Epilepsy and Neuropsychological Comorbidities

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ABSTRACT

Purpose of Review: Epilepsy is a chronic disorder with several associated comorbidities requiring timely recognition and treatment. This article discusses aspects of cognitive impairment; psychiatric disorders including depression, anxiety, and psychosis; and health-related quality-of-life issues pertaining to patients with epilepsy.

Recent Findings: Cognitive problems in epilepsy may be present early in the disease course. Advances in imaging techniques are allowing correlation of structure and function as they relate to cognitive impairment in epilepsy. The relationship between epilepsy, depression, and anxiety is increasingly recognized, and these psychiatric comorbidities may affect suicide risk, patient-reported adverse antiepileptic drug effects, and quality of life. Psychiatric disorders are underrecognized and undertreated in patients with epilepsy.

Summary: Physicians who treat patients with epilepsy should be aware of the major impact that cognitive impairment and psychiatric comorbidities have on these patients. Identifying and treating these comorbidities in epilepsy patients is just as important as seizure treatment.


FACTORS AFFECTING COGNITION IN PATIENTS WITH EPILEPSY

Many factors can affect cognition in patients with epilepsy: etiology of the seizures; seizure type and frequency; age of epilepsy onset; duration and severity of seizures; structural cerebral lesions responsible for the development of epilepsy; cerebral damage due to prolonged seizures or status epilepticus; disturbance of cerebral function in the interictal, ictal, or postictal states; sequelae of epilepsy surgery; side effects of antiepileptic drugs (AEDs); and psychosocial factors. This section reviews some of these factors.

Neuropsychological and Pathologic Substrates in New-Onset and Chronic Epilepsy

Cognitive impairment may be present even before a first seizure. A new study addressing cognition in an adult population with newly diagnosed, untreated epilepsy showed a high frequency of cognitive deficits, with approximately 75% having deficits in attention, executive function, or memory. Patients underreported their cognitive deficits, with only 28.7% reporting attention and 25.1% reporting memory problems, contrasting with objective neuropsychological performance impairments found considerably more frequently; 49.4% had attentional and executive dysfunction, and 47.8% had memory deficits. Lower educational background and the presence of lesional epilepsy were associated with worse objective performance in attention and executive functions, and generalized tonic-clonic seizures were associated with worse objective memory performance.
Cognitive impairment early in the course of epilepsy may relate to many factors, including interictal dysfunction, seizures, and the underlying pathology. Cognitive impairments in epilepsy appear to surpass cognitive deficits seen in the early stages of other cerebral diseases (eg, Parkinson disease, multiple sclerosis). The discrepancy between subjective perception and objective measures of cognitive performance in epilepsy patients suggests that a different approach may be needed when evaluating these patients. Asking patients about cognitive deficits may not be sufficient. Instituting screening tests for cognition at initial clinical presentation could allow later comparisons to detect improvement or progression over the course of the disorder and provide opportunities for early intervention strategies to maximize cognitive functioning.

In a population of adult Veterans Administration (VA) patients with newly diagnosed, untreated epilepsy, there were significant deficits compared to the control population, demonstrating impaired psychomotor speed, decreased sustained attention, and worse mood. Children with recent-onset idiopathic epilepsy show mild diffuse neuropsychological impairment and academic difficulties at the time of diagnosis. Some children had academic underachievement before their first seizure. Although quantitative volumetric MRIs did not differ between groups overall, reductions in the gray matter of the left parietal and occipital lobes correlated with decreased cognitive performance and academic problems in children with epilepsy compared with controls and patients with epilepsy without academic problems. Further, high white matter volumes correlated with better cognitive performance in control patients but not in epilepsy patients.

About 20% of epilepsy patients with chronic temporal lobe epilepsy were found to have adverse cognitive outcomes. Patients with lower baseline IQ, longer epilepsy duration, older age, and smaller baseline left hippocampal volume were most susceptible to cognitive decline. Domains most adversely affected over time were memory, psychomotor speed, executive function, and naming.

Seizure Effects
Recurrent seizures in patients with temporal lobe epilepsy are correlated with hippocampal volume loss and memory impairment. Repeat volumetric MRIs (mean 3.4 years, range 2.5–5.2 years) in 12 patients with unilateral temporal lobe epilepsy revealed progressive hippocampal atrophy (mean 10% volume loss) in patients with continued seizures. Longer epilepsy duration is associated with worse cognition. A cross-sectional study of 209 patients with unilateral temporal lobe epilepsy showed lower IQ in patients having greater than 30-year seizure duration, as compared to those having an epilepsy duration between 15 and 30 years or those with less than 15-year seizure durations. The frequency and severity of continued seizures can also negatively affect cognition. A longitudinal study of 102 patients with non-surgical temporal lobe epilepsy followed for between 2 and 10 years showed loss of memory function in 50% of the patients and loss of executive function in 28%, associated with worsened seizure frequency and severity.

Treatment Effects
Antiepileptic drugs affecting cognitive abilities in adults. Epilepsy patients often report that their AEDs impair their thinking and function at home, work, or school. Patients may
KEY POINTS

- Some antiepileptic drugs have more cognitive side effects than others. Gabapentin, lamotrigine, levetiracetam, and tiagabine affect cognition the least, while benzodiazepines, phenobarbital, topiramate, and zonisamide affect it most. Carbamazepine, oxcarbazepine, phenytoin, and valproate pose an intermediate risk.

- Antiepileptic drug titration rate, final dose, blood levels, the specific antiepileptic drug used, and polytherapy can affect cognition in individual epilepsy patients.

- Cognitive abilities most affected by antiepileptic drugs are processing speed, sustained attention, dual processing, verbal learning, verbal fluency, and memory.

- Patients may not recognize cognitive effects of antiepileptic drugs until after a drug is discontinued.

habituate to the perceived cognitive effects of AEDs and only notice untoward side effects in retrospect after discontinuing an AED. Cognitive side effects of AEDs can depend on titration rate, dose, blood level, and numbers of AEDs used. AED polytherapy increases the risk of cognitive adverse effects compared to monotherapy. Different AEDs have different effects on cognition, and patients have variable susceptibility to AED cognitive side effects. The cognitive abilities most likely affected by AEDs include processing speed, sustained attention, dual processing, verbal learning, verbal fluency, and memory. Barbitalates, benzodiazepines, topiramate, and zonisamide have the most negative cognitive side-effect profiles. A study looking at cognitive effects of older AEDs in healthy adults showed that phenobarbital had greater negative cognitive effects than phenytoin or valproate. Carbamazepine, phenytoin, and valproate have similar modest adverse cognitive effects. Several of the newer AEDs have fewer cognitive side effects than the older AEDs. Studies directly comparing AEDs indicate that gabapentin, lamotrigine, and levetiracetam have less impact on cognition compared to carbamazepine and topiramate. No significant differences were present between oxcarbazepine and phenytoin except for higher score of vigor on the Profile of Mood States scale for oxcarbazepine. Topiramate can produce language problems (word-finding difficulty and impaired language fluency), memory problems, psychomotor slowing, and somnolence. Zonisamide has been associated with sedation, impaired learning, and dose-related negative effects on verbal memory and fluency and executive function. In the VA Cooperative Geriatric Epilepsy Study, which followed almost 600 new-onset elderly epilepsy patients over 1 year, lamotrigine had better overall tolerability than either gabapentin or carbamazepine (which was the worst-tolerated AED).

Antiepileptic drugs, cognition, and children. The cognitive side effects of AEDs in children have not been well studied in prospective randomized trials. Current studies have inadequate length to determine long-term AED effects on neuropsychological function and school performance. An extensive review revealed strong evidence for negative effects of phenobarbital on IQ, attention, and processing efficiency. Carbamazepine, phenytoin, and valproate are essentially equivalent in producing a moderate degree of psychomotor slowing, with smaller effects on IQ and memory than phenobarbital. The effects of newer AEDs in children are essentially unknown because of methodologic limitations, inadequate study duration, and absence of comparative studies. The current studies available show that behavioral side effects can occur. Gabapentin and lamotrigine have been associated with irritability and aggression. Levetiracetam has been associated with somnolence, nervousness, emotional lability, and hyperactivity, although some children actually had improved cognition, concentration, alertness, and behavior. Oxcarbazepine was associated with somnolence. Topiramate has been associated with emotional lability, fatigue, and impaired attention, concentration, and memory. Zonisamide has been associated with a higher risk of psychotic episodes. The long-term cumulative and permanent effects of AED treatment on learning and memory in children remain to be adequately elucidated.

Breast-feeding while on AEDs does not appear to negatively affect cognitive outcomes in children at age 3 who were already exposed in utero. A study
of 199 children exposed to carbamazepine, lamotrigine, phenytoin, or valproate during breast-feeding found no difference in those breast-fed (n = 99) versus non-breast-fed (n = 98) for all AEDs combined and each AED individually.\textsuperscript{22}

Antiepileptic drugs affecting cognitive abilities in the unborn child. Neurodevelopment of children in women with epilepsy can be affected by maternal seizure type, the number of seizures during pregnancy, IQ and educational level of the parents, specific AEDs and other drugs used during pregnancy, and other environmental factors. A large prospective study enrolled 309 mother-child pairs during pregnancy and examined cognitive outcome in children at 3 years old after fetal monotherapy exposure to carbamazepine, lamotrigine, phenytoin, or valproate. Fetal valproate exposure was associated with decreased IQ at age 3. Mean IQs were 98 in carbamazepine, 101 in lamotrigine, 99 in phenytoin, and 92 in valproate (significantly lower than each of the other three drugs). Valproate exhibited dose-related effects, and doses of 900 mg/d or more were related to increased risk of birth deficits and decreased IQ.\textsuperscript{23} A follow-up investigation of the same cohort at 6 years of age revealed that IQ, verbal, nonverbal, memory, and executive abilities were impaired in a dose-dependent manner in children exposed in utero to valproate.\textsuperscript{24} Additional studies are needed to confirm these findings. Fetal exposure to valproate has also been associated with behavioral dysfunction\textsuperscript{25} and increased risk of autistic spectrum disorder.\textsuperscript{26,27} A practice parameter from the American Academy of Neurology recommends avoiding valproate if possible in women with epilepsy during pregnancy to reduce the risk of poor cognitive and verbal outcomes (Level B evidence), and avoiding phenytoin (Level C evidence) and phenobarbital (Level C evidence) in women with epilepsy during pregnancy to reduce the risk of poor cognitive outcomes.\textsuperscript{27} There are not enough data regarding cognitive risk associated with fetal exposure to the newer AEDs as monotherapy, but polytherapy with any of the AEDs should be avoided whenever possible.\textsuperscript{28} Case 6-1 illustrates counseling issues involving a young woman regarding teratogenic and cognitive effects of AEDs on the developing fetus, especially valproic acid.

Epilepsy Surgery
Temporal lobe epilepsy surgery. Temporal lobe epilepsy surgery may improve cognition by rendering the patient seizure free and reducing the overall AED burden over time. However, the removal of nonlesional or normal functioning tissue during standard anterior temporal lobectomy or selective amygdalohippocampectomy can pose cognitive risks and impair postoperative memory function, naming, and facial recognition.\textsuperscript{29,30} Predictors of cognitive decline after epilepsy surgery include (1) anterior temporal lobectomy on the language dominant side, (2) older age at seizure onset, (3) older age at epilepsy surgery, (4) higher preoperative cognitive performance, (5) lack of hippocampal atrophy or sclerosis, and (6) poor postoperative seizure control.\textsuperscript{31} In addition, the lack of evidence for unilateral temporal lobe dysfunction on the side of seizure onset—supported by a normal positron emission tomography (PET) scan, temporal lobe activation on functional MRI (fMRI) memory task, or Wada testing—places the patient at increased risk of postoperative memory decline. Neuropsychological effects after anterior temporal lobectomy on the left side (or language-dominant hemisphere)
may include deficits in naming and verbal memory, and on the right side may include deficits in nonverbal memory, which occur less consistently and are usually less clinically significant. In a recent study, 15 patients without lesions on MRI and negative histopathology underwent temporal lobe epilepsy surgery; nine patients had a standard anterior temporal lobectomy, while six patients had either a partial temporal lobectomy or selective amygdalohippocampectomy. Compared to 15 control patients with lesions on MRI (which includes mesial temporal sclerosis) and positive postoperative histopathology, patients without MRI lesions or positive histopathology had better preoperative memory (ie, baseline performance was close to normal), but had up to a threefold increased risk to show a verbal learning loss compared to the control group. Patients with an MRI lesion and positive histopathology did not have a significant change in pre- or postoperative memory performance. These findings suggest that resecting nonlesional brain tissue puts patients at risk for postoperative memory decline after temporal lobe epilepsy surgery.32

Neurostimulation

Vagus nerve stimulation (VNS), responsive neurostimulation, and deep brain stimulation do not appear to be complicated by cognitive impairments. In a VNS study, there were no cognitive side effects of VNS, and some patients had improved cognition related to decreased seizure frequency and decreased dosages of AEDs.33 Responsive neurostimulation is a device that detects seizure activity within the brain and delivers short electrical pulses to the brain through one to two implanted leads of electrodes,
which can abort a seizure before the patient experiences clinical symptoms. In a responsive neurostimulation study, there was no worsening of neuropsychological performance at the end of the blinded evaluation period or at 1 or 2 years postimplantation. Some patients had statistically significant improvements in cognition at 1 and 2 years, which had a positive impact on their perceived quality of life. In a deep brain stimulation trial, neuropsychological testing did not show any differences between the groups in terms of cognition and mood.

Psychosocial Factors
Epilepsy is associated with many psychosocial challenges, including the potential inability to drive, lack of educational and vocational options, social isolation, physical restrictions, living with stigma, low self-esteem, and impaired family dynamics, all of which can lead to poor quality of life. Driving appears to be a major concern, cited by almost 70% of patients, followed by concerns about independence, work, embarrassment, medication dependence, mood, and safety.

Mood, specifically depression, can also have a major impact on patients with epilepsy. A double-blind, randomized trial of healthy volunteers and epilepsy patients on topiramate or lamotrigine demonstrated that the perception of cognitive side effects was more related to mood disturbance than to actual impairments in objective performance. These data suggest that physicians should consider mood as a significant factor when patients report subjective cognitive problems.

PSYCHIATRIC COMORBIDITIES IN PATIENTS WITH EPILEPSY

Major Depressive Disorder
Features and incidence. About 30% of patients with medically refractory epilepsy develop depressive symptoms that are clinically significant during their lifetime. The frequency of depression among medically refractory epilepsy populations can be as high as 50%, while in patients with controlled seizures the frequency is closer to 10%. Compared to the general population, depression in patients with medically refractory epilepsy is 3 to 10 times more common. There is a bidirectional relationship between depression and epilepsy, such that patients with epilepsy are more likely to develop depression than people in the general population, while patients with major depressive disorder are 4 to 7 times more likely to experience an unprovoked seizure. Factors that can increase the risk of depression in epilepsy patients include the existence of nonlesional partial epilepsy, increased frequency and duration of seizures, and the negative psychotropic effects of some AEDs. Depression in patients with epilepsy is also thought to have an underlying neurobiological basis and not necessarily relate to poor seizure control or other negative psychosocial factors. From a structural and neurobiological standpoint, the pathogenesis of depression in epilepsy may relate to dysfunction in the prefrontal, inferior frontal, striatal, and mesial temporal regions. A neuroimaging study in patients with temporal lobe epilepsy indicated that patients with mesial temporal sclerosis had significantly higher depression scores than other temporal lobe epilepsy patients. In addition, higher Beck Depression Inventory scores correlated with temporal and frontal lobe hypoperfusion on single-photon emission computed tomography (SPECT). Interestingly, treatment of depression via pharmacologic or psychological therapies has been shown to normalize

KEY POINTS
- Neurostimulation in epilepsy patients does not appear to adversely affect cognition.
- Subjective patient cognitive complaints should raise a red flag to the clinician that a possible mood disorder is present.
KEY POINTS

- A bidirectional relationship exists between epilepsy and depression, likely due to dysfunction in overlapping brain systems.
- Depression is underdiagnosed and undertreated in epilepsy patients.
- Most antiepileptic drugs can produce negative behavioral effects. However, some antiepileptic drugs are used in a variety of psychiatric disorders (eg, carbamazepine, lamotrigine, and valproate are used in bipolar disorder).
- A history of a mood disorder or depression is a significant risk factor for developing suicidality in patients with epilepsy.
- Since suicidal ideation is common in outpatient epilepsy clinic settings, physicians should ask about suicidal thoughts during routine visits in order to identify patients for interventions to decrease the risk of suicide in this population.
- Patients with epilepsy frequently experience depression, which should be treated aggressively to improve their quality of life even if they have subsyndromic depressive episodes that do not meet Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria for major depressive disorder.

Brain-metabolic abnormalities in patients without epilepsy.\textsuperscript{38,39} About 30% of patients may experience major depression after epilepsy surgery, with the major risk factors of postsurgical depression being (1) preoperative history of depression and (2) poor family dynamics postoperatively.\textsuperscript{36} Prompt diagnosis and successful treatment of psychiatric comorbidities are important to maximize the benefits of epilepsy surgery.\textsuperscript{50}

Depression is underdiagnosed and undertreated in epilepsy patients. Routine screening for depression and periodic psychiatric and psychosocial assessments during office visits should be done at least once per year to optimize care in epilepsy patients.\textsuperscript{50,51}

Commonly used screening tests for depression are the Beck Depression Inventory-II, the Center for Epidemiologic Study Depression Screen, and the Neurologic Disorders Depressive Inventory in Epilepsy.

The coexistence of epilepsy and psychogenic nonepileptic spells (PNES) is not mutually exclusive. Up to 30% of patients treated at tertiary care epilepsy centers have both disorders. The cause of PNES may be unknown or linked with a previous history of abuse, post-traumatic stress disorder (PTSD) in veterans,\textsuperscript{52} increased rate of some personality disorders, and interestingly a decreased rate of mood and anxiety disorders.\textsuperscript{53} Although there are no evidence-based treatment protocols currently available, the most effective treatment studied for PNES is cognitive behavioral therapy.\textsuperscript{54}

Risk of suicide. Suicide is increased in epilepsy patients, in whom it is seen up to 25 times more frequently than in the general population.\textsuperscript{55} Suicide and suicide attempts occur in between 5.0% and 14.3% of epilepsy patients, compared to 1.0% to 4.6% in the general population.\textsuperscript{56} The most significant risk factor for suicidality is a history of a mood disorder.\textsuperscript{57} Suicidal ideation in epilepsy patients in an outpatient setting is common. A recent study found that 11.9% of epilepsy patients had recent suicidal ideation.\textsuperscript{58} Depression was the only independent predictor of suicidal ideation; other factors such as the patient’s age, gender, seizure type and frequency, duration of epilepsy, medication toxicity, and decreased quality of life were not predictive of it. Interestingly, suicidal ideation was present in only about one-quarter of patients who were euthymic or had only mild depressive symptoms.\textsuperscript{59}

Seizure freedom after epilepsy surgery does not necessarily reduce the risk of suicide. A report of 316 patients who underwent epilepsy surgery noted four suicides in patients who had been seizure free for over 1 year after surgery. Of these four patients, only one patient had Beck Depression Inventory scores in the depressive range, two patients had severe anxiety symptoms, and two had discontinued the potentially mood-stabilizing AED lamotrigine postoperatively. The authors posit that changes in neurotransmitters or injury to the limbic system due to surgery may be possible mechanisms behind suicide after epilepsy surgery.\textsuperscript{58} Asking epilepsy patients about suicidal ideation during their clinical visits is crucial and may mitigate the risk of attempted and completed suicides in this population.

In January of 2008, the US Food and Drug Administration (FDA) issued a class label warning for all AEDs indicating a 1.8-fold increased risk of suicidal ideation or behaviors and recommended that a handout describing this risk should be given to patients when an AED is prescribed. The FDA warning was based on a meta-analysis of data from 199 clinical trials involving patients taking AEDs.
for epilepsy, psychiatric conditions, and pain. However, there are several problems associated with the FDA’s analysis of AEDs and suicide risk: (1) the data were not collected in a systematic and prospective manner; (2) all AEDs were lumped together in the analysis, and the risk of suicidality was treated as a class effect despite three AEDs (carbamazepine, valproate, and felbamate) showing no increased risk; and (3) the risk of suicidality was greatest in epilepsy patients (odds ratio [OR] 3.53) rather than in those taking AEDs for psychiatric disorders (OR 1.51) or other disorders (OR 1.87). Given that suicide and depression are more prevalent among patients with epilepsy, the role of AEDs as an independent factor in promoting suicide remains in doubt.

Preictal, ictal, and postictal major depressive disorder; interictal dysphoric disorder; and subsyndromic depressive episodes. Depression in patients with epilepsy can occur in the preictal, ictal, or postictal state. Preictal depression is characterized by dysphoric mood preceding a seizure for hours or days. Ictal depression is rare and characterized by brief, stereotyped episodes of depression that occur out of context and are the main ictal symptom, manifesting as a simple partial seizure. Postictal depression occurs in almost 50% of patients with medically refractory epilepsy and is characterized by symptoms of depression occurring within 5 days of a seizure and for a median duration of 24 hours after a seizure. Interictal dysphoric disorder (IDD) is a clinically separate entity that has some features overlapping with major depressive disorder (MDD). The term was coined in 2000 and consists of eight key symptoms grouped into three major categories (labile depressive symptoms, labile affective symptoms, and “specific” symptoms) with defined criteria. The Interictal Dysphoric Disorder Inventory (IDDI) is used in clinical studies to diagnose and evaluate IDD symptoms. As opposed to MDD, in which the clinical course is chronic with stable symptoms occurring over a 2-week period, IDD has a rapidly fluctuating course. Overlapping symptoms of IDD with MDD may be depressed mood, fatigue, and changes in sleep pattern. However, IDD is also characterized by prominent irritability, anhedonia, hopelessness, helplessness, fear, labile mood, and anxiety. IDD also needs to be distinguished from peri-ictal dysphoric symptoms. A subsyndromic depressogenic episode (SSDE) is defined as a score of 12 or above on the Beck Depression Inventory-II and a score of 16 or above on the Center for Epidemiologic Study Depression Screen. Patients who meet diagnostic criteria for a SSDE should be aggressively treated to avoid negative impact on quality of life, even when they do not meet Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria for MDD (Case 6-2). Identifying the relationship between MDD, SSDE, and IDD is still a work in progress. IDD as a distinct clinical entity is still a matter of debate and needs to be clarified with future research. Symptoms mimicking SSDE and IDD can also arise due to iatrogenic effects. Case 6-2 illustrates the importance of knowing which AEDs can cause negative mood-related side effects and instead using AEDs that may benefit mood.

Treatment of major depressive disorder. Contrary to common belief, treatment with antidepressants at therapeutic doses rarely causes worsening of seizures in patients with epilepsy, especially with selective serotonin reuptake inhibitors (SSRIs). This risk is very small for SSRIs, and the benefits of...
pharmacotherapy for depression outweigh the risk. When assessing an epilepsy patient with depression, it is important to note whether AEDs with positive psychotropic properties (ie, carbamazepine, lamotrigine, valproate) have recently been discontinued, or whether AEDs with negative psychotropic properties (ie, benzodiazepines, felbamate, levetiracetam, phenobarbital, primidone, tiagabine, topiramate, vigabatrin, zonisamide) have been recently added or the dosage increased.

SSRIs or cognitive behavioral therapy should be considered first-line treatments for MDD in patients with epilepsy. Citalopram and sertraline have no or minimal pharmacokinetic interactions with AEDs. Bupropion should be avoided whenever possible in patients with epilepsy because of its proconvulsant properties; if used, doses should be limited to below 150 mg/d to prevent seizure worsening. Patients in whom SSRI treatment fails can be tried on serotonin and norepinephrine reuptake inhibitors, such as venlafaxine. Tricyclic antidepressants should be considered second-line agents because of their cardiotoxic effects and potential complications resulting from overdoses. There have been reports of tricyclic antidepressant–induced seizures in patients on therapeutic doses who were slow metabolizers of the drug. Tricyclic antidepressants can be used in patients with epilepsy if one “starts low and goes slow” to avoid causing or exacerbating seizures. Monoamine oxidase inhibitors should be considered third-line agents and prescribed by an experienced physician, because of potentially harmful side effects. Patients with severe depression for whom antidepressant treatment fails may be considered candidates for electroconvulsive therapy (ECT), which is not contraindicated.67 Psychological therapies such as cognitive behavioral therapy should also be included, along with pharmacotherapy.

Case 6-2

A self-referred 67-year-old patient presented with a history of esophageal cancer 4 years ago, which was cured by resection and chemotherapy. Six months before presentation, he had the onset of brief spells of unresponsiveness. He had been evaluated by three neurologists and undergone three MRIs, two magnetic resonance angiograms, and three routine EEGs, all of which were normal. He was started on phenytoin 200 mg/d (resulting in a blood level of 10 µg/mL), and his spells, now recognized as likely to be complex partial seizures, completely resolved. However, a month later, he reported cognitive side effects. When offered several alternative antiepileptic drugs (AEDs), he chose levetiracetam. A month later, he remained seizure free on levetiracetam 500 mg twice-daily monotherapy. However, his wife was distraught because the patient had developed irritability shortly after levetiracetam was begun, although he seemed unaware of this change in personality. He was then converted to lamotrigine 100 mg twice a day and remained seizure free, and his irritability and dysphoria resolved.

Comment. This case illustrates the importance of choosing AEDs based on their side-effect profile. Patients may be unable to tolerate specific AEDs because of adverse effects on mood and cognition. In this case, all three AEDs controlled the patient’s seizures, but lamotrigine was the most effective AED in controlling the seizures without cognitive or mood side effects.

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as a helpful treatment strategy for patients with epilepsy, which teaches coping strategies and addresses psychosocial stressors.41

Anxiety Disorders
The prevalence of anxiety disorders in patients with medically refractory partial epilepsy is about 19%.68 The stigma of epilepsy, lack of control over the occurrence of seizures, and lack of education regarding seizures and epilepsy correlate with the development of anxiety.37 In addition, patients with symptomatic partial epilepsy, those with frequent seizures, and women with epilepsy are more prone to develop anxiety disorders.69 Patients may also develop postictal symptoms of anxiety, panic, agoraphobia, compulsions, and self-consciousness that usually last 6 to 24 hours after a seizure.70

Anxiety and mood disorders are frequent comorbidities in patients with epilepsy, and those patients with either anxiety/MDD or anxiety/SSDE have a worse quality of life than those with anxiety or depressive disorders alone.67 The presence of comorbid anxiety and mood disorders increases the frequency of reported AED-related adverse events.71 The treatment of anxiety disorders may include cognitive behavioral therapy, SSRIs, benzodiazepines, or buspirone.

Psychosis
Psychotic disorders occur in approximately 7% of patients with medically refractory partial epilepsy.72 Psychosis may be interictal or postictal. Interictal psychosis in patients with epilepsy is different from schizophrenia. It is chronic and less severe. Patients retain insight and personality, respond better to treatment, and lack the negative symptomatology seen in typical schizophrenia.73 Postictal psychosis occurs most commonly 48 to 72 hours after a seizure cluster and is significantly associated with bilateral independent seizure foci.74 Patients with prior psychiatric hospitalizations75 and a high prevalence of mood disorders in first- and second-degree relatives76 are at higher risk of developing postictal psychosis. Psychosis may also uncommonly occur as an AED adverse effect, due to treatment with zonisamide, topiramate, or levetiracetam, or due to benzodiazepine withdrawal. The treatment of postictal psychosis involves a short course of low-dose benzodiazepines or neuroleptics, such as quetiapine or risperidone. Case 6.3 discusses the rare concept of paradoxical (forced) normalization. In forced normalization, seizures decrease and the EEG recording normalizes (ie, reduced epileptiform activity) during the psychotic episode. The opposite occurs during nonpsychotic periods. Paradoxical normalization is the same phenomenon, but does not require EEG recordings, only the change in seizures.

EPILEPSY AND HEALTH-RELATED QUALITY OF LIFE
Relation to Seizure Freedom and Epilepsy Surgery
Patients with medically refractory partial epilepsy have a poorer health-related quality of life (HRQOL) than seizure-free patients. Epilepsy patients who were seizure free for 12 months or more after epilepsy surgery had better HRQOL than patients with other chronic health conditions (ie, hypertension, diabetes, heart disease, and depression).77 On the contrary, patients with ongoing complex partial or convulsive seizures postoperatively reported a worse HRQOL than patients with other chronic disorders. Even patients with continued simple partial seizures had similar HRQOL scores as diabetic and heart

KEY POINTS
- The US Food and Drug Administration issued a class warning for suicidal ideation and behaviors for antiepileptic drugs used for any purpose. Methodologic concerns have been raised for this conclusion.
- Coexisting depression and anxiety disorders in patients with epilepsy decrease quality of life and are associated with the frequency of reported antiepileptic drug–related adverse events.
disease patients in terms of social function and emotional well-being. Another study demonstrated that seizure freedom within the previous 6 months predicted a better quality of life. Some studies suggest that epilepsy surgery, independent of seizure freedom, can improve HRQOL within the first 6 months. After epilepsy surgery, HRQOL scores increased in relation to the duration of seizure/aura freedom and stabilized after 2 years. After 2 years of seizure freedom, HRQOL scores approach that of a normal age-matched population. However, not all patients after epilepsy surgery experience improved HRQOL. Neuropsychological deficits, particularly verbal memory decline, also appear to interact with seizure outcomes in determining HRQOL after epilepsy surgery. In one pivotal study, HRQOL improved in patients who were rendered seizure free by surgery, despite verbal memory impairments. However, when patients with verbal memory decline did not become seizure free after surgery, HRQOL declined postoperatively.

**Relation to Mood**

Recent studies of HRQOL in refractory epilepsy patients suggest that mood and depression are the strongest predictors of HRQOL. Neuropsychological deficits, particularly verbal memory decline, also appear to interact with seizure outcomes in determining HRQOL after epilepsy surgery. In one pivotal study, HRQOL improved in patients who were rendered seizure free by surgery, despite verbal memory impairments. However, when patients with verbal memory decline did not become seizure free after surgery, HRQOL declined postoperatively.

**Case 6-3**

A 42-year-old woman with medically refractory epilepsy (independent left and right temporal lobe seizure onsets) presented with daily complex partial seizures and weekly generalized tonic-clonic seizures. She also had severe depression, anxiety, and psychosis with paranoid delusions and hallucinations of the devil telling her to harm herself. Her medications on presentation were carbamazepine 200 mg 3 times a day, gabapentin 300 mg 3 times a day, phenobarbital 60 mg at bedtime, and diazepam 1 mg 4 times a day. When treated with tricyclic antidepressants or older neuroleptics, her seizures increased. When treated with increased antiepileptic drug (AED) dosages or additional AEDs, her psychosis worsened. Her history was consistent with the rare phenomenon of paradoxical (or forced) normalization. Over the course of months, the patient underwent several AED and psychotropic medication changes, including addition of risperidone and paroxetine with small dose increases; taper and discontinuation of diazepam, gabapentin, and phenobarbital; dose adjustment of carbamazepine; and gradual titration of adjunctive lamotrigine and clonazepam, resulting in the following final regimen: carbamazepine 400 mg twice a day, lamotrigine 300 mg twice a day, clonazepam 1 mg 3 times a day, paroxetine 40 mg/d, and risperidone 3 mg/d. Her delusions and hallucinations were subsequently well controlled, her depression and anxiety markedly improved, her convulsions were controlled, and her partial seizures were reduced to one per month.

**Comment.** This patient’s case illustrates the complexity of managing epilepsy patients with coexisting mood and psychotic disorders. The rare phenomenon of paradoxical normalization can occur in these patients, whereby psychotic episodes emerge when seizures decrease but resolve when seizures increase. In this patient, finding the right balance of AEDs with positive effects on mood and the treatment of anxiety, depression, and psychosis with appropriate medication at effective doses controlled both the epilepsy and psychiatric disorders more effectively.
of HRQOL. Not only do epilepsy patients with MDD have a worse quality of life than asymptomatic patients, but patients with anxiety disorders, SSDEs, and coexisting MDD and anxiety disorders also have poorer quality of life. Identifying depression in patients with epilepsy, which is currently underdiagnosed and undertreated, can have a significant impact on optimizing treatment outcomes.

Relation to Antiepileptic Drug Toxicity

In addition to seizure, surgery, and mood-related factors, AED side effects and toxicity can negatively affect HRQOL in patients with epilepsy. One study showed that scores on the adverse events profile (AEP) were strongly correlated with Quality of Life in Epilepsy Inventory-89 (QOLI-89) scores, and using the AEP to track the adverse effects of AEDs allowed physicians to make medication adjustments that improved patients’ AEP and HRQOL scores. Identifying AED adverse effects can have a substantial impact on the health status of patients even when medications and epilepsy surgery have failed to do so.

REFERENCES


KEY POINTS

- Psychiatric disorders in epilepsy are common and should be diagnosed and treated to improve patients’ quality of life.
- Identifying and treating depression and adverse effects of antiepileptic drugs can have a major positive impact on the lives of epilepsy patients.
Epilepsy and Neuropsychological Comorbidities


44. Drevets WC. Neuroimaging and neuropathological studies of depression: implications for the cognitive-emotional

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