Anxiety and Depression in Patients with Epilepsy

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EPILEPSY BOARD REVIEW MANUAL

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Statement of Editorial Purpose
The Epilepsy Board Review Manual is a study guide for trainees and practicing physicians preparing for board examinations in epilepsy. Each manual reviews a topic essential to the current management of patients with epilepsy.

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Anxiety and Depression in Patients with Epilepsy

Sheri Cotterman-Hart, MD, PhD, and Amir Adeli, MD

INTRODUCTION

For millennia, epilepsy had been considered a mental disorder, with the link between epilepsy and mood documented more than 2000 years ago.1,2 Even during the middle of the 20th century, epilepsy was classified as a major type of mental disorder.3 Psychological and behavioral phenomena were originally thought to be abortive seizures.3 Initial investigations were devoted to the epilepsy “personality,” and the Minnesota Multiphasic Personality Inventory was a key investigative tool.4,5 Over time our knowledge about and conception of the link between epilepsy and mood has evolved and sharpened, and the anatomical, neurochemical, and psychosocial underpinnings of this link have begun to be explored. This article discusses the current understanding of the relationship between epilepsy and anxiety and depression and reviews therapeutic options for treating these mood disorders in patients with epilepsy (PWE).

ANXIETY

EPIDEMIOLOGY

There is a disproportionate rate of endorsement of anxiety symptoms in PWE as compared to the general population. In a multicenter study performed in the United States, the prevalence of anxiety in patients with chronic epilepsy was 30.4%.6 A Canadian population health study identified a 22.8% lifetime prevalence of anxiety in PWE.7 Anxiety may have a profound impact on an individual’s physical, emotional, and social well-being. Consequently, it has been associated with a significant reduction in health-related quality of life in patients living with epilepsy.8,9 In addition, anxiety may affect the quality of health care a patient receives. Studies have shown that, compared with controls, patients with drug-resistant epilepsy who have anxiety miss more outpatient visits, and those with very severe anxiety symptoms are more likely to have an inpatient admission.10 The efficacy of drug treatment may also be compromised, as patients with anxiety report worse antiepileptic drug (AED)—related adverse effects than asymptomatic patients.11 Poor coping skills likely place PWE at higher risk for developing anxiety. A review of psychosocial predictors of anxiety in PWE identified consistent evidence for the role of poor coping strategies as a significant predictor.12 Age of diagnosis may also serve as an important predictor. Older adults diagnosed post-retirement age were shown to be more
likely than those diagnosed pre-retirement age to report symptoms of anxiety. Proposed reasons for these findings included having less time to adjust to a chronic medical condition and the related restrictions placed on independence. Etiology of the epilepsy syndrome may influence the development of anxiety. Increased anxiety has been identified in patients with cryptogenic epilepsy, possibly as a result of the uncertainty of the etiology, as well as in posttraumatic epilepsy, possibly as a result of neurobiologic changes. Other potential predictors for development of anxiety include comorbid depression, severity of seizures, and patient perception of seizure control.

ETIOLOGY

There is growing neurobiologic support that the amygdaloid complex plays a key role in mediating anxiety. Amygdala ablation in monkeys results in attenuation of fear, whereas direct intracerebral stimulation of either the right or left amygdala in humans has been shown to induce fear. Alteration in amygdala size is associated with anxiety, but the exact mechanism for these changes remains unclear. Studies employing magnetic resonance imaging volumetry techniques have identified fear and anxiety in PWE to be mostly associated with amygdala atrophy, however, amygdala hypertrophy has also been reported. Although this evidence does suggest the amygdala plays a primary role in fear and anxiety, it is unlikely to represent the only neuroanatomical substrate. Stereotactic electroencephalography (EEG) and ictal single photon emission computed tomography recordings in patients whose main seizure symptom was fear have demonstrated a prominent role of the temporal, limbic, prefrontal, anterior cingulate, and orbito-frontal corticies in ictal fear.

Pathologic findings seen in mesial temporal sclerosis have demonstrated neuronal loss and gliosis of the amygdala. Unsurprisingly, of the localization-related epilepsies, temporal lobe epilepsy is commonly associated with ictal fear, panic, and anxiety. Lateralization of anxiety in patients with temporal lobe epilepsy has been studied, with mixed results. A study of patients in Brazil found anxiety to be more common in patients with left mesial temporal lobe epilepsy compared with right. Other studies have found no lateralization differences. Increased anxiety has been identified in patients with frontal lobe epilepsy and generalized epilepsy as well, with increased anxiety in the former when compared to the latter.

Dysfunction of the neurotransmitter gamma-aminobutyric acid (GABA) may represent a potential common pharmacologic etiology for both anxiety and epilepsy. Medications such as benzodiazepines that work at the GABA receptor subtype are highly effective in treatment of both conditions, whereas withdrawal may precipitate either.

From a psychosocial perspective, anxiety may develop as a consequence of living with a chronic, unpredictable, and difficult to treat medical condition. Potential factors include disease stigma, fear of further seizures, fear of significant injury or even death (ie, sudden unexplained death in epilepsy patients), fear of long-term sequelae of epilepsy (ie, memory impairment, adverse effects from AED therapy), loss of relationships, restriction of independence, and loss of income.

CHARACTERISTICS

The term anxiety is often broadly used in clinical contexts but actually represents a group of disorders. Indeed, a variety of anxiety subtypes have been identified in PWE, including social phobia, specific phobia, panic disorder, generalized anxi-
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Anxiety and depression, obsessive-compulsive disorder, posttraumatic stress disorder, and anxiety disorder not further specified.29

Many authors have suggested classifying distinct anxiety syndromes based on the temporal relationship to ictal activity.30,31 Preictal anxiety is characterized as prodromal symptoms prior to the onset of seizure activity. Symptoms of fear and anxiety may occur from several minutes to up to 3 days prior to a complex partial seizure.32 Ictal anxiety typically occurs in the form of a simple partial seizure aura originating from the temporal lobe, more commonly in the mesial region but also seen in the lateral region.30,33 Symptoms may range from a sense of fear, panic, or uneasiness, to extreme agitation or even immobility, often accompanied by a look of horror. Ictal anxiety may be associated with visual hallucinations, oro-alimentary automatisms, and autonomic features such as pallor, piloerection, mydriasis, and tachycardia.22 Postictal anxiety manifests as symptoms of anxiety following a seizure. In a study investigating patients with refractory partial epilepsy, 45% of patients had postictal symptoms of anxiety, with a median duration of 6 to 24 hours.34 Psychotic symptoms may or may not be an associated feature of postictal anxiety.35

Interictal anxiety pertains to symptoms of anxiety separate and distinct from seizures. This represents the most common form of anxiety in PWE, with studies reporting an occurrence of up to 66% in these patients.36 Symptomatic manifestations may be broad, but fear appears to be the most commonly reported symptom.14 This form of anxiety is likely most influenced by psychosocial factors. The importance of recognizing this clinical entity was underscored in 2007, when the International League Against Epilepsy (ILAE) Commission on Psychobiology of Epilepsy developed a proposal for classification of neuropsychiatric disorders in epilepsy. One of the key statements referred to the consideration of interictal anxiety and phobia as a distinct and disabling psychiatric condition.37

SCREENING AND DIAGNOSIS

To date, no validated, widely accepted screening tool exists that can aide in diagnosing anxiety specifically in PWE. Clinicians may utilize one of many screening tools, such as the Generalized Anxiety Disorder 7-item scale (GAD7), a self-reported questionnaire with good sensitivity popular among primary care physicians. Studies are ongoing in developing an optimal screening tool for PWE. Recently, visual analogue tools such as the Emotion Thermometers 7 (ET7), originally developed for screening for depression and anxiety in cancer patients, has been validated in PWE who have depression and anxiety.38

The American Psychiatric Association’s Diagnostic and Statistical Manual of Mental Disorders (DSM-V) is the current standardized guide for classification and diagnosis of mental illnesses. Anxiety disorders are categorized into 12 subtypes. Currently, no specific diagnosis exists for anxiety in PWE. The most analogous classification is represented by the category “Anxiety Due To Another Medical Condition.” This subtype is defined as “panic attacks or anxiety as the predominant symptom with evidence from history, physical examination, or laboratory findings that the disturbance is the direct pathophysiologic consequence of another medical condition. In addition, this disturbance cannot be better explained by another mental disorder, does not occur during the course of delirium, and does cause significant distress or impairment in social, occupational, or other important areas of function.”39 The DSM-V identifies many such medical conditions known to include anxiety as a symptomatic manifestation, including seizures.
In order to provide appropriate treatment and minimize deleterious effects of misdiagnosis, it is essential to differentiate between a primary panic disorder and complex partial seizures. With panic disorder, consciousness is typically preserved, attacks last longer than 5 minutes, anticipatory anxiety is common, and age of onset is typically in the twenties or thirties. The attack may be precipitated by a specific and identifiable external event. With complex partial seizures, the emotion is out of context, consciousness is impaired, and episodes are much briefer, lasting seconds to 1 or 2 minutes; there also may be associated symptoms such as sensory symptoms (ie, déjà vu, olfactory, epigastric) and/or automatisms. Although both patients with primary panic disorder and those with complex partial seizures may experience nocturnal panic, careful history taking may provide clues to differentiate between the 2 conditions. Those with a primary panic disorder experience nocturnal panic attacks during a state of wakefulness, whereas those with panic related to seizures are woken out of sleep with symptoms. If uncertainty remains between the 2 conditions, video EEG monitoring and recording of a typical spell is warranted.

Prior to initiation of treatment, the diagnoses of epilepsy and anxiety disorder should be firmly established. If doubts remain, obtaining additional history and ancillary testing as indicated should be performed. Counseling and education of patients regarding the diagnosis, expectations, and prognosis of living with epilepsy are paramount. This is especially critical in patients newly diagnosed with epilepsy, as this population may be particularly vulnerable for development of mood disorders. Education and counseling should be tailored to the individual patient, but goal setting and promotion of a sense of control have been effective techniques in reducing symptoms of anxiety in PWE.

TREATMENT

In 2011, the ILAE created practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. Clinical consensus for treatment was based on the concept that anxiety in PWE responded to the same pharmacologic and nonpharmacologic treatments used in people without epilepsy. Treatment options utilizing cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitors (SSRI)/serotonin-norepinephrine reuptake inhibitors (SNRI), alone or in combination, were recommended, given the well-established evidence for the efficacy, safety, and tolerability of these therapies in patients with a variety of anxiety disorders. Of note, in the initiation phase of SSRI treatment, a transient paradoxical increase in anxiety and panic symptoms may be seen. In addition to their efficacy for treatment of mood disorders, SSRIs and SNRIs have been shown to have potential anticonvulsive effects as well. No randomized controlled trials have been done to date investigating the efficacy of a particular SSRI in the treatment of anxiety in PWE. A recent evidence-based review of medications for treatment of PWE who have anxiety recommended sertraline or paroxetine as first-choice acute and long-term treatment for social anxiety disorder and posttraumatic stress disorder. For obsessive-compulsive disorder, CBT was determined to be first-choice treatment; however, for symptoms not sufficiently controlled with CBT, sertraline was again recommended as the first-choice selection for pharmacotherapy.

When treating seizures, clinicians may prefer to select an AED that may treat both symptoms of epilepsy and comorbid anxiety. This remains challenging, however, given the current limited understanding of the biochemical and pharmacologic properties of AEDs, as well as individual differences...
in drug response. One theory proposed to aide in AED selection classifies AEDs into 2 groups, those with “sedating” effects and those with “activating” effects. AEDs with sedating effects work via modulation of GABA transmission, and thus may exert potential anxiolytic effects. Examples of such medications include clobazam, vigabatrin, and tiagabine. AEDs with activating effects work on glutamate reduction, and thus may demonstrate anxiogenic effects. Examples include felbamate and lamotrigine. Unfortunately, in clinical practice, there appears to be significant variability in AED effects that cannot be completely explained by this theory. In a relatively recent review of psychotropic effects of AEDs in PWE, decreased anxiety was reported with phenytoin and valproate. Mixed findings were identified with other commonly prescribed AEDs, including levetiracetam, carbamazepine, lamotrigine, topiramate, zonisamide, pregabalin, vigabatrin, and felbamate. A higher prevalence of anxiety was seen with oxcarbazepine and tiagabine. Studies on lacosamide did not identify significant adverse or beneficial psychotropic effects. Gabapentin has also been studied in patients with partial epilepsy and mood disorders. When used as adjunctive treatment with an average dose of 1615 mg/day, no significant change in seizure frequency was noted. Although there was an improvement in depression scores, findings did not support a similar improvement in anxiety scores.

Benzodiazepines are sometimes used as abortive or prophylactic treatment of seizures. Although this class of medications possesses potent anxiolytic effects, it should not be considered first-line treatment, given its adverse effects including sedation and confusion, development of tolerance, risk of seizures with abrupt withdrawal, and paradoxical disinhibition.

Vagus nerve stimulation (VNS) is often used as adjunctive treatment of medically refractory epilepsy. Although no study to date has investigated the efficacy of VNS in PWE who have anxiety disorders, there is promising evidence in patients with medically refractory anxiety that VNS may have both acute and long-term treatment benefits.

Clinicians and patients must be vigilant regarding potential new-onset anxiety or exacerbation of anxiety with discontinuation or withdrawal of antiepileptic therapy. This is commonly done in the setting of controlling seizures and adjusting the AED regimen, when the patient is experiencing intolerable side effects, or during an admission to an epilepsy monitoring unit. Withdrawal of AED therapy, even if done gradually, may result in symptoms of anxiety, and symptoms may take several days to resolve following reinitiation of AED therapy.

Individualized CBT utilized in conjunction with pharmacologic therapies provides added treatment...
benefit with minimal adverse effects to the patient. Group therapies may also be effective. A study of PWE who underwent 10 weeks of group CBT demonstrated improvement in measures of depression and anxiety as well as increases in knowledge and achievement of CBT skills.53

Surgery for medically refractory epilepsy remains a highly efficacious, albeit underutilized, treatment option for select patients.54 Theorized benefits that may improve anxiety include improved sense of self-control, reduced fear of seizures, greater activity levels, and reduced AED burden.55 In reality, the relationship between epilepsy surgery and anxiety is much more complex, with mixed findings for improvement. A review of psychiatric outcomes following epilepsy surgery identified results suggesting improvement of anxiety, no change in anxiety, as well as new-onset anxiety status post surgery.56

Key clinical features of anxiety in PWE are summarized in Table 1.

**Table 1. Anxiety in Patients With Epilepsy: Key Clinical Features**

<table>
<thead>
<tr>
<th>Symptomatology</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preictal</td>
<td>Symptoms of anxiety can precede a seizure by hours to days</td>
</tr>
<tr>
<td>Ictal</td>
<td>Ictal fear possible from simple partial seizure; typically felt out-of-context; associated with autonomic features; needs to be differentiated from panic attack</td>
</tr>
<tr>
<td>Intercital</td>
<td>Fear is the most common symptom reported</td>
</tr>
<tr>
<td>Occurrence</td>
<td>Up to 66% of patients with epilepsy report anxiety</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosocial</td>
<td>Poor coping skills; coexisting depression</td>
</tr>
<tr>
<td>Physiologic</td>
<td>Age, etiology; severity of seizures; withdrawal of antiepileptic drugs</td>
</tr>
<tr>
<td>Screening</td>
<td>Generalized Anxiety Disorder-7</td>
</tr>
<tr>
<td>Quality of life</td>
<td>Significantly impacted; may impact quality of health care received</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment options</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>Antiepileptic drugs</td>
<td>Pregabalin</td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>Selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor</td>
</tr>
<tr>
<td>Therapy-based</td>
<td>Cognitive behavioral therapy</td>
</tr>
</tbody>
</table>

**DEPRESSION**

**EPIDEMIOLOGY**

There has been considerable debate about increased risk of depression in PWE. Depression is certainly the most frequent psychiatric comorbidity that occurs with epilepsy.57–59 The significant variability of reported depression in PWE is likely dependent on population selection (community vs. tertiary care center populations), how depression is defined, what tools are used to assess depression, and whether prevalence versus incidence of depression is assessed.7,60–62 Despite some questions as to the methods used to assess the presence of depression in PWE,63 there is support for the increased incidence and prevalence of depression in PWE.

In various adult populations with epilepsy, estimates of depression prevalence vary. Community and population survey samples with patient self-report have demonstrated prevalence rates ranging
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from 13% to 25%.

In a subpopulation analysis of a community sample, patients with controlled seizures endorsed the presence of depression at a rate of 4%, while patients with medically refractory epilepsy endorsed the presence of depression at a rate of 27% to 58%. Data show that, compared to patients with other chronic disabilities, the rate of depression in PWE is greater than expected. A study of veterans demonstrated a prevalence of 48%. In a study of patients with treatment-refractory epilepsy, 15% of patients met DSM criteria for axis I active clinical depression; however, when using a measure of prevalence rather than active diagnosis in a presumably similarly refractory population preparing for surgical intervention, patients had a 43% lifetime prevalence for depressive disorder. The diagnosis of major depressive disorder was carried by 7.5% of one population. Use of screening scales such as the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HDRS), and the Hospital Anxiety and Depression Scale yield estimates of symptoms of depression ranging from 20% to 80%. Consistent with data suggesting that depression is 17 times more common in patients with focal onset seizures than in patients without epilepsy, when populations were sorted by refractory complex partial seizures or temporal lobe epilepsy the reported prevalence ranged from 45% to 62%. For patients with mesial temporal lobe epilepsy in the postsurgical state, 27% to 37% reported postoperative depression, with 13% having new-onset major depressive disorder. Studies not relying on self-report data also support an increased prevalence of depression in PWE. One study found PWE were 4 times more likely to be hospitalized for depression than the comparison population. In a study of a national database, PWE had a higher rate of prescription of antidepressant medications than the general population. The pooled odds ratio of active depression in PWE has been documented at 2.77.

Children and adolescents with epilepsy also have reported increases in behavioral disorders, including those associated with mood disorders. Parents of children with epilepsy consistently report more behavioral problems. Although some studies have demonstrated no difference between children with epilepsy and controls on structured psychiatric interviews, 30% of children with epilepsy score at risk on the Child Behavior Checklist, 12% to 34% score at risk on the Child Depression Inventory, and more than 30% reach a score consistent with psychiatric diagnosis on the Kiddie Schedule for Affective Disorders and Schizophrenia. In one study, 40% of children and adolescents with epilepsy reported depression, while 62% reported chronic distress and social impairment. Separate reports in different countries/cultures documented depression in 23% and 28% of adolescents with epilepsy.

Suicidal ideation and attempt are also more prevalent in adults, adolescents, and children with epilepsy. PWE are estimated to carry a 5-fold increased risk for suicide compared to the general population, with patients with temporal lobe epilepsy carrying a 25-fold increased risk. Documented rates of actual history of suicide attempts in PWE range from 14.6% to 30%. Suicide accounts for 10% of all deaths in PWE, and the standardized mortality rate for PWE and a history of suicide attempt is 5.1.

RISK FACTORS

Factors associated with development of depression in PWE, including psychosocial, familial predisposition, epilepsy-related variables, and medications, have been debated and inconsistently demonstrated in the literature. The variables most
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consistently associated with the development of depression in PWE include stressful life events, seizure type, and neuroradiographic measurements of metabolism/blood flow.59

Psychosocial

Psychosocial factors reported to have an association with depression include receiving disability benefit payments,79,84 lack of employment,76 lower socioeconomic status,79,101,102 frequent hospitalization,76 being a visible minority,65 stressful life events,1,102 poor adjustment/acceptance of the disease state,1,101,102 and an external attributional style.102,103 In children, psychosocial risk factors include family organizational skills, family adaptation to illness, over-controlling parenting style, parent-child relationship, family stress,93 and maternal depression.86,93 The data regarding higher rates of depression in women compared to men with epilepsy is mixed,1,79,102 Family history of depression has also been reported to be associated with depression in PWE.84,102,104 Additionally, patient characteristics in children such as low IQ, learning disabilities, and neurological disabilities were associated with an increased risk for depression.86

Epilepsy-Related Variables

Epilepsy-related variables have also demonstrated associations with the development of depression in PWE. Polytherapy in antiepileptic regimens has been associated with an increased risk of depression,70,93 although the medications may function in concert with other risk factors in the development of symptoms.12 There has been inconsistent evidence showing that age of onset,105 duration of epilepsy,59,106 seizure focus and laterality,83,102,107 and imaging abnormalities106 or neurological lesion102,108 are associated with comorbidity of depression in PWE. The data regarding the relationship between the degree of seizure control and the presence of depression is mixed, and the hypothesis that poorer control of seizures is associated with increased risk of depression is controversial.59,105,109 Seizure frequency of less than 1 per month predicted postictal depression.110 However, many studies in children,93 adolescents,94 and adults64,74,111 have documented that uncontrolled seizures were a positive risk factor in developing depression or depressive symptoms.

A separate variable from seizure frequency is seizure type, the predictive value of which has also been debated.90 Focal epilepsy was documented to be more frequent in PWE who have comorbid psychiatric diagnoses.112 Complex partial seizures were overrepresented in a population of PWE who required hospitalization for depression.77 Complex partial seizures,76,110 specifically those without secondary generalization,70,76 had a high association with comorbid depression. However, it remains unclear if this higher representation of complex partial seizures in the psychiatric population results from the condition itself or from temporal lobe epilepsy being the most common type of epilepsy.108 Patients with temporal lobe epilepsy did not differ significantly from patients with focal extratemporal epilepsy on overall score on the Clinical Interview Schedule, but were more impaired than patients with primary generalized epilepsy.113 In the same study, the diagnosis of depression was greater in patients with temporal lobe epilepsy (36%) compared to the focal extratemporal (18%) and primary generalized (15%) epilepsy groups. Similarly, mesial temporal sclerosis has been closely associated with depression.114 However, in a study of patients with temporal lobe epilepsy with and without mesial temporal sclerosis, high scores on the BDI were predictive of mesial temporal sclerosis, but the reverse was not true, causing the investigators to postulate that mesial
temporal sclerosis was a facilitating but not causative agent for depression in PWE.107

**Surgery**

The onset of depression in the postoperative period following surgical intervention for epilepsy control usually occurs within the first 2 to 3 months following surgery75,84 and is usually transient, with a duration of up to 6 months. Risk factors include preoperative depression and poor family adjustment.84

**Risk Factors for Suicide**

Suicide and suicide attempts carry their own set of purported risk factors.105,115 Decreased adaptive ability,115,116 early onset during adolescence,105,115 comorbid psychiatric diagnosis,105,115 and inadequate neurological follow up115 are several risk factors cited. More psychotic symptoms are reported in patients who complete suicide,1 and use of antipsychotic medications increases risk of suicide attempt.105 The relative risk of suicide in PWE who have a diagnosed psychiatric condition is 13.7, with this estimate more than doubling to 29.2 in the 6 months following the diagnosis of epilepsy if the psychiatric condition was present prior to seizure presentation.117 AEDs have been reported to increase postictal suicide attempts.105,118 Severity of epilepsy does not appear to be a factor.105,115 A case report reported on 5 suicides in PWE in the 13 months following full seizure control. Of these patients, 3 were controlled with surgical intervention, 1 with medication, and 1 with VNS. Four of the patients had a history of suicidal ideation.119

**CHARACTERISTICS**

Depressive disorders in PWE have unique characteristics.120 Mood is classified as ictal, peri-ictal, and interictal.1 There is an unclear relationship between ictal, postictal, and interictal depressive disorders, and the most clinically relevant disorder may be interictal depressive disorders.121 Although many PWE meet criteria for major depressive disorder, many also present with atypical features.1

Many PWE experience preictal dysphoria. These patients experience prodromal dysphoric symptoms prior to seizure, with the mood change proceeding the seizure by up to 72 hours.4,101 In some cases, the mood can be relieved by seizure onset.122

Another facet of depressive disorders in PWE is ictal and postictal mood changes. Ictal depression occurs infrequently,60 with ictal depressive symptoms reported in 1%.4 Between 15% and 25% of auras have psychiatric symptoms.57,73 These are, however, usually anxiety related. The symptoms are brief and out of context.57 Nevertheless, simple partial nonmotor seizures can masquerade as an interictal disorder,123 and clinicians should consider the possibility that subclinical seizures can promote behavioral issues before clinical seizures present.90 Postictal depression is defined as depressive mood lasting for days following a seizure.122 These symptoms meet criteria for major depressive disorder, but with a duration of less than 2 weeks.110 Postictal depression increases risk for suicide attempt,73,75,105 and suicidal ideation can be a habitual postictal symptom.57,101

Interictal depressive disorders in PWE can be major depressive disorder, atypical depression, or dysthymia.60 Interictal depressive disorder is the most common presentation of affective disorder in PWE.60,124 Its atypical features and intermittent nature may contribute to underrecognition of the disorder.60,73,125 PWE reportedly demonstrate moods with sudden onset/offset, brief duration, and markedly increased irritability,122 with more chronic dysthymia between major depressive epi-
sodes. A classic dysthymic background with fewer “neurotic” traits (eg, somatization), periods of peri-ictal agitation, more paranoia, more irritability, disengagement, hopelessness, brooding, and less guilt has been described. This has been labeled subsyndromic depression and minor depression and has been proposed to be a forerunner to early major depressive disorder relapse. PWE who have minor depression have atypical features, the most prevalent of which is anhedonia. Interictal dysphoric disorder, a term coined by Blumer, is characterized by decreased mood, anergy, pain, insomnia, irritability, fear, and anxiety. These interictal dysthymic-like episodes, however, do not meet DSM criteria. In a study of psychiatric patients, patients with acute unstable depressive syndrome with fluctuating psychiatric symptoms, suicidal ideation, motor agitation, and lack of ability to understand/explain symptoms were more likely to have a past medical history positive for seizures. There is little data regarding the expression of depression in children with epilepsy being different from that in children without epilepsy. On the Child Behavior Checklist, children with epilepsy score high on internalizing, attention, thought, and somatic complaints. Children with epilepsy are more likely to present with irritability than with sadness.

ETIOLOGY

Consideration regarding the etiology of depressive disorders in PWE centers on the reactive or endogenous nature of depression in these patients. Depression in epilepsy likely results from a multifactorial process in which biologic (genetics, seizure focus, neurochemical and neurophysiologic changes in limbic structures), psychosocial (reaction to chronic disease, stigma, adverse life events, perceived social support, learned helplessness, disengaged coping strate-
alternative psychosis. Forced normalization is neither uniform nor common. However, this theory of antagonism has also been applied to the acute relationship between seizures and mood, termed by some self-electroconvulsive therapy, in which increased depression is seen with decreased seizure burden. Prodomal dysphoric states are noted to be relieved by seizure onset in some patients. As noted in the section on epidemiology, one of the risk factors associated with development of an interictal depressive disorder is the presence of complex partial seizures without generalized tonic-clonic seizures. Control of seizures by medication can precipitate mental symptoms, including depression. Depression following epilepsy surgery can occur in up to one third of patients, with the size of surgical resection being positively correlated with emotional lability. This can presumably result from postoperative lessening of excitatory activity along with enhanced prominence of inhibition favoring worsening and new emergence of dysphoric disorders.

Strong evidence for a common endogenous substrate for epilepsy and depression is the increased risk for seizures seen in patients with depression. Symptoms of depression can antedate the first seizure, and a history of depression increases the risk of seizures, especially complex partial seizures. This risk is even higher if the patient has a history of suicide attempt. Multiple studies have measured the increased risk for new-onset seizure in patients with a history of depression and/or suicide attempt. Depression scores and seizure frequency were significant predictors of each other at a single time point and longitudinally. Children who present with seizures have behavioral problems present on the Child Behavior Checklist. Major depressive disorder in the absence of a known prior neurological insult is associated with a 6-fold increase in risk for unprovoked seizures. In a case-control study involving patients aged 10 years and older with newly diagnosed unprovoked seizures, depression diagnosis was 1.7 to 3.7 times more common among cases before seizure diagnosis, while 10 depressive symptoms were twice as common in those with epilepsy. The odds ratio of patients with a history of depression developing an unprovoked seizure has been measured at 1.4 to 7.0, while the incidence rate ratios for depression and suicidality prior to the diagnosis of epilepsy have been documented at 1.5 to 15.7 and 3.1 to 4.5, respectively. In the elderly, major depression has an even stronger association with new unprovoked seizures. A history of suicide attempt is 5.1 times more common in patients presenting with a new-onset unprovoked seizure, with a reported odds ratio of 4.7.

This relationship of psychiatric dysfunction to presentation of seizures carries over into the disease course. Higher seizure frequency and symptomatic focal epilepsy were demonstrated to contribute significantly to the variance observed in BDI scores; higher Neurologic Disorders Depression Inventory for Epilepsy (NDDIE) scores were associated with higher seizure frequency; and poor seizure control was associated with increased number of depressive symptoms. Severe epilepsy is more common in mental health groups. Patients with epilepsy and comorbid depression report higher levels of perceived seizure severity and worse seizure recovery. Psychiatric diagnosis has a negative impact on seizure control. A history of depression is predictive of development of pharmacoresistant epilepsy. Pharmacoresistance is associated with current or prior depression, with an odds ratio of 2.17. Depression is also predictive of worse response to surgical treatment of epilepsy. Absence of psychiatric history was an
independent predictor of all 3 types of Engel class I outcomes (free of disabling seizures) following epilepsy surgery.\textsuperscript{150}

**Psychosocial**

Initially, depression was seen as a normal reaction to the diagnosis of epilepsy.\textsuperscript{125} Although clearly there is some neurophysiologic underpinning to the comorbid existence of depression and epilepsy, psychosocial issues and their role in the genesis of depression in chronic epilepsy should not be ignored.\textsuperscript{126} Neurophysiologic variables are the most frequently investigated in predicting the development of depression, but these investigations have yielded the fewest positive findings, while psychosocial variables have been evaluated less frequently but have been found to be more commonly associated with depression.\textsuperscript{59} Indeed, individual psychological variables are the best predictors of other psychological variables. However, when individual psychological variables were factored out, seizure severity was a significant predictor of self-esteem and locus of control,\textsuperscript{15,64} which in themselves are associated with development of depression. It is perhaps partly true that limbic activation by seizure increases the patient’s vulnerability to stressors.\textsuperscript{5}

As covered in the section on risk factors, there are many variables that have been studied in relationship to the development of depression in PWE. The difficulty with associations, however, is the direction of causality and even the presence of a causal relationship is difficult to define. General factors such as the burden of epilepsy, the burden of normality following surgery, and resilience have been postulated.\textsuperscript{106} Low self-esteem and perceptions of stigma, risk of physical harm, and death have also been felt to play a role.\textsuperscript{63,66,72,75,104} More concrete factors have also been studied, with financial distress, disability, joblessness, isolation, low levels of social support, increased number of stressful life events, and frequent hospitalization\textsuperscript{59,63,66,72,76,101} all demonstrating correlations with the development of depressive disorders in PWE.

A conceptual framework of styles of perception and adaption in interactions with life events is also an important determinant of mental health. Both lack of acceptance of and poor adjustment to the diagnosis of epilepsy have been demonstrated to be associated with the development of depressive disorders.\textsuperscript{73,75,101,104} It has further been proposed that poor adaptation to their disease state predisposes PWE to have lower levels of engagement in healthy behaviors and coping styles.\textsuperscript{151} Depression is most closely associated with the use of escape-avoidance and self-controlling coping styles.\textsuperscript{109} Moreover, the viewpoint with which a PWE interprets his or her life events is an equally important determinant of mental health. Much of this viewpoint revolves around a sense of control that can be affected by seizure frequency. Data demonstrate seizure control is positively correlated with a greater perception of life control.\textsuperscript{151} It is a lack of a sense of control that is associated with developing psychopathology and depression.\textsuperscript{66,72,73,75,104,151} This lack of control has been variously placed in the contexts of a model of learned helplessness\textsuperscript{72,125} and external locus of control.\textsuperscript{72} Attributional style, specifically a pessimistic style, has also been demonstrated to be associated with the development of depressive disorders.\textsuperscript{75,152,153}

The relationship of psychosocial variables with depression in children with epilepsy is also complex. Both epilepsy-related and preexisting family variables correlated with behavioral problems in children with epilepsy.\textsuperscript{86} However, as the prevalence of depression in children with epilepsy has not changed despite significant advances in the
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Diagnosis and treatment of seizures, psychosocial factors must be examined. Depression in children with epilepsy can only partially be attributed to the chronic disease state. Although some studies have demonstrated no differences between mothers of children with epilepsy and no correlation of mother-child scores, comparisons between children with epilepsy and their siblings suggest family factors may contribute significantly. Features of the family which are associated with the development of depression include family ability to organize, family adaptation to illness, over-controlling parenting style, parent-child relationship, and maternal depression. Indeed, the parent-child relationship and parenting style have the strongest influence on psychopathology in children with epilepsy when other seizure and child characteristics are controlled.

Anatomy

Evaluation of anatomic commonalities between epilepsy and depression focus on laterality, temporal lobe dysfunction including mesial temporal sclerosis, and frontal lobe dysfunction. There have been mixed results regarding the role of temporal laterality in the etiology of depression, and although either side can be associated with depression, a left-sided focus is more highly associated with depressive symptoms. Some have suggested that the observed association with a left-sided focus, rather than being causative, reflects a trait of persistent vulnerability. Among a population of PWE hospitalized for depression and with EEG abnormality, there was a predominance of left-sided EEG changes. In a separate population, more of the patients with left-sided onset complex partial seizures had a history of depression. In a study of patients undergoing epilepsy surgery, there was no difference in depression between the patients with temporal lobe or extratemporal epilepsy. However, postoperatively 13% of patients with mesial temporal lobe epilepsy developed depression compared with none in the extratemporal resection group. In a mixed seizure type population, no association was found between laterality and history of depression. Lateralization was not found to be significantly associated with the presence of major depressive disorder or with increased scores on screening tools for depressive symptoms. Additionally, the presence of mesial temporal sclerosis was also not found to be significantly associated with the presence of depression or depression screening tool scores. One study found that scores on the BDI were a predictor of mesial temporal sclerosis, but the reverse was not true. However, when hippocampal neuronal dysfunction was evaluated rather than mesial temporal sclerosis, the ¹H-MRSI data did correlate with severity of depression in patients with temporal lobe epilepsy. ¹H-MRSI data did correlate with severity of depression in patients with temporal lobe epilepsy. It has been suggested that subsequent frontal lobe dysregulation secondary to seizure focus may explain some of the inconsistencies in the data. Left orbital frontal and left anterior cingulate thinning was found to be associated with symptoms of depression in patients with temporal lobe epilepsy. Moreover, in patients with lesions but without mesial temporal sclerosis, unilateral left hemisphere lesions were over represented in the depressed population.

Other anatomic regions have been explored in relationship to development of depressive disorders in PWE. Depression is more frequent in patients with limbic seizure focus, and much study revolves around dysfunction in the temporal lobe including the amygdala and hippocampus as well as dysfunction in the frontal lobe. Moreover, most neuroimaging studies have found that lesions or functional abnormalities were associated with
more severe symptoms of depression, usually revolving around hippocampal, amygdalar, temporal, and frontal structures. Independent data from patients without epilepsy have linked depression and suicide to anatomic and biochemical changes in the amygdala and hippocampus, with similar changes seen in patients with temporal lobe epilepsy. Amygdalar volumes were significantly reduced in patients with dysphoric disorder of epilepsy and correlated with core symptoms of dysphoria, emotional instability, irritability, and aggression. More patients with documented temporal lobe hypometabolism had a history of depression. In patients with temporal lobe epilepsy, serotonin 5HT1A receptor binding is decreased in the hippocampus, amygdala, anterior cingulate, and lateral temporal cortex. Grey matter loss has been documented in patients with mesial temporal lobe epilepsy and is greater in patients diagnosed with depression via BDI and DSM-IV structured interview. Furthermore, a known postoperative complication of anterior temporal lobectomy is the development of depression. Multiple studies have documented frontal lobe dysfunction as key in the development of depression in PWE, but it is unclear if this is secondary to the epileptic process itself or a finding for depression in general.

**Neurochemical**

Multiple neurochemical mechanisms have been proposed to contribute to the comorbidity of epilepsy and depression. Norepinephrine, serotonin, GABA, glutamate, acetylcholine, and dopamine have all been linked to depression in epilepsy. Additional mechanisms have also been proposed for interleukin-1β, corticosteroids, and folic acid deficiency.

Interleukin-1β, as part of a neuroinflammatory process, has been proposed as potentially contributing to the comorbidity of epilepsy and depression. Release of interleukin-1β and activation of its receptor in the hippocampus are established hallmarks of temporal lobe epilepsy. Interleukin-1β has also been demonstrated to lead to depression via the hypothalamic-pituitary-adrenal (HPA) axis. Blockade of interleukin-1β receptors attenuates behavioral, endocrine, and biochemical markers of depression.

The close tie between medial temporal lobe structures and the HPA axis is implicated in depression in PWE. Life stressors are associated with triggering both seizures and depression, and dysregulation of the HPA axis has been demonstrated in both disease states. A feedback cycle between depression and seizures via corticosteroid release has been proposed wherein seizure-induced HPA dysfunction may increase the risk of depression and excess hormone from chronic stress may exacerbate epileptogenesis. Data from animal models support this. Following status epilepticus, animals demonstrate positive dexamethasone suppression tests, a hallmark of depression in humans and indicative of HPA axis dysfunction. Additionally, seizures increase interictal corticosteroid concentrations, which are correlated with severity of depressive equivalent behaviors, while conversely corticosteroids accelerate amygdalar kindling.

Serotonin and norepinephrine are both well studied as potential common pathological substrates to account for the comorbidity of depression and epilepsy. Experiments in which serotonergic or noradrenergic transmission is decreased exacerbate seizures while increases are associated with a reduction in seizure expression. Blockade of norepinephrine or serotonin reuptake has been demonstrated to be a key mechanism in the anticonvulsant properties of antidepressants.
Moreover, several AEDs, including carbamazepine, lamotrigine, zonisamide, valproate, and vigabatrin, increase extracellular serotonin.\textsuperscript{104,171} Evidence suggests that the anticonvulsant effect of VNS is partially derived from activation of monoaminergic transmission, as lesioning of noradrenergic and serotoninergic neurons in rats decreases the anticonvulsant effect of VNS.\textsuperscript{104,160} Positron emission tomography studies have documented decreased serotonin transmission in patients with primary depressive disorders and in PWE.\textsuperscript{57}

Multiple studies have been performed on 5HT\textsubscript{1A}-receptor binding in relation to the expression of depression in PWE. Decreased binding of 5HT\textsubscript{1A} has been seen in both epilepsy and depression.\textsuperscript{167} In patients with temporal lobe epilepsy, decreased 5HT\textsubscript{1A} binding was found in the hippocampus, amygdala, anterior cingulate, and insular and temporal cortex ipsilateral to the seizure focus, as well as in the contralateral hippocampus and raphe nucleus.\textsuperscript{131,157,162,172} The degree of decreased binding in the epileptic focus is proportional to the degree in which each area is involved in seizure generation as defined on intracerebral recording. Binding is lowest in the seizure-onset zone, less impaired in areas of propagated discharges, and even less affected in areas with spike detection only or no epileptic activity recorded.\textsuperscript{173} Comorbid depression detected by formal psychiatric interview was associated with more pronounced extension of binding deficits to nonlesional limbic regions.\textsuperscript{157}

These serotonin and norepinephrine results are consistent with those seen in animal models of epilepsy and depression. Augmentation of serotonin and norepinephrine in mouse models of epilepsy raises the seizure threshold,\textsuperscript{1} while depletion of synaptic serotonin and norepinephrine in genetic epilepsy-prone rats, epileptic baboons, and nonepileptic rats aggravates seizures.\textsuperscript{174} Rats demonstrate decreased serotonergic raphe and hippocampal transmission following status epilepticus.\textsuperscript{133} Genetically epilepsy prone rats demonstrate deficits in norepinephrine and serotonin and show depressive equivalent behaviors.\textsuperscript{160} Behavioral equivalents of despair and anhedonia in animals following status epilepticus are reversible with 5HT\textsubscript{1A} blockers.\textsuperscript{133}

**Antiepileptic Drug Therapy**

Use of AEDs can precipitate mood disorders in PWE. In fact these medications may have either positive or negative effects on mood.\textsuperscript{101} Proposed mechanisms for negative mood effects are varied, and AEDs have multiple, incompletely understood mechanisms that may or may not be related to their multiple clinical effects.\textsuperscript{165} GABA modulation, monoamine changes, forced normalization, folic acid deficiency, and withdrawal states have all been proposed.\textsuperscript{72,101,175} Some authors have proposed a division of agents into GABA, sedative, anxiolytic and glutamatergic, antidepressive, and activating types,\textsuperscript{121,165} with GABA associated with a higher risk of depression. However, many studies in children with epilepsy did not find AED type a consistent predictor of depression.\textsuperscript{90} AEDs may act in combination with other risk factors in the development of depressive symptoms.\textsuperscript{12,62}

Perceived medication side effects is a significant predictor of scores on depression subscales.\textsuperscript{64} When a PWE first endorses depressive symptoms, it is important to screen for any recent changes in the AED regimen.\textsuperscript{73,129,176} Iatrogenic depression from AEDs does respond to antidepressant treatment.\textsuperscript{101}

A risk factor for AED-associated changes in mood is medication load, including the number of medications used, the strength of the medication, and how quickly titration was performed.\textsuperscript{177} Rapid
dose escalation and high dosing are associated with depression. Although there is evidence that polytherapy is associated with mood disorders, this finding is not universal. In children with epilepsy, high doses and a high number of AEDs were associated with behavior problems. Higher number of AEDs is associated with higher scores on the BDI and on the NDDIE. Changes from polytherapy to monotherapy or just decreasing the number of medications can improve mood. Decreasing the number of AEDs from an average of 2.8 to 1.6 resulted in lower anxiety and depression scores.

There are case reports of suicide or overdose related to carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, primidone, tiagabine, topiramate, vigabatrin, zonisamide, and valproate. Additionally, the FDA has issued a warning regarding an excessive risk of suicidality in patients taking AEDs. This warning referred to a meta-analysis that included clinical trials of AEDs in which there was a 2-fold increased risk of suicide in patients taking AEDs. However, the validity of the meta-analysis has been questioned. In adjusted analysis, the use of AEDs was not associated with an increased risk of suicide in PWE, but AED use was associated with increased risk among patients with depression and among those without epilepsy, depression, or bipolar disorder.

Of the individual AEDs, several stand out in relation to mood changes. Phenobarbital and other barbiturates have long been associated with increased risk of depression and suicide, with reported rates up to 40% and 47%, respectively. Prior psychiatric history may increase the likelihood of this reaction. Other consistently reported associations (reported percent incidence) include felbamate (40%), levetiracetam (2.5–3.8%), tiagabine (3%–5%), vigabatrin (10%–12%), and zonisamide (7.4%). Topiramate has been linked to depression (15%) and mood lability (17%), although coadministration of lamotrigine can be protective. Interestingly, patients with hippocampal sclerosis are more likely to develop topiramate-associated depression. Withdrawal from carbamazepine, phenytoin, and valproate may precipitate psychiatric symptoms in up to 40% of patients.

**QUALITY OF LIFE**

Depression has a significant impact, in multiple ways, on the quality of life of PWE. Depression has been associated with decreased general quality of life, increased social disability, and increased mortality. Indeed, primary predictors of poor quality of life were ongoing seizures and comorbid psychiatric diagnosis. However, quality of life scores are more affected by subjective depression than short-term seizure control, with mood being the strongest predictor of quality of life. Depression is associated with decreased reported quality of life and subjective health assessment. Patients with increased scores on depression screening tools have worse scores on quality of life measures than asymptomatic patients. Depression is a predictor of dramatic worsening of subjective health states, and is a powerful predictor of quality of life after adjusting for seizure variables. In patients with refractory epilepsy, depression was the key determinant of quality of life. Furthermore, scores on depression screening tools have been shown to be the strongest and most consistent predictor of quality of life without interactions with other variables. In PWE, those with depression report 25% lower health status compared to those without. Domains of quality of life concerns in PWE include driving, employment,
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social embarrassment, medication dependence, independence, stress, and safety. Depression in PWE is associated with worse adverse effects of AEDs, more severe seizures, and a more difficult time recovering from seizures. Depression, especially in drug refractory patients, doubles the overall costs of medical care in epilepsy.

SCREENING

Detection of depression can add additional benefits of $10,000 to $35,000 per year and can positively impact the patient's quality of life. However, depression in PWE frequently is under-recognized. Possible reasons why depression goes unrecognized include patient or physician minimization, atypical presentation, or failure of physician inquiry. Rates of detecting depression increases by 10% to 47% when reliable and valid screening tools are used during normal care. Simple inquiry about anhedonia is a good predictor of depression, and there are multiple short screening tools available for use, which, although not diagnostic, can suggest the need for further examination. The Hospital Anxiety and Depression Scale is available for use. The BDI and Center for Epidemiologic Studies Depression Scale (CES-D) are both validated in PWE. The NDDIE has the advantage of being specifically designed to minimize confounders seen from AED side effects and separate cognitive problems associated with epilepsy. This simple tool asks the patient if listed descriptors are self-applicable over the previous 2 weeks. These descriptors are: Everything is a struggle, Nothing I do is right, Feel guilty, I'd be better off dead, Feel frustrated, I have difficulty finding pleasure. The NDDI-E is 81% sensitive and 90% specific. In children with epilepsy, one can administer the Diagnostic Interview Schedule for Children or the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS). Additionally, self-reporting tools that can be used include the Children's Depression Inventory, Multidimensional Anxiety Scale for Children, and Child Behavior Checklist. Patients with newly diagnosed epilepsy have a significant likelihood of having a history of depression or current depressive symptoms, and screening should be performed at all stages of care rather than just in the chronic setting.

TREATMENT

Given the significant impact of depression on quality of life and utilization of health care services, as well as the risk of long-term pathophysiologic consequences of untreated depression and the high incidence of suicide in PWE, early detection and treatment are imperative. In a study of patients with high BDI scores, only 5% were diagnosed and treated, while in a separate study using the CES-D, 38.5% of the patients with a positive screen had never been evaluated for depression. In a wider national epidemiological study population, 38% of patients who endorsed depression were not assessed by a mental health professional. In one study, 40% of children with epilepsy who scored high on the K-SADS received no mental health assessment. Interictal depressive symptoms respond to medication in a manner similar to idiopathic depression symptoms. The standard of care is for neurologists to screen for depressive symptoms and initiate therapy, including psychopharmacological treatment. The presence of suicidal ideation, psychotic symptoms, or symptoms of bipolar disorder should prompt immediate referral. Key clinical features of depression in PWE are summarized in Table 2.
Antiepileptic Drugs

AED use can be altered to address symptoms of depression in PWE. If a patient becomes depressed, recent changes in the antiepileptic regimen should be analyzed for temporal correlation with the new symptoms. Simplification of the antiepileptic regimen may also have positive benefits. Decreasing the number or AEDs decreases depression scores. Clinicians can also choose to use AEDs with more favorable effects on mood. Many AEDs elevate indices of serotonin transmission. Of note, carbamazepine, lamotrigine, and valproate have favorable effects on mood. Early studies with the substitution of carbamazepine for other antiepileptics demonstrated improvement in psychopathology. This positive affective effect is supported by animal data, with mixed results found in human studies. Lamotrigine is used to treat bipolar depression in patients without epilepsy and has data supporting a favorable effect in PWE. Lamotrigine has antidepressant properties and has demonstrated a positive effect on BDI scores. Valproate has antidepressive properties in animal models; in humans it may relieve mood and agitation and is used as a mood stabilizer.

Antidepressants

Depression, depressive symptoms, and iatrogenic depression from AEDs respond to antidepressants. Use of amitriptyline or nomifensine improved scores on the HDRS and BDI, and citalopram treatment decreased total HDRS score. Patients with temporal lobe epilepsy were effectively treated for depression with citalopram, mirtazapine, or reboxetine. SSRIs are the first-line agent in the treatment of depression in adults and children with epilepsy. Antidepressants should be started at a low dose and advanced slowly. A consensus statement from the Epilepsy Foundation’s Mood Disorders Initiative recommends starting the SSRI escitalopram at 5 mg/day with titration.
Effect of antidepressants on seizure control. Risk of antidepressants causing seizures is overestimated.\textsuperscript{175,193,194} What risk is present is associated with rapid dose escalation and high dosing.\textsuperscript{63,122} Historically, attempts to predict which antidepressants are more likely to cause seizures have been complicated by the definition of seizure used, the concomitant use of other medications, and withdrawal from drugs or alcohol.\textsuperscript{195} Additionally, data on antidepressant-induced seizures is based on samples from the psychiatric population, not PWE,\textsuperscript{192} and there is a lack of evidence that PWE are more likely to experience antidepressant-induced seizures.\textsuperscript{170} Studies have suffered from methodological flaws including small sample size, case reports of overdoses, and failure to distinguish between incidence and prevalence.\textsuperscript{145,194,196} No change in seizure control was seen with the use of amitriptyline or nomifensine\textsuperscript{189} in one study or with the use of citalopram, mirtazapine, or reboxetine in another.\textsuperscript{191} Summary analysis of seizure incidence from FDA phase I and II clinical trials documented a significantly lower seizure frequency in patients treated with antidepressants compared with placebo.\textsuperscript{197} However, fear of seizure induction remains the most cited reason for not treating PWE.\textsuperscript{198}

As noted, SSRIs are the first-line choice for treatment of depression in PWE. SSRIs have a positive effect on both mood and seizures,\textsuperscript{199} and SSRIs have preclinical profiles similar to AEDs.\textsuperscript{200} Experimentally induced increases in norepinephrine or serotonin decrease seizure expression,\textsuperscript{1,160} SSRIs decrease seizure frequency in genetically prone rats.\textsuperscript{57} These anticonvulsant effects may be region- and seizure subtype–specific as models of chronic partial epilepsy are more likely to respond than models of acute generalized seizures.\textsuperscript{200} In a study in 36 children with epilepsy treated with sertraline or fluoxetine, only 2 children experienced an increase in seizure frequency.\textsuperscript{201} Studies with citalopram treatment of PWE have documented no change in seizure frequency.\textsuperscript{190,191} Sertraline use was associated with 6% of patients endorsing any increase in seizure frequency, and only one of these met criteria for definite causality. All patients returned to baseline seizure frequency after adjustment of antiepileptic dosing.\textsuperscript{202}

Tricyclic antidepressants (TCAs) have also been used in PWE. TCAs have a higher risk for provoking seizures when compared to SSRIs,\textsuperscript{170} but lowering seizure threshold with therapeutic doses of a TCA remains rare.\textsuperscript{122} Although in a population-based study use of a TCA was associated with a 2.5-fold risk for seizures,\textsuperscript{140} the estimated incidence of seizures with TCAs ranges from 0.1% to 4%. Patients with temporal lobe epilepsy were effectively treated for depression with mirtazapine with no change in seizure frequency.\textsuperscript{191} Factors that increase risk for TCA-produced seizures include high plasma concentrations and rapid dose escalation.\textsuperscript{104} Plasma concentrations should be followed if TCAs are used in PWE.\textsuperscript{73,125} The TCAs consistently associated with decreased seizure threshold include amoxapine, clomipramine, maprotiline, and mianserin.\textsuperscript{1,121,145,176,194,196,199}

Data regarding the effect of the norepinephrine-dopamine reuptake inhibitor bupropion on seizure threshold is mixed. The seizure rate for bupropion in patients without epilepsy is 0.4%. Many of the seizures first reported were associated with the immediate-release formulation, and it remains unclear if the same increased risk applies to the sustained-release preparation.\textsuperscript{192,194}
Pharmacokinetic interactions. When treating PWE for depression, the clinician should be aware of potential pharmacokinetic interactions between the AEDs and the antidepressants. Mostly these interactions occur between TCAs and first-generation antiepileptic medications, but select SSRIs may also have interactions. Carbamazepine, phenobarbital, phenytoin, and valproate levels can be increased with use of TCAs. Conversely, the first-generation AEDs may alter the pharmacokinetics of TCAs. Valproate can inhibit the metabolism of TCAs, leading to higher plasma levels, while carbamazepine and phenobarbital can induce their metabolism. Additionally, carbamazepine affects the protein binding of TCAs, leading to an increased free fraction. Stopping AEDs can lead to a subsequent increase in TCA plasma levels. When using TCAs in PWE, monitoring of blood levels of both the antiepileptic and TCA agent may be necessary.

Select SSRIs also have pharmacokinetic interactions with AEDs, with the most frequently reported of these being fluoxetine and fluvoxamine. Carbamazepine levels can be increased with the coadministration of fluoxetine or fluvoxamine. Additionally, the combination of fluoxetine and carbamazepine may result in a serotonin syndrome. Lamotrigine levels can increase with the use of sertraline. Again, the antiepileptic medications can affect the metabolism of SSRIs as well. Carbamazepine induces the metabolism of citalopram, and phenobarbital has been demonstrated to decrease levels of paroxetine. Valproate increases fluvoxamine levels. As citalopram does not alter the CYP450 system, it is less likely to have interactions with the AEDs.

Various other classes of antidepressants also have pharmacokinetic interactions with AEDs. Carbamazepine is a potent inducer of bupropion metabolism, while bupropion markedly inhibits valproate and phenytoin metabolism. Toxicity has been reported with the combination of carbamazepine and nefazodone. The combination of carbamazepine and a monoamine oxidase inhibitor can increase the concentration of the former and has been associated with hypertension.

Therapy

Although patients frequently have difficulty accessing mental health resources, the augmentation of pharmacological treatment with alternative treatment strategies should be used in the management of depression in PWE. In many cases, alterations in the patient’s perception of the world and his or her role in it may be needed. Children with epilepsy need supportive therapy to improve problem solving and coping skills, while cognitive behavioral therapy can moderate learned helplessness/external locus of control. CBT, interpersonal psychotherapy, and family therapy have all demonstrated efficacy with the combination of therapy with pharmacological treatment being superior to medications alone. A consensus statement from the Epilepsy Foundation’s Mood Disorders Initiative recommends the use of therapy as a treatment modality.

Vagal Nerve Stimulation

VNS has been approved for the treatment of depression and can reduce symptoms of depression independent of seizure attenuation. Evidence suggests that the anticonvulsant effect of VNS is partly derived from activation of monoaminergic transmission, consistent with an antidepressant function. In one study, fewer emotional and physical problems were reported in the VNS group compared with the control group at 12 to 16
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weeks. However, efficacy for depression in PWE has not been conclusively established.

Electroconvulsive Therapy

Although spontaneous seizures have occurred after electroconvulsive therapy, it is still considered a safe treatment for PWE. There is even data suggesting that the inter-treatment seizure threshold is increased. If electroconvulsive-induced seizure is too short for efficacy, the clinician can consider a temporary decrease in dosing of the antiepileptic agent. Electroconvulsive therapy remains a safe and efficacious treatment for pharmacoresistant depression.

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