psychiatric illness
patients with epilepsy

Appropriate treatment of mental health problems can improve the global prognosis for the patient who has a seizure disorder.

Patients who have epilepsy have a higher incidence of psychiatric illness than the general population—at a prevalence of 60%. Establishing a temporal association and making a psychiatric diagnosis can be vexing, but awareness of potential comorbidities does improve the clinical outcome (Box, page 32). As this article discusses, psychiatric presentations and ictal disorders can share common pathology and exacerbate one another. Their coexistence often results in frequent hospitalization, higher treatment cost, and drug-resistant seizures. Risk factors for psychopathology in people who have epilepsy include psychosocial stressors, genetic factors, early age of onset of seizures, and each ictal event. Among ictal disorders, temporal-lobe epilepsy confers the highest rate of comorbidity.

Mood disorders

Mood disorders are the most common psychiatric disorder comorbid with epilepsy (irrespective of age, socioeconomic status, and ethnicity), affecting 43% of patients who have a seizure disorder. These disorders present as an ictal aura in 1% of cases; the presence of a comorbid mood disorder implies a more severe form of epilepsy. Most mood disorders are underdiagnosed in epilepsy, however, because of the mistaken assumption that depression is a normal reaction to having a seizure disorder.

Interictal depression is the most commonly reported complaint, although dysphoria also can present peri-ictally. The severity of depression and the seizure disorder often are directly proportional to each other. Decreased levels of serotonin and norepinephrine, or
abnormalities in their transport or postsynaptic binding, have been reported in epilepsy and in affective illness. MRI studies have documented that patients who have a depressive disorder have more gray-matter loss compared with healthy controls. Depression diminishes the quality of seizure remission after medical and surgical interventions for epilepsy.

Taking a multidisciplinary approach to treating a mood disorder in a patient who has epilepsy might improve ictal and mood outcomes. Anhedonia is the most common presenting symptom, but some patients do not meet DSM-5 criteria. Anhedonia is the most common presenting symptom in depressed patients with epilepsy, but some do not meet DSM-5 criteria.

**Clinical Point**

Anhedonia is the most common presenting symptom in depressed patients with epilepsy, but some do not meet DSM-5 criteria.

**Box**

**Key observations about psychiatric comorbidity in epilepsy**

- Rule out a seizure disorder in a patient who has new-onset attention-deficit/hyperactivity disorder or memory impairment
- Individual or family psychotherapy, or both, can be beneficial when epilepsy and psychiatric illness coexist
- Prompt recognition and treatment of psychiatric comorbidity can:
  - diminish the rate of recurrence of seizures
  - enhance quality of life, mood, sleep
  - improve adherence to a drug regimen
  - decrease the potential for substance abuse
- Because surgery for epilepsy increases susceptibility to depression and anxiety, preoperative assessment and, if warranted, management of these 2 conditions is necessary to take preventive measures and provide intervention quickly.

Electroconvulsive therapy and vagus nerve stimulation are effective interventions in treatment-resistant depression. The efficacy of transcranial magnetic stimulation remains to be clarified.

AEDs can produce psychiatric effects, even in nonconvulsive epilepsies. Twenty-eight percent of cases of depression that are comorbid with epilepsy have an iatrogenic basis, and can be induced by barbiturates, topiramate, vigabatrin, tiagabine, and levetiracetam. These adverse effects are a common reason that patients discontinue drug treatment and obtain psychiatric consultation.

Neurosurgical management of epilepsy carries a low risk of depression compared with pharmacotherapy because the surgery offers better ictal control. Because some AEDs have mood-stabilizing properties, discontinuing one might unmask an underlying mood disorder.

The incidence of adjustment disorder with depressed mood in persons who have epilepsy is 10%; with dysthymia, the incidence is 4%. Adjustment problems with an adverse psychosocial outcome are documented more often in patients who have a long-standing, chronic disorder than in those with a more recent diagnosis.

Postictal suicidal ideation is more common in persons who have a preexisting mood disorder. The rate of suicide among epilepsy patients is 5%, compared with 1.4% in the general population—which is the same rate seen among patients with other psychiatric conditions, but higher than what is observed in many chronic medical conditions. Attempted suicide is not a direct result of epilepsy, but is significantly related to underlying psychopathology; anxiety comorbid with a mood disorder increases the risk of suicide.

The incidence of bipolar disorder among epilepsy patients is 1.4%. Although some interactions between antiepileptic drugs (AEDs) and antidepressants; sertraline, citalopram, and escitalopram have the lowest incidence of adverse effects. Because tricyclic antidepressants have proconvulsant properties, they are not commonly prescribed in these patients (Table 1).
AEDs can induce mania and hypomania, valproate and lamotrigine each have mood-stabilizing properties that might prevent such episodes.²³

**Anxiety disorders**

**Anxiety.** Approximately one-third of epilepsy patients report anxiety. In contrast to what is seen with depression, AEDs do not alleviate anxiety.¹⁶,¹⁹ Anxiety or fear is the most common ictal-related psychiatric symptom making it difficult to differentiate anxiety and a seizure.²⁴

Antidepressants, especially an SSRI, often are the treatment of choice; patients must be warned about the risk of an exacerbation of anxiety precipitated by an antidepressant. Such an adverse reaction might prompt cognitive-behavioral therapy (CBT) or limited use of a benzodiazepine.²⁵

**Obsessive-compulsive disorder.** The incidence of OCD in epilepsy is 14% to 22%.²⁶ Damage to the orbitofrontal cortex or temporal lobe epilepsy surgery can induce OCD; neurotransmitters involved

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations for treating depression when epilepsy is comorbid</strong></td>
</tr>
</tbody>
</table>

1. **Is your patient at risk of depression?**
   - Evaluate for risk factors
     - History of a psychiatric disorder, suicide attempt, or both
     - Family history of affective illness
     - Peri-ictal psychiatric disturbance
     - Psychosocial difficulties or trauma

2. **Treat the epilepsy**
   - Gain seizure control
   - Minimize polypharmacy
   - Make use of the positive psychotropic effects of antiepileptic drugs (AEDs)
   - Carefully titrate the dosage of any depressogenic AEDs that you prescribe, and monitor those patients for development of depression
   - Check the serum level of AEDs as indicated

3. **Treat the depression**
   - Select an antidepressant that has 1) minimal proconvulsive properties and 2) a favorable pharmacokinetic profile
   - Start at a low dosage; titrate slowly
   - Monitor for suicidal ideation, using collateral information

Source: Reference 13

**Clinical Point**

Anxiety or fear is the most common ictal-related psychiatric symptom making it difficult to differentiate anxiety and a seizure.
are serotonin, glutamate, dopamine, and \( \gamma \)-aminobutyric acid (GABA).\(^{27}\) Patients may report obsessive thoughts in the peri-ictal period as well; some AEDs, such as topiramate, have been reported to induce such behaviors.\(^{28}\) Treatment options include CBT, an antidepressant, and, in refractory cases, neurosurgery.\(^{29}\)

### Psychosis

The prevalence of psychosis is approximately 10% among persons who have epilepsy, and is observed most often in patients who have complex partial seizures.\(^{30}\) Risk factors include a family history of epilepsy or psychosis, temporal lobe epilepsy, a long seizure history, and significant neuropathology.\(^{31}\) Structural abnormalities in the limbic system, especially the hippocampus, predispose patients to psychosis. Abnormal activity of GABA and dopamine are implicated in psychotic symptoms in these patients.\(^{32}\)

Depending on the type and focus of the seizure, ictal psychoses present with cognitive and affective symptoms or hallucinations. Delusions can be associated with comorbid traumatic brain injury.\(^{32}\) Post-ictal psychosis is differentiated from other peri-ictal confusional states by:

- presence of more organized thinking
- absence of EEG changes.\(^{33}\)

Alteration of an AED regimen can induce post-ictal psychosis. Iatrogenic psychosis sometimes is observed after right-sided temporal lobe surgery.\(^{34}\)

Interictal psychoses probably occur as a result of aberrant nerve regeneration, with an increased concentration of dopamine in the brain after long-term seizure control. Epileptic psychosis is distinguished from schizophrenia by the predominance of visual hallucinations, no alteration of personality or affect, and glial proliferation.\(^{35}\) Some patients exhibit “forced normalization,” in which psychotic features appear after epilepsy has been treated successfully and EEG findings are normalized.\(^{36}\)

Management of psychosis in epilepsy includes ensuring the patient’s safety, ruling out medical causes of psychosis, and preventing relapse. Prescribe antipsychotics with caution because many of these agents have epileptogenic potential or can interfere with the hepatic metabolism of AEDs. Quetiapine, risperidone, and haloperidol have low potential for seizure induction; chlorpromazine and clozapine are more likely to precipitate an ictal event.\(^{37}\) Ziprasidone, quetiapine, and aripiprazole often are prescribed for post-ictal and interictal psychoses.\(^{38}\)

### Sleep disorders

Epilepsy patients often complain about difficulty sleeping, namely:

- 10% to 33% exhibit restless leg syndrome or periodic limb movement disorder
- 10% to 65% have obstructive sleep apnea
- 11% to 28% report excessive daytime sleepiness.\(^3\)

Convulsive activity and the rate of generalization of partial seizures are increased by sleep, especially non-rapid eye movement sleep. Rapid eye movement (REM) sleep suppresses ictal activity, but the pattern of REM sleep is disrupted in epilepsy. Seizures and some sleep disorders present with similar symptoms, such as confusion and amnesia (Table 2).\(^{39}\)

---

### Table 2

<table>
<thead>
<tr>
<th>Sleep disorders can be confused with epilepsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Wakefulness disorders</strong></td>
</tr>
<tr>
<td>Sleep attacks</td>
</tr>
<tr>
<td>Cataplexy</td>
</tr>
<tr>
<td><strong>Non-REM sleep disorders</strong></td>
</tr>
<tr>
<td>Sleep terrors</td>
</tr>
<tr>
<td>Somnambulism</td>
</tr>
<tr>
<td>Sleep enuresis</td>
</tr>
<tr>
<td>Somniloquy</td>
</tr>
<tr>
<td><strong>REM sleep disorders</strong></td>
</tr>
<tr>
<td>Hypnagogic hallucinations</td>
</tr>
<tr>
<td>Sleep paralysis</td>
</tr>
<tr>
<td>REM sleep behavior disorder</td>
</tr>
<tr>
<td>Nightmares</td>
</tr>
</tbody>
</table>

**Source:** Reference 39
Management of comorbid sleep problems includes:
- effective control of seizures
- avoidance of polypharmacy
- assuring sleep hygiene.

Disordered sleep resulting from an AED might be relieved by switching to another medication.39

**Substance abuse**
Abuse of substances is a significant risk factor for recurrence of seizures.

**Alcohol**, at a low dose, has antiepileptic properties; intoxication rarely induces a seizure, although seizures often accompany alcohol withdrawal.40

Acute alcohol abuse increases the free level of AEDs by inhibiting 1) microsomal enzyme systems and 2) binding of albumin by metabolites, such as acetaldehyde. These effects can lead to the dangerous outcome of respiratory depression, especially with drugs like phenobarbital.

Chronic alcohol use induces hepatic enzymes, which augments clearance of AEDs, except benzodiazepines. Metabolism of AEDs is decreased because of reduced hepatic blood flow.

Moderate drinking does not increase the incidence of seizures in medication-adherent patients. People who have recurrent alcohol-withdrawal seizures do not have a heightened risk of epilepsy.41

**Cannabis.** Animal studies have documented the anticonvulsant effect of Cannabis in partial and generalized epilepsy and a proconvulsant effect in absence (petit mal) seizures.42

**Tramadol, caffeine.** Patients who abuse tramadol or who have an excessive intake of caffeine have a decreased seizure threshold.43

---

**Clinical Point**
Alcohol intoxication rarely induces a seizure, although seizures often accompany alcohol withdrawal.
Opiates can exert a proconvulsant or anticonvulsant action, depending on the type of endorphin receptors involved.

Cocaine decreases the seizure threshold by 1) blocking cerebral GABA receptors and 2) inhibiting dopamine reuptake, thus elevating excitatory neurotransmitters. Cocaine can cause a generalized or focal seizure; the latter is caused by intracerebral stroke or hemorrhage.

The AEDs topiramate and lamotrigine tend to decrease the desire to abuse alcohol by enhancing inhibitory control by way of decreasing dopamine activity in the mesocorticolumbic system.

Memory deficits

The relative risk of dementia among epilepsy patients is greater compared with the general population. Recurrent seizures can result in cognitive deficits; epilepsy has been documented in 2% to 64% of Alzheimer’s disease patients.

Progressive amnesia, with an associated decline in cognition in epilepsy patients despite AED therapy, warrants a dementia workup. Patients with an ictal disorder often have difficulty with memory, especially if the hippocampus is affected, such as in temporal lobe epilepsy. Seizures are a common manifestation of several neurodegenerative conditions, and may be associated with a treatable dementia or psychosis in patients with cyanocobalamin deficiency.

Several memory deficits are associated with seizure disorders:

• **Transient epileptic amnesia** can be ictal or post-ictal, or can be a manifestation of an underlying seizure disorder. The condition is associated with isolated memory deficits; other cognitive functions usually are intact.

• **Accelerated long-term memory deficit** occurs when patients forget skills acquired over the past few days or weeks. The problem can be reduced with sleep.

• **Remote memory impairment** is characterized by inability to recall personal information from the past.

When considering a diagnosis of a memory deficit as a manifestation of dementia, keep in mind that cognitive impairment also can develop after epilepsy treatment—although most newer medications cause relatively few such problems.

2-pronged management. It is difficult to establish a temporal association between epilepsy and dementia. When the conditions coexist, appropriate treatment of both is important, because inadequate control of seizures can heighten release of amyloid toxins in the hippocampus. This results in rapidly progressive cognitive decline.

Neurodevelopmental disorders

The incidence of epilepsy in children who have an autism spectrum disorder is 5% to 38%; the disorder is more common in the presence of mental retardation or cerebral palsy.

A significant percentage of youth who are referred for evaluation of attention-deficit/hyperactivity disorder (ADHD) eventually are given a diagnosis of absence seizures. The incidence of ADHD in children with epilepsy is 20%; these patients display epileptiform EEG changes, and require meticulous screening, which includes ictal induction by hyperventilation to differentiate ADHD from a seizure disorder. Many AEDs, especially GABAergic drugs, can cause symptoms of ADHD. Methylphenidate is safe in children whose seizures are well-controlled, and has no significant interactions with AEDs.

Management. Adequate seizure control is the only effective means to slow regression in cases of epilepsy comorbid with autism spectrum disorder, mental retardation, and cerebral palsy.

References


Related Resources


Drug Brand Names

- Aripiprazole • Abilify
- Chlorpromazine • Thorazine
- Citalopram • Celexa
- Clozapine • Clozaril, FazaClo
- Escitalopram • Lexapro
- Haloperidol • Haldol
- Lamotrigine • Lamictal
- Levetiracetam • Keppra
- Methylphenidate • Ritalin
- Quetiapine • Seroquel
- Risperidone • Risperdal
- Topiramate • Topamax
- Tiagabine • Gabitril
- Valproate • Depakote
- Vigabatrin • Sabril
- Ziprasidone • Geodon

Clinical Point

Progressive amnesia, with an associated decline in cognition in epilepsy patients despite AED therapy, warrants a dementia workup.

Clinical Point
Adequate seizure control can slow regression in epilepsy comorbid with autism spectrum disorder, mental retardation, and cerebral palsy

Do you wrestle with the complex problems of your bipolar disorder patients?

Then visit the Current Psychiatry Bipolar Disorders Resource Page at CurrentPsychiatry.com

Here, find collected Current Psychiatry Pearls, audiocasts, video interviews, and review articles—such as Deputy Editor Dr. Joseph F. Goldberg speaking on how best to treat patients with suspected ultra-rapid cycling bipolar disorder.


Providing psychiatrists with peer-reviewed, practical, and up-to-date advice by leading authorities on common clinical challenges