Neuropsychiatric and Cognitive Comorbidities in Epilepsy

By Marco Mula, MD, PhD, FRCP, FEAN; Honor Coleman, MPsych, PhD; Sarah J. Wilson, PhD, FAHMS, FASSA

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

CITE AS:
CONTINUUM (MINNEAP MINN) 2022;28(2, EPILEPSY):457–482.

Address correspondence to Dr Marco Mula, Epilepsy Group, Atkinson Morley Regional Neuroscience Centre, St George's University Hospital NHS Foundation Trust, Blackshaw Road, London SW17 0QT, United Kingdom, mmula@sgul.ac.uk.

RELATIONSHIP DISCLOSURE:
Dr Mula has received personal compensation in the range of $500 to $4999 for serving on a speakers bureau for Eisai Co, Ltd, and UCB, Inc, and for serving as an Associate Editor for *Epilepsy & Behavior*; has received publishing royalties from Elsevier and Springer Publishing Company; and has a compensated relationship with the Korean League Against Epilepsy and the Philippine League Against Epilepsy. Dr Coleman has received personal compensation for serving as a research lead for the Epilepsy Foundation of Australia. Dr Wilson has received personal compensation in the range of $0 to $499 for serving on a speakers bureau for Pretola Global Health Consulting Limited. The institution of Dr Wilson has received research support from the Austin Medical Research Foundation, Australian Research Council, Australian Government National Health and Medical Research Council, and the Epilepsy Foundation.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Mula, Coleman, and Wilson report no disclosures.

© 2022 American Academy of Neurology.

ABSTRACT

PURPOSE OF REVIEW: This article discusses psychiatric and cognitive comorbidities of epilepsy over the lifespan and illustrates opportunities to improve the quality of care of children and adults with epilepsy.

RECENT FINDINGS: One in 3 people with epilepsy have a lifetime history of psychiatric disorders, and they represent an important prognostic marker of epilepsy. Contributors are diverse and display a complex relationship. Cognitive comorbidities are also common among those living with epilepsy and are increasingly recognized as a reflection of changes to underlying brain networks. Among the cognitive comorbidities, intellectual disability and dementia are common and can complicate the diagnostic process when cognitive and/or behavioral features resemble seizures.

SUMMARY: Comorbidities require consideration from the first point of contact with a patient because they can determine the presentation of symptoms, responsiveness to treatment, and the patient's day-to-day functioning and quality of life. In epilepsy, psychiatric and cognitive comorbidities may prove a greater source of disability for the patient and family than the seizures themselves, and in the case of essential comorbidities, they are regarded as core to the disorder in terms of etiology, diagnosis, and treatment.

INTRODUCTION

In addition to seizures, psychiatric and cognitive problems represent potential major sources of disabilities in children and adults with epilepsy, and this is reflected in the new International League Against Epilepsy (ILAE) definition of epilepsy.[1] In fact, epilepsy is now defined as a disorder of the brain characterized not only by recurrent seizures but also by its neurobiological, cognitive, and psychosocial consequences.[1]

Epidemiologic studies have shown that 1 in 3 people with epilepsy have a lifetime diagnosis of any psychiatric disorder, and 1 in 4 patients have a current psychiatric problem.[2] As for all brain disorders, epilepsy is also burdened by potential impairment in some aspects of cognition. Community-based studies in pediatric samples suggest an increased prevalence of cognitive abnormalities in

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

children with epilepsy, even in those with uncomplicated epilepsies, compared with children without epilepsy.[3]

The reasons for psychiatric and cognitive problems in epilepsy are complex. The epilepsy syndrome and the core features of the epilepsy, such as the age of onset, duration of the disease, interictal epileptiform discharges, seizure frequency, and side effects of antiseizure medications, are obviously crucial. At the same time, brain development and aging, as well as the underlying brain disorder and cause of the epilepsy, are equally important. This article discusses psychiatric and cognitive comorbidities of epilepsy over the lifespan, illustrating opportunities to improve the quality of care of children and adults with epilepsy.

PSYCHIATRIC DISORDERS IN EPILEPSY

Good data are now available on the epidemiology of psychiatric disorders in adults and children with epilepsy, and studies concur that all psychiatric disorders occur more frequently in patients with epilepsy than in the general population.[4]

In adults, a meta-analysis of 14 population-based studies including more than 1,000,000 participants showed an overall prevalence of active (current or in the past 12 months) depression in epilepsy of 23.1% with an increased overall risk of 2.7 compared with the general population.[5] A meta-analysis of 27 studies of anxiety disorders in more than 3000 people with epilepsy showed a pooled prevalence of 20.2% with generalized anxiety disorder being most common (10.2%).[6] A meta-analysis of the prevalence of psychosis, schizophrenia, and schizophreniform illness in 57 studies with a total of more than 40,000 participants showed a pooled prevalence of psychosis of 5.6% in unselected individuals increasing to 7% in people with temporal lobe epilepsy, with a pooled odds ratio for risk of psychosis compared with the general population of 7.8.[7] A meta-analysis of the prevalence of psychogenic nonepileptic seizures (PNES) in people with epilepsy showed a pooled prevalence of 12% whereas the prevalence of epilepsy in those with PNES was 22%.[8]

Data from children with epilepsy are not different despite an obvious emphasis on developmental disorders. A population-based study in 85 children and adolescents (aged 5 to 15 years) with active epilepsy in England reported that the prevalence of attention deficit hyperactivity disorder (ADHD) was around 33%, autism spectrum disorder was 21%, depression was 7%, and anxiety was 13%.[9] A nationwide Norwegian registry study in an unselected pediatric population of more than 1,000,000 children reported developmental and psychiatric comorbidities in 43% of children with epilepsy with overall odds ratios (compared with the general child population) of 10.7 for autism, 5.4 for ADHD, 2.3 for anxiety disorders, and 1.8 for depression.[10]

The relationship between epilepsy and psychiatric disorders is complex and reflects a combination of psychosocial and biological factors. Epilepsy is still a highly stigmatized condition, leading to discrimination and marginalization.[11] The social limitations (eg, loss of driving privileges), the unpredictable nature of seizures, and the potential social embarrassment associated with them can lead to poor self-esteem, social withdrawal, isolation, and distress. At the same time, several biological factors contribute to the increased occurrence of psychiatric disorders. Neuroimaging studies have identified network abnormalities involving particularly the limbic structures in patients with epilepsy and depression or psychosis.[12,13] However, data from prospective observational

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

studies have indicated that the relationship between epilepsy and psychiatric disorders is bidirectional, meaning that not just patients with epilepsy are at increased risk of developing psychiatric disorders but patients with psychiatric disorders have an increased risk of developing epilepsy. This has been demonstrated for major depression, psychoses, ADHD, and autism spectrum disorder.[14] For example, a large observational cohort study in the United Kingdom involving more than 10,000,000 participants found that depression is associated with a 2.5-fold increased risk of developing epilepsy.[15] Two retrospective, large cohort studies, one in England and the other in Taiwan, reported that individuals with schizophrenia have a twofold to threefold increased risk of developing epilepsy[16] with an incidence rate of 7 per 1000 person-years.[17] Taken together, all these findings suggest the existence of common pathogenic mechanisms operating in epilepsy and major psychiatric disorders. However, data on these common mechanisms are scant. Low serotonin levels have been described in animal models of epilepsy, such as genetically epilepsy-prone rats, the pilocarpine status epilepticus model, and rhesus monkeys. Hyperactivation of the hypothalamic-pituitary-adrenal axis and high cortisol levels have been associated with plastic changes in the hippocampi, such as γ-aminobutyric acid (GABA) receptor downregulation in the hippocampi, which may increase the propensity for spontaneous seizures.[18] However, all these fascinating hypotheses need to be verified and tested.

Finally, psychiatric symptoms may be biologically linked to the neurobiology of seizures themselves. On one hand, peri-ictal psychiatric symptoms may occur either before or after a seizure and are considered to be caused by the brain network changes operating during specific seizure types. On the other hand, psychiatric symptoms may arise because of the modulation of these neurobiological systems through epilepsy treatments, such as antiseizure medications or epilepsy surgery.[19]

WHY NEUROLOGISTS SHOULD PAY ATTENTION TO PSYCHIATRIC DISORDERS IN EPILEPSY

Psychiatric comorbidities have been historically associated with poor quality of life in adults[20] and children[21] with epilepsy, and strong data now point out their role as potential prognostic indicators.

A population-based cohort study suggested that depression is associated with high comorbidity rates as measured by the Charlson Comorbidity Index and that the severity of the depression itself (based on the type of treatment received) correlates with lower odds of achieving seizure remission.[15] Moreover, psychiatric disorders are associated with a high risk of side effects of antiseizure medication,[22] especially cognitive[23] and psychiatric symptoms,[24] whereas psychiatric comorbidities have been associated with 4 times the risk of drug resistance in focal[25] and generalized epilepsies.[26]

The impact of psychiatric comorbidities in terms of seizure outcome and psychiatric outcome in epilepsy surgery is complex and yet to be established. Regarding seizure outcome, some studies have found a lower probability of achieving seizure freedom after temporal lobectomy in patients with preexisting psychiatric comorbidity,[27,28] whereas other authors have refuted these findings.[29] The same holds true for psychiatric outcomes, with some studies showing an increased risk of recurrence of depression or anxiety during the first

KEY POINTS

- Psychiatric disorders occur more commonly in epilepsy than in the general population and are increasingly recognized as a major source of disability in epilepsy.
- The etiology of psychiatric disorders in epilepsy is complex and can include both biological and psychosocial factors, including altered functioning of brain networks, stigma, social limitations, and distress.
- The relationship between epilepsy and psychiatric disorders is bidirectional, including depression, psychogenic nonepileptic seizures, attention deficit hyperactivity disorder, autism spectrum disorder, and schizophrenia.
- Consideration of psychiatric comorbidities is clinically relevant for neurologists because comorbid psychiatric conditions have been associated with poorer treatment outcomes, as well as increased health care utilization and increased mortality.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

3 to 12 months after surgery in people with epilepsy,[30] whereas others have shown improvement over the long term.[31]

Psychiatric comorbidities are associated with premature mortality in epilepsy.[32] This may be caused by a variety of reasons, including increased risk of substance or alcohol abuse,[33] increased risk of injury,[34] and increased suicide rates.[35] Data from a nationwide, population-based study showed that female patients with epilepsy and psychiatric comorbidities had a fivefold increased risk of sudden unexpected death in epilepsy (SUDEP) compared with those without such comorbidities.[36]

It is evident that psychiatric comorbidities increase the global burden of epilepsy from a public health perspective with increased health costs.[37] People with epilepsy and psychiatric disorders have high health care resource utilization, including increased emergency department admissions and outpatient visits.[38] Data from a nationwide US inpatient analysis showed that psychiatric comorbidities, in particular depression and psychosis, increase length-of-stay and inpatient costs for people with epilepsy.[39]

Combined, these data show that the identification of these problems can inform clinicians of the long-term prognosis of the epilepsy itself.

SCREENING FOR PSYCHIATRIC DISORDERS AND DIAGNOSTIC CHALLENGES

Despite the epidemiologic evidence, psychiatric comorbidities are still underdiagnosed and undertreated in epilepsy. Barriers to diagnosis and treatment are complex and multifactorial, including, among other things, cultural barriers to mental health issues in general, a lack of training of neurologists and psychiatrists in the psychiatric aspects of neurologic disorders, and a lack of clinical resource allocation to support a multidisciplinary approach.[40]

In the general population, screening tools are available in primary and secondary care settings for almost all major psychiatric conditions. These tools have been shown to be cost-effective because they are short, standardized against *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) criteria, and less resource-intensive than a full clinical interview. In the past, the validity of these instruments in people with epilepsy was a major barrier to their use in routine clinical practice. However, good data are now available on the validity of clinical instruments for depression and anxiety in adults and for ADHD in children.

A systematic review of studies validating depression screening tools in adults with epilepsy showed that the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) is, at present, the most cost-effective screening instrument, validated in a variety of settings and available in 13 languages.[41] The NDDI-E has also been validated for suicidality screening with good sensitivity and specificity.[42] Other well-known self-rating scales, such as the Beck Depression Inventory II (BDI-II) and the Patient Health Questionnaire 9-item depression scale (PHQ-9), have also been shown to be valid in epilepsy but require the use of cutoff scores higher than those adopted in the general population (general population BDI-II = 10, PHQ-9 = 5; epilepsy BDI-II = 15, PHQ-9 = 10).[41] This can be partly explained by the heterogeneity of clinical presentations of depression in epilepsy but also highlights the need to adapt these questionnaires to the specific needs of people with epilepsy to maximize their sensitivity and specificity.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Lastly, the Hamilton Depression Rating Scale has also been validated for use in people with epilepsy.[43]

Regarding anxiety, the validity of the Hospital Anxiety and Depression Scale (HADS) and the Generalized Anxiety Disorder Scale (GAD-7) has been investigated in adults with epilepsy. Although studies on the HADS in epilepsy provide conflicting results,[44,45] the validity and cost-effectiveness of the GAD-7 seem to be well established.[46,47] Inconsistencies among studies can arise for several reasons, including the fluctuating nature of anxiety symptoms and the pleomorphic and atypical phenomenology of psychiatric symptoms in epilepsy.[48] Epilepsy-specific instruments, the 18-item Epilepsy Anxiety Survey Instrument (EASI) and its briefer version the 8-item EASI demonstrated a sensitivity of 76% and a specificity of 84% for the identification of *DSM-5* diagnosis of anxiety disorders.[49]

Data on screening instruments in children with epilepsy are still limited. A systematic review from an ad hoc task force of the ILAE supports the use of the Strength and Difficulties Questionnaire (SDQ) for ADHD.[50] Data on clinical instruments for depression and anxiety in the pediatric population are scant. A 12-item self-report screening tool for children aged 12 to 17 years, the NDDI-E-Youth, has been validated in epilepsy,[51] but further studies in this area are still needed.

As for any medical condition, after a positive screen, it is important to establish the diagnosis. As already alluded to, psychiatric symptoms in epilepsy can arise for a variety of reasons, such as peri-ictal symptoms, side effects of epilepsy treatments, or comorbid psychiatric disorders. However, it is important to point out that the boundaries between these scenarios are often blurred, and patients may develop symptoms due to multiple contributing factors. In fact, people with a psychiatric comorbidity are also those at risk of psychiatric side effects of antiseizure medication, and they may also present a worsening of their background psychiatric comorbidity during, for example, the postictal phase.[52] The first challenge is, therefore, the identification of different contributing factors to develop the best management plan for the individual patient. For this reason, neurologists need to be aware of peri-ictal symptoms and side effects of epilepsy treatments.

Despite many historical notes and several anecdotal reports, the prevalence and pathophysiology of peri-ictal symptoms are largely unknown, and most data come from adults. Postictal psychoses are probably those with the largest literature; they seem to have a point prevalence of 2%[7] and represent around 25% of all cases of psychosis in epilepsy. Postictal psychoses are typically observed in temporal lobe epilepsy, they can last for a few weeks, and they are associated with higher rates of violent behaviors and suicide attempts than interictal psychoses.[53] For this reason, they need to be promptly recognized and managed. Nonpsychotic postictal symptoms are largely unrecognized because they are short-lasting and difficult to identify. However, data from a telemetry unit showed that 43% of patients with drug-resistant focal epilepsy present with postictal symptoms of depression, 45% with postictal anxiety, and 7% with psychotic symptoms.[52] These occurred following more than half of the seizures captured and lasted for a median of 24 hours.[52]

Regarding psychiatric symptoms as side effects of epilepsy treatments, a retrospective study from a large, unselected sample of more than 4000 adults with epilepsy showed that 1 in 6 individuals develop drug-related psychiatric side

KEY POINTS

- **Barriers to diagnosis and treatment can include a lack of training of neurologists and psychiatrists in the psychiatric aspects of neurologic disorders and a lack of clinical resource allocation to support a multidisciplinary approach, as well as broader stigma and cultural barriers to mental health support.**
- **Some useful tools to screen for psychiatric conditions in epilepsy include the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), Epilepsy Anxiety Survey Instrument (EASI), the brief Epilepsy Anxiety Survey Instrument, the Beck Depression Inventory II (BDI-II), Patient Health Questionnaire 9 (PHQ-9), the Hospital Anxiety and Depression Scale (HADS), and the Generalized Anxiety Disorder Scale (GAD-7).**
- **Diagnosis of psychiatric conditions in epilepsy involves careful consideration of the timing of symptom onset and progression to determine the presence of postictal symptoms and/or possible contribution of antiseizure medications.**

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

effects.[54] Another retrospective study of more than 2600 people showed that 1 in 7 cases of psychosis are due to antiseizure medications.[55] In 2008, the US Food and Drug Administration (FDA) issued an alert to health care professionals about an increased risk of suicide ideation and suicidal behavior in people treated with antiseizure medications (known as *antiepileptic drugs* when the alert was issued). In 2013, an ad hoc task force of the ILAE published an expert consensus

TABLE 8-1 **Common Psychiatric Side Effects of Antiseizure Medications**[a]

Drug	Psychiatric side effects
Barbiturates (primidone and phenobarbital)	Depression In children and individuals with intellectual disabilities: hyperactivity, irritability, aggression
Benzodiazepines	In children, older adults, and individuals with intellectual disabilities: hyperactivity, irritability, aggression
Brivaracetam	Aggressive behavior, depression, psychosis, but better tolerated than levetiracetam
Carbamazepine	Not reported
Eslicarbazepine	Not reported
Ethosuximide	Psychosis
Felbamate	Anxiety, psychosis
Gabapentin	In children and individuals with intellectual disabilities: hyperactivity, aggression, irritability
Lacosamide	Not reported
Lamotrigine	In individuals with intellectual disabilities: hyperactivity, irritability, aggression
Levetiracetam	Irritability, aggression, anxiety, depression, psychosis
Oxcarbazepine	Not reported
Phenytoin	Psychosis (particularly at high serum levels)
Pregabalin	Depression
Rufinamide	Not reported
Stiripentol	Hyperactivity, irritability, aggression
Tiagabine	Irritability
Topiramate	Depression, psychosis, irritability
Valproate	Not reported
Vigabatrin	Psychosis, depression In children and individuals with intellectual disabilities: hyperactivity, aggression, agitation
Zonisamide	Psychosis, depression, irritability

[a] Modified with permission from Mula M, et al, Neurol Clin Pract.[2] © 2021 American Academy of Neurology.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

statement pointing out the complexities of the relationship between suicide and epilepsy.[56] Although some, but not all, antiseizure medications can be associated with psychiatric manifestations that can lead to suicide ideation and suicidal behavior, the risk of stopping or refusing to start antiseizure medications is significantly worse and can actually result in serious harm to the patient, including death. Suicidality in epilepsy is multifactorial, and different variables are involved.[57] Sodium channel blockers seem to be less frequently associated with psychiatric side effects,[24,54] but no robust head-to-head trials provide strong evidence of this. For this reason, clinicians should consider the possibility of psychiatric side effects with any drug in predisposed individuals, such as those with psychiatric comorbidities. Psychiatric side effects of antiseizure medications reported to have a prevalence higher than 1% are summarized in TABLE 8-1.

The phenomenology of psychiatric disorders in epilepsy has itself been a matter of debate.[58,59] People with epilepsy may develop psychiatric disorders that are clinically identical to those in individuals without epilepsy. However, it is now established that some develop psychiatric syndromes characterized by atypical features poorly captured by conventional classification systems such as *DSM-5* and *International Classification of Diseases, Tenth Revision* (*ICD-10*).[58] This has led to attempts to develop clinical instruments tailored for people with epilepsy. However, apart from their use in research settings, the relative benefits of these various instruments in the assessment of common psychopathology in routine clinical practice are the subject of ongoing debate.

KEY POINT

- Further research is needed to examine the efficacy of treatment approaches for psychiatric disorders in epilepsy, but first-line treatment involves psychoeducation and psychological interventions.

MANAGEMENT OF PSYCHIATRIC DISORDERS IN EPILEPSY

Full symptom remission should always be the ultimate goal of any psychiatric intervention. Current evidence on the management of psychiatric comorbidities in epilepsy is limited. There is, however, no reason to consider that internationally adopted guidelines for treatment of psychiatric disorders may not be valid in epilepsy. It seems reasonable, therefore, to follow standards of care in psychiatry, taking into account the distinctive needs of people with epilepsy, including interactions between psychotropic drugs and antiseizure medications, as well as seizure risk (TABLE 8-2). The management plan should consider a combination of interventions depending on the origin of symptoms. Although guidelines of treatment of psychiatric disorders should be adopted for psychiatric comorbidities or the acute treatment of psychiatric symptoms, seizure control is the obvious long-term intervention for peri-ictal symptoms[60,61] and drug optimization for side effects of antiseizure medications.

In the general population, psychological interventions, alone or in combination with drugs, are the first-line treatment for all anxiety disorders[62] and for mild to moderate depression.[63] It is reasonable to apply this guidance also to people with epilepsy, but the evidence is still limited and mainly based on quality-of-life data.[64,65] A 2018 ILAE report confirmed that psychological interventions are recommended in people with epilepsy and mild to moderate depression, although again the evidence level is still moderate.[66]

Psychoeducation and psychological interventions still represent first-line treatments in people with PNES.[67] Explaining the diagnosis and educating individuals and caregivers about the differences between epilepsy and PNES are extremely important.[68] However, no studies on the management of PNES in patients with epilepsy exist. Outside epilepsy, controlled trials in patients with PNES are also limited. Data from a US, multicenter, pilot, randomized, clinical

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

TABLE 8-2 **Management of Psychiatric Comorbidities in Epilepsy**[a]

	Management	Comments
Peri-ictal symptoms (psychiatric symptoms occurring around seizures)	Improve seizure control Consider surgery where appropriate Treat psychiatric comorbidity if present	Psychiatric opinion in multidisciplinary approach to clarify diagnosis and management plan
Paraictal symptoms (alternating psychiatric symptoms and seizures)	Consider reducing the dose of antiseizure medicine or eventually switch to alternative medication	Psychiatric opinion in multidisciplinary approach to clarify diagnosis and management plan
Major depression	Mild to moderate: psychological treatment Severe: selective serotonin reuptake inhibitors (SSRIs) (either sertraline 50 mg daily or citalopram 20 mg daily) with or without psychological treatment If two antidepressants fail, refer patient to psychiatry If suicidal ideation or psychotic symptoms, urgent referral to psychiatry	Consider interaction with enzyme inducers Consider side effects of SSRIs (ie, hyponatremia, sexual dysfunction, osteoporosis, bleeding, weight gain)
Anxiety disorders	Mild to moderate: psychological treatment Severe: SSRIs (either sertraline 50 mg daily or citalopram 20 mg daily) with or without psychological treatment If fails two interventions refer to psychiatry	Consider interaction with enzyme inducers Consider side effects of SSRIs (ie, hyponatremia, sexual dysfunction, osteoporosis, bleeding, weight gain)
First-episode psychoses	Urgent referral to psychiatry First choice: risperidone Second choice: olanzapine or quetiapine	Consider interaction between quetiapine and enzyme inducers (ie, undetectable levels of quetiapine up to 700 mg total daily dose when in combination with carbamazepine) Consider side effects of antipsychotics (eg, sedation, weight gain with olanzapine)
Attention deficit hyperactivity disorder	Methylphenidate Psychological interventions	Review at transition to discuss opportunity of continuing treatment during adulthood
Psychogenic nonepileptic seizures (PNES)	Explain diagnosis Educate patients and caregivers about differences between PNES and epileptic seizures Psychoeducational and psychotherapeutic interventions as in people with PNES only Always refer to psychiatry to identify other psychiatric disorders in comorbidity Treat other psychiatric comorbidities (eg, depression, anxiety)	Individualized multidisciplinary approach is always recommended

[a] Reprinted with permission from Mula M, et al, Neurol Clin Pract.[2] © 2021 American Academy of Neurology.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

trial of cognitive-behavioral therapy (CBT)-informed therapy with or without sertraline in people with PNES showed a significant seizure reduction compared with treatment with sertraline only.[69] However, a UK pragmatic, parallel-arm, multicenter, randomized controlled trial failed to show any benefit of CBT in addition to standard medical care for the reduction of monthly seizures.[70] Further studies are needed to identify what patient group may benefit from specific interventions.[71]

In the general population, antidepressants are recommended for moderate to severe depression and for all anxiety disorders in combination with psychological treatments.

An ad hoc task force of the ILAE is developing the first clinical practice recommendations for the pharmacologic treatment of depression in adults with epilepsy.[72] Selective serotonin reuptake inhibitors (SSRIs) can be considered as first-line treatment when a pharmacologic treatment is needed. All enzyme-inducing antiseizure medications seem to reduce SSRI blood levels by around one-quarter, but it is unclear whether dose adjustments are needed.[73] Clinical monitoring is recommended, and antiseizure medication dose adjustments should be considered depending on clinical response. However, fluoxetine, fluvoxamine, and, to a lesser extent, sertraline may potentially increase phenytoin blood levels and valproate blood levels, though to a lesser extent.[73,74] The most important interaction of enzyme-inducing antiseizure medications is with bupropion for which blood levels can be reduced by up to 90% when combined with, for example, carbamazepine.[74] Side effects of antidepressants include weight gain, sexual dysfunction, hyponatremia, osteopenia, and heart problems. Coprescription of antidepressants with antiseizure medications with a similar spectrum of side effects may be obviously associated with an increased likelihood of developing such side effects (TABLE 8-2).[74]

Regarding seizure risk, antidepressants have long been considered to be associated with an increased risk of seizures. However, this is not a drug class effect, and individual drugs or drug groups should be considered. An analysis of seizure incidence in phase 2 to 3 clinical trials of psychotropic drugs approved by the FDA between 1985 and 2004 involving more than 75,000 individuals found that seizure incidence was not different from that associated with placebo for SSRIs. Clomipramine at high doses (>150 mg) showed a standardized incidence ratio of 4 (95% confidence interval [CI], 2.6 to 6.0).[75] Bupropion immediate-release formulation showed also a slightly increased incidence with a standardized incidence ratio of 1.58 (95% CI, 1.03 to 2.32).[75] However, the seizure rate for the sustained-release formulation was reported similar to that of SSRIs and in the region of 0.1% at doses of up to 300 mg/d.[76] These findings have been confirmed in a 2018 systematic review.[77]

Data on antipsychotics in epilepsy are almost nonexistent despite the fact that this class of medications is used in several clinical contexts, from psychoses to challenging behavior in people with learning disabilities and autism. For this reason, internationally adopted guidelines of treatment of psychotic disorders should be adapted, again taking into account specific issues of people with epilepsy such as interactions with antiseizure medications and increased risk of side effects.[78]

The choice of antipsychotic drug for a first episode of psychosis should consider the likely benefits and possible side effects of each option, including metabolic (ie, weight gain and diabetes), extrapyramidal (ie, akathisia,

KEY POINT

- Choice of medication for psychiatric conditions should include consideration of metabolic, extrapyramidal cardiovascular, and hormonal side effects and interactions with antiseizure medications, including the possibility of amplifying side effects of antiseizure medications.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

dyskinesia, and dystonia), cardiovascular (ie, long QT interval), and hormonal (ie, increased prolactin levels) side effects.[79] Olanzapine, quetiapine, and risperidone are often regarded as first-line treatments for first-episode schizophrenia to balance safety and efficacy.[80] In fact, clozapine and haloperidol have the same level of evidence in terms of efficacy, but they are both burdened by a low tolerability and safety profile.[43]

In epilepsy, postictal psychoses represent an epilepsy-specific problem, and for this reason, it is not possible to apply evidence from other clinical populations. Historically, a combination of benzodiazepines (ie, clobazam) and atypical antipsychotics has been used,[81] but no controlled trials have been conducted. Similarly, no controlled studies have been performed on the use of antipsychotics in people with epilepsy and autism and challenging behavior.

Regarding interactions, antiseizure medications with enzyme-inducing properties (eg, phenytoin, carbamazepine, barbiturates) reduce blood levels of all antipsychotics,[73] and this interaction is particularly evident for quetiapine, where the prescription with enzyme inducers such as carbamazepine can lead to undetectable blood levels of quetiapine even at dosages of 700 mg/d.[82] Although valproate is usually considered an enzyme inhibitor, it seems to mildly induce the metabolism of olanzapine, aripiprazole, clozapine, and quetiapine.[83] Because the clinical relevance of this interaction is not certain, it should be considered on an individual basis. Antipsychotics do not seem to affect blood levels of antiseizure medications. As discussed for antidepressants, neurologists should bear in mind combining drugs with a similar spectrum of side effects. Sedation, weight gain, and risk of arrhythmias or aplastic anemia are side effects to be considered for specific combinations (TABLE 8-2).

Finally, regarding the seizure risk of antipsychotics, clozapine has a 9.5-times increased risk compared with placebo,[75] and such a risk is dose and titration dependent.[84] Olanzapine and quetiapine also seem to carry some risk, although to a lesser extent than clozapine; risperidone does not seem to increase the risk of seizures compared with placebo.[75]

An ad hoc ILAE task force reviewed studies on treatment of ADHD in children with epilepsy.[50] Response rates for methylphenidate in children with ADHD and epilepsy range between 65% and 83% whereas only anecdotal evidence is available for atomoxetine and amphetamines. Data on potential interactions between methylphenidate and antiseizure medications are limited to older compounds, but no evidence of clinically relevant interactions exists. A Swedish study involving more than 21,000 children with seizures showed no evidence of increased risk of seizures from ADHD medications,[85] and this was endorsed by the ILAE report.[50]

COGNITION AND EPILEPSY

Cognitive comorbidities represent a common aspect of the experience of living with epilepsy and can detrimentally impact patient psychosocial functioning, including educational and vocational trajectories, emotional and social competence, and well-being.[86,87] In general, difficulties with attention, executive functioning, and memory are commonly reported by patients with epilepsy and found in up to 70% of untreated patients before the onset of seizures or early in the diagnostic process.[88] These findings point to shared mechanisms that may underlie cognitive and behavioral impairments as well as seizures in people with epilepsy, referred to as *essential* comorbidities. This is further reflected in the

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

current understanding of epilepsy as a "network disease," involving changes in underlying brain networks beyond a specific identifiable lesion. Because the primary function of these networks is to support specific cognitive processes and behaviors, this suggests that epilepsy is as much a disorder of cognition and behavior as it is of seizures.[89]

Significant variation exists in the manifestation and functional impact of network changes on cognition and behavior.[90,91] Even when considering a particular type of epilepsy, individuals may exhibit heterogeneous cognitive profiles. For example, recent research has described three empirically derived cognitive phenotypes in temporal lobe epilepsy, namely those with (1) minimally impaired cognition, (2) intact language and intelligence with a primary memory impairment, and (3) generalized cognitive compromise.[91] These groups also demonstrate differences in the presence and severity of neuroanatomic abnormalities in networks.[92]

Further complicating the picture, cognitive difficulties in epilepsy can occur transiently as a result of seizure activity, may relate to interictal spikes, the side effects of antiseizure medications, and can be exacerbated by mood and behavioral difficulties.[23,93-95] In an effort to address these complexities, the Neuropsychology Task Force of the ILAE has introduced the development of a new International Classification of Cognitive Disorders in Epilepsy to advance our understanding of the essential cognitive comorbidities of epilepsy.[96]

KEY POINTS

- Cognitive comorbidities are common among people living with epilepsy and can range from generalized cognitive impairment to relatively circumscribed deficits.
- The International Classification of Cognitive Disorders in Epilepsy seeks to advance the understanding of the essential cognitive comorbidities of epilepsy.

Epidemiology of Intellectual Disability and Dementia in Epilepsy

Because intellectual disability and dementia are common comorbidities of epilepsy, they are particularly important for the neurologist to bear in mind and, thus, form the focus of the remainder of this article.

In *DSM-5*, the presence of an intellectual disability is typically defined as a full-scale IQ of ≤65 to 75, reflecting cognitive functioning significantly below the population mean of 100 (CASE 8-1).

By highlighting the "network" nature of epilepsy as discussed earlier, the relationship between epilepsy and intellectual disability appears bidirectional. This is supported by research findings indicating that children with epilepsy are more likely to be diagnosed with a comorbid intellectual disability[98] and prevalence estimates of 1 in 5 individuals with intellectual disability diagnosed with comorbid epilepsy.[99] The prevalence of comorbid epilepsy typically increases with increasing severity of intellectual disability. Pooled estimates of epilepsy in moderate intellectual disability have been identified at 16.7% (95% CI, 10.8 to 25.0) compared with 27.0% (95% CI, 16.1 to 41.5) for severe intellectual disability and 50.9% (95% CI, 36.1 to 65.5) for profound intellectual disability.[99]

Underscoring the importance of comprehensive care for this group compared with those with intellectual disability without epilepsy, people living with intellectual disability and epilepsy are at increased risk of a range of other impairments. This can include increased risk of a speech handicap (73.6% versus 50.0%), motor handicap (54.4% versus 14.4%), joint disease (29.3% versus 16.8%), gastrointestinal disease (34.5% versus 23.4%), and stroke (5.2% versus 1.9%).[99]

Among children living with epilepsy, rates of psychiatric and behavioral issues are 2.5 times greater than for their healthy peers.[98] For those living with moderate to severe intellectual disability, the detection of psychiatric disorders can often be "overshadowed" by behavioral issues such as aggression or self-injurious behaviors.[100] In this way, the presentation of anxiety and depression among

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

individuals with epilepsy and intellectual disability will often be "atypical," and it is important to assess any changes to behavior that may indicate mood changes.

When looking to treat psychiatric and behavioral issues among those living with epilepsy and comorbid intellectual disability, it is important to consider that the impact of intellectual disability is not necessarily restricted to cognitive changes, such as difficulty with processing of new information, reasoning, and problem-solving, but it also affects emotional intellect and the ability to express and regulate one's emotions.[101,102] How differences in emotional intellect present can vary and may be exacerbated by the nature of the intellectual disability and cognitive difficulties. For example, research in this area has found that people with intellectual disability are more able to identify an emotion than verbally express it,[103] which may be linked to underlying poor verbal intellect and difficulty with complex cognitive functions such as abstract verbal reasoning. Research identifying that 75% of adults with intellectual disability can successfully link emotions to situations[104] shows the benefit that people with intellectual disability may get from "scaffolding," or providing cues to support correct emotion recognition and discussion.

A syndromic approach to classifying epilepsy can be particularly useful when considering childhood epilepsies, with a syndrome diagnosis at presentation possible in up to three-quarters of children.[105] Several childhood epilepsy syndromes involve significant developmental delay, intellectual disability, and

CASE 8-1

A 28-year-old woman was referred for surgical workup in the context of temporal lobe epilepsy with hippocampal sclerosis. Preoperative language functional MRI (fMRI) was inconclusive, showing bilateral activation on some language tasks. This was due to a combination of difficulty the patient experienced with the language tasks given, as well as poor-quality imaging due to movement artifact. A preoperative neuropsychological assessment confirmed intellectual disability, with an estimated full-scale IQ of 68, as well as relative further reductions in verbal new learning and memory. Collateral history from the family aligned with the objective cognitive findings. The patient lived at home with her parents and relied on her family for support with activities of daily living. As such, both the patient and her family were included in the preoperative counseling process. When asked about their expectations for surgery, the family voiced concerns about the possible severe risks of surgery, including stroke, and wondered if surgery would result in significant loss of autobiographic memory (eg, forgetting people within the family and where they live).

Presurgical counseling involved counseling regarding the typical changes seen after a left anterior temporal lobectomy (eg, increased word-finding difficulties and a possible drop in verbal memory) and tailored counseling for this patient's likely risks and benefits. Given the patient's premorbid intellectual disability, presurgical counseling also included consideration of external supports, such as occupational therapy, social work, and clinical psychology.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

severe drug-resistant epilepsy (TABLE 8-3).[106] These are often referred to as the *developmental epileptic encephalopathies* and include syndromes such as Lennox-Gastaut syndrome and Landau-Kleffner syndrome. Briefly, an epileptic encephalopathy has been defined by the ILAE as "a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function."[107] Distinct from a neurodegenerative condition, the epileptic encephalopathies can vary significantly over the course of disease, and effective seizure control may be able to improve the overall prognosis.[108] Although antiseizure medications remain the first line of treatment, other types of treatment such as vagus nerve stimulation and the ketogenic diet are also used and more commonly among the epileptic encephalopathies than among other epilepsy syndromes.[109]

Advances in genetics have also shed light on rare genetic epilepsy syndromes that involve significant cognitive comorbidities, such as *KCNQ2* and *SYNGAP1*. These syndromes are rarely encountered in the clinic, with only approximately 200 individuals with *SYNGAP1* identified, although more individuals are suspected to have the gene.[108,110] Improvements in genetic testing that have allowed the provision of a diagnosis are important for identifying appropriate treatment and can provide families with some sense of relief and a direction forward, as well as a sense of community and peer support if they are able to connect with others in a similar situation.[110]

COMMENT

This patient is a good candidate for epilepsy surgery, given she is young and has lesion-positive temporal lobe epilepsy with hippocampal sclerosis and a memory deficit identified before surgery. As such, she is less likely to notice a significant drop in her verbal memory postoperatively. However, the case also illustrates how the presence of an intellectual disability can complicate the preoperative workup because (1) the patient may not be a reliable historian (necessitating a collateral report from the family); (2) disentangling specific cognitive deficits (eg, language) can be difficult when generalized cognitive impairment is present; this may have impacted fMRI findings in this case, as the patient found typically "straightforward" language tasks challenging; and (3) the presence of an intellectual disability raises considerations in terms of gaining informed consent.

The International League Against Epilepsy (ILAE) currently recommends the commencement of "prehabilitation" prior to surgery. In contrast to traditional cognitive rehabilitation, which occurs after a neuropsychological deficit has been sustained, candidates for epilepsy surgery can engage in prehabilitation. This is the process of utilizing still-intact functions prior to surgery to proactively establish compensatory strategies and routines in preparation for postoperative changes.[97] This process of presurgical counseling should include expectation management for both the patient and the family, as well as discussion of broader supports and cognitive strategies that could be implemented in the household. Establishing rapport and routine with support workers before surgery will help maximize adjustment and postsurgical recovery.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

An increasingly important cognitive comorbidity of epilepsy to consider is dementia. Because of the aging population, dementia is a national health priority for many countries and the focus of a significant amount of research. Epilepsy and seizures are commonly associated with the occurrence of both stroke and dementia, two of the most common neurologic conditions in an aging population.[111] The relationship between dementia and epilepsy appears bidirectional, with an increased risk of seizures among those with dementia and an increased risk of dementia for those with epilepsy.[90,112] For example, the period prevalence of an individual with epilepsy developing dementia has been estimated between 8.1 and 17.5 per 100 people, and the period prevalence of epilepsy among those with dementia has been estimated at 5 per 100 people in

TABLE 8-3 **Childhood Epilepsy Syndromes Associated With Significant Developmental Delay and/or Intellectual Disability**

Epilepsy syndrome	Description
Lennox-Gastaut syndrome	Etiology: two of three cases are symptomatic of a variety of diffuse, multifocal, or focal brain insults including some metabolic disorders Prevalence: Lennox-Gastaut syndrome constitutes 1-2% of the epilepsies and 1-10% of childhood-onset epilepsies (depending on the age considered); Lennox-Gastaut syndrome is more common in boys than girls Onset: from infancy to late childhood but peaks at 3-5 years of age Seizure types: atonic, tonic, atypical absence Comorbidities: developmental delay, severe intellectual disability, behavioral problems; a good prognosis with normal cognitive functioning is reported in 10-15% of cases
Doose syndrome	Etiology: considered a form of idiopathic generalized epilepsy Prevalence: Doose syndrome constitutes approximately 1-2% of childhood-onset epilepsies and is more common in boys than girls Onset: early to midchildhood, peaking around 2-4 years Seizure types: febrile and afebrile generalized tonic-clonic seizures, myoclonic-astatic seizures, atonic, myoclonic, and absence Comorbidities: cognitive comorbidities can vary in occurrence and severity; approximately half eventually will achieve seizure freedom and normal or near-normal developmental trajectories
Dravet syndrome (severe myoclonic epilepsy of infancy)	Etiology: approximately 80% of those with Dravet syndrome have a mutation in the *SCN1A* gene; Dravet syndrome lies at the severe end of the manifestation of this gene Prevalence: Dravet syndrome affects 1 in 15,700 individuals Onset: in infancy (within the first year) Seizure types: include myoclonic, hemiclonic, and/or generalized tonic-clonic; seizures are frequent and prolonged Comorbidities: developmental delay is not always evident until the first or second year of life. Comorbidities include delayed language, behavioral difficulties, movement and balance disorders, orthopedic disorders, sleeping difficulties, and chronic infections and dysautonomia

CONTINUED ON PAGE 471

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

population-based settings.[113] To highlight the importance of understanding cognitive comorbidities in epilepsy, those with epilepsy and intellectual disability are also at greater risk of developing dementia than are individuals with epilepsy without intellectual disability.[99]

When examining specific types of dementia, research often points to vascular dementia and Alzheimer disease as particularly associated with the risk of developing seizures.[90,113] Other forms of dementia, such as frontotemporal dementia or dementia with Lewy bodies (DLB), have received less attention in the literature[112]; however, one 2020 study suggested a reasonably consistent prevalence of epilepsy across dementia types, with a prevalence of recent-onset epilepsy among those with Alzheimer disease at 1.82% versus 1.28% for frontotemporal

CONTINUED FROM PAGE 470

Epilepsy syndrome	Description
Landau-Kleffner syndrome	Etiology: a rare form of epilepsy, sometimes called *progressive epileptic aphasia* or *aphasia with convulsive disorder*; develops in children with no structural brain abnormalities
	Prevalence: estimates from a Japanese study indicate prevalence between 44.2 and 59.2 per 18 million[106]; affects twice as many boys as girls
	Onset: early neurodevelopment is typically normal; onset is usually in early to midchildhood, peaking at 5-7 years, and manifests as a slow or sudden loss of receptive and expressive language
	Seizure types: approximately 70% of children with Landau-Kleffner syndrome will have seizures; seizures may be of different types (most commonly focal motor seizures) and are typically infrequent
	Comorbidities: cognitive comorbidities occur in a triad of symptoms, namely acquired language problems, as well as general cognitive and behavioral abnormalities; approximately half will experience remittance of symptoms and function normally in adult life
Rasmussen encephalitis	Etiology: a rare, chronic neuroinflammatory condition; typically affects only one hemisphere (half of the brain), but it can sometimes progress to involve the whole brain
	Prevalence: estimates of prevalence are between 1.7 and 2.4 per 10 million
	Onset: most commonly occurs before the age of 10 years but can also occur in adolescence and adulthood
	Seizure types: focal onset and frequent and severe; approximately half of those with Rasmussen encephalitis will experience epilepsia partialis continua (recurrent and unrelenting focal seizures with retained awareness that can last hours, days, or even years)
	Comorbidities: progressive loss of neurologic functioning, including motor skills, speech, and cognitive functioning; as it progresses, it may cause a hemiparesis; children with Rasmussen encephalitis frequently enter a phase of permanent, but stable, neurologic deficits after 8 to 12 months; the disease in adults and adolescents may continue to progress slowly.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

dementia and 2.47% for DLB.[112] Given the more common presentation of Alzheimer disease and vascular dementia in the clinic, however, these will likely be the most encountered forms of dementia with epilepsy seen by clinicians.

A commonly considered mechanism for epileptogenesis in dementia is thought to be increased cortical excitability caused by cortical deposition/aggregation of pathologic proteins; however, the precise cause of epileptic seizures in patients with dementia remains unknown.[112] Researchers have also highlighted several common underlying risk factors, including vascular risk factors that may predispose to atherosclerosis and raised inflammatory markers, as well as lifestyle factors such as decreased social interaction and reduced physical activity.[90]

Implications of Cognitive Comorbidities in the Diagnosis of Epilepsy

The presence of cognitive comorbidities has implications for the diagnostic process and clinical decision making around treatment, including gaining

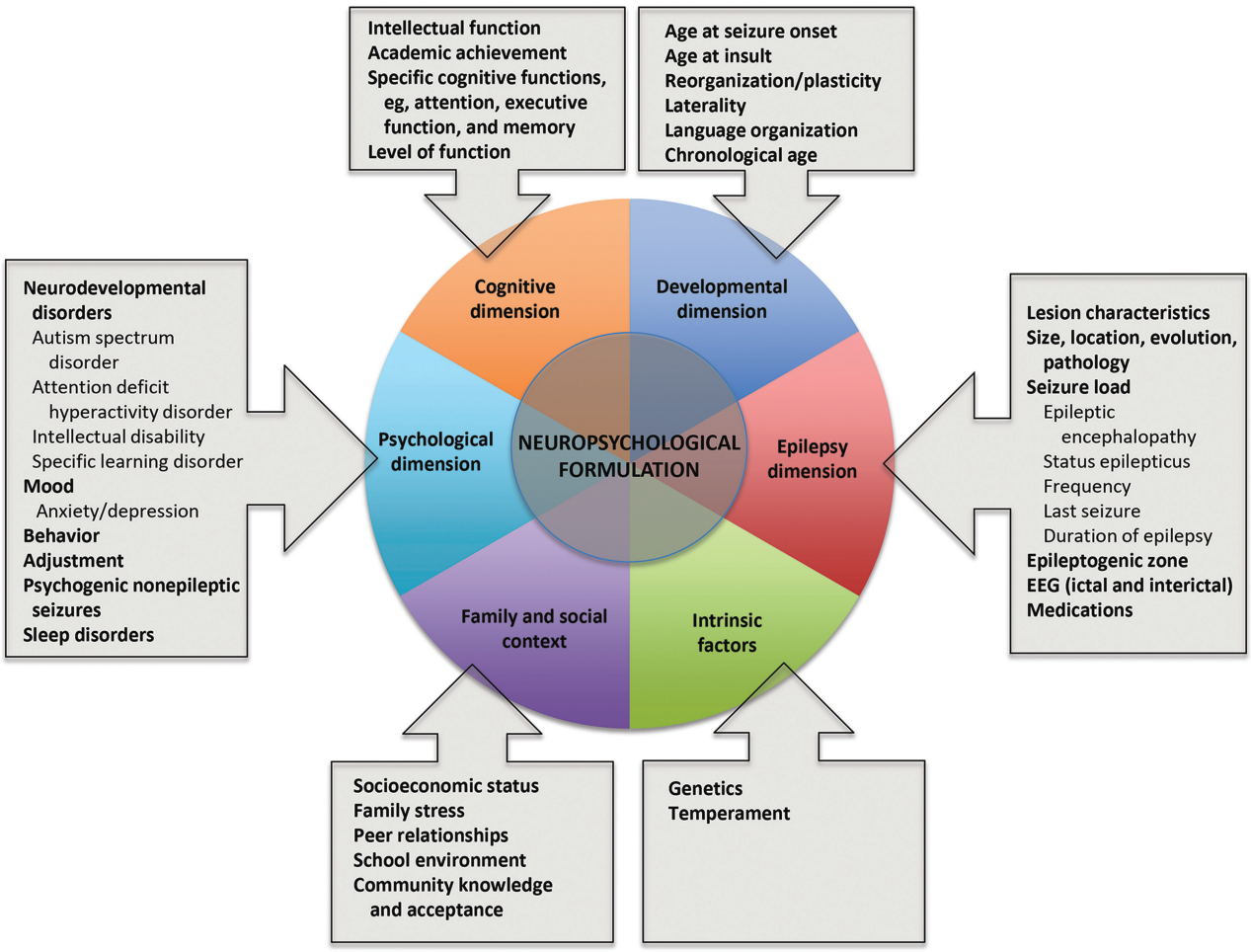

FIGURE 8-1

An overview of the process of neuropsychological formulation, taking into consideration not only neurophysiologic factors (epilepsy dimension) but also developmental, intrinsic, cognitive, psychological, and social factors.

EEG = electroencephalogram.

Reprinted with permission from Gonzales LM and Wrennall JA, Seizure.[123] © Elsevier Ltd.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

informed consent and assessment of decision-making capacity. An understanding of cognitive capacity should be fundamental to how clinicians structure clinical interactions, including establishing rapport, ensuring an adequate understanding of diagnostic information and treatment recommendations, and engaging family members/caregivers as part of the extended clinical care team (CASE 8-1).[114]

Subjective cognitive concerns are common among people living with epilepsy,[115] and identifying whether an objective cognitive deficit is present can sometimes be difficult to determine at face value. The weight of the evidence to date has indicated generally poor to modest (at best) associations between subjective memory concerns and tested memory functions.[116] In general, memory concerns have been found to be more related to factors such as mood and anxiety disorders, general psychological distress beyond depression, and illness perceptions.[116] Memory symptoms may also be linked to objective cognitive performance in nonmemory domains, including language and attention.[117] For patients with dementia, strident cognitive symptoms are often seen in the early stages of disease when the individual is experiencing mild cognitive impairment. In the later stages of disease progression, the memory symptom is often vague and muted, reflecting loss of insight.[118]

Cognitive deficits may be detected at several points during the interview and assessment of a patient. In conversation, it may be possible to notice changes in speech, including dysnomia or anomia (word-finding difficulties), a sense of vagueness and difficulty providing a clear history, confabulation,[119] inappropriate or disinhibited behaviors, and emotional lability. As such, it is often important to gain permission to speak with a family member or caregiver to obtain further insights into the patient's cognitive functioning and how it impacts daily living (CASE 8-1).

Cognitive screening measures, such as the Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE), can also be useful in identifying patients who require more detailed neuropsychological assessment to diagnose a cognitive comorbidity.[120,121] Here, it is important to remember that screening measures are not diagnostic instruments, and individuals may obtain low scores on these measures for a range of reasons.[122]

To properly diagnose a cognitive deficit, a formal neuropsychological assessment should be conducted; it is a collaborative and holistic process that takes into account biological, neurodevelopmental, psychological, and broader social factors when considering the patient's cognitive presentation (FIGURE 8-1).[122,123] Obtaining an accurate neuropsychological assessment at baseline is important for identifying changes following treatment, including the addition of new medications or surgery or both, as well as tracking progression over time if a neurodegenerative process is suspected.[124] Neuropsychological assessment of intellectual and communication skills also provides important data on a patient's ability to comprehend, communicate, and problem-solve, as well as their level of insight and ability for self-reflection. This is relevant to how well the patient can understand and retain new information and their level of readiness for certain treatments, such as epilepsy surgery or psychological therapy or both. Some practical considerations for working with people with epilepsy and cognitive comorbidities are summarized in TABLE 8-4.

In the diagnostic process, cognitive comorbidities may impact a person's ability to recall and/or describe seizure experiences well to the clinician, or they

KEY POINTS

- Cognitive difficulties may extend beyond intellectual functions, such as attention and memory, and may include difficulties with emotional expression and regulation.
- Several specific childhood epilepsy syndromes typically involve significant developmental delay and/or intellectual disability. Many of these syndromes represent rare genetic epilepsy syndromes.
- An epileptic encephalopathy has been defined by the International League Against Epilepsy as "a condition in which the epileptiform abnormalities themselves are believed to contribute to the progressive disturbance in cerebral function."
- The recognition of a bidirectional relationship between epilepsy and dementia is growing, with an increased risk of dementia among people living with epilepsy and an increased risk of seizures in dementia.
- Increased risk of seizures has been identified across several different dementia syndromes, including Alzheimer disease, frontotemporal dementia, and dementia with Lewy bodies.
- Risk factors for seizures in dementia include poor cardiovascular health, raised inflammatory markers, decreased physical fitness, and decreased social interaction.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

TABLE 8-4 **Recommended Adaptations to Psychological Therapy in Adults With Intellectual Disabilities**[a]

Therapeutic element	Adaptations recommended
Establishing patient abilities	
Assessment	Full neuropsychological assessment (eg, intellect, language, memory)
	Emotion recognition and cognitive regulation of emotions
Developmental level	Intellectual ability, communication, and social skills
	Treatment readiness: internal motivation and self-reflective capacity
Diagnosis	Risk of diagnostic overshadowing (see text for details)
	Consider both patient self-report and validation from other stakeholders in patient care (eg, support services, other health practitioners)
Adaptations focused on improving cognitive and emotional skills	
Scaffolding	Reduce complexity of therapy
	Use psychoeducation as building blocks to therapy goals
Self-reflection	Reinforce and utilize positive influences (eg, friendships, hobbies)
	Encourage areas where self-management is evident
	Acknowledge challenges (may include disability-specific factors)
Adaptations focused on improving communication and patient "buy-in"	
Language	Appropriate for the patient's level of understanding
Rapport	Paraphrasing to aid reflection and probe questions to confirm mutual understanding of discussion content
	Use of pictorial representations, games, and nonverbal methods
External support (eg, caregivers)	A more directive approach may be required
	Providing a space for, and encouragement of, self-efficacy
	Build self-motivation
	Awareness of influential psychosocial factors (eg, finances)
	Possible administrative engagement with community services
	Involvement can support therapeutic goals
	Therapy with and without supporters present enhances autonomy
Flexibility	Dynamic engagement strategies (eg, therapy setting, involvement of others, small goals to foster self-belief and "buy-in")

[a] Reprinted with permission from Trevis KJ, Wilson SJ, Springer International Publishing.[114] © 2016 Springer International Publishing.

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

may manifest in ways that resemble seizure activity (eg, attentional or language difficulties). Moreover, epilepsy can often go undetected among those with dementia because of diagnostic overshadowing or misattribution of the side effects of medications.[125]

Some have suggested that the variable clinical presentation of seizures in older adults is increased because of the relatively high prevalence of underlying cerebrovascular disease, resulting in heterogeneity of the epileptogenic focus.[90] Several common seizure mimics can also be seen in older adults including syncope, transient ischemic attacks, migraine, panic attacks, and sleep disorders, as well as staring or behavioral spells in patients with static encephalopathy or dementia.[90,125]

Management of Cognitive Comorbidities in Epilepsy

Despite the large amount of literature on cognitive problems in epilepsy, a relatively small number of studies directly assess the efficacy of pharmacologic or neuromodulatory interventions on cognition. As pointed out in a systematic review on this subject, available studies are limited by the small sample size, the heterogeneity of epilepsy types and antiseizure medications prescribed, variability in cognitive assessment tools, and inconsistent consideration of possible moderating factors such as mood.[126] Studies that investigated cognitive enhancement in epilepsy per se showed a lack of efficacy of classic acetylcholinesterase inhibitors.[127] This is probably because of the etiology of memory dysfunction in epilepsy being mediated via mechanisms other than loss of cholinergic neurons. Noninvasive neuromodulation in epilepsy is appealing because of the potential to have an impact on seizure frequency and/or interictal epileptiform discharge frequency, but data on cognition are still limited.[126] Data on the management of epilepsy in patients with cognitive disorders are also limited. Some authors suggested that epilepsy in Alzheimer disease responds better to antiseizure medications compared with other types of dementia, although these results may be affected by the relatively small numbers of those with other types such as frontotemporal dementia and DLB.[112] The treatment of epilepsy in dementia will no doubt be an area of much ongoing investigation in the future.

When surgical treatment for epilepsy is considered, it is important for the team to have thorough discussions with patients and their families, weighing the risks and benefits of undergoing surgery (CASE 8-1).[128] In obtaining informed consent for surgery, the clinician should consider alternative ways of communicating possible risks and benefits to scaffold the patient's understanding. This could include diagrams and written information, as well as connecting the patient with a "peer," or someone with epilepsy who has been through surgery before. This can provide them with a more concrete and tangible understanding of some of the possible benefits and/or risks of surgery. It is also important to include the family throughout the presurgical workup and counseling process so that the family can (1) understand and retain the relevant information to discuss with the patient later, (2) support the patient in asking questions in what might feel like an intimidating clinical environment, and (3) be provided with the opportunity to ask their own questions. The expectations of both the patient and the family should be carefully explored and addressed in the presurgical counseling process because the family may be expecting surgery to produce changes in the individual's cognitive and psychosocial functioning as well as their seizure frequency.[129,130]

KEY POINTS

- **Subjective cognitive concerns are not always correlated with objective cognitive performance and may be influenced by mood, lack of insight, and other psychological factors.**
- **Different cognitive screening measures may include the Montreal Cognitive Assessment (MoCA) or the Mini-Mental State Examination (MMSE). However, cognitive comorbidity can only be properly diagnosed following a comprehensive workup that includes formal neurologic, neuropsychological, and/or neuropsychiatric assessment.**
- **Consideration of a patient's cognitive functioning is crucial in the workup to epilepsy surgery. This is important not only in considering the possible cognitive risks of surgery but also in how clinicians discuss the surgery with patients and their family members and obtain informed consent. Cognitive aids, such as written and/or simplified information, may be helpful for some patients.**

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

Although seizures and cognitive dysfunction are often symptomatic of shared underlying network disease, postoperative improvement in seizure frequency does not automatically translate to improved cognitive and/or behavioral functioning. In some cases, seizure reduction can bring to the fore other signs of cerebral dysfunction previously not noticed by the family because of their focus or misattribution to seizures.[129,130] This can add to the experience of caregiver burden or stress and increase the likelihood of poor postoperative adjustment.[114,129,130]

If epilepsy is to be recognized as more than a seizure disorder, treatment choices need to consider more than antiseizure medications. Dementia, intellectual disability, and epilepsy are all conditions where real and perceived personal control over the environment is reduced. Loss of control, whether real or perceived, is often associated with heightened anxiety and distress.[131]

In the field of psychology, a growing body of research points to the benefits of adapted therapeutic approaches, such as CBT, for the treatment of anxiety and depression in patients with cognitive deficits.[132] These approaches can help foster greater self-awareness and insight, as well as increased emotional, behavioral, and social self-regulation among those with epilepsy and mild intellectual disability.[114] For those with more severe cognitive deficits, treatments may also need to involve behavioral interventions aimed at reducing challenging behaviors, as well as psychoeducation and support for the family.[133]

In the general population, psychosocial risk factors for cognitive decline in older age can include decreased physical and mental activity.[90] These factors are more common among people living with epilepsy because of the associated psychosocial restrictions of seizures, such as the inability to drive, unemployment or underemployment, and experiences of stigma and discrimination.[134] This may have a cumulative effect over the course of a lifetime for those with early-onset epilepsy but can also be a significant impediment to socializing among those with older-onset epilepsy and cognitive comorbidities.

For people with epilepsy and intellectual disability, the experience of psychosocial challenges is often reported to be heightened, including higher rates of trauma and abuse, family stressors, unemployment and poverty, less participation in the community, a lack of meaningful friendships or intimate relationships, and elevated rates of mental health difficulties.[114] These psychosocial challenges significantly impact a person's day-to-day functioning and quality of life and are often perceived as more detrimental than seizures.[122]

People with epilepsy and intellectual disability face the added challenge of living with often "hard-to-treat" epilepsy, for which information is limited on the long-term effects of seizures on their cognitive and behavioral functioning.[114] Both patients and their families, then, can often have apprehension about the future, possible progression of cognitive symptoms, and the provision of long-term care. For patients with dementia and epilepsy, although a degenerative cognitive trajectory is expected, this is equally challenging for both patients and their family/caregivers, particularly as patients become increasingly reliant on those around them to manage their epilepsy. Beyond the individual, it is also important to consider systemic factors that may present barriers to effective care. Prevalence estimates suggest that nearly 80% of people living with epilepsy are in low- or middle-income countries, with a rate of new cases up to twofold higher

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

than that of high-income countries.[135] Limitations in resources mean that many of these patients will not be able to access specialist care to optimize medical treatment of their epilepsy or have access to allied health support to manage the cognitive and psychosocial sequelae of epilepsy. Further barriers to care may include cultural factors and illness beliefs and increased stigmatization around epilepsy, as well as practical barriers such as difficulty traveling to clinics or accessing alternatives such as telehealth.[135-137]

CONCLUSION

People living with epilepsy are at increased risk of both psychiatric and cognitive comorbidities. These are now thought to represent "essential comorbidities" (ie, the manifestation of changes to underlying brain networks). Consideration of comorbidities should occur throughout the clinical interview, diagnostic, and treatment process.

KEY POINT

- **Consideration of psychiatric well-being is important not only for patients' general well-being but also for their subjective cognitive functioning, because the reduced physical and social activity that may be prompted by low mood can be detrimental to cognition.**

REFERENCES

1 Fisher RS, Acevedo C, Arzimanoglou A. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(4):475-482. doi:10.1111/epi.12550

2 Mula M, Kanner AM, Jetté N, Sander JW. Psychiatric comorbidities in people with epilepsy. Neurol Clin Pract 2021;11(2):112-120. doi:10.1212/CPJ.0000000000000874

3 Lin JJ, Mula M, Hermann BP. Uncovering the neurobehavioural comorbidities of epilepsy over the lifespan. Lancet 2012;380(9848):1180-1192. doi:10.1016/S0140-6736(12)61455-X

4 Salpekar J, Mula M. Common psychiatric comorbidities in epilepsy: how big of a problem is it? Epilepsy Behav 2019;98:293-297. doi:10.1016/j.yebeh.2018.07.023

5 Fiest KM, Dykeman J, Patten SB. Depression in epilepsy: a systematic review and meta-analysis. Neurology 2013;80(6):590-599. doi:10.1212/WNL.0b013e31827b1ae0

6 Scott AJ, Sharpe L, Hunt C, Gandy M. Anxiety and depressive disorders in people with epilepsy: a meta-analysis. Epilepsia 2017;58(6):973-982. doi:10.1111/epi.13769

7 Clancy MJ, Clarke MC, Connor DJ. The prevalence of psychosis in epilepsy; a systematic review and meta-analysis. BMC Psychiatry 2014;14(75):1-9. doi:10.1186/1471-244X-14-75

8 Kutlubaev MA, Xu Y, Hackett ML, Stone J. Dual diagnosis of epilepsy and psychogenic nonepileptic seizures: systematic review and meta-analysis of frequency, correlates, and outcomes. Epilepsy Behav 2018;89:70-78. doi:10.1016/j.yebeh.2018.10.010

9 Reilly C, Atkinson P, Das KB. Neurobehavioral comorbidities in children with active epilepsy: a population-based study. Pediatrics 2014;133:e1586-e1593. doi:10.1542/peds.2013-3787

10 Aaberg KM, Bakken IJ, Lossius MI. Comorbidity and childhood epilepsy: a nationwide registry study. Pediatrics 2016;138(3):e20160921. doi:10.1542/peds.2016-0921

11 Mula M, Kaufman KR. Double stigma in mental health: epilepsy and mental illness. BJPsych Open 2020;6(4):E72. doi:10.1192/bjo.2020.58

12 Elkommos S, Mula M. A systematic review of neuroimaging studies of depression in adults with epilepsy. Epilepsy Behav 2021;115(107695). doi:10.1016/j.yebeh.2020.107695

13 Allebone J, Kanaan R, Wilson SJ. Systematic review of structural and functional brain alterations in psychosis of epilepsy. J Neurol Neurosurg Psychiatry 2018;89(6):611-617. doi:10.1136/jnnp-2017-317102

14 Hesdorffer DC, Ishihara L, Mynepalli L. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. Ann Neurol 2012;72(2):184-191. doi:10.1002/ana.23601

15 Josephson CB, Lowerison M, Vallerand I. Association of depression and treated depression with epilepsy and seizure outcomes: a multicohort analysis. JAMA Neurol 2017;74(5):533-539. doi:10.1001/jamaneurol.2016.5042

16 Wotton CJ, Goldacre MJ. Coexistence of schizophrenia and epilepsy: record-linkage studies. Epilepsia 2012;53(4). doi:10.1111/j.1528-1167.2011.03390.x

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

17 Chang YT, Chen PC, Tsai IJ. Bidirectional relation between schizophrenia and epilepsy: a population-based retrospective cohort study. Epilepsia 2011;52(11):2036-2042. doi:10.1111/j.1528-1167.2011.03268.x

18 Kanner AM. Can neurobiological pathogenic mechanisms of depression facilitate the development of seizure disorders? Lancet Neurol 2012;11(12):1093-1102. doi:10.1016/S1474-4422(12)70201-6

19 Mula M. Neuropsychiatric symptoms of epilepsy. Springer; 2016.

20 Agrawal N, Bird JS, Oertzen TJ. Depression correlates with quality of life in people with epilepsy independent of the measures used. Epilepsy Behav 2016;62:246-250. doi:10.1016/j.yebeh.2016.07.020

21 Sano F, Kanemura H, Tando T. Depressive symptoms contribute to quality of life in children with epilepsy. Eur J Paediatr Neurol 2014;18(6):774-779. doi:10.1016/j.ejpn.2014.08.002

22 Panelli RJ, Kilpatrick C, Moore SM. The Liverpool Adverse Events Profile: relation to AED use and mood. Epilepsia 2007;48(3):456-463. doi:10.1111/j.1528-1167.2006.00956.x

23 Velissaris SL, Wilson SJ, Newton MR. Cognitive complaints after a first seizure in adulthood: influence of psychological adjustment. Epilepsia 2009;50(5):1012-1021. doi:10.1111/j.1528-1167.2008.01893.x

24 Stephen LJ, Wishart A, Brodie MJ. Psychiatric side effects and antiepileptic drugs: observations from prospective audits. Epilepsy Behav 2017;71(pt A):73-78. doi:10.1016/j.yebeh.2017.04.003

25 Nogueira MH, Yasuda CL, Coan AC. Concurrent mood and anxiety disorders are associated with pharmacoresistant seizures in patients with MTLE. Epilepsia 2017;58(7):1268-1276. doi:10.1111/epi.13781

26 Stevelink R, Koeleman BPC, Sander JW. Refractory juvenile myoclonic epilepsy: a meta-analysis of prevalence and risk factors. Eur J Neurol 2019;26(6):856-864. doi:10.1111/ene.13811

27 Koch-Stoecker SC, Bien CG, Schulz R, May TW. Psychiatric lifetime diagnoses are associated with a reduced chance of seizure freedom after temporal lobe surgery. Epilepsia 2017;58(6):983-993. doi:10.1111/epi.13736

28 Bell GS, Tisi J, Gonzalez-Fraile JC. Factors affecting seizure outcome after epilepsy surgery: an observational series. J Neurol Neurosurg Psychiatry 2017;88(11):933-940. doi:10.1136/jnnp-2017-316211

29 Altalib HH, Berg AT, Cong X. Presurgical depression and anxiety are not associated with worse epilepsy surgery outcome five years postoperatively. Epilepsy Behav 2018;83:7-12. doi:10.1016/j.yebeh.2018.01.040

30 Wrench JM, Rayner G, Wilson SJ. Profiling the evolution of depression after epilepsy surgery. Epilepsia 2011;52(5):900-908. doi:10.1111/j.1528-1167.2011.03015.x

31 Ramos-Perdigués S, Baillés E, Mané A. A prospective study contrasting the psychiatric outcome in drug-resistant epilepsy between patients who underwent surgery and a control group. Epilepsia 2016;57(10):1680-1690. doi:10.1111/epi.13497

32 Fazel S, Wolf A, Långström N. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet 2013;382(9905):1646-1654. doi:10.1016/S0140-6736(13)60899-5

33 Keezer MR, Bell GS, Neligan A. Cause of death and predictors of mortality in a community-based cohort of people with epilepsy. Neurology 2016;86(8):704-712. doi:10.1212/WNL.0000000000002390

34 Gur-Ozmen S, Mula M, Agrawal N. The effect of depression and side effects of antiepileptic drugs on injuries in patients with epilepsy. Eur J Neurol 2017;24(9):1135-1139. doi:10.1111/ene.13346

35 Hesdorffer DC, Ishihara L, Webb DJ. Occurrence and recurrence of attempted suicide among people with epilepsy. JAMA Psychiatry 2016;73(1):80-86. doi:10.1001/jamapsychiatry.2015.2516

36 Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: a nationwide population-based cohort study. Neurology 2017;89(2):170-177. doi:10.1212/WNL.0000000000004094

37 Wilner AN, Sharma BK, Soucy A. Common comorbidities in women and men with epilepsy and the relationship between number of comorbidities and health plan paid costs in 2010. Epilepsy Behav 2014;32:15-20. doi:10.1016/j.yebeh.2013.12.032

38 Hamilton KT, Anderson CT, Dahodwala N. Utilization of care among drug resistant epilepsy patients with symptoms of anxiety and depression. Seizure 2014;23(3):196-200. doi:10.1016/j.seizure.2013.11.012

39 Patel RS, Elmaadawi A, Mansuri Z. Psychiatric comorbidities and outcomes in epilepsy patients: an insight from a nationwide inpatient analysis in the United States. Cureus 2017;9:e1686. doi: 10.7759/cureus.1686

40 Lopez MR, Schachter SC, Kanner AM. Psychiatric comorbidities go unrecognized in patients with epilepsy: "you see what you know." Epilepsy Behav 2019;98(pt B):302-305. doi:10.1016/j.yebeh.2019.01.027

41 Gill SJ, Lukmanji S, Fiest KM. Depression screening tools in persons with epilepsy: a systematic review of validated tools. Epilepsia 2017;58(5):695-705. doi:10.1111/epi.13651

42 Mula M, McGonigal A, Micoulaud-Franchi JA. Validation of rapid suicidality screening in epilepsy using the NDDIE. Epilepsia 2016;57(6):949-955. doi:10.1111/epi.13373

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

43 Mula M, Iudice A, La Neve A. Validation of the Hamilton Rating Scale for Depression in adults with epilepsy. Epilepsy Behav 2014;41:122-125. doi:10.1016/j.yebeh.2014.08.029

44 Gandy M, Sharpe L, Perry KN. Anxiety in epilepsy: a neglected disorder. J Psychosom Res 2015; 78(2):149-155. doi:10.1016/j.jpsychores.2014.12.002

45 Wiglusz MS, Landowski J, Cubała WJ. Validation of the Polish version of the Hospital Anxiety and Depression Scale for anxiety disorders in patients with epilepsy. Epilepsy Behav 2018;84: 162-165. doi:10.1016/j.yebeh.2018.04.010

46 Seo JG, Cho YW, Lee SJ. Validation of the generalized anxiety disorder-7 in people with epilepsy: a MEPSY study. Epilepsy Behav 2014;35: 59-63. doi:10.1016/j.yebeh.2014.04.005

47 Micoulaud-Franchi JA, Lagarde S, Barkate G. Rapid detection of generalized anxiety disorder and major depression in epilepsy: validation of the GAD-7 as a complementary tool to the NDDI-E in a French sample. Epilepsy Behav 2016; 57(pt A):211-216. doi:10.1016/j.yebeh.2016.02.015

48 Mula M. The interictal dysphoric disorder of epilepsy: a still open debate. Curr Neurol Neurosci Rep 2013;13(6):1-6. doi:10.1007/s11910-013-0355-2

49 Scott AJ, Sharpe L, Thayer Z. Design and validation of two measures to detect anxiety disorders in epilepsy: the Epilepsy Anxiety Survey Instrument and its brief counterpart. Epilepsia 2019;60(10):2068-2077. doi:10.1111/epi.16348

50 Auvin S, Wirrell E, Donald KA. Systematic review of the screening, diagnosis, and management of ADHD in children with epilepsy. Consensus paper of the Task Force on Comorbidities of the ILAE Pediatric Commission. Epilepsia 2018;59(10): 1867-1880. doi:10.1111/epi.14549

51 Wagner JL, Kellermann T, Mueller M. Development and validation of the NDDI-E-Y: a screening tool for depressive symptoms in pediatric epilepsy. Epilepsia 2016;57(8): 1265-1270. doi:10.1111/epi.13446

52 Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. Neurology 2004;62(5):708-713. doi:10.1212/01.wnl.0000113763.11862.26

53 Hilger E, Zimprich F, Pataraia E. Psychoses in epilepsy: a comparison of postictal and interictal psychoses. Epilepsy Behav 2016;60:58-62. doi:10.1016/j.yebeh.2016.04.005

54 Chen B, Choi H, Hirsch LJ. Psychiatric and behavioral side effects of antiepileptic drugs in adults with epilepsy. Epilepsy Behav 2017;76: 24-31. doi:10.1016/j.yebeh.2017.08.039

55 Chen Z, Lusicic A, O'Brien TJ. Psychotic disorders induced by antiepileptic drugs in people with epilepsy. Brain 2016;139(pt 10):2668-2678. doi:10.1093/brain/aww196

56 Mula M, Kanner AM, Schmitz B, Schachter S. Antiepileptic drugs and suicidality: An expert consensus statement from the Task Force on Therapeutic Strategies of the ILAE Commission on Neuropsychobiology. Epilepsia 2013;54(1): 199-203. doi:10.1111/j.1528-1167.2012.03688.x

57 Mula M. Depression in epilepsy. Curr Opin Neurol 2017;30(2):180-186. doi:10.1097/WCO.0000000000000431

58 de Araújo Filho GM, Tarifa B, Santos RE, et al. Clinical and sociodemographic variables associated with interictal dysphoric disorder and interictal personality in patients with drug-resistant temporal lobe epilepsy: a controlled study. Epilepsy Behav 2017;69:100-103. doi:10.1016/j.yebeh.2017.01.021

59 Labudda K, Illies D, Bien CG, Neuner F. Interictal dysphoric disorder: further doubts about its epilepsy-specificity and its independency from common psychiatric disorders. Epilepsy Res 2018;141:13-18. doi:10.1016/j.eplepsyres.2018.01.020

60 Buranee K, Teeradej S, Chusak L, Michael M. Epilepsy-related psychoses and psychotic symptoms are significantly reduced by resective epilepsy surgery and are not associated with surgery outcome or epilepsy characteristics: a cohort study. Psychiatry Res 2016;245:333-339. doi:10.1016/j.psychres.2016.08.020

61 Trebuchon A, Bartolomei F, McGonigal A. Reversible antisocial behavior in ventromedial prefrontal lobe epilepsy. Epilepsy Behav 2013; 29(2):367-373. doi:10.1016/j.yebeh.2013.08.007

62 National Institute for Health and Care Excellence. Generalised anxiety disorder and panic disorder in adults: management. Accessed December 8, 2021. nice.org.uk/guidance/cg113

63 National Institute for Health and Care Excellence. Depression in adults: recognition and management. Accessed December 8, 2021. nice.org.uk/guidance/cg90

64 Michaelis R, Tang V, Wagner JL. Cochrane systematic review and meta-analysis of the impact of psychological treatments for people with epilepsy on health-related quality of life. Epilepsia 2018;59(2):315-332. doi:10.1111/epi.13989

65 Michaelis R, Tang V, Wagner JL. Psychological treatments for people with epilepsy. Cochrane Database Syst Rev 2017;10(10):CD012081. doi:10.1002/14651858.CD012081.pub2

66 Michaelis R, Tang V, Goldstein LH. Psychological treatments for adults and children with epilepsy: evidence-based recommendations by the International League Against Epilepsy Psychology Task Force. Epilepsia 2018;59(7): 1282-1302. doi:10.1111/epi.14444

67 Gasparini S, Beghi E, Ferlazzo E. Management of psychogenic non-epileptic seizures: a multidisciplinary approach. Eur J Neuro 2019; 26(2):e205-e215. doi:10.1111/ene.13818

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

68 Kanemoto K, LaFrance WC, Duncan R. PNES around the world: where we are now and how we can close the diagnosis and treatment gaps-an ILAE PNES Task Force report. Epilepsia Open 2017;2(3):307-316. doi:10.1002/epi4.12060

69 LaFrance WC, Baird GL, Barry JJ. Multicenter pilot treatment trial for psychogenic nonepileptic seizures: a randomized clinical trial. JAMA Psychiatry 2014;71(9):997-1005. doi:10.1001/jamapsychiatry.2014.817

70 Goldstein LH, Robinson EJ, Mellers JDC. Cognitive behavioural therapy for adults with dissociative seizures (CODES): a pragmatic, multicentre, randomised controlled trial. Lancet Psychiatry 2020;7(6):491-505. doi:10.1016/S2215-0366(20)30128-0

71 Agrawal N, Gaynor D, Lomax A, Mula M. Multimodular psychotherapy intervention for nonepileptic attack disorder: an individualized pragmatic approach. Epilepsy Behav 2014;41:144-148. doi:10.1016/j.yebeh.2014.09.041

72 Mula M, Brodie MJ, de Toffol B, et al. ILAE clinical practice recommendations for the medical treatment of depression in adults with epilepsy. Epilepsia 2022;63(2):316-334. doi:10.1111/epi.17140

73 Mula M. The pharmacological management of psychiatric comorbidities in patients with epilepsy. Pharmacol Res 2016;107:147-153. doi:10.1016/j.phrs.2016.03.022

74 Italiano D, Spina E, Leon J. Pharmacokinetic and pharmacodynamic interactions between antiepileptics and antidepressants. Expert Opin Drug Metab Toxicol 2014;10(11):1457-1489. doi:10.1517/17425255.2014.956081

75 Alper K, Schwartz KA, Kolts RL, Khan A. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry 2007;62(4):345-354. doi:10.1016/j.biopsych.2006.09.023

76 Dunner DL, Zisook S, Billow AA, Batey SR, Johnston JA, Ascher JA. A prospective safety surveillance study for bupropion sustained-release in the treatment of depression. J Clin Psychiatry 1998;59(7):366-373. doi:10.4088/JCP.v59n0705

77 Steinert T, Fröscher W. Epileptic seizures under antidepressive drug treatment: systematic review. Pharmacopsychiatry 2018;51(4):121-135. doi:10.1055/s-0043-117962

78 Agrawal N, Mula M. Treatment of psychoses in patients with epilepsy: an update. Ther Adv Psychopharmacol 2019;9(2045125319862968). doi:10.1177/2045125319862968

79 National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults: prevention and management. Accessed December 8, 2021. nice.org.uk/guidance/cg178

80 Hasan A, Falkai P, Wobrock T. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry 2012;13(5):318-378. doi:10.3109/15622975.2012.696143

81 de Toffol B, Trimble M, Hesdorffer DC, et al. Pharmacotherapy in patients with epilepsy and psychosis. Epilepsy Behav 2018;88:54-60. doi:10.1016/j.yebeh.2018.09.001

82 Nickl-Jockschat T, Paulzen M, Schneider F, Grözinger M. Drug interaction can lead to undetectable serum concentrations of quetiapine in the presence of carbamazepine. Clin Neuropharmacol 2009;32(1):55. doi:10.1097/WNF.0b013e31816a1cc6

83 de Leon J, Santoro V, D'Arrigo C, Spina E. Interactions between antiepileptics and second-generation antipsychotics. Expert Opin Drug Metab Toxicol 2012;8(3):311-334. doi:10.1517/17425255.2012.660918

84 Williams AM, Park SH. Seizure associated with clozapine: incidence, etiology, and management. CNS Drugs 2015;29(2):101-111. doi:10.1007/s40263-014-0222-y

85 Brikell I, Chen Q, Kuja-Halkola R. Medication treatment for attention-deficit/hyperactivity disorder and the risk of acute seizures in individuals with epilepsy. Epilepsia 2019;60(2):284-293. doi:10.1111/epi.14640

86 Kerr MP, Mensah S, Besag F. International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. Epilepsia 2011;52(11):2133-2138. doi:10.1111/j.1528-1167.2011.03276.x

87 Quintas R, Raggi A, Giovannetti AM. Psychosocial difficulties in people with epilepsy: a systematic review of literature from 2005 until 2010. Epilepsy Behav 2012;25(1):60-67. doi:10.1016/j.yebeh.2012.05.016

88 Witt JA, Helmstaedter C. Cognition in epilepsy: current clinical issues of interest. Curr Opin Neurol 2017;30(2):174-179. doi:10.1097/WCO.0000000000000430

89 Wilson SJ, Baxendale S. The new approach to classification: rethinking cognition and behavior in epilepsy. Epilepsy Behav 2014;41:307-310. doi:10.1016/j.yebeh.2014.09.011

90 Sen A, Capelli V, Husain M. Cognition and dementia in older patients with epilepsy. Brain 2018;141(6):1592-1608. doi:10.1093/brain/awy022

91 Hermann B, Seidenberg M, Lee EJ. Cognitive phenotypes in temporal lobe epilepsy. J Int Neuropsychol Soc 2007;13(1):12-20. doi:10.1017/S135561770707004X

92 Dabbs K, Jones J, Seidenberg M, Hermann B. Neuroanatomical correlates of cognitive phenotypes in temporal lobe epilepsy. Epilepsy Behav 2009;15(4):445-451. doi:10.1016/j.yebeh.2009.05.012

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

93 Agah E, Asgari-Rad N, Ahmadi M. Evaluating executive function in patients with temporal lobe epilepsy using the frontal assessment battery. Epilepsy Res 2017;133:22-27. doi:10.1016/j.eplepsyres.2017.03.011

94 Elliott IM, Lach L, Smith ML. I just want to be normal: a qualitative study exploring how children and adolescents view the impact of intractable epilepsy on their quality of life. Epilepsy Behav 2005;7(4):664-678. doi:10.1016/j.yebeh.2005.07.004

95 Harden J, Black R, Chin RFM. Families' experiences of living with pediatric epilepsy: a qualitative systematic review. Epilepsy Behav 2016;60:225-237. doi:10.1016/j.yebeh.2016.04.034

96 Norman M, Wilson SJ, Baxendale S, et al. Addressing neuropsychological diagnostics in adults with epilepsy: Introducing the International Classification of Cognitive Disorders in Epilepsy: The IC CODE Initiative. Epilepsia Open 2021;6(2):266-275. doi:10.1002/epi4.12478

97 Baxendale S. Cognitive rehabilitation and prehabilitation in people with epilepsy. Epilepsy Behav 2020;106:107027. doi:10.1016/j.yebeh.2020.107027

98 Oh A, Thurman DJ, Kim H. Comorbidities and risk factors associated with newly diagnosed epilepsy in the U.S. pediatric population. Epilepsy Behav 2017;75:230-236. doi:10.1016/j.yebeh.2017.07.040

99 Robertson J, Hatton C, Emerson E, Baines S. Prevalence of epilepsy among people with intellectual disabilities: a systematic review. Seizure 2015;29:46-62. doi:10.1016/j.seizure.2015.03.016

100 Eaton C, Tarver J, Shirazi A. A systematic review of the behaviours associated with depression in people with severe-profound intellectual disability. J Intellect Disabil Res 2021;65(3):211-229. doi:10.1111/jir.12807

101 Murray G, McKenzie K, Murray A. The impact of contextual information on the emotion recognition of children with an intellectual disability. J Appl Res Intellect Disabil 2019;32(1):152-158. doi:10.1111/jar.12517

102 Ho FC, Lam CSC, Lo SK. Differences between students with comorbid intellectual disability and autism spectrum disorder and those with intellectual disability alone in the recognition of and reaction to emotions [published online August 5, 2020]. J Autism Dev Disord. doi:10.1007/s10803-020-04630-0

103 Joyce T, Globe A, Moody C. Assessment of the component skills for cognitive therapy in adults with intellectual disability. J Appl Res Intellec Disabil 2006 Mar;19(1):17-23. doi:10.1111/j.1468-3148.2005.00287.x

104 Dagnan D, Chadwick P, Proudlove J. Toward an assessment of suitability of people with mental retardation for cognitive therapy. Cognit Ther Res 2000;24(6):627-636. doi:10.1023/A:1005531226519

105 Scheffer IE, Berkovic S, Capovilla G. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512-521. doi:10.1111/epi.13709

106 Makiko K, Masumi I, Reiko O. Epidemiological study of Landau-Kleffner syndrome (LKS) in Japan. Brain Dev 2014;36(4):284-286. doi:10.1016/j.braindev.2013.04.012

107 Scheffer IE, Liao J. Deciphering the concepts behind "Epileptic encephalopathy" and "Developmental and epileptic encephalopathy." Eur J Paediatr Neurol 2020;24:11-14. doi:10.1016/j.ejpn.2019.12.023

108 Specchio N, Curatolo P. Developmental and epileptic encephalopathies: what we do and do not know. Brain 2021;144(1):32-43. doi:10.1093/brain/awaa371

109 McTague A, Cross JH. Treatment of epileptic encephalopathies. CNS Drugs 2013;27(3):175-184. doi:10.1007/s40263-013-0041-6

110 Weldon M, Kilinc M, Holder JL, Rumbaugh G. The first international conference on SYNGAP1-related brain disorders: a stakeholder meeting of families, researchers, clinicians, and regulators. J Neurodev Disord 2018;10(1):1-6. doi:10.1186/s11689-018-9225-1

111 Béjot Y, Yaffe K. Ageing population: a neurological challenge. Neuroepidemiology 2019;52(1-2):76-77. doi:10.1159/000495813

112 Arnaldi D, Donniaquio A, Mattioli P. Epilepsy in neurodegenerative dementias: a clinical, epidemiological, and EEG study. J Alzheimers Dis 2020;74(3):865-874. doi:10.3233/JAD-191315

113 Subota A, Pham T, Jetté N. The association between dementia and epilepsy: a systematic review and meta-analysis. Epilepsia 2017;58(6):962-972. doi:10.1111/epi.13744

114 Trevis KJ, Wilson SJ. Nonpharmacological management of epilepsy in adults with intellectual disabilities. In: Prasher VP, Kerr M, eds. Epilepsy and intellectual disabilities. Springer International Publishing; 2016:197-223.

115 Feldman L, Lapin B, Busch RM, Bautista JF. Evaluating subjective cognitive impairment in the adult epilepsy clinic: effects of depression, number of antiepileptic medications, and seizure frequency. Epilepsy Behav 2018;81:18-24. doi:10.1016/j.yebeh.2017.10.011

116 Rayner G, Siveges B, Allebone J. Contribution of autobiographic memory impairment to subjective memory complaints in focal epilepsy. Epilepsy Behav 2020;102:106636. doi:10.1016/j.yebeh.2019.106636

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.

117 Madore KP, Khazenzon AM, Backes CW. Memory failure predicted by attention lapsing and media multitasking. Nature 2020;587(7832): 87-91. doi:10.1038/s41586-020-2870-z

118 Buckley RF, Saling MM, Frommann I. Subjective cognitive decline from a phenomenological perspective: a review of the qualitative literature. J Alzheimers Dis 2015;48(suppl 1): S125-S140. doi:10.3233/JAD-150095

119 Mendez MF, Fras IA, Kremen SA, Tsai PH. False reports from patients with frontotemporal dementia: delusions or confabulations? Behav Neurol 2011;24(3):237-244. doi:10.3233/BEN-2011-0335

120 Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005;53(4):695-699. doi:10.1111/j.1532-5415.2005.53221.x

121 Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12(3):189-198. doi: 10.1016/0022-3956(75)90026-6

122 Wilson SJ, Baxendale S, Barr W. Indications and expectations for neuropsychological assessment in routine epilepsy care: report of the ILAE Neuropsychology Task Force, Diagnostic Methods Commission, 2013-2017. Epilepsia 2015;56(5):674-681. doi:10.1111/epi.12962

123 Gonzalez LM, Wrennall JA. A neuropsychological model for the pre-surgical evaluation of children with focal-onset epilepsy: an integrated approach. Seizure 2020;77:29-39. doi:10.1016/j.seizure.2018.12.013

124 Baxendale SA, Wilson SJ, Baker GA. Ten things every neurologist needs to know about neuropsychological assessments and interventions in people with epilepsy. Eur J Neurol 2020;27(2):215-220. doi:10.1111/ene.14104

125 Sirven JI, Ozuna J, America EF. Diagnosing epilepsy in older adults: what does it mean for the primary care physician? Geriatrics 2005; 60(10):30-35.

126 Jacobs CS, Willment KC, Sarkis RA. Non-invasive cognitive enhancement in epilepsy. Front Neurol 2019;10(167). doi:10.3389/fneur.2019.00167

127 Hamberger MJ, Palmese CA, Scarmeas N. A randomized, double-blind, placebo-controlled trial of donepezil to improve memory in epilepsy. Epilepsia 2007;48(7):1283-1291. doi:10.1111/j.1528-1167.2007.01114.x

128 Baxendale S, Thompson P. Red flags in epilepsy surgery: identifying the patients who pay a high cognitive price for an unsuccessful surgical outcome. Epilepsy Behav 2018;78:269-272. doi:10.1016/j.yebeh.2017.08.003

129 Ozanne A, Verdinelli C, Olsson I. Callosotomy in children—parental experiences reported at long-term follow-up. Epilepsy Behav 2018;86: 91-97. doi:10.1016/j.yebeh.2018.06.020

130 Ozanne A, Verdinelli C, Olsson I. Parental experiences before and long-term after their children's hemispherotomy—a population-based qualitative study. Epilepsy Behav 2016;60: 11-16. doi:10.1016/j.yebeh.2016.04.025

131 Wilson SJ, Rayner G, Pieters J. Positive illusions determine quality of life in drug-resistant epilepsy. Epilepsia 2020;61(3):539-548. doi:10.1111/epi.16455

132 Ponsford J, Lee NK, Wong D. Factors associated with response to adapted cognitive behavioral therapy for anxiety and depression following traumatic brain injury. J Head Trauma Rehabil 2020;35(2):117-126. doi:10.1097/HTR.0000000000000510

133 Lloyd BP, Kennedy CH. Assessment and treatment of challenging behaviour for individuals with intellectual disability: a research review. J Appl Res Intellect Disabil 2014;27(3): 187-199. doi:10.1111/jar.12089

134 Kerr C, Nixon A, Angalakuditi M. The impact of epilepsy on children and adult patients' lives: development of a conceptual model from qualitative literature. Seizure 2011;20(10):764-774. doi:10.1016/j.seizure.2011.07.007

135 Trinka E, Kawn P, Lee B, Dash A. Epilepsy in Asia: disease burden, management barriers, and challenges. Epilepsia 2019;60(S1):7-21. doi:10.1111/epi.14458

136 Cross JH, Kwon C, Asadi-Pooya AA, Balagura G, Gomez-Iglesias P, et al. Epilepsy care during the COVID-19 pandemic. Epilepsia 2021;62: 2322-2332. doi:10.1111/epi.1704

137 Sanchez N, Kajumba M, Kayegira J, et al. Stakeholder views of the practical and cultural barriers to epilepsy care in Uganda. Epilepsy Behav 2021;114:107314. doi:10.1016/j.yebeh.2020.107314

Copyright © American Academy of Neurology. Unauthorized reproduction of this article is prohibited.