By Steven Karceski, MD

Exploring the Connection Between Mood Disorders and Epilepsy

The interaction between seizures and depression is more complex than you might think, ranging from the psychological to the cellular level. Here's the latest thinking.

Depression and epilepsy are comorbid conditions. By definition, *comorbidity* means that the associated illness occurs more often than would be expected compared to populations of patients who do not have the other illness. However, *comorbidity* does not imply *causality*.[1] In other words, because the two illnesses occur together does not mean that one *causes* the other. However, the conditions may share a common underlying pathological mechanism. Neurotransmitters (or abnormalities in neurotransmitters) may be the "link." In any case, it has become very clear that the comorbid illness can significantly affect quality of life. In fact, the quality of life of people with epilepsy is influenced *more* by the presence of depression than the frequency of their seizures.[2]

Mood Disorders and Epilepsy

The association between depression and anxiety has been observed for centuries: Hippocrates in 400 B.C. said, "Melancholics ordinarily become epileptics."[3] In more recent years, this association has been carefully studied. First, to understand the extent to which the two illnesses are related. Second, to illuminate the underlying causes of both. And third, to evaluate therapies which may be effective for *both* conditions. If monotherapy is the goal, it is logical to select a single treatment in order to optimize the quality of life of persons who suffer from both conditions.

The answer to the first question is simply this: many people with epilepsy are also depressed. A recent survey of over 85,000 people evaluated the prevalence of bipolar symptoms in person with chronic illnesses compared to healthy controls.[4] The surveys included questions from the Mood Disorder Questionnaire. Results were used to compare the rates of bipolar symptoms in people with epilepsy (1,236 respondents), migraine (8,994 respondents), asthma (7,951 respondents), and diabetes (7,342 respondents) versus healthy controls (57,172 respondents). Symptoms of bipolar disorder were found in 12.2 percent of people with epilepsy, 7.2 percent of migraineurs, 6.3 percent of asthmatics, 3.2 percent of diabetics and 1.7 percent of the controls. In other words, the prevalence of the symptoms of bipolar disorder was *six times higher* in people with epilepsy than in the control group!

Major depressive disorder (MDD), which is defined as having symptoms of depression for more than two weeks, is estimated to occur in 5.8 percent of the population. In those with epilepsy, the number with MDD is eight to 48 percent (an average of 29 percent).[1] In a community-based study of people with epilepsy, the rate of depression was 37 percent. In patients referred to an epilepsy center—generally a group of people whose seizures are very refractory to medications—the rate of depression was 50 percent.[3]

The number of people who have epilepsy and anxiety is a little more difficult to discern. Although a higher prevalence has been observed,[5] the association has been less well studied. Gabb stated that the rate of anxiety was 13.3 percent in the general population. In persons with epilepsy, up to 52 percent also reported symptoms of anxiety.[1] Like depression, anxiety often occurs in people with seizures. In fact, in people who had epilepsy and reported depression, 72.9 percent *also* reported having anxiety.[1]

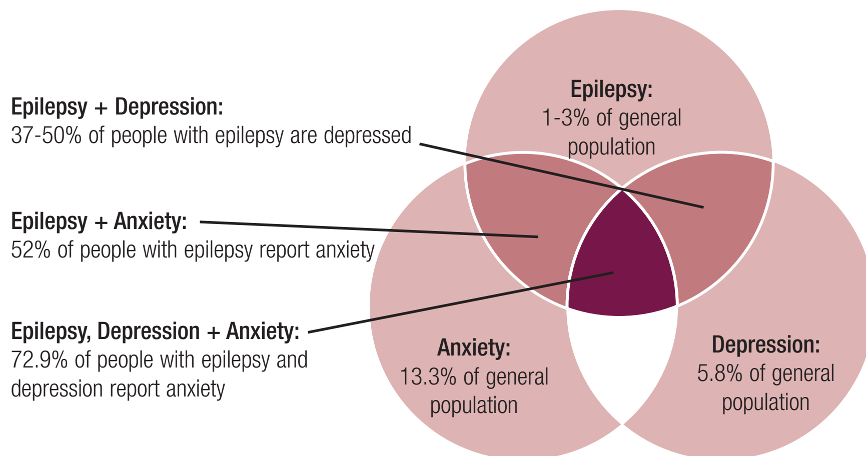
What's the Common Denominator?

It is interesting that epilepsy, anxiety, depression and especially bipolar disorder all cause symptoms which emerge episodically. The conditions tend to be chronic (though not always). Although there are many different classes of medications for each illness, it is interesting that antiepileptic drugs (AEDs) are effective *both* for seizures and certain mood disorders. Is there a common underlying cause? Or do these illnesses share a common pathological mechanism? The answers remain vague; however, further research may uncover the answers.

One possible connection between these illnesses occurs on the level of neurotransmitters. We know, for instance, that in rats, low levels of serotonin and norepinephrine can cause seizures. Positron emission tomography, using ligands that bind to serotonin receptors (5-HT_{1A}), have demonstrated decreased binding ipsilateral to the seizure focus in persons with temporal lobe epilepsy.[3] In addition, certain medications (*e.g.*, reserpine) which effectively deplete stores of norepinephrine are known to cause seizures. One antidepressant medication, imipramine, which causes an increase in *both* serotonin and norepinephrine, reduced the frequency of myoclonic seizures in a double-blind study.[3] Although none of these studies conclusively proves this "link," the evidence is compelling.

Another possible connection between mood disorders and epilepsy may be at the level of the cell (or neural network). Both epilepsy and depression can occur after

Figure 1. Epilepsy, Depression and Anxiety: Estimates of Their Occurrence



injury to either the frontal or temporal lobes. Reduced cerebral blood flow to the mesial frontal lobe has been reported in persons with depression. Atrophy of certain deep temporal structures (like the hippocampus) has also been reported in depression.[1,3] Mesial temporal sclerosis, a specific type of scarring in the hippocampus, is a well-known cause of temporal lobe epilepsy. In addition to alterations in neurotransmitter levels, injury to certain areas of the brain may predispose people to developing both seizures and depression.

It has long been known that some AEDs also have mood-stabilizing effects. Carbamazepine, lamotrigine and valproate are commonly used by both psychiatrists and neurologists. These medications have one common mechanism of action: they increase serotonin levels. One possible reason that these agents work for both conditions is simple: serotonin has *both* anti-seizure and anti-depressant effects. The vagus nerve stimulator, a device used in the treatment of refractory seizures, was just approved by the FDA as a treatment for medication-resistant depression. Although its mechanism of action remains largely unknown, one effect is to increase the release of norepinephrine via connections through the locus coeruleus. Here again, the treatment affects a neurotransmitter which has been implicated in both illnesses.

Treating the Co-morbid Illness Improves Quality of Life

It is now recognized that in patients with epilepsy, the presence of depression correlates more strongly with a poor quality of life than the frequency of the seizures.[2] A person with seizures requires therapy for his or her epilepsy; however, if the depression is left untreated, the individual may continue to do very poorly. This translates into greater numbers of doctor's visits, use of medical systems and a higher cost of care. For the patient, this may result in ongoing difficulties with work (*e.g.*, underemployment) or education. In other words, the psychosocial impact is great.

At each office visit, neurologists will often ask questions about seizures and side effects. Unfortunately, patients are not always asked about their mood. In addition, because of the stigma associated with "mental illness," they may be less likely to volunteer information in this area. However, if asked, patients are more likely to discuss their mood. One possible way to address this is to screen patients (perhaps in the waiting area with a questionnaire) for signs and symptoms of depression or anxiety. When identified, the next question is: what should be done?

Many treatments are now available for depression. Some anti-seizure medications may help both disorders. If monotherapy is sought, preferentially selecting one of these agents may be the answer. Other patients may require both an anti-seizure medication and an anti-depressant. Finally, some patients will require medicines for both illnesses as well as psychotherapy. Once depression (or anxiety) has been identified as a comorbid illness, it is reasonable to ask for help from our colleagues in psychiatry. With all of the available medications, which one(s) is best for an individual patient? Does this person also require psychotherapy? In other words, a team approach may be needed in order to optimize the person's quality of life.

Conclusions

Epilepsy, depression, anxiety and bipolar disorder commonly co-exist. Although there are many possible explanations, it is becoming increasingly evident that both mood and seizure disorders require treatment to achieve the best quality of life.

Some antiepileptic drugs are effective for both illnesses; in some instances, selection of one of these agents may result in improvements in both conditions. Other patients may require combination therapy. Finally, some people will need psychotherapy to cope with their mood disorders. A team approach that involves the neurologist, psychiatrist and psychologist may help to optimize the evaluation and treatment of people with epilepsy and mood disorders. **PN**

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Steven Karceski, MD is Assistant Clinical Professor of Neurology at the College of Physicians & Surgeons of Columbia University and Director of the Columbia Epilepsy Center at the Atlantic Neuroscience Institute.