed that the intervention (15 adolescents) was effective compared with treatment

as usual (15 adolescents) to decrease depressive symptoms (BDI [Beck Depression Inventory], CES-D, HAMD) and preventing depressive disorder (Class I, SOE for CBT was low). Two NRCTs (Jones, Blocher) using a computerized form of CBT (Camp-Cope-A-Lot) for 12 weeks showed a decrease in anxiety symptoms (MASC-C, SCARED-C and P [Screen for Child Anxiety Related Disorders Versions Children and Parents], CBCL Internalizing Symptoms) and social anxiety/social phobia (SCARED-Social Anxiety). (Class IV, SOE for CBT low). Systemic family therapy was used in one RCT [45] to treat 104 children with epilepsy and symptoms of anxiety (HADS-A) or depression (HADS-D). Systemic family therapy was effective compared to the inactive control group (using antiseizure medication [ASM]). (Class III; SOE was Low).

Two RCTs with non-pharmacological treatment included psychoeducation in a group intervention [46] and physical activity [47]. These two trials had depression and/or anxiety symptoms as secondary goals. They were both ineffective (Class III; SOE low).

Considering **pharmacological studies**, one NRCT [48] in children and adolescents with focal epilepsy and major depressive disorder (MDD) did not have seizure worsening with fluoxetine and sertraline (primary goal). The treatment was effective in decreasing MDD in 97.2% of all participants. (Class IV; SOE low for efficacy). All treatment studies had a high risk of bias (**Figures 3 and 4**) and low level of evidence according to the **GRADE** system [51] (**Supplementary Material 4B**). The categorization according to the AAN therapeutic classification of evidence scheme is shown in **Table 6**.

4.RECOMMENDATIONS FOR DIAGNOSIS OF ANXIETY AND DEPRESSION IN CHILDREN AND ADOLESCENTS WITH EPILEPSY

The assessment of anxiety and depression in pediatric epilepsy comprises different aspects such as the timing (when), the source of information (who), and the instrument used for evaluation (how). The Task Force acknowledges that physicians need support and training to identify and manage mental health disorders in this population.

4.1. GENERAL RECOMMENDATIONS FOR DIAGNOSIS OF ANXIETY AND DEPRESSION IN CHILDREN WITH EPILEPSY

IDENTIFICATION AND SURVEILLANCE

Recommendation 1: Universal screening for anxiety and depression is recommended in all children and adolescents with new-onset epilepsy age seven years or older (baseline) and annually thereafter [52]. **Level of Agreement:** Very Strong (97%)

High-quality guidelines for non-specialists recommend universal screening for anxiety and depression with some differences in age group [18, 53]**.**
Since there is a paucity of data on children with epilepsy, recommendations from the general population were adopted. The need for early screening and identification is corroborated by the presence of psychiatric or behavioral disorders before the first seizure [54, 55], in new-onset pediatric epilepsy [56, 57]or at the first appointment [58, 59]. In chronic epilepsy, regardless of the severity, periodic screening is reinforced by the knowledge that children with chronic disorders have higher rates of psychopathology [3-5]**.**

CLOSER SURVEILLANCE

Recommendation 2. In line with the Guidelines of the American Academy of Pediatrics [24], closer surveillance with more frequent screening or clinical evaluation for anxiety and/or depression in children and adolescents with epilepsy is recommended:

1. In adolescents, specifically after the age of 12 years;
2. In those with risk factors such as previous history or family history of psychiatric disorder (e.g., depression, anxiety, bipolar disorder, suicide-related behaviors, substance use, and other psychiatric illness);
3. In the setting of significant psychosocial stressors (e.g., family crises, physical and sexual abuse, neglect, and other trauma histories, foster care, adoption); and
4. In those with frequent somatic complaints.

Level of Agreement: Very Strong (97%)

Recommendation 3. Closer surveillance is also recommended for children and adolescents with epilepsy experiencing seizure worsening or therapeutic modifications (e.g., introducing antiseizure medication with negative psychotropic effects or withdrawing antiseizure medication with positive psychotropic effects). **Level of Agreement:** Very Strong (97%)

In the general population, risk factors mentioned above indicate that children at higher risk require closer surveillance [24, 27, 60-70]. Additionally, in children with epilepsy, modifications of therapeutic strategies and epilepsy aggravation are additional concerns and demand attention [71-74].Health care providers must consider that vigilant recognition and active monitoring for psychiatric morbidity in children and adolescents with epilepsy represents the cornerstone of management since earlier interventions may decrease symptoms of depression and anxiety [58, 59] and prevent disorders in children with milder symptoms [44].

SOURCE OF ASCERTAINMENT OF DEPRESSION & ANXIETY

Recommendation 4. When interviewing a child/adolescent with epilepsy about depression and anxiety, it is recommended that both the child/adolescent with epilepsy and their parents be interviewed, whenever possible. **Level of Agreement:** Very Strong (97%)

The child's interview is desirable but cannot be assessed in isolation since the child's functioning and psychological well-being depends highly on the environment. Age and intellectual level must be considered. Young children may need their parents, especially in the first contact. On the other hand, adolescents may need an explanation about the relevance of their parent’s information. The assessment of children and adolescents with moderate to severe/profound intellectual disability is beyond the scope of this work.

Obtaining a diagnostic picture of the child requires multisource information, including the family, and whenever possible, the school [27]. Therefore, this Task Force, in line with previous clinical practice guidelines (CPGs)[24, 27, 38-40] and evidence from children with epilepsy [75, 76], recommends that the caregiver must be involved in the process of diagnosis. When family/caregiver are involved in the assessment providing information, attention should be given to the limits of adolescents’ confidentiality. Parents and adolescents must be aware of the information that can be disclosed or not.

RECOMMENDATIONS FOR CHOICE OF INSTRUMENTS FOR FORMAL ASSESSMENT OF DEPRESSIVE AND ANXIETY SYMPTOMS

Clinicians and researchers aiming to assess either depression or anxiety face the difficult task of choosing from many symptom checklists and rating scales or interviews. These checklists or

rating scale are widely used since they are a time-effective method of obtaining clinical information with a small burden to respondents. They can also be administered in almost any setting to multiple informants (e.g., parents, teachers, and youth) using various modes of administration (e.g., on-site, online, by mail, computer) [77, 78]**.** Healthcare providers must be aware that checklists and scales represent a first-level screening for mental health disorders. All have limitations and are not designed to diagnose disorders, but rather to assess and score symptoms identifying those who need more in-depth evaluation for mental health disorders. Considering this scenario, healthcare providers may base the selection on their own expertise and clinical supports in their practices.

BEHAVIORAL CHECKLIST

Recommendation 5. A formal screening questionnaire, either on paper or electronically, is recommended as a first-level screen to assess for symptoms of depression and anxiety in children and adolescents with epilepsy. **Level of Agreement:** Very Strong (93.9%)

Recommendation 6: In busy clinical settings, it is recommended that a staged approach be used, beginning with a shorter behavioral checklist (e.g., Strengths and Difficulties Questionnaire [SDQ]). If the screen is positive, it must be followed by a more comprehensive checklist (e.g., Child Behavior Checklist [CBCL], Behavior Assessment System for Children [BASC]) or specific rating scales for depression and anxiety, with additional questions on suicidal ideation for children and adolescents with epilepsy who screen positive. **Level of Agreement:** Strong (87.9%)

Recommendation 7: Health care providers must choose the most appropriate checklist based on feasibility (e.g., time required to complete it), availability in the interviewee's language, cost, assessment (parents [young children] or parents and children [older children and adolescents]) with epilepsy and familiarity with the questionnaire. **Level of Agreement:** Very Strong (97%)

Broadband behavioral checklists/questionnaires - longer and shorter - are measures of behavior and personality across age groups and have been used in children with epilepsy. The review conducted by the **TF on Psychiatric Conditions in Pediatric Epilepsy** identified the Child Behavioral Checklist (CBCL) [79] [80]followed by the Behavior Assessment System for Children (BASC) [80] [81] [82] as the most frequently used longer broadband behavioral checklists. The analysis of the CBCL validity for children with new-onset [83] and chronic epilepsy [84] showed that the difference between scores was evident mainly for the narrowband scales (Attention Problems, Withdrawal, and Thought Problems), but negligible for the broadband scales (Internalizing Problems and Total Problems). Therefore, ambiguity seems to be negligible for the assessment of anxiety and depression. When CBCL internalizing and anxiety/affective subfactors were calibrated against K-SADS PL, these narrowband scales showed higher sensitivity than the CDI, but not than the MASC [42].

The Task Force acknowledges that longer broadband checklists/ questionnaires are useful yet not feasible in under-resourced clinical settings. For the non-specialist, a staged approach beginning with a shorter behavioral checklist followed by a more comprehensive checklist, specific rating scales, or whenever possible a clinical interview may be helpful.

RATING SCALES

More narrowly focused depression or anxiety symptom rating scales have been developed to permit valid and reliable quantitative assessment of specific symptoms. The **Task Force on**

Psychiatric Conditions in Pediatric Epilepsy identified that the most frequently used were Children Depression Inventory (CDI) and Beck Depression Inventory (BDI I and II).

Recommendation 8: Depression and anxiety symptom scales are recommended to quantify the presence and severity of a symptom in children and adolescents with epilepsy; this serves to establish a baseline against which response to therapeutic intervention, such as medication, can then be compared. **Level of Agreement:** Very Strong (97%)

Recommendation 9: In the clinical and research setting, it is recommended to use an instrument of choice to quantify self-reported symptoms of depression and anxiety in children and adolescents with epilepsy. The instrument of choice must be translated and validated for the interviewee's language. **Level of Agreement:** Very Strong (90.6%)

Recommendation 10: The choice of questionnaire for the assessment of symptoms of depression and anxiety in children and adolescents with epilepsy must consider the expertise of every health care provider, the available resources, and the feasibility in every setting. **Level of Agreement:** Very Strong (96.9%)

Recommendation 11: The health care provider involved in the care of children and adolescents with epilepsy must always explain that identifying symptoms is essential to optimize treatment outcome and reduce morbidity using language understandable to lay people. **Level of Agreement:** Very Strong (100%)

Recommendation 12: Children and adolescents with epilepsy and subthreshold symptoms that do not meet the criteria for a diagnosis of depression or anxiety, are at higher risk to develop these disorders and must be assessed more often. **Level of Agreement:** Strong (84.8%)

The **Task Force on Psychiatric Conditions in Pediatric Epilepsy** identified eight self-administered questionnaires for anxiety symptoms in children with epilepsy. The most frequently used questionnaires for anxiety symptoms are: STAI-CH (State and Trait Anxiety Inventory for Children), RCMAS (Revised Children's Manifest Anxiety Scale), SCARED (Screen for Child Anxiety Related Disorders), and MASC (Multidimensional Anxiety Scale for Children). There is no clear evidence of the superiority of one anxiety questionnaire over the other in children with epilepsy. The MASC (sensitivity of 0.87 and specificity of 0.72 in a sample of 57 children and adolescents with epilepsy) is the only questionnaire validated against a gold standard measure (K-SADS). [42]. Based on the current evidence and expert-opinion, the TF cannot recommend one checklist or one rating scale over the other. In this context, physicians must consider feasibility, their expertise with the questionnaire, and translation for the language of the interviewee.

SPECIAL CONSIDERATIONS REGARDING SEIZURE CONTROL AND ANTISEIZURE MEDICATION

Recommendation 13: Interictal and peri-ictal symptoms require distinct therapeutic strategies. The health care provider must actively ask if symptoms of anxiety or depression are related to seizure worsening/control in children and adolescents with epilepsy. **Level of Agreement:** Very Strong (100%)

Recommendation 14: It is recommended when assessing for symptoms of anxiety and depression that the health care provider ask whether the child or adolescent with epilepsy had

a seizure in the past 24 hours, as this could reflect an adjustment reaction rather than an anxiety or depressive disorder. **Level of Agreement:** Strong (84.4%)

Recommendation 15: The direct questioning of parents/caregivers and adolescents with epilepsy about new behavioral adverse effects of ASMs, pre-existing symptoms aggravated by ASMs, and interictal depressive/anxious symptoms is recommended. **Level of Agreement:** Very Strong (100%)

Recommendation 16: Parents and adolescents must be informed about the psychotropic properties of an ASM and possible behavioral adverse effects before it is prescribed to a child or adolescent with epilepsy. **Level of Agreement:** Very Strong (97%)

Once the presence of anxiety and depressive symptoms is recognized, the next step is to identify whether the symptoms are exclusively peri-ictal since these symptoms may not reflect the child's current state. Peri-ictal symptoms are not rare, but clinicians need to specifically enquire because they may not be reported by parents [85].

When the interviews and scales are used in a clinical context, the examiner has, in principle, the opportunity to clarify and to interpret the meaning of the critical items [84].
In addition, the effect of ASMs on mood is widely documented (e.g., levetiracetam, phenobarbital) and should be considered [86]. Depressive disorder have been identified in children with epilepsy treated with phenobarbital[87], but not in those with carbamazepine. Similar findings were reported with phenytoin but not with carbamazepine. [88](26).

The Task Force acknowledges and reinforces that transient worsening that are seizure and ASM-behavioral adverse effects must be evaluated. However, it is advisable to inform the caregiver that seizure symptoms and ASM mood and behavioral adverse effects should not be included in the rating [74, 86].

PSYCHIATRIC INTERVIEWS

Recommendation 17: Specialized clinical evaluation by a provider with expertise in mental health (e.g., psychiatrist or psychologist) is highly advisable when possible if clinical concerns for anxiety and depression are noted on history or screening in a child or adolescent with epilepsy. **Level of Agreement:** Very Strong (90.6%)

Recommendation 18: A structured and semi-structured psychiatric interview remains advisable for some research settings (e.g., screening tool validation studies) in children and adolescents with epilepsy. **Level of Agreement:** Very Strong (100%)

Using structured or semi-structured interviews is infrequent in non-research settings since they demand training, time, cost, and thus can be a burden to patients and caregivers. The **Task Force on Psychiatric Conditions in Pediatric Epilepsy** acknowledges that although standardized screening instruments are helpful for diagnosis, they do not replace a direct interview by a specialized clinician.

4.2. TREATMENT OF DEPRESSION AND ANXIETY IN CHILDREN AND ADOLESCENTS WITH EPILEPSY

GENERAL PRINCIPLES OF TREATMENT

Recommendation 19: Health care providers must develop a pragmatic treatment plan for anxiety and/or depression in children and adolescents with epilepsy and their caregivers. The treatment plan consists of deciding the treatment setting and determining the type of treatment - pharmacological and/or psychological. **Level of Agreement:** Very Strong (100%)

Recommendation 20: The treatment plan for anxiety and/or depression must be feasible and practical, addressing the needs, fears, beliefs, religion, cultural background, and resources of children and adolescents with epilepsy and primary caregivers. **Level of Agreement:** Very Strong (100%)

Recommendation 21: A health care provider must monitor children and adolescents with epilepsy who have been prescribed antidepressants for adverse effects, self-harm, and suicide risk. Onsite or online interviews with children and family members is recommended.***Level of Agreement:** Very Strong (93.8%)

*Comment added (modified) based on the Delphi Panel comments (2nd Round of Delphi)

Treatment of mental disorders in youth with epilepsy may add an extra burden to the patient and their family, due to stigma as well as practical aspects, such as additional medication, appointments, and new health care providers (e.g., psychologist, psychiatrist). There was consensus that patients with epilepsy and their families need a treatment plan for anxiety and/or depression which includes treatment type and setting, providing information about the severity, the impact, and the risks [89-94]. It is well-known that treatment plans lead to greater adherence and better outcomes in chronic disorders [24, 95-97]. [98] Panelists were unanimous that the treatment plan must be child and family-centered, and cultural beliefs must be respected to enhance the alliance between the patient/family and healthcare providers. Assessment during any treatment is mandatory. According to the American Academy of Child and Adolescent Psychiatry [27, 41], standardized symptom rating scales can supplement clinical interviews since these scales optimize therapists' abilities to assess treatment response and remission [99]

MONITORING AND TREATMENT INITIATION

MILD DEPRESSION AND ANXIETY

Recommendation 22. In line with previous Guidelines (National Institute for Health and Care Excellence [NICE] [38], American Academy of Pediatrics [AAP] [18, 24, 100] , American Psychological Association [APA] [101] [18, 24], a period of watchful and active monitoring (4-6 weeks) for mild depression or anxiety must be considered in children and adolescents with epilepsy. (This recommendation does not apply for moderate to severe symptoms). **Level of agreement:** Very Strong **(**96.9%)

Recommendation 23: If possible, psychological support or programs to increase resilience and coping must be offered during the period of monitoring for children with mild symptoms of depression and anxiety.* **Level of Agreement:** Strong (96.9%)

*Comment added based on the Delphi Panel comments (2nd Round of Delphi)

Recommendation 24: It is recommended that the watchful "active" monitoring in children and adolescents with epilepsy and mild symptoms of depression or anxiety, provided by a team member (e.g., nurses, social workers, junior fellows, residents) with basic training, include:

1. weekly or biweekly visits (onsite, by phone, or online) with regular symptom checking.

2. behavioral activation techniques (the prescription of exercise and leisure activities),
3. sleep monitoring (sleep deterioration can aggravate depression and anxiety),
4. a peer support group (whenever possible),
5. self-management goals for depression/anxiety and epilepsy, and
6. educational materials (paper/ website) for families and patients.

Level of Agreement: Strong (80.6%)

According to current CPGs for non-specialists in children and adolescents with mild depressive or anxiety disorder without additional burdens, active monitoring for 4 to 6 weeks is usually sufficient – provided that patients can manage their daily lives [18, 24, 38, 102, 103]. Active monitoring includes consultation and mental health education based on behavioral therapy to improve the understanding and management of depression and anxiety [104]. Measures to improve mental health should be offered and reinforced, such as regular exercise, sleep hygiene, mindfulness, relaxation techniques, a balanced diet, everyday activities, and social interaction [105].

During this period, the patient must be reassessed with a formal screening (onsite, online, or by phone). Active monitoring with mental health education is not an "independent" treatment method such as psychotherapy. Therefore, according to the stepped-care model [38], psychological support can be provided whenever possible. The Task Force acknowledges the shortage of mental health professionals to assist these patients by providing proper support [106, 107]. For this reason, we stress the importance of basic mental health training for healthcare providers caring for children if psychological support is unavailable or if there is a lengthy waiting list for milder cases.

According to the American Academy of Child and Adolescent Psychiatry (AACAP) [27, 41], therapeutic task-sharing with a primary care provider, particularly for mild and moderate cases, expands access and conserves the time of the child psychiatrist for managing complex and severe presentations.

MODERATE TO SEVERE DEPRESSION AND ANXIETY

Recommendation 25. In moderate to severe depression, anxiety and/or comorbid psychiatric conditions (e.g., substance abuse) in children and adolescents with epilepsy, the health care provider must refer to a mental health specialist (e.g., psychiatrist, psychologist) whenever possible. **Level of Agreement:** Very Strong (90.6%)

Recommendation 26. In the case of a lengthy wait time for mental health services for children and adolescents with epilepsy, the health care provider in charge must support active monitoring (onsite, online, by phone). **Level of Agreement:** Very Strong (90.6%)

Recommendation 27: Epilepsy clinics/centers must develop clinical care pathways to facilitate access to mental health services for children and adolescents with epilepsy. **Level of Agreement**: Very Strong (100%)

There was a uniform agreement for both the referral of severe cases to the specialist and the need to develop paths to mental health care. It is recommended to establish a collaboration with mental health care specialists to refer at-risk children and adolescents in advance. The collaborative care model with interdisciplinary team-based care consisting of a consultant psychiatrist for advice or consultation in the primary care clinic may be helpful in high, middle, and low-income countries [108-110]. The Task Force acknowledges that integrated healthcare approaches are resource-intensive to implement and maintain. Therefore, it may not be feasible to adopt such a model fully.

PSYCHOTHERAPY

Recommendation 28. Due to the limited evidence about the benefits of psychotherapy in children and adolescents with epilepsy, mental health providers are encouraged to base their treatment on trials conducted in children with depression and anxiety without epilepsy. **Level of Agreement:** Strong (87.1%)

Recommendation 29. The psychosocial intervention in children and adolescents with epilepsy should be tailored to the person's needs and severity of the depressive/anxious episode. Where available and indicated, cognitive behavioral therapy should be offered after assessing its suitability (e.g., personality characteristics, coping skills, family support, intellectual level, and social environment). **Level of Agreement:** Very Strong (93.8%)

In adolescents with epilepsy and subthreshold depressive symptoms, one RCT [44] compared CBT with psychotherapy (treatment as usual). Despite the limited sample (30 adolescents), treatment with CBT was superior at improving depressive symptoms and preventing depressive disorder compared with psychotherapy as usual (Class I study; High Risk of Bias [RoB-II]; Quality of Evidence for CBT: Low [GRADE]).
In children with epilepsy and anxiety disorder (generalized anxiety disorder, separation anxiety, and social phobia), a manual-based, computer-assisted CBT intervention for 12 weeks showed significant reductions in symptoms of anxiety and depression reported by the children at completion of the intervention and at the three-month follow-up [49, 50]. Similarly, parents reported fewer symptoms of anxiety and a reduction in behavior problems. Therefore, this CBT intervention for children with epilepsy and anxiety disorders was safe, effective, and feasible. This finding has a low SOE due to the limited sample and high risk of bias. There was a significant reduction in symptoms of anxiety and depression (Class IV, High Risk of Bias [Robins], Low Quality of Evidence [GRADE] [49, 50]. In children with depression and anxiety without epilepsy, psychotherapy is recommended as first-line treatment [27, 41]. According to current AACAP guidelines for children with depression or anxiety without epilepsy, there is stronger evidence for CBT compared to other forms of therapy, including interpersonal therapy and familial therapy [27, 41] . Ongoing RCTs with large samples may help to determine the clinical and cost-effectiveness of adding a modular psychological intervention to usual care for the mental health disorders in comparison to assessment-enhanced usual care alone in children and adolescents with epilepsy.

Recommendation 30: Psychotherapy must be age-appropriate, and for younger children with epilepsy, the family must be involved directly or via family therapy and counseling. **Level of Agreement:** Very Strong (93.8%)

The Task Force acknowledges that family involvement in the treatment of children with depression and anxiety is of undeniable importance. Treatment is characterized by a collaboration between patient, family, and therapist [27, 41]. Strategies that promote the relationship, communication, parenting style, and parent modeling of mood dysregulation may provide additional benefits to the child's treatment [27, 41].

In children without epilepsy, there are some inconsistencies regarding the importance of family therapy in isolation. NICE [38] guidelines recommend family therapy as a first-line option, but other CPGs for primary care physicians do not comment on this modality [18, 24, 39, 40]. According to the AACAP [27, 41], family based interpersonal therapy (vs. active control) improved clinician, parent, and self-reported symptoms of depression in children MDD and/ or

PDD. For adolescents or children with MDD, dysthymia, or DD NOS, family therapy improved depression response when compared with active control. However, the SOE for family therapy benefit in isolation is low.

In adolescents with epilepsy, one RCT with systemic family therapy applied to 104 adolescents (52 intervention and 52 inactive controls [receiving ASM only]) was identified. The primary aim was to document if systemic family therapy decreases symptoms of anxiety ([Hamilton Anxiety Scale (HAMA) score ≥14 points] and depression ([Hamilton Anxiety Scale (HAMA) score ≥20 points]. Scores of anxiety and depression were significantly decreased with systemic family therapy; meanwhile, the family dynamics and family functions were significantly improved, and the social support was also increased [45]. This Class III study had a high risk of bias and provided low SOE. Therefore, the current evidence is insufficient to judge the effectiveness of family therapy in adolescents with epilepsy.

Recommendation 31. Peri-ictal symptoms in children and adolescents with epilepsy respond poorly to antidepressant medication, and psychological support for the child and family is advisable when symptoms are related to loss of control associated with seizure unpredictability**.** **Level of Agreement:** Strong (81.3%)

*Comment modified based on the Delphi Panel comments (2nd Round of Delphi)

Current treatment strategy for peri-ictal anxiety and depression is to try to improve seizure control as remission is not always possible and thus, reduce the symptoms [111, 112].

PHARMACOLOGICAL TREATMENT

Recommendation 32: Health care providers (neurologists and epileptologists with training/ skills for mental disorders) faced with treating interictal depression/ anxiety in children and adolescents with epilepsy should use principles established for patients without epilepsy, considering the possible interaction with antiseizure medications and risk of seizure exacerbation. **Level of Agreement:** Strong (96.8%)

Recommendation 33: Selective serotonin reuptake inhibitors **(**SSRIs) must be regarded as first-line pharmacologic treatment of anxiety and/or depression in children/adolescents with epilepsy as they have a low seizure propensity and favorable side-effect profile. **Level of Agreement:** Strong (86.7%)

Recommendation 34. Slow titration of selective serotonin reuptake inhibitors **(**SSRIs) associated with careful and appropriate follow-up and monitoring is recommended for the treatment of anxiety and/or depression in children and adolescents with epilepsy. **Level of Agreement:** Strong (83.9%)

The Task Force acknowledges that medical education, training, and experience are necessary to prescribe antidepressant medications safely and effectively. In addition, an emergency risk plan and referral pathways must exist. By including recommendations for pharmacological treatment, the Task Force does not rule out the need for mental health care providers but recognizes the shortage of mental health services in high, middle, and low-income settings [106, 107, 113]. Current high-quality CPGs for children and adolescents without epilepsy recommend SSRIs (except paroxetine), preferably fluoxetine, as a first-line medication for major depressive disorder [18, 24, 27, 38-41]. For anxiety, SSRIs are recommended for children and adolescents from 6 to 18 years with social anxiety, GAD, separation anxiety, and panic disorders [27, 38, 41].

The **Task Force on Psychiatric Conditions in Pediatric Epilepsy** systematic review identified one open-label study (Class IV) using fluoxetine and sertraline for children and adolescents with epilepsy and major depressive disorder. The efficacy was high, and seizure worsening was rare [48]. (Class IV; Risk of Bias: High [Robins]; Quality of the Evidence: Low [GRADE]).

In line with current recommendations, the Task Force strongly suggests increased monitoring for increases in suicidal ideation in the weeks following medication initiation [18, 24, 27, 38-41].

Recommendation 35. Tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors are not recommended as first-line treatment for the treatment of anxiety and/or depression in children and adolescents with epilepsy. **Level of Agreement:** Strong (87.5%**)**

*Recommendation modified after the 2nd Round of Delphi

The Task Force acknowledges that availability of SSRIs may be limited in low-resource settings. Some local CPGs actively recommend against TCAs use [38-40], and others do not provide any comment about it.

COMBINATION THERAPY

Recommendation 36: Psychotherapy should be associated with pharmacotherapy if considered appropriate for the treatment of anxiety and/or depression in children and adolescents with epilepsy. **Level of Agreement:** Strong (87.1%)

The combination treatment (Combined Therapy) of SSRIs and CBT could be offered for MDD, GAD, social anxiety disorder, social anxiety, separation anxiety, or panic disorder whenever possible. In one RCT with adolescents with MDD without epilepsy, fluoxetine combined with CBT improved depressive symptoms (low SOE) [114].

In anxiety, two RCTs showed that combination therapy, compared with therapy alone and sertraline alone, improved primary anxiety and global function [115]. Combination therapy may represent a more effective short-term treatment than either treatment alone. The Task Force acknowledges the major difficulties that healthcare providers face in accessing combined therapy but understand that such recommendation may be useful for policymaking.

Recommendation 37: Epileptologists and/or pediatric neurologists should communicate with other healthcare providers, especially mental health providers, if they are prescribing a new antiseizure medication with negative psychotropic effect. **Level of Agreement:** Strong (81.3%)

Appropriate management of ASMs is another component in the management of children and adolescents with epilepsy with symptoms of depression or anxiety. Healthcare providers should aim for the cautious selection of ASMs with a lower likelihood of psychiatric/behavioral adverse effects [8, 74, 102, 116-119]. The Task Force acknowledges the importance of balancing such considerations against the primary objective of seizure control. Consideration must also be given toward the accumulative impact of polytherapy in this context and should be avoided where possible and minimized when required.

ONGOING MANAGEMENT

Recommendation 38: A health care provider must monitor children and adolescents with epilepsy prescribed with antidepressants for adverse effects, self-harm, and suicide risk.

Onsite or online interviews with children and family members are recommended. **Level of Agreement:** Very Strong (93.8%)

Recommendation 39. In busy clinical settings, a checklist with the most common antidepressant/anxiolytic adverse effects is recommended in children and adolescents with epilepsy. **Level of Agreement:** Strong (80.7%)

Recommendation 40. Education of family/primary caregivers is essential to guarantee adherence to antidepressant/anxiolytic and adequate monitoring of psychiatric symptoms and adverse effects in children and adolescents with epilepsy. **Level of Agreement**: Very Strong (96.8%)

Recommendation 41. Clinical trials have shown that symptoms and functioning do not improve at the same time. Therefore, the assessment of treatment strategy in children and adolescents with epilepsy and depression or anxiety must consider several domains, including:

1. Efficacy
2. Global functioning (social and academic)
3. Risk of suicide
4. Possible adverse effects from treatment with adverse-effect scales
5. Treatment adherence
6. New or ongoing environmental stressors (e.g., family conflict/dysfunction, academic issues, bullying).

Level of Agreement: Very Strong (100%)

In the ideal scenario, a mental health care provider with expertise must monitor for adverse effects, especially at the beginning of treatment. However, patients and families may report adverse effects or worsening symptoms during their appointment with the epileptologist, pediatric neurologist, pediatrician, or other healthcare providers. Therefore, healthcare providers in charge of these children and adolescents must be aware of the treatment and its risks. In collaborative care or shared-care model of care, the role of every care provider must be established, including monitoring [16, 23, 120-122]. There is no evidence to support the that in-person monitoring is more effective than virtual monitoring after treatment initiation. More importantly, a regular and frequent schedule should be developed to obtain input from the adolescents and families to ensure adherence with the monitoring strategy [123-126]. This may include monitoring depressive symptoms, risky behaviors, and global functioning (e.g., school setting, interaction with peers). The contact with the family will ensure appropriate monitoring and enhance adherence [24].

Recommendation 42. In line with the American Academy of Child and Adolescent Psychiatry (2022) and the American Academy of Pediatrics (2018) Guidelines, it is recommended that children and adolescents with epilepsy treated for 12 months for anxiety and/or depression should be monitored every month for 6 to 12 months after full resolution of psychiatric symptoms. **Level of Agreement:** Strong (80.6%)

Recommendation 43: In case of recurrence of anxiety and/or depressive symptoms,healthcare providers must treat and monitor children and adolescents with epilepsy monthly for up to 2 years, given the high recurrence rates. In case of recurrence, referral to a mental health provider is recommended. **Level of Agreement:** Strong (87.1%)

Recommendation 44: If antidepressant/anxiolytic treatment inefficacy (i.e., symptoms, functioning) or partial efficacy is detected over a period of six to eight weeks in a child or

adolescent with epilepsy, referral to a mental health provider (e.g., psychiatrist, psychologist) is recommended. **Level of Agreement:** Strong (90%)

Recommendation 45. The presence of new psychiatric conditions not previously identified (i.e., anxiety, mania, substance abuse) or imminent suicidal risk in children and adolescents with epilepsy require immediate referral or treatment in a specialized setting (e.g., inpatient treatment). **Level of Agreement:** Strong (83.9%)

For anxiety disorder, improvement is expected within two weeks of treatment initiation, clinically significant improvement by week 6 and maximal improvement by 12 weeks or later [127]. For depression, a significant improvement in depression symptoms is expected within the first month of treatment initiation, with two-thirds of SSRI benefits by week 2 and maximal benefit by week 4-6 [128]. [27]. The optimal duration of treatment with an initial depressive disorder is uncertain, but it is generally accepted to continue therapy for 6-12 months after remission to reduce relapse. Depression with severe symptoms, longer duration, and relapses may benefit of longer treatment [129]. Referral to a mental healthcare provider or, at least, consultant with an expert is recommended for cases of inefficacy, recurrence/relapses, the emergence of a new psychiatric condition (namely, those with moderate to severe symptoms), self-harm or suicidal ideation/planning.

SHARED-CARE MODEL

Recommendation 46. The ongoing involvement of the managing epilepsy team in the treatment of depression and anxiety is recommended to ensure acceptance, adherence to treatment, counseling, and support**.** A shared-care model is recommended in children and adolescents with epilepsy and mental health disorders. **Level of Agreement: Very** Strong (96.8%)

Children and adolescents with epilepsy and their families are familiar with their primary care provider (child neurologist, epileptologist, or the epilepsy team), but may not be familiar with mental healthcare providers (psychiatrists, psychologists, counselors, social workers). It may represent an extra burden to the complex scenario of chronic conditions (double stigma) and a challenge for diagnosis and treatment. Integrated behavioral healthcare is defined as “the care a patient experiences as a result of a team of primary care and behavioral health clinicians, working together with patients and families, using a systematic and cost-effective approach to provide patient-centered care for a defined population” [130]. In this context, the epileptologist introduces the patient to the behavioral health provider, and the behavioral health provider then engages the patient and begins the assessment and treatment process. The team follows a "stepped care" approach allowing immediate and appropriate treatment without referral to mental health services. Higher levels of care are reserved for patients who are not improving or who have a more complicated presentation [131]. The team refines the diagnosis throughout treatment and provides medication adjustments, brief behavioral interventions, and education. Adjusting treatment, including referral to specialty mental healthcare if needed, continues until treatment targets are accomplished. The process allows a sophisticated application of mental health skills, in short supply, to be leveraged across larger populations of patients.

CONCLUSION

This manuscript, with consensus-based recommendations, addressed common but important aspects of the diagnosis and treatment of anxiety and depression in children and adolescents with epilepsy.

Although depression and anxiety disorders and symptoms are common in children and adolescents with epilepsy, our systematic review showed that the strength of evidence is meager to put forward clinical guidelines. Regarding diagnosis, validation studies are scarce. Considering treatment, more controlled, randomized, double-masked studies with large samples and follow-ups are needed.

The Delphi method, used to generate recommendations, provides expert consensus in a structured process. It offers several strengths that make it a valuable tool for decision-making, such as anonymity and iterative process, minimizing personal biases' impact, and allowing geographical representation. An overreliance on expert opinions and limited group dynamics are common weaknesses of the Delphi process. We took measures to minimize the bias introduced by expert selection (e.g., experts from the same group) and facilitators. We considered experts from all ILAE regions and revised recommendations based on their opinions during three rounds. Recommendations that achieved at least 80% agreement were included in our final recommendations.

Children and adolescents with epilepsy are at a higher risk of experiencing psychiatric disorders, such as depression and anxiety, compared to children without epilepsy and non-neurological chronic disorders [4] [3]. Therefore, they must be routinely and systematically screened for these conditions. The treatment for these disorders should follow the same guidelines used to treat children and adolescents without epilepsy. However, due to the unpredictability of seizures and the potential adverse effects of antiseizure medication on behavior, special care is required if seizures worsen or if the therapy requires modification.

The Task Force acknowledges the shortage of mental health providers, which makes it necessary to adopt an integrated model of care with shared responsibilities. Education is necessary for primary and secondary care centers and pathways of referral for severe cases.

This study has identified areas in the management of depression and anxiety of children and adolescents with epilepsy that lack a solid evidence base and require more targeted research. Moreover, it has provided a practical guide to address challenging areas in the care of children and adolescent with epilepsy who are at a higher risk of developing depression and anxiety.

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Table 1. Demographic and Epilepsy Characteristics of Diagnostic Studies

Study	Psychiatric Interview	Ascertainment Source	Questionnaire under Validation	N	N included for validation	Sex (%)	Age (years) Age Range Mean [SD]	Age of epilepsy onset (years) Mean [SD]	Duration of epilepsy (years) Mean [SD]	Epilepsy Type (%)		Antiseizure medication (%)	
Caplan et al. *Epilepsia* USA, 2005	KSADS-PL KSADS-E	Tertiary and community	CDI MASC CBCL - Internalizing - Anxiety / Depression	171	57	M: 47 F: 53	5-16 10.3 [2.7]	5.7 [3.21]	4.7 [3.21]	Focal Generalized*	58.5 41.5	0 01 ≥02	8 68 24
Wagner et al.# *J of Child Neurol* USA, 2013	KSADS Depression Module	Tertiary	NDDI-E-Y (11-item)	93	5	M: 53 F: 47	10 - 17 14 [2.0]	8 [5.01] Age range: 0-16 yrs	-	Focal Generalized Unknown	59.1 34.4 7.5	0 1 ≥2	2 65 34

*Childhood Absence Epilepsy
Data available for the whole group (93) *Childhood absence epilepsy
CBCL: Child Behavior Checklist; CDI: Children's Depression Inventory; **F:** Female; **K-SADS-E:** Kiddie-Schedule for Affective Disorders and Schizophrenia - Epidemiological Version; **K-SADS-PL**: Kiddie-Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version; **M:** Male; **MASC:** Multidimensional Anxiety Scale for Children; **N:** Number of patients; **NDDI-E-Y:** Neurological Disorders Depression Inventory for Epilepsy in Youth; **SD:** Standard Deviation

Table 2. Diagnostic Accuracy Studies – Validation Studies Using Psychiatric Interviews

Study	N	Tool	Cut-point	Reference Standard	Sensitivity	Specificity	PPV	NPV	AUC
Caplan et al. *Epilepsia* USA, 2005	57	CDI	≥50	KSADS-PL and E[1]	0.583	0.733	NR	NR	NR
		MASC	≥50		0.867	0.718	NR	NR	NR
		CBCL Internalizing	≥67		0.627	0.694	NR	NR	NR
		CBCL Anxiety + Depression	≥67		0.38	0.919	NR	NR	NR
Wagner et al., *J of Child Neurol* USA, 2013	93	NDDI-E-Y 11 items	≥ 27	KSADS-PL[2]	0.80	0.71	0.14	0.98	0.79 (0.58-0.99)

AUC: Arrea under the curve; **CBCL:** Child Behavior Checklist; **CDI:** Children's Depression Inventory; **K-SADS-E:** Kiddie-Schedule for Affective Disorders and Schizophrenia - Epidemiological Version; **K-SADS-PL:** Kiddie-Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version; **MASC:** Multidimensional Anxiety Scale for Children; **NDDI-E-Y**: Neurological Disorders Depression Inventory for Epilepsy in Youth; **NR**: Not Reported by the Authors. **NPV**: Negative Predictive Value; **PPV**: Positive Predictive Value

[1]The primary author or a trained research assistant administered the K-SADS to each child and parent. A consensus DSM-IV diagnosis was reached after reviewing videotapes of the child's interviews and audiotapes of the parent's interviews. A child was excluded from the study if a diagnostic consensus was not reached. [2] KSADS-PL Module for Depression was applied by a phone.

Table 3. Characteristics of Treatment Studies

Author	Year of Publication	Retrospective or Prospective	Study Design	Location (Country)	Location (Region)	Ascertainment	Sample Size	Age range [mean (SD)]	Gender (%F)
Martinovic, Simonovic & Djokic *Epilepsy & Behavior*	2006	Prospective	Randomized controlled trial	Serbia	Europe	Tertiary	Total:30 IG: 15 CG:15	13-19 [17.4 (1.6)] IG(CBI): 17.2 (2.5) CG(TAU): 17.6 (2.2)	60 IG: 60 CG:60
Li et al. *Psychiatry Investigation*	2016	Prospective	Randomized controlled trial	China	Asia	Tertiary, single center	Total: 104 IG: 52 CG:52	13-20 IG: 17.14 (± 1.82) CG:16.98 (± 2.06)	55.3 IG: 50 CG:51.9
Dorris et al. *Epilepsy & Behavior*	2017	Prospective	Randomized controlled trial	United Kindom	Europe	Tertiary, multicentric	Total: 83 IG: 40 CG:43	12–17 IG:14.4 (± 1.5) CG: 14.3 (± 1.4)	60.24 IG: 65.4 CG:66.7
Brown et al. *Epilepsy & Behavior*	2019	Prospective	Randomized controlled trial	Canada	North America	Secondary, multicentric	Total: 115 IG: 56 CG:59	08-14 [11.37 (± 1.91)] IG: 11.54 (±1.93) CG: 111.20 (± 1.86)	50.8 IG: 50 CG:50.8
Thome-Souza, Kuczynki, Valente *Epilepsy & Behavior*	2007	Prospective	Non-randomized observational	Brazil	Latin America	Tertiary single center	Total: 36	5-18 [12.78 (± 3.04)]*	52.8
Blocher et al. *Epilepsy & Behavior*	2013	Prospective	Non-randomized observational	United States of America	North America	Secondary and tertiary centers	Total: 15	8-13 [11 (± 1.51)]	53.3
Jones et al. *Seizure*	2014	Prospective	Non-randomized observational	United States of America	North America	Secondary and tertiary centers	Total: 15	8-13 [11 (± 1.51)]	53.3

*Provided by the authors

CG: Control Group; **F:** Female; **IG**: intervention Group; **SD**: Standard Deviation

Table 4. Clinical and demographic data of RCTs and NRCTs

	Sample	Age range (years) Mean [SD]		Sex (F%)	Mean age of epilepsy onset (years) Mean [SD]		Duration of epilepsy (years) Mean [SD]		Type of Epilepsy** N[%]			Number of ASM (% of Patients)		
		IG	CG		IG	CG	IG	CG		IG	CG		IG	CG
Martinovic *Epilepsy & Behavior* Serbia and Montenegro, 2006	30 children with subthreshold depression IG: 15 CG: 15	17.2 [2.5]	17.6 [2.2]	Total: 60*	UD	UD	0.7 [0.4]	0.8 [0.3]	Focal (Partial) Generalized	9[60] 6[40]	9[66.7] 5[33.3]	0 1 ≥2	0 46.7 53.3	0 60 40
Li *Psychiatry Investigation* China, 2016	104 children with anxiety and depression IG: 52 CG: 52	17.14 [1.82]	16.98 [2.06]	CG: 51.9 IG: 50	UD	UD	5.38 [5.0]	6.59 [5.20]	Focal (Partial) Generalized Other seizure types[#]	NR 33[63.5] 19[36.5]	NR 34[65.4] 18[34.6]	1 ≥2	50 50	51.92 48.1
Dorris *Epilepsy & Behavior* United Kingdom, 2017	83 children without psychiatric comorbidity IG:40 CG:43	14.4 [1.5]	14.3 [1.4]	GC: 66.7 IG: 65.4	UD	UD	7.4 [3.9]	5.6 [3.5]	Genetic Generalized Focal Unspecified Benign Rolandic Epilepsy Unknown	20 [50] 15[37.5] 03[7.5] 02[5]	21[48.8] 18 [41.9] 03[7] 01[2.2]	1 2 3	52.3 32.5 10	69.8 25.6 4.6
Brown *Epilepsy & Behavior* Canada, 2019	115 children without psychiatric comorbidity IG: 56 GC: 59	11.54 [1.93]	11.20 [1.86]	Total: 62*	7.74 [3.32]	7.04 [3.0]	3.8 [3.2]	4.22 [2.79]	Partial (Simple+ Complex) #Generalized	23[41.7] 48[85.7]	20[33.9] [89.8]	0 1 2 3	8.9 64.3 17.8 5.3	11.9 55.9 25.4 5.1
Thome-Souza *Epilepsy & Behavior* Brazil, 2007	36 children with major depressive disorder	6-16 11.97 [3.04]		47.22	6.1 [6.8] Age range: 0.1-16 yrs		6.4 [5.1] Age Range:0.25-16 yrs		Focal Generalized	100 0		1 2 3	66.7 19.4 13.9	
Blocher *Epilepsy & Behavior* USA, 2013	15 children with anxiety disorder	8-13 11.0 [1.51]		53.3	7.0 [3.0]		4.12 [2.82]		Focal Generalized	73.3 27.7		0 1	20 80	
Jones *Seizure* USA, 2014	15 children with anxiety disorder	8-13 11.0 [1.51]		53.3	7.0 [3.0]		4.12 [2.82]		Focal Generalized	73.3 27.7		0 1	20 80	

*There was no difference of biological sex among the groups, only in the total group.**;** ** Terminology used by the authors**;** # Generalized includes generalized tonic-clonic,absence, myoclonic, atonic
ASM: Antiseizure Medication; **UD:** unavailable data; **CG:** control group; **IG:** intervention group; **NR:** not reported by the authors; **NRCT:** Non-Randomized Controlled Trials; **RCT**: Randomized Controlled Trials.

Table 5. Characterization of outcome variables of depressive and anxious symptoms in non-randomized studies

Study	Type of Intervention	Treatment Method	Primary Outcome	Secondary Outcome	Baseline Period Mean [SD]	End of Study Mean [SD]	Follow-up Mean [SD]	p	AAN Class	SOE
						6 months	9 months			
Martinovic *Epilepsy & Behavior* Serbia and Montenegro, 2006	Psychotherapy	Cognitive-Behavioral Intervention	BDI		IG:8.2 [0.94] CG:8.1 [0.96]	IG: 5.4 [2.97] CG: 7.8 [2.66]	IG: 5.60 [3.03] CG: 7.7 [1.76]	P < 0.05	I	Low
			CES-D		IG:14.1 [4.52] CG: 13.9 [4.51]	IG:9.8 [4.20] CG: 13.6 [4.64]	IG: 10.5 [5.32] CG: 13.8 [4.79]	P < 0.05		
			HAMD		IG:5.9 [0.80] CG: 5.7 [0.70]	IG:3.3 [1.29] CG: 5.8 [1.98]	IG: 3.5 [1.73] CG: 6.73 [2.76]	P < 0.05		
				QOLIE-31 Total Score	IG:36.95 [11.05] CG: 38.48 [10.18]	IG:52.78 [6.40] CG: 41.35 [8.26]	IG: 56.40 [5.51] CG: 42.23 [9.23]	P < 0.01		
				Cognitive risk factors	IG: 9.4 (1.2) CG: 9.2 (1.4)	IG: 4.6 (0.8) CG: 7.8 (1.3)	IG: 4.9 (1.1) CG: 7.5 (1.8)	P < 0.05		

Li *Psychiatry Investigation* China, 2016	Psychotherapy	Systemic Family Therapy	Seizure Frequency		IG:6.50[6.77] CG:7.00[6.85]	IG:4.22[3.54]*† CG:6.20[5.86]*		P<0.05	III	Low
			HAMA		IG:13.41 [7.83] CG:13.76 [8.76]	IG:9.52±6.28*† CG:13.48 [8.47]		P<0.05		
			HAMD		IG:22.55 [9.76] CG: 20.35[9.55]	IG: 13.86±9.17*† CG: 18.89[8.73]		P<0.05		
			SSRS		IG:31.34[12.97] CG: 34.83[11.53]	IG: 41.41[10.61]*† CG: 34.52[9.97]		P<0.05		
			FAD		IG: 19.03[7.17] CG: 19.33[7.46]	IG: 17.59[5.10]* CG: 18.91[7.12]		P<0.05		
			SSFD (Family Atmosphere)		IG: 25.78[11.29] CG: 28.70[12.02]	IG: 19.83[7.30]*† CG: 29.37[11.82]		P<0.05		
			Total Family Function Score		IG:94.81 [13.58] CG:94.98 [22.40]	IG:90.91 [17.71]*† CG:100.85 [19.75]		P<0.05		
				Self-fulfilling prophecy	NR	NR				
Dorris *Epilepsy & Behavior* United Kingdom, 2017	Psychoeducational	Group therapy				Post	3 months		III	Low
			EKP-G		IG:39.15 [5,28] CG: 39.87 [4.69]	IG: 41.36 [5.05][a] CG: 40.29 [3.75]	IG: 43.36 {3.24][b] CG:41.10 [4.41]			
			SSEC-C		IG: 57.15 [14.72} CG: 59.26 [12.80]	IG:60.23 [10.34] CG: 60.84 [9.91]	IG:60.69 [8.23] CG: 60.55 [10.45]			

			B-IPQ		IG: 36.26 [12.32] CG: 34.47 [13.54]	IG: 36.38 [12.77] CG: 34.87 [12.75]	IG: 35.72 [12.0] CG: 34.95 [13.33]			
			PedsQL		IG: 70.93 [15.41] CG: 69.36 [19.42]	IG: 67.61 [14.10] CG: 66.93 [17.28]	IG: 67.79 [11.74] CG: 69.19 [17.70]			
			GEOS-YP		IG: 62.61 [14.85] CG: 66.20 [13.95]	IG: 63.82 [14.43] CG: 66.83 [11.85]	IG: 65.83 [11.62] CG: 66.16 [12.13]			
				PI-ED	IG: 14.49 [6.61] CG: 12.76 [7.84]	IG: 14.95 [6.39] CG: 13.39 [6.69]	IG: 13.72 [5.86] CG: 13.95 [7.76]			
				BAI-Y	IG: 51.8 [11] CG: 49.5 [10.4]	NR				
				BDI-Y	IG: 51.2 [10.3] CG: 47.8 [9.7]	NR				
Brown *Epilepsy & Behavior* Canada, 2019	Psychoeducational	Behavioral counseling to increase physical activity	CDI-S CHEQOL KIDSCREEN-27 Mood Physical activity				12 months [&] t-Value, p-Value −0.43, 0.67 1.82, 0.07 0.98, 0.33 0.16, 0.87	P=0,07	III	Low
Thome-Souza *Epilepsy & Behavior* Brazil, 2007	Pharmacological	SSRIs (Fluoxetine and Sertraline)	Worsening of Seizures (Seizure Diary)		NA	1 month NA	≥12 months		VI	Low
				Adverse effects	NA	NA	-	NA		
				KSADS-PL (MDD)	NA	NA	Complete remission 72.2 Partial improvement	NA		

							25			
Blocher *Epilepsy & Behavior* USA, 2013	Psychotherapy	Computer-assisted CBT	MASC(C)		57.33 [+15.21]	12 weeks 47.93 [±14.44]	3 months 47.43 [±12.28]	p<0.05	IV	Low
			SCARED(C)		30.87 [±18.22]	17.60 [±12.39]	16.71 [±12.50]	p<0.05		
			SCARED(P)		29.93 [±10.95][#]	22.29 [±8.77]	22.79 [±12.84]	p^1=0.02/ p^2=0.18		
			CBLC Total (P)		60.20 [+8.36]	55.07 [±9.57]	56.93 [±8.18]	p<0.05		
			CBCL Internalizing		67.27 [±5.57]	62.07 [±7.05]	DI	P=0.039		
				CDI	48.53 [±11.34]	42.87 [±8.76]	41.36 [±7.11]	p<0.01		
Jones *Seizure* USA, 2014	Psychotherapy	Computer-assisted CBT	SCARED- Social Anxiety		6.67 [±3.37]	12 weeks 3.80 [±2.81]	3 months --	P<0.05		

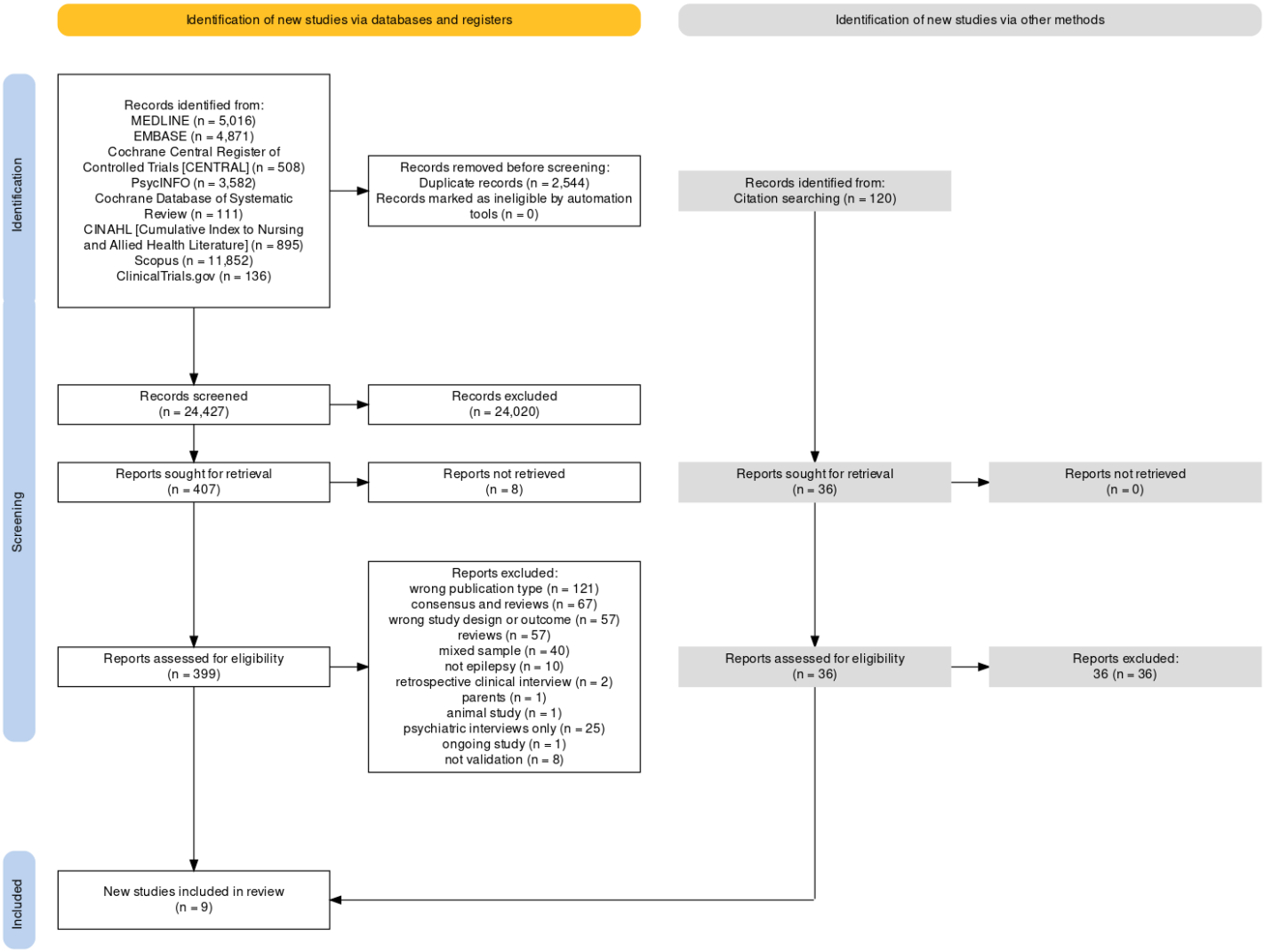
*p<0.05; compared with the endpoint of the control group, †p<0.05;
[a] Cohen's d= 0.25; [b] Cohen's d = 0.58
&: Scores reflect Control group in reference in Intervention group. Estimates are derived from linear mixed-effects model that adjusts for Baseline score, age, gender, and BMI. p values are from t-tests for null hypotheses that parameter estimates were set to zero.
p^1:12 weeks p^2: 3 months follow-up; [#]corresponds to week 7
BDI: Beck Depression Inventory; **B-IPQ**: Brief - Illness Representations Questionnaire; **CBCL**: Child Behavior Checklist; **CBLC total (P)**: Child Behavior Checklist total score– Parent Version; **CBT**: Cognitive Behavioral Therapy; **CDI**: Children's Depression Inventory; **CBI**: Cognitive Behavioral Intervention; **CES-D**: Center for Epidemiological Studies- Depression Scale; **EKP-G**: Epilepsy Knowledge Profile-General; **FAD:** Family Assessment Device;
GEOS-YP: Glasgow Epilepsy Outcome Scale for Young Persons; **HAMA:** Hamilton Anxiety Scale; **HAMD:** Hamilton Depression Scale; **K-SADS-PL:** Kiddie-Schedule for Affective Disorders and Schizophrenia – Present and Lifetime Version; **MASC**: Multidimensional Anxiety Scale for Children; **MASC(C):** Multidimensional Anxiety Scale for Children _ Child Version; **MDD**: major depressive disorder; **NA**: not applicable; **NR**: overall score not reported by author, only the subscales; **PedsQL**: Paediatric Quality of Life Inventory**;** **PIED**: Paediatric Index of Emotional Distress; **QOL:** Quality of Life; **SCARED**: Screen for Child Anxiety Related Disorder; **SCARED (C)**: Screen for Child Anxiety Related Disorder – Child Version; **SCARED (P)**: Screen for Child Anxiety Related Disorder – Parent Version; **SSEC-C**: Seizure Self Efficacy Scale for Children; **SSFD**: Scale of Systemic Family Dynamics; **SOE**: Strength of Evidence; **SSRIs**: selective serotonin reuptake inhibitors; **SSRS:** Scale of systemic family dynamics; **TAU:** Treatment as usual; **UD**: unavailable data; **USA**: United States of America
C: children; **P**: parents;

Table 6. American Academy of Neurology Level of Evidence Class (AAN LOE Class)

Intervention		Study	Comparison CG	Treatment Allocation	Completeness of Follow-up	Masking	Number of Primary Outcome	Secondary Outcome	AAN LOE Class
Psychological Treatment	CBT	Martinovic, 2006	↑ CBT *vs.* TAU	↑	↑	↑	↑ **≤2**	↑	I
		Jones, 2014	↓	N/A	N/A	N/A	N/A	N/A	IV
		Blocher, 2013	↓	N/A	N/A	N/A	N/A	N/A	IV
	STF	Li, 2016	↑ SFT *vs.* Inactive control	?	?	↓	↑ ≤2	↑	III
Physical Treatment	Fitbit®	Brown, 2019	↑ Fitbit®+ counseling *vs.* Fitbit®	↑	?	↓	↑ ≤2	↑	III
Psychoeducational (Self-management)		Dorris, 2017	↑ Psychosocial intervention *vs.* Waiting List	↑	↓ **(>20% drop out)**	↓	↓ ≥3	↑	III
Pharmacological	SSRIs	Thomé-Souza, 2017	↓	N/A	N/A	N/A	N/A	N/A	IV

N/A: not applicable; **CBT**: Cognitive Behavior Therapy; **CG**: Control Group; **SFT**: Systemic Family Therapy; **SSRIs**: Selective Serotonin Reuptake Inhibitors; **TAU**: Treatment as usual

Figure 1. PRISMA



Figures 2A and B. Summary of QUADAS assessment of included studies

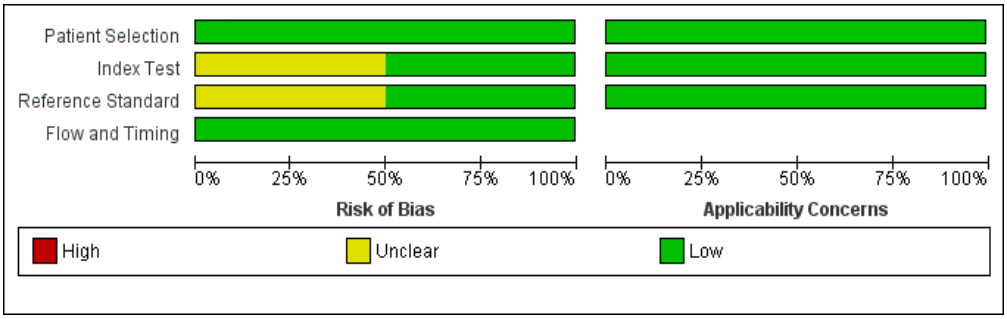


Figure 2A.'Risk of bias' graph: review authors' judgements about each 'risk of bias' domain presented as percentages across all included studies.

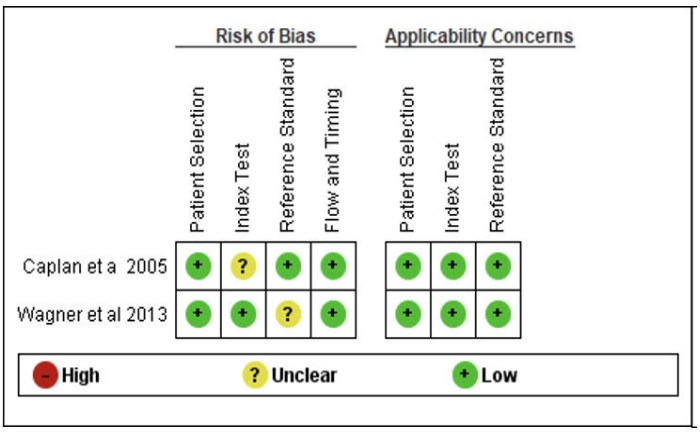


Figure 2B. 'Risk of bias' summary: review authors' judgements about each 'risk of bias' domain for each included study.

Figures 3A and B. Summary of RoB 2.0 assessment of included RCTs

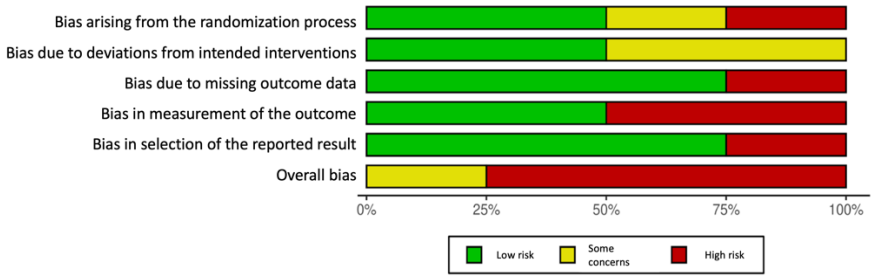


Figure 3A. 'Risk of bias' graph: review authors' judgements about each 'risk of bias' domain presented as percentages across all included RCTs.

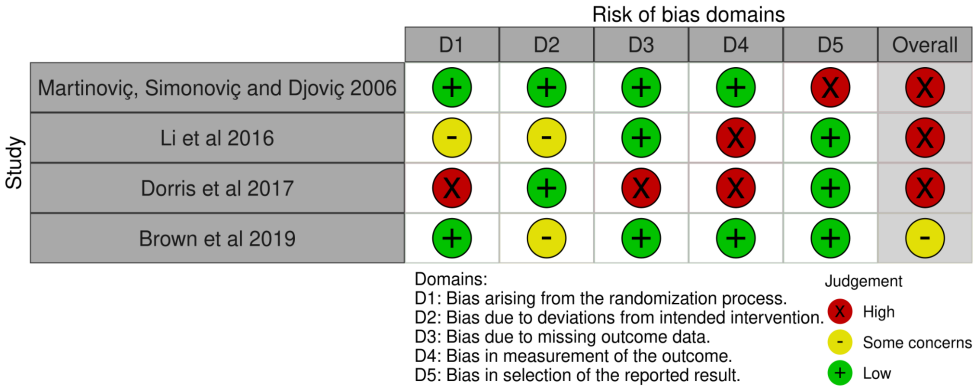


Figure 3B. 'Risk of bias' summary: review authors' judgements about each 'risk of bias' domain for each included RCT.

Figures 4A and B. Summary of ROBINS-I assessment of included NRCTs

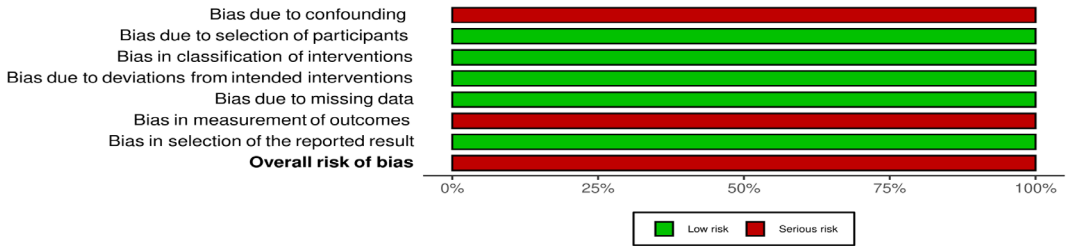


Figure 4A.'Risk of bias' graph: review authors' judgements about each 'risk of bias' domain presented as percentages across all included NRCTs.

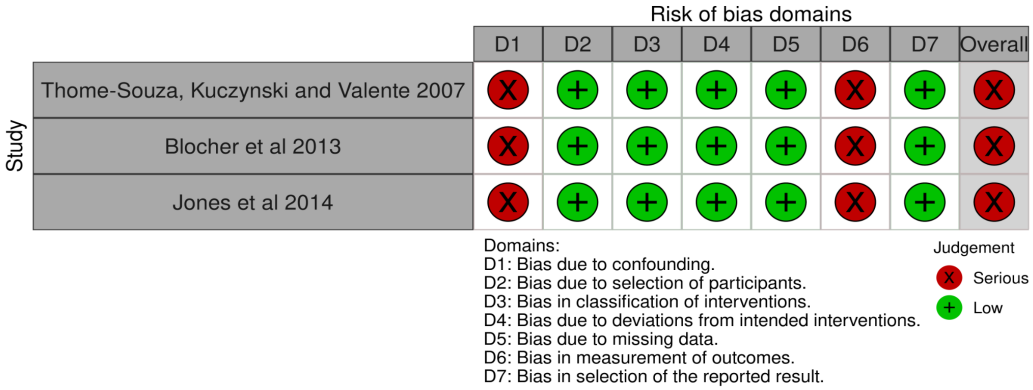


Figure 4B. 'Risk of bias' summary: review authors' judgements about each 'risk of bias' domain for each included NRCT.