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ACCEPTED FOR PUBLICATION IN EPILEPSIA

Psychological treatments for adults and children with epilepsy: Evidence-based recommendations by the ILAE Psychology Task Force

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Summary

Given the significant impact that psychosocial factors and epilepsy treatments can have on the health-related quality of life (HRQOL) of individuals with epilepsy and their families, there is great clinical interest in the role of psychological evaluation and treatments to improve HRQOL and comorbidities. Therefore, the ILAE charged the Psychology Task Force with the development of recommendations for clinical care based on evaluation of the evidence from their recent Cochrane review of psychological treatments in individuals with epilepsy. The literature search for a recent Cochrane review of Randomized Controlled Trials (RCTs) investigating psychological treatments for individuals with epilepsy constitutes the key source of evidence for this article. In order to provide practical guidance to service providers, we provide ratings on study research designs based on 1) the American Academy of Neurology's (AAN) Level of Evidence (LOE) system and 2) the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. This paper is the culmination of an international collaboration process involving pediatric and adult psychologists, neurologists, psychiatrists and neuropsychiatrists. The process and conclusions were reviewed and approved by the ILAE Executive Committee. The strongest evidence for psychological interventions was identified for the most common mental health problems, including depression, neurocognitive disturbances, and medication adherence. Psychological interventions targeting the enhancement of HRQOL and adherence and a decrease in comorbidity symptoms (anxiety, depression) should be incorporated into comprehensive epilepsy care. There is a range of psychological strategies (i.e., CBT and mindfulness-based therapies), which show promise for improving the lives of persons with epilepsy, and clinical recommendations are provided to assist epilepsy health care providers in treating the comorbidities and challenges associated with epilepsy and its treatments.

Key words: Screening, psychoeducation, depression, anxiety, stigma

Key points

- There are no previous specific recommendations for clinical practice based on the quality of the evidence for psychological treatments in patients with epilepsy
- Ratings on study research designs were based on the American Academy of Neurology's (AAN) Level of Evidence (LOE) system
- Evidence-based recommendations were based by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system
- The best evidence of effectiveness of psychological interventions was identified for depression, medication non-adherence, and neurocognitive disturbances.
- Evidence supports that psychological therapies should be considered in the treatment of individuals with epilepsy to improve HRQOL and comorbidities.

1. Introduction

Among the treatment tools for individuals with epilepsy, which include medication, diet, surgery, neuromodulation and psychological interventions, the latter most specifically aim to improve health-related quality of life (HRQOL). Individuals with epilepsy have a lower HRQOL than healthy individuals and individuals with other chronic diseases¹. Even a single seizure is associated with reduced HRQOL². Several factors contribute to poor HRQOL, especially when seizure freedom cannot be achieved, including medication side effects^{3, 4, 5}, the number of anti-epileptic drugs (AEDs)^{4, 6}, psychological symptoms (e.g., depression^{7, 8}; and psychosocial difficulties (e.g., unemployment)⁹.

Given the significant impact that psychosocial factors and epilepsy treatments can have on the HRQOL of individuals with epilepsy and their families, there is great clinical interest in the role of psychological evaluation and treatments to improve HRQOL. While several recent systematic and meta-analytic reviews of psychological treatments for individuals with epilepsy have been conducted^{10, 11, 12, 13}, and consensus statements regarding psychological/psychiatric care for individuals with epilepsy have been published^{14, 15}, specific recommendations for clinical practice based on the quality of the evidence for psychological treatments have not yet been developed.

Therefore, the ILAE charged the Psychology Task Force with the development of recommendations for clinical care based on the evaluation of the evidence from their recent Cochrane review of psychological treatments to improve HRQOL in individuals with epilepsy^{12, 13}. This paper is the culmination of a process of international collaboration involving pediatric and adult psychologists, neurologists, psychiatrists and neuropsychiatrists. The process and conclusions were reviewed and approved by the ILAE Executive Committee. The findings are intended for health care practitioners around the world.

2. Method of evaluating the quality of for psychological treatments

2.1 Operational definition of psychological treatments

“Psychological treatment” refers to a broad range of interventions for children and adults that encompass psychological or psychiatric non-pharmacological interventions for individuals, families and groups, as well as self-/family management, adherence and educational interventions (see Table 1). Intervention elements may be administered on their own or in combination. While some intervention elements are universally applicable, other elements address epilepsy and seizures more specifically. Interventions can target specific mental health disorders (anxiety, depression) or particular behaviors related to the management of epilepsy (adherence, coping). Even though differences in theoretical underpinnings and treatment targets limit the scope of comparisons¹¹, there is overlap among the psychological treatments that can be applied to individuals with epilepsy.

2.2 Source of evidence for recommendations

The literature search for a recent Cochrane review of Randomized Controlled Trials (RCTs) investigating psychological treatments for individuals with epilepsy constitutes the key source of evidence for this article^{12, 13}. While the Cochrane review focused on HRQOL and therefore excluded studies that did not include HRQOL as an outcome parameter, the present evidence-based recommendations included all RCTs investigating psychological interventions in individuals with epilepsy (figure 1).

2.3 Method of evaluation

In order to provide practical guidance to service providers, we provide ratings on study research designs based on 1) the American Academy of Neurology’s (AAN) Level of Evidence (LOE)¹⁶ system and 2) the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system^{17, 18}. GRADE has been modified by Tolin et al. (2015) to include three levels (very strong, strong, and weak recommendation) for evaluation of the quality of evidence for RCTs in the clinical psychology literature¹⁹. Using

Tolin's three levels (see Table 2), we evaluate the quality of evidence for psychological treatments for specific disorders (e.g., depression, anxiety) in addition to seizure outcomes, adherence, and epilepsy education and provide clinical recommendations for use of indicated treatments. If the evidence base for a given treatment is of low quality or lacking entirely, we highlight the need for further research in this area. We also provide a brief overview of treatment delivery, including options for resource-poor settings, as well as service considerations including recommendations for inpatient and outpatient treatment facilities and for training.

2.4 Notable considerations

Psychological treatments tend to be complex multicomponent interventions, i.e., several intervention components may be incorporated in diverse therapeutic approaches (e.g., education plus skills training) and studies with different treatment targets and, therefore, the same intervention components will be mentioned in various sections throughout this article. Special issues relating to pediatric populations will be included in each subsection. Level 3 and Level 4 Specialized Epilepsy Centers are required to have a psychologist and social worker as part of their centers; however, which psychosocial services are offered are not specified²⁰. Because psychological treatment delivery varies within and across countries and settings, we will mostly refer to “mental health care providers” without specifying their professional groups. Mental health care providers can include psychiatrists, psychologists, psychotherapists, licensed clinical social workers, neurologists with therapy training, neuropsychiatrists, and psychiatric nurses, among other mental health professionals. Cultural issues and differences that may affect implementation, and utilization will be mentioned; however, an elaborate discussion of cultural considerations and implications is beyond the scope of this paper.

The authors are aware of the challenges of clinical translation marked by the gap between ideal care and real care constraints in busy clinical settings, in which trained staff often necessary to deliver evidence-based interventions are lacking. However, it is relevant for all providers to focus on early identification and prevention of comorbidity, which could be time-and cost-effective, as HRQOL is a significant predictor of healthcare charges in epilepsy, with poorer HRQOL predicting greater healthcare charges^{21, 22, 23}.

3. Available evidence for psychological treatment across the epilepsy spectrum:

Relevance to clinical practice and recommendations

3.1 Evidence-based screening: Selecting patients for psychological treatment in the clinical setting

3.1a Evaluation of the evidence for psychological screening. Psychological disorders are at least twice as common in individuals with epilepsy than the general population^{24, 25}; therefore, standard screening procedures for patients newly diagnosed with epilepsy, as well as for patients with chronic epilepsy, should be integrated into routine epilepsy care^{15, 21, 26}. Symptom screening assists in the identification of individuals who may benefit from psychological treatments. To address the issue, the AAN has included screening for psychiatric or behavioral disorders at each epilepsy encounter as a new quality measure for the delivery of optimal care and better outcomes for individuals with epilepsy²⁷.

Epilepsy-specific measures are now available to evaluate psychosocial functioning, including depressive symptoms and HRQOL. For example, the six-item self-report survey, Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), is an epilepsy-specific screening tool for major depression²⁸ and its feasibility has been demonstrated in a routine clinical setting²⁹. Annual use of the NDDI-E has previously been recommended by the ILAE neuropsychiatric commission²⁶. It has been validated in many languages, is freely available, and has been tailored for use in young people (NDDI-E-Y)³⁰.

Screening measures for other aspects of psychological functioning (e.g., HRQOL, AED side effects) may provide beneficial information regarding patient well-being.

Psychometrically sound and free epilepsy specific HRQOL tools include the QOLIE adult (QOLIE-10, QOLIE-31, QOLIE-89) and adolescent (QOLIE-48) measures^{31, 32} and the newer PedsQL Epilepsy Modules^{33, 34}. Parent-proxy report of their child's HRQOL can also be obtained via the Quality of Life in Childhood Epilepsy questionnaire (4-18 years old)^{35, 36}. Additionally, the assessment of psychiatric/psychological symptoms at baseline can inform the choice of an AED, given that a history of psychological symptoms increases the vulnerability to subsequent behavioral/emotional side effects^{37, 38}. Subsequently this baseline information can help determine if psychological symptoms arising during the course of treatment could be an AED side effect or an exacerbation of a premorbid or comorbid psychological disorder. Continued assessment of AED side effects over the course of epilepsy can inform changes to medications and/or alternative treatments (e.g., diet) and is important to consider at each epilepsy visit given the relationship between side effects, adherence, and HRQOL³⁹. Standardized evaluation of side effects is available through use of the Pediatric Epilepsy Side Effects Questionnaire (PESQ)⁴⁰ and the Liverpool Adverse Event Profile^{41, 42}.

3.1b Considerations for pediatric populations. Multi-informant screening is ideal for pediatric populations. While children are often better reporters of their own internalizing symptoms⁴³, caregivers can provide a unique and beneficial perspective for some behaviors/deficits, such as executive functioning and oppositional or hyperactive behaviors⁴⁴. Caregivers are also critical reporters when children have cognitive impairment developmental delays, or are too young to provide valid responses.

3.1c Recommendations for psychological screening. Psychological screening is indicated given the high prevalence of mental health disorders in individuals with epilepsy.

According to the AAN practice guideline, patients with epilepsy should complete mental health screenings as part of routine epilepsy care²⁷. Specific clinical recommendations include:

1. Each epilepsy visit should include, at a minimum, a clinical question regarding mental health and quality of life. Screening is encouraged at epilepsy diagnosis, prior to and following AED initiation or changes and at routine time intervals (e.g., yearly).
2. Practitioners should consider multi-informant screenings for children and also for adults, when indicated and available.
3. A measure of psychological functioning should be administered prior to AED initiation and over the course of AED treatment.
4. Practitioners should consider including a standardized evaluation of AED side effects.
5. Practitioners are encouraged to consider a measure of HRQOL.
6. If screening identifies significant symptoms or a problem, patients should undergo a formal mental health assessment to inform the selection of the appropriate treatment elements based on individual needs. Family members may provide key details of past events during this evaluation.

3.2 Psychoeducation for patients, parents and caregivers

Psychoeducational interventions involve the dissemination of knowledge and education regarding seizures, treatments, comorbid conditions, and lifestyle challenges. While most psychological interventions involve an aspect of education, this next section is reserved solely for interventions that focus primarily on education and not on the development of behavioral, cognitive, or meditation skills.

3.2a Evaluation of the evidence for psychoeducational interventions. According to several national guidelines (e.g., Scottish Intercollegiate Guidelines Network, National

Institute of Clinical Health and Care Excellence, United Kingdom, American Epilepsy Society), additional personalized information on treatment, possible outcomes, and specific risks must be provided to patients and families following an epilepsy diagnosis. Patients may experience challenges with adjustment to and worries about the epilepsy diagnosis after learning about potential legal, psychosocial and health ramifications⁴⁵. Additionally, research indicates that individuals with epilepsy and/or their caregivers frequently misunderstand basic information about epilepsy, including knowledge about their diagnosis, seizure precipitants or triggers, purpose and potential side effects of AEDs, safety concerns, and the risks of seizures^{46, 47, 48, 49, 50}. A large amount of the variance in HRQOL is explained by individuals' perceptions of their illness^{51, 52}, and educational interventions may modify illness perceptions and improve an individual's HRQOL. Therefore, it is prudent to follow-up the initial communication of an epilepsy diagnosis with (psycho-) education about seizures, treatments and their side effects, comorbid conditions, and self-management and quality of life issues²⁶. Indeed, the AAN recommends providing *personalized* epilepsy safety information and education on a yearly basis²⁷.

Of the 15 RCTs investigating educational interventions, four studies were level of evidence (LOE) II^{53, 54, 55, 56}, four studies^{57, 58, 59, 60} were LOE III, and seven studies^{61, 62, 63, 64, 65, 66, 67} were LOE IV. All four LOE II studies reported improvements in their various primary outcomes: medication adherence⁵³, epilepsy knowledge and satisfaction with information and support⁵⁴, medication-related problems⁵⁴, and HRQOL⁵⁶. The LOE II studies investigated psychoeducational interventions that were delivered by specialized epilepsy nurses or trained medical doctors to individuals and included personalized information during routine visits or a general information package during a series of scheduled sessions.

3.2b. Psychoeducational interventions for epilepsy receive a GRADE recommendation of STRONG (Table 3). *There is moderate- to high-quality evidence that*

psychoeducational interventions produce a clinically meaningful improvement in health related outcomes in individuals with epilepsy, including medication adherence, satisfaction with information and support, and HRQOL.

3.2c Considerations for pediatric populations. Clinicians are encouraged to take into consideration the developmental abilities of children and level of understanding when discussing an epilepsy diagnosis with children and their families. Material should be presented in child-friendly terms with pictorial representations when possible or game-based formats. Depending on the child's developmental level and chronological age, clinicians may wish to discuss some aspects of epilepsy with caregivers only (e.g., SUDEP).

3.2d Specific clinical recommendations for epilepsy psychoeducation include:

1. Each patient with epilepsy should receive psychoeducation.
2. Because a diagnosis of epilepsy may create fear and shock in individuals and/or families, a follow up to the initial diagnosis is recommended to provide specific details regarding psychoeducation for a particular patient's epilepsy symptoms, characteristics, and needs.
3. Psychoeducation may focus on seizure knowledge and treatments, information needs and support, and/or comorbid conditions.
4. Psychoeducation may be provided individually or in a group setting.
5. Psychoeducation should be provided to patients with consideration for their developmental level, health literacy, and information and support needs.
6. Clinicians are encouraged to select an evidence-based educational intervention that suits the needs of their patients (adult vs child, group vs individual) and to assess pre- and post- outcomes (e.g., knowledge) to monitor whether their patients are learning from the intervention.

7. Clinicians are encouraged to continue to routinely assess their patient's needs for psychoeducation about epilepsy, its treatments, and comorbid conditions across the lifespan.

3.3. Depressive symptoms

There is substantial evidence supporting the idea of a bidirectional relationship between epilepsy and depression. Shared neurobiological mechanisms, for example lesion of mesial temporal structures and hippocampus volume loss⁶⁸ shed light on the reasons for their co-existence and interlinking relationship. Depression may predate the onset of epilepsy: A history of depression is associated with a 2- to 4-fold increase in the risk for an unprovoked seizure^{69, 70, 71}. Depression can also be a psychological reaction to epilepsy, and it is a significant predictor of seizure outcomes with pharmacological and surgical treatments^{72, 73}. There is newer evidence for specific clusters of depressive symptoms in persons with epilepsy, with the more common cluster consisting of a cognitive phenotype (e.g., self-critical cognitions, such as ineffectiveness)⁷⁴.

3.3a Evaluation of the evidence for interventions for depressive symptoms. Nine RCTs investigated psychological interventions for individuals with epilepsy with depression symptoms^{75, 76, 77, 78, 79, 80, 81, 82, 83} or as a preventative intervention for clinical depression in patients with subthreshold depressive symptoms⁸⁴. The following seven studies measured depressive symptoms as secondary outcome: Four RCTs investigated psychological interventions^{85, 86, 87, 88}, one RCT investigated a self-management⁸⁹ and two RCTs investigated educational programs^{55, 65}.

Of these 15 studies, one study was LOE I⁸⁴ (84), five studies were LOE II^{55, 75, 76, 79, 86, 89}, two studies were LOE III^{78, 85} and the remaining eight studies were LOE IV^{53, 65, 77, 81, 82, 83, 87, 88}. Most LOE I and II studies reported significant reduction in depressive symptoms except for one depression-specific intervention LOE II study that reported a reduction in suicidal

ideation but no other significant changes on a generic depression scale^{75, 76} and the educational program⁵⁵ that did not find any significant changes in depressive symptoms. The highest level of evidence pertains to skill-based training and behavioral interventions. Techniques comprised behavioral and social activation, problem solving and goal setting skills, training of social competencies, and identifying social support. These were particularly effective in addressing behavioral symptoms of depression and its associated limitations, such as social withdrawal, hypersomnia, physical inactivity, and unemployment^{75, 76, 84} (Table 4).

3.3b Interventions for depressive symptoms in epilepsy receive a GRADE recommendation of STRONG (Table 4): *There is moderate- to high-quality evidence that skill-based and behavioral psychological interventions produce a clinically meaningful effect on depressive symptoms, including suicidal ideation in individuals with epilepsy.*

3.3c Considerations for pediatric populations. There are limited data for the treatment of depression or depressive symptoms in pediatric epilepsy populations⁸⁴, thus clinicians are encouraged to base treatment on the results of treatment trials conducted with children with depression in non-epilepsy populations⁹⁰. Treatment may include psychoeducation to children and family as well as cognitive-behavioral therapy for children⁹⁰, and most child focused depression protocols include strong family involvement in treatment (e.g., encouragement of mastery of skills). Notably, similar to adults, negative cognitions (ineffectiveness) may be more relevant than mood symptoms in youth with epilepsy, and interventions should target such symptoms⁹¹. Those who have risk factors for depression (e.g., family history of mood disorders, coexisting medical condition, psychosocial adversities) should be evaluated by clinicians at regular intervals⁹² for the prevention of clinical depression, early diagnosis, and treatment.

3.3d Specific clinical recommendations for depressive symptoms include:

1. Depression should be assessed in routine epilepsy care following epilepsy diagnosis regardless of drug-responsiveness.
2. Psychological interventions can be provided individually or in a group format.
3. Treatment components may include behavioral intervention (e.g., social activation) and skill-based interventions (e.g., problem solving, social skills training).
4. Treatment outcomes should be monitored using standardized inventories/rating scales.

3.4 Treatment non-adherence and self-management

Adherence is defined as the extent to which a person's behavior coincides with medical or health advice⁹³. In contrast, self-management is defined as the interaction of health behaviors and related processes that patients and families engage in to care for a chronic condition⁹⁴. AED non-adherence ranges from 25-50%^{95, 96} in adults and 43-58%^{39, 97} in children with epilepsy. The consequences of non-adherence can be severe, including continued seizures^{39, 98}, poor HRQOL⁹⁹, higher healthcare costs and utilization¹⁰⁰, pharmacoresistance¹⁰¹, and even death¹⁰².

3.4a Evaluation of the evidence for interventions for adherence and self-management. Three RCTs investigated psychological interventions specifically aiming at increasing medication adherence^{103, 104, 105}. Two studies investigated self-management interventions that measured medication adherence as a secondary outcome^{106, 107}. Two studies^{104, 107} were LOE II, and the three remaining studies were LOE IV^{103, 105, 106}. Significant results were reported for the LOE II pediatric adherence intervention while no significant changes were reported for the self-management program. Thus, the highest level of evidence pertains to education and teaching families of children with epilepsy about problem solving strategies.

3.4b Adherence/Self-management interventions for epilepsy receive a GRADE recommendation of STRONG (Table 5): *There is moderate- to high-quality evidence that*

multi-component interventions that include education and problem-solving produce a clinically meaningful effect on medication adherence in children with epilepsy.

3.4c Considerations for pediatric populations. Parents are encouraged to partner with the children and adolescents to manage the treatment regimen, including supervision around taking AEDs and avoidance of seizure triggers. Parental involvement can aid in ensuring that adherence does not decline in adolescents, a vulnerable developmental period. Technology-focused adherence solutions may be particularly salient for adolescents¹⁰⁸.

3.4d Specific clinical recommendations for adherence/self-management include:

1. Adherence should be assessed during routine clinical practice in a non-judgmental and open dialogue
2. Clinicians are encouraged to assess barriers to adherence and problem-solve ways to improve adherence
3. Use of technology focused solutions that enhance reminders and that may be well-received and beneficial in establishing good adherence behaviors

3.5 Seizures

The aim of non-pharmacological seizure management techniques is to increase life quality as well as decrease seizure frequency and/or duration. Seizure management techniques could pragmatically be divided into three different approaches: 1) interventions to influence the consequences of seizures, e.g. mindfulness training on awareness and non-judgmental acceptance of seizure-related physical symptoms, 2) interventions to affect the onset of seizures, e.g. discrimination of seizure triggers through a functional analysis of individual seizure development, lifestyle recommendations for stress coping, and 3) techniques to abort ongoing seizures, e.g. aura interruption techniques i.e. countermeasures to stop seizures from developing^{109, 110, 111, 112}.

3.5a Evaluation of the evidence for interventions for seizure-related outcomes. Four RCTs investigated psychological interventions aimed to primarily decrease seizure frequency^{88, 113, 114, 115, 116}. Five studies investigated psychological interventions^{75, 76, 82, 86, 109, 110} and two studies^{58, 59} investigated an educational program that targeted non-seizure outcomes and included seizure frequency as a secondary outcome. Two studies^{75, 76, 86} were LOE II, three studies were LOE III^{58, 59, 113}, the remaining six studies were LOE IV^{82, 88, 110, 109, 114, 115, 116}. A significant decrease in seizure frequency was reported in one LOE II study⁸⁶ that focused on mindfulness training together with a set of lifestyle recommendations that facilitated coping with seizure-related disturbances and stressful situations; and in one of the two educational programs⁵⁸ that were both rated LOE III. Therefore, the highest level of evidence pertains to mindfulness-based therapies as well as lifestyle recommendations that facilitated stress coping. These allow patients to notice and acknowledge their emotional processes and physical symptoms related to their seizures, so as to facilitate acceptance and coping.

3.5b Psychological interventions for seizure-related outcomes receive a GRADE recommendation of WEAK (Table 6): *The evidence is inconclusive, suggesting an important area for future research. While there is moderate- to high-quality evidence that mindfulness-based therapies and lifestyle modifications that focus on improving HRQOL produce a clinically meaningful effect on seizure frequency in individuals with epilepsy, there is also evidence that CBT-based interventions focused on improving depressive symptoms do not have a clinically meaningful effect on seizure-related outcomes in individuals with epilepsy.* **3.5c Considerations for pediatric populations.** The development of psychological seizure management techniques may have to involve an assessment of the child's family background and family dynamics⁹⁹. Since parents and teachers may observe pre-seizure events, they may be taught to reinforce stress reduction and other healthy behaviors^{114, 115}.

3.5d Specific clinical recommendations for seizure-related outcomes include:

1. Clinicians are encouraged to inquire about their patients' interest in learning mindfulness training on awareness and non-judgmental acceptance of seizure-related physical symptoms
2. Clinicians should provide education to patients and family members on the interlinking relationship between psychological factors and seizures, and therefore psychological treatments could be included as part of the epilepsy care.
3. Clinicians are encouraged to investigate into details of seizure development (e.g. seizure precipitants, coping) and to make lifestyle recommendations relevant to individual patient.
4. Mindfulness training designed for patients with epilepsy should be an adjunctive treatment option where resources allowed.

3.6 Anxiety

Panic and generalized anxiety are more frequent in adults and older adolescents with epilepsy than in the corresponding general population and may have a marked negative impact on the HRQOL¹¹⁷. In the assessment of anxiety disorders clinicians need to consider the temporal relationship of anxiety symptoms and seizures. This subsection focuses on interictal anxiety symptoms that may be related to a fear of future seizures as well as fears epilepsy-related consequences (psychosocial worries) and complications (such as injury, brain damage, memory impairment). The anticipatory anxiety about seizures may also take the form of seizure phobia, which may lead to maladaptive avoidance and isolation. It is, however, important to note that equally disabling anxiety symptoms (e.g., social phobia, generalized anxiety) may also occur separately from seizure-related worries and are also important to address¹¹⁸. Perceived stigma is a risk factor for increased anxiety, which, again, illustrates the interrelatedness of psychological issues^{119, 120}.

3.6a Evaluation of the evidence for interventions for anxiety symptoms. Only one RCT investigated a psychological intervention specifically aiming to decrease anxiety symptoms⁸². Four studies investigating psychological interventions^{77, 78, 86, 87}, one study a self-management⁸⁹ and one an educational program⁵⁵, measured anxiety symptoms as a secondary outcome. Three studies^{55, 86, 89} were LOE II, and one study⁷⁸ was LOE III, while the remaining three studies were LOE IV^{77, 82, 87}. Of all LOE II studies, only the psychological intervention that measured anxiety symptoms as a secondary outcome reported a significant decrease in anxiety symptoms⁸⁶. Hence the highest level of evidence pertains to the implementation of mindfulness exercises that may facilitate the process of awareness, experience, and finally acceptance of feelings of anxiety.

3.6b Interventions for anxiety symptoms in epilepsy receive a GRADE recommendation of WEAK (Table 4): *The evidence is somewhat inconclusive, suggesting this is an important area for future research. While there is moderate- to high-quality evidence that mindfulness-based interventions produce a clinically meaningful effect on anxiety symptoms in individuals with epilepsy, several other moderate to high quality studies did not demonstrate a meaningful effect. Notably, in many of these interventions, anxiety was a secondary outcome.*

3.6c Considerations for pediatric populations. Many parents refer to the experience of their child's first seizure as traumatic which may lead to anxieties concerning the condition⁵⁷. As a consequence, children may develop a fear of seizures by observing anxious parental reactions¹²¹. Psychological interventions that aim at alleviating anxiety in children may also have a secondary goal of addressing parents' fear of seizures^{114, 115}. Similar to depression, caregiver involvement in encouragement of skill rehearsal is important to skill mastery in children.

3.6d Specific clinical recommendations for anxiety symptoms include:

1. Clinicians are encouraged to assess interictal anxiety symptoms that may be related to a fear of future seizures and fear of epilepsy-related complications
2. Complex psychosocial worries, such as perceived stigma, may exacerbate symptoms of anxiety, and should be evaluated and addressed.
3. The highest level of evidence pertains to the implementation of mindfulness exercises that may facilitate the process of awareness, experience, and finally acceptance of feelings of anxiety. Therefore, health care providers are encouraged to refer patients with anxiety symptoms for mindfulness-based interventions to alleviate their anxiety symptoms.

3.7 Neurocognitive disturbances

Cognitive impairment can be associated with epilepsy and adds to disability beyond seizures alone, particularly in those with temporal lobe epilepsy and drug-resistant epilepsy^{122, 123}. The details of cognitive assessment and training in epilepsy were thoroughly discussed in separate recommendation statements¹²⁴. Instead of providing rehabilitation or training that targets objective cognitive deficits, psychological treatments may aim at managing the interrelationship between mood, anxiety and subjective cognitive complaints, which may not necessarily be reflected in objective evidence of cognitive impairment¹²⁵.

3.7a Evaluation of the evidence for interventions for neurocognitive disturbances.

Only one RCT investigated a psychological intervention specifically focused on cognitive symptoms (LOE III)⁸⁵, and one other study⁸⁶ measured cognitive functions as secondary outcome (LOE II). The highest level of evidence pertains to a mindfulness-based training for individuals with epilepsy, aiming to cultivate patients' self-awareness and focused attention. The completion of this treatment was associated with significant improvements in objective measures of delayed verbal memory in patients with drug-resistant epilepsy compared to controls⁸⁶; however, no changes were reported in other cognitive measures, including

attention, non-verbal memory and executive functions. A home-based self-management program (HOBSCOTCH) incorporating psychoeducation, self-awareness training, compensatory strategies and cognitive training has been developed and has been shown to be associated with significant improvement in objective cognitive performance⁸⁵.

Using Acceptance and Commitment Therapy tailored for individuals with epilepsy, Lundgren et al. (2006; 2008) guided individuals to develop a non-judgmental acceptance of their memory functions and refocused patients on the achievement of valued life goals despite the preconceived obstacle of impaired cognitive functioning^{109, 110}. In a controlled study (LOE IV), this intervention was found to be associated with significantly improved HRQOL^{109, 110}.

3.7b Interventions for neurocognitive disturbances in epilepsy receive a GRADE recommendation of STRONG: *There is moderate- to high-quality evidence that mindfulness-based interventions produce a clinically meaningful effect on neurocognitive disturbances in individuals with epilepsy.*

3.7c Considerations for pediatric populations. The prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD) is higher in pediatric epilepsy than in the general population, with rates of 30-40% in children with epilepsy¹²⁶. There are very few studies examining the benefit of psychological interventions for children with epilepsy and comorbid ADHD¹²⁷ and our search did not yield RCTs of psychotherapy for epilepsy and ADHD. Expert reviews on treatment of ADHD in individuals with epilepsy emphasizes the need to address cognition¹²⁸. Moreover, the general child literature has a strong evidence base for the efficacy of behavioral interventions in reducing ADHD symptoms in children¹²⁹. Given the comorbid learning disabilities and the neurocognitive deficits common in children with epilepsy, it is also important to discuss potential learning problems, provide access to resources (e.g., educational interventions), communicate with school personnel, and facilitate

referrals for neuropsychological evaluations. Commercially available products have also been recently tested in epilepsy and may prove to be beneficial¹³⁰. A new web-based executive functioning intervention for adolescents is currently being tested and may be one way to aid youth with epilepsy around cognitive skill deficits¹³¹.

3.7d Specific clinical recommendations for neurocognitive disturbances.

1. Clinicians are encouraged to be aware of the interrelationship between mood, anxiety and subjective cognitive complaints, which may not necessarily be reflected in objective evidence of cognitive impairment.
2. Cognitive assessment and training may complement a mindfulness-based training aiming to increase patients' self-awareness and focused attention.
3. Several strategies can be built into psychological interventions for individuals with epilepsy with subjective neurocognitive disturbances to enhance a sense of self-reliance. These techniques include incorporating written handouts, joint reviews of the preceding sessions to reinforce memory for session content, shortening treatment sessions, and audio-recording sessions to enable the individuals to review the content between sessions. Such techniques have been found to be beneficial⁷⁷.
4. In the absence of data to support the efficacy of behavioral interventions tailored to children with epilepsy and ADHD, clinicians are encouraged to apply the evidence-based behavioral techniques supported in the general child literature.

3.8 Social and family problems and stigma

Having epilepsy may be associated with vocational, educational, social and personal difficulties¹³². Indeed, individuals with epilepsy are less likely to be well educated, employed, and/or have a romantic partner¹³³. They also experience social difficulties, including social isolation, social competence, and other social skills deficits¹³⁴. Family functioning, including communication, social support, adaptation, mastery, and conflict is often impacted

by epilepsy¹³⁵. Personal experiences with epilepsy may involve perceived stigma, defined as a set of negative and often unfair beliefs about something¹³⁶. Perceptions of stigma can lead to concealment in order to avoid the anticipated negative consequences of epilepsy disclosure in societies at all stages of economic development^{120, 137}. While the strength of the perception of stigma may be associated with internal factors, such as low self-esteem¹³², there are also external factors, including cultural and religious differences contributing to stigma¹³⁸. The extent to which independence and autonomy are encouraged also varies considerably between cultures. Regardless of these cultural differences, epilepsy may result in significant restrictions in an individual's social functioning and independence, which may be self-imposed or imposed by others⁶¹.

3.8a Evaluation of the evidence for interventions for social and family problems and stigma. Regardless of their primary outcome measure, most psychological treatments employ strategies to actively strengthen the social network and build social support, to limit overprotection or inappropriate dependence and to enhance self-responsibility, to improve communication and the acceptance of the diagnosis and deal with emotional difficulties. Specific to the social domain, one LOE I psychological intervention study emphasized social skills⁸⁴, while one LOE II psychological intervention study focused on social activation^{75, 76}, and one LOE II self-management intervention focused on community integration and optimizing epilepsy-related communication⁸⁹. A LOE II intervention incorporated family components to adherence and utilized an outcome measure that included an aspect of family functioning- parenting (child support, autonomy, discipline)¹⁰⁴. LOE III and IV psychological interventions included assertion training⁸¹, communication skills⁷⁷, identification of social support⁸⁰, anger management⁸⁷ and motivational interviewing¹³⁹. LOE II educational programs included information about social, family and occupational issues^{53, 55}, and LOE III educational programs included content/skills for communication, self-responsibility, and self-

management⁵⁷, self-advocacy topics⁶², coping^{59, 60}, as well as psychosocial and occupational issues⁵⁸. One LOE IV educational program in Nigeria⁶⁵ addressed specific cultural misconceptions about seizures and their treatment. Of note, most of the interventions addressing family components are targeted towards pediatric patients and their caregivers, and none of the identified studies measured outcomes relating explicitly to stigma.

3.8b Interventions for social and family problems and stigma in epilepsy receive a GRADE recommendation of STRONG: *There is moderate- to high-quality evidence that psychological interventions, adherence and self-management interventions produce a clinically meaningful effect on symptoms related to social and family problems and stigma.*

3.8c Considerations for pediatric populations. Children and adolescents with epilepsy are at greater than average risk of having increased dependence on parents¹⁴⁰. Parents are often overly restrictive and overprotective of their children with epilepsy, which can influence social growth and independence^{141, 142}.

3.8d Specific clinical recommendations for social problems and stigma

1. Clinicians should inquire about the extent to which individuals with epilepsy feel affected by interpersonal and social problems, including problems affecting individuals with epilepsy at their workplace, in school or in their private lives
2. This assessment may include evaluation of barriers to open communication about epilepsy to avoid anticipated negative consequences of disclosure
3. Incorporate treatment components that address internal factors contributing to social and family problems and stigma such as social and communication skills (e.g. assertion training, training of epilepsy-related communication), social activation (e.g. community integration, identification of social support), and parenting skills.

4. Treatment delivery and service considerations

The described treatment elements may be delivered face-to-face or via telehealth technology (e.g., computer, smartphone, tablet, telephone) in an individual or group setting or in a combination of these modalities.

4.1a Evaluation of the treatment delivery and implementation modalities.

A group setting used by itself or as an adjunct to individual sessions may not only be more cost-effective than individual sessions, it also offers some unique advantages such as group role modeling to practice skills and the solicitation and exchange of individual experiences, perspectives and self-management strategies. Group interventions were investigated by one LOE I psychological intervention study⁸⁴, one LOE II psychological intervention study⁸⁶, and one LOE II self-management intervention study⁸⁹. All of these studies reported significant improvements in their primary outcome measures. Over half of all investigated educational interventions were delivered in a group setting^{55, 57, 58, 59, 62, 63, 64, 65}.

In addition to the face-to-face delivery by trained health professionals, telehealth options have been explored in one LOE II psychological intervention study⁷⁹ investigating a web-based treatment aiming to decrease depressive symptoms (Deprexis), one LOE IV web-based self-management program (WebEase)¹⁰⁶, and one LOE IV SMS-based educational program (Mobile Epilepsy Educational System, MEES)⁶¹. Interactive engagement can be promoted by questions and quizzes^{79, 106} or the opportunity to send personal inquiries that are answered by program providers⁶¹, which allows for the personalized delivery of educational materials (e.g., tailoring). One LOE IV study⁸⁰ investigated the telephone-based delivery of a psychological intervention in a group setting. All of these aforementioned studies reported significant results regarding their primary outcome measures. Since limited access to psychological treatments that are specifically designed to address the needs and concerns of people with epilepsy seems to be the rule rather than the exception¹⁴³, telehealth modalities may

help break down barriers to delivering psychological treatments in some resource-poor settings and help facilitate treatment for individuals with active seizures who live in areas with poor public transportation. Some studies in pediatric epilepsy suggest that telehealth modalities have similar outcomes and therapeutic alliance as face-to-face interventions^{144, 145}. In fact, a meta-analysis found no differences between face-to-face and telehealth in the general population¹⁴⁶. Similarly, home-based delivery of multimodal interventions may eliminate barriers and promote the collaboration between community/public health care professionals and epilepsy specialists. One LOE II study^{75, 76} and one LOE III study⁸⁵ reported significant improvements in primary outcomes

Optimal treatment implementation remains an ongoing area of development. Since the development of new skills and the formation of new habits requires time and regular practice, most interventions aim to increase participants' practice of relevant skills by embedding knowledge into treatment sessions spread out over time. Education protocols can, for example, either be delivered en bloc as a two-day course or in a weekly format. Half of all 14 studies investigating educational programs^{53, 54, 55, 61, 62, 63, 66} had chosen to deliver their interventions using at least two sessions that were at least one month apart. LOE I and II studies of psychological interventions and one self-management intervention⁸⁹ reporting significant primary outcome results were implemented in at least four sessions⁸⁶ that were delivered with a maximum frequency of weekly sessions⁸⁴ and a minimum frequency of two to three weeks between sessions^{75, 76}. Depending on their primary treatment method, these interventions included practice assignments between sessions. Booster sessions following a more intense treatment period may increase skills retention^{109, 110}.

4.1b Home-based, group-based and telehealth intervention delivery in epilepsy
receive a GRADE recommendation of STRONG: *There is moderate- to high-quality evidence that home-based, group-based and telehealth-based treatments produce a clinically*

meaningful effect on a broad range of symptoms in individuals with epilepsy, including suicidal ideation and depressive symptoms, as well as HRQOL.

4.1c Considerations for pediatric populations. Electronic and telehealth treatment modalities (e.g., telephone, computer, mobile health, electronic health) may be particularly beneficial to families of children with epilepsy, who must consider balancing the needs of the child with epilepsy and other children, difficulty taking time off from work/school, etc. to engage in psychological treatment. Adolescents have a strong preference for technology and are thus also more likely to be amenable to telehealth treatment modalities¹⁴⁷.

4.1d Specific clinical recommendations for treatment delivery and implementation

1. The described treatment elements may be delivered face-to-face in clinical settings or home-based, via telehealth technology.
2. Psychological interventions can be provided individually or in a group format.
3. Clinicians are encouraged to choose treatment delivery modalities based on local treatment resources (e.g. community/public health care professionals) and barriers (e.g. poor public transportation).
4. A group setting may be more cost-effective than individual sessions and offer unique advantages (e.g. exchange of individual experiences, elicitation of group support and encouragement).
5. While it is beyond the scope of this paper to discuss the differences in treatment implementation and delivery across cultures, we encourage the implementation of basic elements of psychological interventions, including education and self-help resources (including, e.g., relaxation CDs, seizure tracking devices etc.)
6. While providers and patients may wish to compress intervention content, they are encouraged to consider the dose(s) of treatments suggested by the empirical literature

to permit sufficient scope for consolidating change by including practice by participants between sessions.

7. In order to decrease anxieties in non-medical mental healthcare professionals over treating patients with seizures, a protocol should be generated for individual patients, detailing how seizures that may occur during treatment sessions should be managed.

5. Training recommendations

Mental health providers who have had extensive professional training in the delivery of psychological interventions may have greater capacity to deliver psychological treatment for people with epilepsy than epilepsy-specific providers who have had very limited (if any) training in providing non-educational psychological interventions. Medical professionals, such as epilepsy nurses are equipped to provide educational and basic self-management interventions and can be equipped for other psychological interventions (cognitive behavioral, mindfulness) with specific training (e.g., psychiatric nursing degree, completed training on a specific treatment protocol). Thus, we would recommend the following:

1. It is important to acknowledge that the required training for specific interventions depends on the professional background and expertise of the person delivering the intervention, the nature of the treatment package, and how well the treatment has been described and manualized.
2. A mental health professional delivering the intervention elements should have basic knowledge regarding epilepsy – etiology and classification of seizures, treatment options and psychopathology²⁶.
3. Conversely, a medical professional delivering any psychological intervention elements should receive training in the administration of psychological interventions in general as well as specific, detailed training in the implementation of the specific intervention protocol being administered.

4. Epilepsy-specific psychological interventions should ideally be implemented by professionals in direct contact with the diagnostician and the treating medical epilepsy specialist.
5. Some interventions, such as PEARLS, UPLIFT, or MOSES/FAMOSEs, offer and require the completion of program-specific training prior to implementation, with variability in the extent and mode of training^{58, 59, 60, 75, 76, 80, 83, 148, 149, 150} to ensure the treatment is delivered as intended.

Conclusion

All patients should be screened for mental health comorbidities, and patients with psychological symptoms should be referred for further evaluation and treatment of indicated or at-risk psychological symptoms. Evidence supports that psychological therapies which target comorbid mental health symptoms and HRQOL should be considered in the comprehensive treatment of individuals with epilepsy. The strongest evidence was identified for the most common mental health problems, including depression, as well as health behaviors, such as adherence. Treatments for these disorders and challenges received **STRONG** recommendations. Treatment protocols and training on the intervention techniques and delivery is available for many of the interventions discussed. Few treatments have been evaluated with the same rigor in children and adolescents compared to adults, and we lack studies focusing on anxiety as an intervention target and primary outcome. In addition, RCTs investigating psychological interventions in other common comorbidities, such as ADHD and substance abuse in adults and children with epilepsy, are absent. However, there is a strong evidence base for the benefit of psychological interventions in treating these disorders in the general population, which can be used to inform the development of epilepsy specific intervention protocols and RCT designs to evaluate the efficacy of these interventions in the epilepsy population. Epilepsy health care providers are encouraged to promote psychological

treatments as an integral part of epilepsy care and to know the resources available in their area.

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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.

Figure 1: Flow chart of study selection

Table 1: Terminology for psychological interventions

Intervention	Goal	Type of Therapies Used
Psychological interventions	<ul style="list-style-type: none"> • To reduce psychological distress (e.g., depressive or anxiety symptoms) • To improve adjustment and coping with epilepsy and its treatments 	<ul style="list-style-type: none"> • Cognitive-behavioral therapies • Behaviorally-based therapies • Acceptance and Commitment Therapy • Motivational interviewing
Self-/family management and adherence intervention	<ul style="list-style-type: none"> • Activities or steps that an individual or family can perform that are known to either influence the frequency of seizures or promote the well-being of the person with seizures. • Activities or steps can lie within the individual, family, community, or healthcare system domains 	<ul style="list-style-type: none"> • Cognitive-behavioral • Motivational interviewing • Family therapy
Adherence interventions	<ul style="list-style-type: none"> • Helping patients adhere to the advice of healthcare providers, including taking antiepileptic drugs, following a ketogenic diet, and avoiding seizure triggers. • Medication taking can be broken down into several components, including optimal dose timing and adequate frequency of dosing. 	<ul style="list-style-type: none"> • Problem-solving • Intention • Motivational interviewing • Family therapy
Educational interventions	<ul style="list-style-type: none"> • Increase knowledge of epilepsy and its treatments or the working of the brain 	<ul style="list-style-type: none"> • Psychoeducation (group or individual formats)

Table 2. Modified GRADE recommendations for psychological treatments based on systematic reviews (adapted from Guyatt et al., 2008)

Recommendation	
Very strong recommendation	<p>All of the following:</p> <ul style="list-style-type: none"> • There is high-quality evidence that the treatment produces a clinically meaningful effect on symptoms of the disorder being treated. • There is high-quality evidence that the treatment produces a clinically meaningful effect on functional outcomes. • There is high-quality evidence that the treatment produces a clinically meaningful effect on symptoms and/or functional outcomes at least 3 months after treatment discontinuation. • At least one well-conducted study has demonstrated effectiveness in non-research settings.
Strong recommendation	<p>At least one of the following:</p> <ul style="list-style-type: none"> • There is moderate- to high-quality evidence that the treatment produces a clinically meaningful effect on symptoms of the disorder being treated. • There is moderate- to high-quality evidence that the treatment produces a clinically meaningful effect on functional outcomes.
Weak recommendation	<p>Any of the following:</p> <ul style="list-style-type: none"> • There is only low- or very low-quality evidence that the treatment produces a clinically meaningful effect on symptoms of the disorder being treated. • There is only low- or very low-quality evidence that the treatment produces a clinically meaningful effect on symptoms of the disorder being treated as well as on functional outcomes. • There is moderate- to high-quality evidence that the effect of the treatment, although statistically significant, may not be of a magnitude that is clinically meaningful.

Table 2: The recommendations are either rated as very strong, strong or weak.

Table 3: AAN LOE of studies investigating psychoeducation

	Study	Treatment method	Primary outcomes	Secondary outcomes	Blinding	Randomization	Concealed Allocation	Masked Assessment	Attrition	AAN LOE
Educational Interventions	Aliasgharpour 2012 (63)	Epilepsy (psycho-)education program	ESMS ↑		↑	↓	?	?	↓	Class IV
	Dash 2015 (53)		MMAS ↑		↑	↓	↓	↓	↓	Class II
	Helgeson 1990 (64)		Misinformation about epilepsy ↓	Fear of seizures ↓	↑	?	?	?	↑	Class IV
	Jantzen 2009 (57)		DISABKIDS ↑	Disclosure of epilepsy ↑	↑	↑	↑	↓	↓	Class III
	Lua 2013 (61)		MQOLIE-30 ↑		?	↓	?	?	↓	Class IV
	May 2002 (58)		SF-36 ↔	D-S' ↔	↑	↓	↑	↓	↑	Class III
	Olley 2001 (65)		Knowledge about illness ↑	BDI ↓	↑	↑	↑	↑	?	Class IV
	Pfäfflin 2012 (60)		Epilepsy knowledge ↑		↑	↑	↑	↓	↑	Class III
	Pramuka 2007 (62)		QOLIE-89 ↔		↑	↓	?	↑	↑	Class IV
	Rau 2006 (59)		KINDL ↔	Seizure frequency ↔	↑	↑	↑	↓	↑	Class III
	Ridsdale 2000 (66)		Satisfaction with advice ↑	Knowledge of epilepsy ↔	↑	↓	↑	↑	↓	Class IV

	Yadegray (2015) (67)		QOLIE-31-P ↑	?	↓	?	?	?	Class IV
	Pfäfflin 2016 (55)	Counseling	Satisfaction with information and support ↑ QOLIE-31 ↔, HADS-D ↔, HADS-A ↔	↑	↓	↓	↓	↑	Class II
	Beretta 2014 (54)	Patient-tailored medication education	Drug-related problems ↓ QOLIE-31 ↔	↑	↓	↓	↓	↓	Class II
Mixed	Helde 2005 (56)	Epilepsy education +Nurse-led counseling	QOLIE-89 ↑	↑	↓	↓	↓	↓	Class II

Table 3: ↑: significant increase, ↓: significant decrease, ↔: result was not significant; red ↑: high risk of bias, green ↓: low risk of bias, yellow ↔: unclear risk of bias; AAN: American Academy of Neurology, BDI: Beck Depression Inventory, D's: Depressive Mood Scale, DISABKIDS: Quality Of Life in children and adolescents with disabilities and their family, ESMS: Epilepsy Self-Management Scale, HADS-D/A: Hospital Anxiety Depression Scale-Depression/Anxiety, KINDL: Gesundheitsbezogene Lebensqualität und psychosoziale Auswirkungen der Epilepsie (Health-related Quality of Life and psychosocial consequences of epilepsy), LOE: Level of Evidence, MMAS: modified Morisky Medication Adherence Scale, MQOLIE-30: Malay Quality of Life Inventory in Epilepsy-30, QOLIE-31/-31-P/-89: Quality of Life Inventory in Epilepsy-31/-31-P/-89, SF-36: Short-Form 36

Table 4: AAN LOE of studies investigating interventions investigating depression and anxiety

	Study	Treatment method	Primary outcomes	Secondary outcomes	Blinding	Randomization	Concealed Allocation	Masked Assessment	Attrition	AAN LOE
Psychological Treatments	Ciechanowski 2010 & Chaytor 2011 (75 & 76)	Cognitive Behavioral Therapy (CBT)	HSCL-20 ↔, suicidal ideation ↓		↑	↓	↓	↓	↓	Class II
	Davis 1984 (81)		DACL ↓, BDI ↔		↑	?	?	?	↓	Class IV
	Gandy 2014 (77)		NDDI-E ↓, HADS-D ↓	HADS-A ↔,	↑	↓	↓	↑	↑	Class IV
	Martinovic 2006 (84)		BDI ↓, CES-D ↓, HAMD ↓		↓	↓	↓	↓	↓	Class I
	Orjuela-Rojas 2015 (78)		BDI ↓, HADS-D ↔, MINI ↔	HADS-A ↔	↑	↑	↑	↓	↑	Class III
	Schröder 2014 (79)		BDI ↓		↑	↓	↓	↓	↑	Class II
	Tan 1986 (88)			BDI ↔, MMPI ↔		?	?	?	↓	Class IV
	Thompson 2010 (80)		BDI ↓		↑	?	↑	?	↑	Class IV
	Thompson 2015 (83)		BDI ↓, NDDI-E ↓		↑	?	?	?	↓	Class IV
	Li 2016 (82)	Systemic family therapy (SFT)	HADS-D/-A ↓		?	?	?	?	?	Class IV
	Tang 2015 (86)	Mindfulness Therapy (MT)		BAI ↓, BDI ↓	↑	↓	↓	↓	↓	Class II

Self- Management	Tajrishi 2015 (87)	Attribution retraining	↓ GHQ	↑	?	?	?	?	Class IV
	Fraser 2015 (89)	Comsumer-driven Psycho-education	PHQ-9 ↓	↑	↓	↓	↓	↓	Class II
	Olley 2001 (65)	Psycho-education	BDI ↓	↑	↑	↑	↑	?	Class IV
	Pfäfflin 2016 (55)	Counseling	HADS-D ↔, HADS-A ↔	↑	↓	↓	↓	↑	Class II
	Caller 2016 (85)	Cognitive, memory + self-management training	PHQ-9 ↔, NDDI-E ↔	↑	↓	↑	↓	↑	Class III

Table 4: ↑: significant increase, ↓: significant decrease, ↔: result was not significant; red ↑: high risk of bias, green ↓: low risk of bias, yellow ↔: unclear risk of bias; BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, CES-D: Center for Epidemiological Study on Depression scale, DACL: Depression Adjustment Checklist, ESMS: Epilepsy Self-Management Scale, GHQ: General Health Questionnaire, HAMD: Hamilton Depression Scale, HADS-A/-D: Hospital Anxiety Depression Scale, HSCL-20: Hopkins Symptom Checklist-20, MINI: Mini International Neuropsychiatric Interview, MMPI: Minnesota Multiphasic Personality Inventory, NDDI-E: Neurological Depressive Disorders Inventory-Epilepsy, PHQ-9: Patient Health Questionnaire-9

Table 5: AAN LOE of studies investigating interventions aiming at improving medication adherence

	Study	Treatment method	Primary outcomes	Blinding	Randomization	Concealed Allocation	Masked Assessment	Attrition	AAN LOE
Self-management Interventions	Dilorio 2009 (107)	Motivational Interviewing (MI)	AGAS ↔, MEMS ↔	↑	↑	↓	↑	↑	Class IV
	Dilorio 2011 (106)		MAS ↑	↑	↓	↓	↓	↓	Class II
Adherence Interventions	Modi 2016 (104)	Family-tailored problem-solving intervention	MEMS ↑	↑	↓	↓	↓	↑	Class II
	Pakpour 2015 (103)	Motivational Interviewing (MI)	MAS ↑	?	↓	?	?	↓	Class IV
	Peterson 1984 (105)	Counseling	AED plasma levels ↑, prescription refill frequency ↑	↑	↓	?	?	↓	Class IV

Table 5: ↑: significant increase, ↓: significant decrease, ↔: result was not significant; red ↑: high risk of bias, green ↓: low risk of bias, yellow ↔: unclear risk of bias; AGAS: Antiretroviral General Adherence Scale, MEMS: Medication Event Monitoring System, MAS: Medication Adherence Scale, MAS: Medication Adherence Scale

Table 6: AAN LOE of studies investigating intervention investigating seizure-related outcomes

Study	Treatment method	Primary outcomes	Secondary outcomes	Blinding	Randomization	Concealed Allocation	Masked Assessment	Attrition	AAN LOE
Au 2003 (113)	Cognitive Behavioral Therapy (CBT)	Seizure frequency ↔		?	↑	↑	↓	↓	Class III
Ciechanowski 2010 & Chaytor 2011 (75 & 76)			seizure frequency ↔	↑	↓	↓	↓	↓	Class II
Dahl 1985 (114)		Seizure index ↓		↑	?	?	↑	↓	Class IV
Mc Laughlin 2011 (116)		Seizure frequency ↓		↑	↓	?	?	↓	Class IV
Tan 1986 (88)		Seizure frequency ↔		↑	?	?	?	↓	Class IV
Lundgren 2006 (109)	Acceptance and Commitment Therapy (ACT)		Seizure frequency ↓, seizure index ↓	↑	↓	↓	↑	↓	Class IV
Lundgren 2008 (110)			Seizure frequency ↓, seizure index ↓	↑	↓	↓	↑	↓	Class IV
Li 2016 (82)	Systemic family therapy (SFT)		Seizure frequency ↓	?	?	?	?	?	Class IV

Psychoeducation	Tang 2015 (86)	Mindfulness Therapy (MT)	seizure frequency ↓, SSI ↔	↑	↓	↓	↓	↓	Class II
	May 2002 (58)	Psychoeducation	Seizure frequency ↓	↑	↓	↑	↓	↑	Class III
	Rau 2006 (59)		Seizure frequency ↔	↑	↑	↑	↓	↑	Class III

Table 6: ↑: significant increase, ↓: significant decrease, ↔: result was not significant; red ↑: high risk of bias, green ↓: low risk of bias, yellow ↔: unclear risk of bias; seizure index: (seizure frequency x seizure duration in seconds), SSI: Seizure Severity Index

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