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How seizure disorders change depression treatment

Suicide risk is high in depressed patients with epilepsy, especially the temporal lobe form

Ms. A, age 29, has had depression for 6 years and has taken antidepressants with inconsistent response. For 3 weeks, while not taking any antidepressant, she reports loss of energy; feeling sad, subdued, and tearful; poor concentration; and reduced interest in enjoyable activities including sex, the same symptoms she first reported 6 years ago. She has no appetite but has not lost weight.

Several times a month Ms. A “loses” short periods of time. For example she says sometimes she cannot remember what happens between parking her car and sitting at her desk at work. After these episodes, which began 9 years ago, her speech is slightly slurred, and coworkers tease her about being “hungover.” She feels fuzzy-headed, but her speech and thinking clear after a few hours. At other times she smells burning rubber and feels that everything she does repeats what she has done before. Sometimes she feels “out of body” and can watch herself from the ceiling.

Ms. A’s symptoms suggest a seizure disorder. Her depressive features appeared after these ictal episodes began 9 years ago.

Recognizing mood disorders in patients with epilepsy is important because these disorders can be successfully treated within the context of the medical condition.

Many cases of comorbid depression in epilepsy are undiagnosed. A study of

100 patients with refractory epilepsy and depression severe enough for pharmacotherapy found that referral for psychiatric treatment was delayed >1 year in 75% of patients with spontaneous mood disorders and 89% of patients with depression secondary to antiepileptic drugs (AEDs).¹

Psychiatrists often are called on to evaluate and treat depression in epilepsy patients or to assess for nonadherence to AEDs. Successfully treating these patients requires understanding:

- the relationship between epilepsy and depression
- the etiology of depression in patients with seizure disorder
- how to treat depression in this population.

High comorbidity

Depression rates are higher in epilepsy patients than in the general population (1% to 3% of men, 2% to 9% of women).² Depression can be diagnosed in:

- 20% to 30% of patients with recurrent seizures
- 6% to 9% of patients in remission
- 50% to 55% of patients attending hospital epilepsy clinics and video telemetry units.³

Major depressive disorder is more common and severe in patients with a seizure

disorder than in those with other neurologic and chronic medical conditions.⁴ Men with epilepsy have a higher risk of developing depression, whereas in the general population depression is more prevalent in women.⁵ Major depression may be more common in patients with complex partial seizures—specifically temporal lobe epilepsy (TLE), the most common form of epilepsy in adults.⁴ An estimated 3% to 21% of epileptic patients have dysthymic disorder.⁵ The prevalence of bipolar disorder in this population is unknown.

Temporal relationship. Depression can be preictal, ictal, postictal, or interictal.⁴ One-third of patients with partial seizures report premonitory symptoms, usually before secondary generalized tonic clonic seizures.⁵

- Preictal depression occurs hours to days before a seizure and often is relieved by the convulsion.

- Ictal depression—more common in TLE—occurs as an aura in approximately 1% of patients. Onset is sudden and ranges from mild sadness to profound helplessness and despair. Treating the seizures also treats the depression.

- Postictal depression in TLE patients lasts hours to days after a seizure.

- Interictal depression affects up to two-thirds of epilepsy patients, especially those with severe or frequent seizures. Treat interictal depression separately from the seizures.

Differential diagnosis

Assessing and treating a depressive episode is similar in patients with or without epilepsy. In medically ill patients, DSM-IV-TR recommends using diagnostic criteria for major depression and treating the depression whatever its cause.

Search for seizure cause. Although 70% of epilepsies are idiopathic, search for the cause of a patient's seizures. Neuroimaging can rule out a stroke, cerebral tumor, or traumatic brain injury as the cause of both depression and epilepsy.⁴ Even after exhaustive study, 10% to 20% of epilepsy cases cannot be identified by electroencephalography (EEG).

Seizure type and location, severity, laterality of seizure focus, and frequency are important variables in the etiology of depression in patients with epilepsy.⁶ Similar changes in neurotransmitters—serotonin, noradrenaline, dopamine, and gamma-aminobutyric acid—are observed in both depression and epilepsy.⁵

Characterize depressive symptoms.

Consider involving the patient's spouse or partner in the discussion to validate and augment the patient's report. Often patients describe depressive symptoms—such as sleep problems, changes in appetite, loss of libido, and impaired cognition—that could be side effects of AEDs or symptoms of epilepsy.

Depression associated with epilepsy has distinct features. Blumer⁷ coined the term interictal dysphoric disorder (IDD), characterized by these types of symptoms:

- somatoform (anergia, pain, and insomnia)
- affective (irritability, euphoric moods, fear, and anxiety).

The Neurological Disorders Depression Inventory for Epilepsy, an online, 6-item, self-assessment tool, can help identify a possible major depressive episode (see *Related Resources*, page 41).

Is it bipolar depression? Determine if your patient's depression might be part of a bipolar disorder. This diagnosis may modify your treatment plan because antidepressants could trigger a manic or hypomanic episode. Also look for untreated psychotic features, which are associated with a suicide completion rate of 19% in bipolar epilepsy patients.⁶

Screen for suicidal behavior. Ask about suicidal ideation, plans, and attempts within the past month and in the patient's lifetime.⁴ Compared with the general population, the risk of suicide is 4 to 5 times higher in depressed persons with epilepsy⁸ and 25 times higher in those with TLE (*Table 1*, page 30).⁹ Overdoses are used in 80% to 90% of suicide attempts among patients with epilepsy, perhaps because of the availability of AEDs.³

Clinical Point

Often patients describe depressive symptoms that could be side effects of antiepileptic drugs or symptoms of epilepsy

continued

Clinical Point

Compared with the general population, the risk of suicide is 4 to 5 times higher in depressed persons with epilepsy

Table 1
Risk factors for suicide among epilepsy patients

Age 25 to 49 years
Male gender
Coexisting psychopathology, including personality disorders
Temporal lobe epilepsy
Personal difficulties such as social or work-related problems
Prolonged duration of epilepsy
Poor seizure control
Source: Reference 3

Perceived social stigma, inability to drive, AEDs' effects on cognition, and interpersonal and psychosocial issues may contribute to the patient's depression. Ask about social support, recent stressful events, and financial and vocational impact of the seizure disorder.⁶

CASE CONTINUED

Searching for a cause

Previously Ms. A worked steadily and led an active life. She does not have a history of mania or hypomania. She is alert, neat, and cooperative. She sits calmly, gestures appropriately when speaking, and has no abnormal movements. She is subdued but says she is a bit anxious.

Her workup includes routine hematologic and biochemical parameters, EEG, and brain MRI. All are negative.

We look for signs of psychosis, mania, or personality disorder, which can affect the clinical presentation and influence diagnosis and management. Ms. A's depressive episodes meet DSM-IV-TR criteria for nonmelancholic recurrent depression, but she has atypical features such as feeling "fuzzy-headed," having slurred speech, and losing track of time.

Her episodes are sudden, brief, and involve altered awareness followed by amnesia. She describes déjà vu, perceptual changes, and motor speech problems.

Ms. A's behavioral syndrome is consistent with complex partial seizure with frontal and temporal foci. Her dominant brain hemisphere likely is involved because speech is affected.

We classify her depression as postictal because of the temporal relationship with the seizures. Thus, controlling the seizures should prevent the depression.

Depression as a side effect

Depression in epilepsy is multifactorial, and pharmacotherapy is one of many biologic and psychosocial risk factors.

AED's negative effects such as depression and cognitive changes may be caused by polypharmacy, drug-induced folate deficiency, drug titration and dosage, or withdrawal.⁶ Patients receiving combination therapies are more likely to be depressed.⁴ AED polypharmacy might be a marker for refractory epilepsy, and thus depression can be caused by both the neurologic illness and its treatment. Shorvon et al¹⁰ reported improved alertness, concentration, drive, mood, and sociability after patients' polytherapy was reduced to monotherapy, especially carbamazepine monotherapy.

Onset or worsening of depression could coincide with starting a new AED.⁶ Phenytoin and topiramate are most closely associated with acute depression during initial treatment.³ One study noted that depressed patients taking barbiturates as part of polytherapy were significantly more depressed than those taking carbamazepine.⁸ Phenytoin can produce depression, suicidal ideation, and suicidal and parasuicidal behavior.

Patients starting tiagabine might develop agitation, withdrawal, and mood disturbance that could suggest depression.³ With topiramate the rate of affective symptoms is dose-dependent, with an incidence of 9% with 200 mg/d and 19% with 1,000 mg/d.¹¹

Some patients (11% to 15%) receiving polytherapy that includes liver enzyme-inducing AEDs (carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, and topiramate) present with decreased serum, erythrocyte, and cerebrospinal fluid folate levels, which is associated with depression.⁴

Bipolar depression. AEDs such as carbamazepine, valproic acid, and lamotrigine

continued on page 35

continued from page 30

are used for bipolar maintenance therapy in patients without a seizure disorder. Lamotrigine is used to treat bipolar depression in non-epilepsy patients. Therefore, these AEDs are first-line treatment for comorbid epilepsy and bipolar depression.¹²

Using antidepressants

Effectively treating depression in epilepsy patients (*Algorithm*) encompasses assessment of prescribed AEDs and the use of antidepressants, electroconvulsive therapy (ECT), and psychotherapy. No evidence indicates that any 1 antidepressant is more effective than others for treating depression in patients with epilepsy. When starting an antidepressant, consider the drug's effect on seizure threshold, its efficacy, and drug-drug interactions.

Seizure risk. Seizures are a rare but serious adverse effect of most antidepressants (*Table 2, page 36*).¹³ Compared with the incidence of first seizures in the general population (<0.1%), the prevalence of seizures occurring with therapeutic doses of antidepressant is increased (0.1% to 4%).⁴ Generalized tonic-clonic seizures are associated with increased mortality in tricyclic antidepressant (TCA) overdose, especially with amitriptyline, maprotiline, and clomipramine.

Desipramine, monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and trazodone are preferred options for depressed epilepsy patients because these drugs lower the seizure threshold less than other antidepressants, with a 1% to 1.5% incidence of seizures during the first 2 years of treatment.¹⁴ Because most seizures reported with these medications are dose-related, blood level monitoring is helpful. Avoid bupropion, which has a seizure rate double that of other antidepressants.⁶

Clinical trial experience and EEG studies suggest that the SSRIs are less epileptogenic than TCAs. MAOIs also are less likely than TCAs to cause seizures but can cause excessive sedation when coadministered with barbiturates. The only double-blind trial of antidepressants (amitriptyline, nomifen-

Algorithm

Stepwise approach to treating comorbid psychiatric disorders and epilepsy

Step 1

Determine the etiology of depression

Step 2

Assess AED regimen

Avoid polytherapy

Consider the adverse psychotropic effects with phenobarbital and primidone

Consider changing to carbamazepine or valproic acid, if clinically appropriate; modified release preparations usually are better tolerated

Monitor total plasma levels of AEDs

Screen erythrocyte folate levels

Step 3

Start the antidepressant at a low dose and then increase slowly

Start with drugs of choice such as selective serotonin reuptake inhibitors

Bupropion, maprotiline, and clomipramine are contraindicated in patients with a history of seizures, brain injury, or EEG abnormality

Assess for antidepressant-AED interactions

Continue to monitor plasma levels of AEDs

Remember that all antidepressants can lower the seizure threshold

Step 4

Consider ECT for refractory or severe depression

Step 5

Recommend support groups and cognitive-behavioral therapy

Communicate regularly with patient's neurologist, primary care physician, and other specialists involved in his or her care

AEDs: antiepileptic drugs; ECT: electroconvulsive therapy; EEG: electroencephalography

Clinical Point

Desipramine, MAOIs, SSRIs, and trazodone are preferred options because they lower the seizure threshold less than other antidepressants

sine, and placebo) to treat comorbid depression and epilepsy found no significant differences among drugs or placebo.⁸

Drug-drug interactions. Consider the cytochrome P450 enzyme system when choosing an antidepressant for an epilepsy

Clinical Point

Antidepressants can alter serum levels of phenobarbital and carbamazepine, and antiepileptic drugs usually reduce antidepressant levels

Table 2

Antidepressants' seizure potential in any patient

Antidepressant	Risk of seizures (%)
High risk (not indicated for epilepsy patients)	
Bupropion <450 mg	0.4
450 to 600 mg	0.6 to 2.19
Clomipramine	0.5 to 1.66
Maprotiline	0.4 to 15.6
Intermediate risk	
Tricyclics	0.1 to 4
Amitriptyline	0.4 to 0.5
Imipramine	0.6 to 0.9
Low risk	
Citalopram	<0.1
Fluoxetine	<0.1 to 0.2
Fluvoxamine	0.2
Paroxetine	0.1
Sertraline	< 0.1
Trazodone	< 0.1
Venlafaxine	0.1 to 0.2
Mirtazapine	< 0.1
Duloxetine	0.2

Source: References 6,13

patient.⁶ Antidepressants can alter serum levels of phenobarbital and carbamazepine, and AEDs usually reduce antidepressant levels.⁸ For example, carbamazepine could lower TCA levels, valproic acid might elevate TCA levels,¹⁵ and imipramine and nortriptyline might increase phenytoin levels. Similarly, monitor TCA levels during AED withdrawal, as increased TCA concentrations can result in toxicity and concomitant behavioral effects.¹³

SSRIs may cause a dramatic rise in AED levels, leading to dizziness, ataxia, confusion, and somnolence. Sertraline and citalopram seem less likely to increase AED levels than fluvoxamine or fluoxetine.⁶ Fluvoxamine inhibits carbamazepine and phenytoin metabolism.³ Among SSRIs, most case reports of drug-drug interactions involve fluoxetine, which inhibits cyto-

chrome enzymes and may increase carbamazepine or phenytoin levels, sometimes with clinical consequences.⁶ Monitor electrolytes when prescribing carbamazepine or oxcarbazepine with an SSRI because the combination may cause hyponatremia.

Start antidepressants at doses lower than used in patients without epilepsy, and gradually increase until depression remits. Periodically check AED levels during antidepressant treatment, and adjust dosages to maintain a therapeutic level.

Nondrug therapies

ECT. Consider ECT for patients with refractory or severe depression. ECT can be lifesaving—especially in patients with psychotic depression—and is a viable and safe alternative to antidepressants for patients with epilepsy.³

ECT can raise a patient's seizure threshold.¹³ Unilateral nondominant electrode placement is recommended to minimize the combined cognitive side effects of AEDs and ECT. Except for those at high risk of status epilepticus, advise patients not to take their AEDs the morning of ECT treatments.

Support groups. Epilepsy can affect many aspects of a patient's life, including education, employment, family life, and self-esteem.¹³ Epilepsy support groups can provide emotional support by introducing patients to others with a seizure disorder. Patients often experience a sense of relief when they discover that they are not alone and other group members share similar dilemmas. Becu et al¹⁶ reported that self-help group intervention characterized by education, support, and socialization significantly reduced depression scores in epilepsy patients. These groups often offer education about the nature of the patient's illness.

Psychotherapy. Because psychosocial factors can play a role in the expression of depression in patients with epilepsy, cognitive, behavioral, and interpersonal therapy may be useful.⁶ These treatment modalities provide an opportunity to educate patients and

continued on page 41

continued from page 36

families about epilepsy, explore emotional reactions to the condition, and correct false beliefs about the illness. Goldstein¹⁷ showed that after 12 sessions of cognitive-behavioral therapy, 6 patients with chronic, poorly controlled epilepsy reported reduced depression scores. Their initial epilepsy-related problem had less impact on their daily lives and self-rated work and social adjustment improved significantly.

CASE CONTINUED

Seeing results

We treat Ms. A's mood episodes with carbamazepine, titrated up to 400 mg bid. Her seizures decrease in frequency, and after 1 month her depressive symptoms subside. Her coworkers describe Ms. A as more outgoing and full of energy.

We refer Ms. A to an epilepsy support group that meets twice a month, and she is relieved to know other patients experience similar symptoms. She continues individual psychotherapy, which helps her adjust to epilepsy's chronic nature and complications.

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Related Resources

- Epilepsy Foundation. Epilepsy and mood disorders. www.epilepsyfoundation.org/programs/mood.
- Epilepsy Foundation. Neurological Disorders Depression Inventory for Epilepsy Screening Tool. www.epilepsyfoundation.org/about/related/mood/nddi-tool.cfm.

Drug Brand Names

Amitriptyline • Elavil	Maprotiline • Ludiomil
Amoxapine • Asendin	Mirtazapine • Remeron
Bupropion • Wellbutrin	Nefazodone • Serzone
Carbamazepine • Tegretol	Nortriptyline • Aventyl, Pamelor
Citalopram • Celexa	Oxcarbazepine • Trileptal
Clomipramine • Anafranil	Paroxetine • Paxil
Desipramine • Norpramin	Phenytoin • Dilantin
Doxepin • Sinequan	Primidone • Mysoline
Duloxetine • Cymbalta	Sertraline • Zoloft
Fluoxetine • Prozac	Tiagabine • Gabitril
Fluvoxamine • Luvox	Topiramate • Topamax
Imipramine • Tofranil	Trazodone • Desyrel
Lamotrigine • Lamictal	Valproic acid • Depakote
Lithium • Eskalith, Lithobid	Venlafaxine • Effexor
Nomifensine • Merital	

Disclosure

The authors report no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Clinical Point

Self-help groups characterized by education, support, and socialization significantly reduced depression scores in epilepsy patients

Bottom Line

Determining if your patient's depression occurs before, during, or immediately after a seizure will guide your treatment plan. Avoid antiepileptic drug (AED) polypharmacy, which may exacerbate depressive symptoms. Depression is the primary risk factor for suicide in patients with epilepsy. Evaluate the risk of seizures associated with antidepressants, and watch for drug-drug interactions between AEDs and antidepressants.