ABSTRACT

Depression commonly is comorbid with epilepsy and, of the depressive disorders, major depression is most common. Depression is often comorbid with an anxiety disorder (e.g., generalized anxiety, social phobia, post-traumatic stress disorder, panic disorder, or obsessive-compulsive disorder), in the general public and in persons with epilepsy (PWE). This discussion will focus on mood disorders in PWE and treatment options for those adult PWE with a unipolar mood disorder. The presentation of mood disorders forms a spectrum across patients. Mood disorders remain undiagnosed and undertreated in PWE, in part, because many healthcare providers think these disorders are a normal reaction to a chronic illness. However, recent epidemiologic studies suggest that the relationship may be bidirectional (i.e., causal instead of merely comorbid), but the nature of this relationship is unclear. Undertreating depression in PWE not only jeopardizes patients' psychiatric health but also undermines the patients' ability to habituate to their medical illness or follow and comply with treatment regimens. Depression in epilepsy also has been shown to decrease the patient's quality of life and increase the patient's risk for suicide. Therefore, it is important to continue research into the mechanisms of mood/anxiety disorders and epilepsy and to make their diagnoses a higher priority in the management of PWE. There are limited evidence-based data for treating depression specifically in PWE. However, the psychiatric literature provides a framework for treatment strategies. As with treatment of depression in the general public, total remission is the treatment goal because residual symptoms are strong predictors of relapse.

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DEFINING THE PROBLEM

Mood disorders usually fall into 1 of 4 categories: major depressive disorder, dysthyemic disorder, minor depression, or depression not otherwise specified. Major depressive disorder is a severe form of depression and is defined by the presence of at least 5 of the following symptoms for at least 2 weeks: depressed mood, anhedonia, worthlessness or guilt, fatigue, substantial weight loss or gain (5% in 1 month), insomnia or hypersomnia, difficulty concentrating, agitation or retardation, and suicidal ideation. The symptoms usually are acute and may resolve, at least partially, but frequently recur. Dysthymic disorder is a milder but more persistent form of depression (symptoms are present frequently for at least 2 years); residual symptoms can occur between episodes and significantly affect the patient. Minor depression is also a milder but more persistent form of depression and is marked by at least 2 but fewer than 5 of the symptoms listed earlier in this section.1 Mood disorders can also be described as having a unipolar or bipolar presentation. Unipolar depression is characterized by depressive episodes with periods of partial or complete remission to normal mood states (euthymia). Bipolar depression is defined by the...
occurrence of at least 1 manic episode or episode of abnormal mood elevation in the context of a depressive disorder. Because bipolar depressive disorders appear to have unique features from unipolar depressive disorders, their treatments also must be individualized. These issues have been commented upon elsewhere. For simplicity, treatment issues in this article will refer only to unipolar depression.

Depression is an important problem among the general public, and even more so among persons with epilepsy (PWE). The lifetime prevalence estimate from the Epidemiological Catchment Area study was 5.8%, but other studies indicate that up to 26% of women and 12% of men will experience a depressive disorder in their lifetime. Depression commonly is comorbid with epilepsy and, of the depressive disorders, major depression is most common. Mean lifetime-to-date prevalence of major depression in PWE is estimated to be 29% based on 7 studies (ranging from 8%–48%). In 5 of these studies, approximately 25% of PWE reported symptoms associated with an adjustment disorder with depressed mood, dysthymic disorders, or depressive disorder not otherwise specified.

In the general population and in PWE, depression often is comorbid with an anxiety disorder (eg, generalized anxiety, social phobia, post-traumatic stress disorder, panic disorder, or obsessive-compulsive disorder). Anxiety disorders are the most common mental illness in the United States, affecting 19.1 million (13.3%) of the adult population. In a study involving 174 PWE, 48.9% of the participants had a current Axis I disorder, of which 24.1% had a mood disorder and 52.3% had an anxiety disorder. Of note, 72.9% of the PWE with a depressive disorder also had an anxiety disorder. Thus, as with the general population, mood and anxiety disorders form a spectrum across PWE.

Clinically, epilepsy and affective disorders are episodic illnesses. In fact, the symptoms of depression in epilepsy can be classified by their temporal relation to seizure occurrence: preictal (before seizure onset), postictal (after a seizure), ictal (during a seizure), and interictal (unrelated to seizure occurrence). Intercital depression is the most common affective disorder in PWE, but frequently the symptoms do not meet any of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria. PWE can meet the criteria for Axis I mood disorders, but they also may have lower levels of depression that significantly diminish their quality of life and functioning. The focus of the remaining section of this review article will be concerned with depressive disorders.

The frequency and severity of depression in PWE remains underdiagnosed and undertreated. In studies involving 76 adult PWE, 43% of those participants with a current major depressive disorder and 68% of those PWE with a current minor depressive disorder were untreated; 38% of those participants who had a history of lifetime episodes of major depression had never received therapy for depression. Unfortunately, these discrepancies also exist for pediatric PWE. In a study involving 44 pediatric PWE, of whom 26% had significantly increased depression scores (based on the Child Depression Inventory) and 16% met the criteria for significant anxiety symptomology (based on the Revised Children’s Manifest Anxiety Scale), none of the study participants had been previously identified as having depression or anxiety.

A Link Between Epilepsy and Depression?

It is unclear why depression and anxiety are underdiagnosed in PWE. These disorders are common in other chronic illnesses, such as heart disease, cancer, type 2 diabetes mellitus, multiple sclerosis, and stroke. The frequent presence of depression and anxiety in chronic conditions may be considered erroneously as an expected reaction to the illness rather than as an underlying disorder. Therefore, patients may not seek treatment, and clinicians may not inquire about a treatment. Nonetheless, there is a clear relationship that must be addressed. The exact nature of this comorbid relationship has not been defined. Comorbidity does not necessarily imply causality. Intuitively, clinicians understand that epilepsy begets depression, but does depression beget epilepsy? Is the link bidirectional? Recent data from epidemiologic studies suggest that there may be a link between depression and epilepsy, but the nature of this relationship is unclear.

In a community-based epidemiologic study of incident cases of a patient whose first unprovoked seizure occurred at the age of at least 55 years, a history of depression (using DSM-III-R criteria) was 6 times more frequent in those patients with seizure than among control subjects (95% confidence interval, 1.56–22; P = .003), even when controlling for age, sex, length of medical follow-up, and medical therapies for
depression. Similar findings have been found in pediatric patients.

Genetics and experience appear to play a role in the onset of depression and epilepsy. However, the modes of inheritance likely are complex and multifactorial. In general, genetic predisposition may be important in the development of seizure disorders, and stress also may be a factor in activating these vulnerabilities.

Because mood and anxiety disorders form a spectrum across PWE, they can be difficult to detect and to diagnose. In 2 studies describing interictal depression, a substantial portion of the study population had to be classified as having atypical depression (25%) or as having depressive disorder not otherwise specified (50%). In interictal depression, the symptom cluster may mimic dysthymic disorder with symptomatic periods lasting from hours to days with intermittent symptom-free periods of similar duration. Kanner et al described this as “dysthymic-like disorder of epilepsy” characterized by anhedonia (with or without hopelessness), fatigue, anxiety, irritability, poor frustration tolerance, and mood lability with bouts of crying—all severe enough to disrupt activities, interpersonal relationships, and overall quality of life and to cause patients to seek treatment. Of note, PWE and a dysthymic-like disorder of epilepsy may also be unrecognized and undertreated.

**Shared Neural Mechanisms of Epilepsy and Depression**

Diminished serotonin and noradrenaline appear to be important in the development of idiopathic depression. The benefits of selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) in treating depression are well established. Emerging evidence suggests that low levels of these 2 neurotransmitters also may play a role in epilepsy, and that noradrenergic and/or serotonergic transmission may describe, at least in part, a causal relationship between epilepsy and depression. As reviewed by Jobe, experimentally induced noradrenergic and serotonergic deficits can contribute to epileptic episodes and affective disorders, and experimentally induced increases in noradrenaline and serotonin can be anticonvulsant and antidepressive. Antiepileptic drugs (AEDs) can be used to treat depression; noradrenergic or serotonergic activation appears to contribute to the anticonvulsant effects of AEDs. Also, positron emission tomography studies of PWE and control subjects show that patients with severe temporal lobe epilepsy (TLE) showed reduced 5-HT1A receptor binding potential in the electroencephalogram focus and its limbic connections.

Paradoxically, SSRIs and SNRIs can lower the seizure threshold in some patients, and clinicians who prescribe these drugs for their patients with epilepsy should be aware of this important potential adverse effect. The seizure-inducing property of antidepressants appears to be caused by mechanisms other than those involving noradrenergic or serotonergic elevation. However, some antidepressants appear to be more of a risk than others.

Although the mounting evidence for the role of noradrenaline and serotonin is compelling, other factors most likely are involved in these 2 disorders. Brain-derived neurotrophic factor (BDNF) is expressed at lower levels in depression, and animal models show that BDNF appears to exert an antidepressant effect. BDNF expression in the central nervous system is modified by various insults to the brain, including stress, ischemia, seizure activity, and hypoglycemia. The amygdala and hippocampus interpret stressful stimuli and regulate appropriate responses; the hippocampus is affected by exposure to seizures. Glucocorticoids released in response to stress appear to damage the CA3 region of the hippocampus. Chronic TLE is associated with severely declined dentate neurogenesis in the adult hippocampus.

**The Importance of Treating Depression**

Undertreating depression in PWE not only jeopardizes the patient’s psychiatric health but also undermines the patients’ ability to habituate to their medical illness or follow and comply with treatment regimens. In all of the chronic illnesses mentioned in this article, depression is a major risk factor for the development of a physical illness.

There are several models to explain the role of depressive disorders in exacerbating disease progression in PWE. A model of “allostatic load” considers the hippocampal response to stressors. In patients with psychiatric disorders, the hippocampus may be damaged by repeated stressors (perhaps because of increased glucocorticoids and suppression of neurogenesis) that may result in hippocampal atrophy. The amygdala also may be affected with initial hyperacti-
vation and enlargement but with shrinkage during recurrent long-term depression (ie, the brain adapts to short periods of stress [allostasis], but prolonged stress [allostatic load] can impair neural plasticity). These models are speculative and suggest that stress in the form of depression may promote the hippocampal atrophy seen in PWE. In the integrative model of depression and chronic medical illness, major depression may decrease a patient’s ability to habituate to a chronic medical illness through a catch-22: the progressive functional decline associated with chronic medical illness may cause depression, and depression can precipitate additional functional impairment. Depression is associated with an approximately 50% increase in the medical costs related to chronic medical illness, even after controls are set for the severity of physical illness. The adverse effect of major depression on chronic illness can occur through health habits (eg, smoking, diet, and sedentary lifestyle), detrimental effect on adherence to medical regimens, and/or adverse physiologic effects (ie, decreased heart rate variability and increased adheresiveness of platelets).

Depression in epilepsy also has been shown to decrease patients’ quality of life and to increase their risk for suicide. Depression is among the most important factors affecting the quality of life of PWE and refractory disease. In one study, depression correlated with (and predicted most strongly) a patient’s quality of life. Depression also has been shown to be more important than is seizure rate in those patients with refractory epilepsy (Figure 1). In one study, depression was found to be the only predictor of quality of life (among comparisons to age, sex, marital status, seizure frequency, duration and type of seizure disorder, seizure localization, and number of AEDs).

In this study, depression in PWE (as measured by the self-report Beck Depression Inventory) was common (54%), severe (19% with suicidal thoughts), underdiagnosed (37%), and largely untreated (17% on antidepressants).

Therefore, not surprising, is the increased suicide prevalence among PWE compared to the general population (lifetime prevalence rates of 5%–14% vs 1.1%–1.2%). In a multicenter study, 12.2% of PWE had current suicidal ideation and 20.8% of patients had attempted suicide in their lifetime.

**DIAGNOSIS AND TREATMENT**

Depression not only is commonly comorbid with epilepsy but also is treatable. The first challenge is

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**Figure 1. Scatterplots Showing Correlation of Seizure Rate or Depression Rating Score with Health-Related Quality of Life**

A total of 195 consecutive patients at the Washington University in St. Louis Adult Outpatient Epilepsy Clinic were screened. Reprinted with permission from Gilliam. Neurology. 2002;58(suppl 5):S9-20.
diagnosis. There are several reliable, validated tools that can help to diagnose depression accurately and quickly in the general population—notably the Beck Depression Inventory and the Hamilton Depression Rating Scale. There has been some concern about the over-representation of somatic symptoms in these tools—in which nearly 33% of the items have a somatic focus—and their use in PWE. However, it appears that both psychometric tools have a valid use for treating PWE. The Neurological Disorders Depression Inventory, a newly developed psychometric evaluation instrument designed to diagnose depression in PWE, was tested involving 200 patients at 5 comprehensive epilepsy centers. The diagnostic tools were chosen according to their lack of association to medication or disease-related adverse effects. The result is a 6-item screening tool for rapid diagnosis, which may be available soon.38

Because depression has been recognized only recently as a common comorbid condition with epilepsy, there are limited evidence-based data for treatment in this population. Thus, the psychiatric literature is used for guidance on treatment algorithms. Once depression is diagnosed and defined according to seizure activity (ie, preictal, ictal, postictal, or interictal), clinicians must determine if the depressive symptoms are AED-related, particularly with phenobarbital, and should assess any psychosocial issues or need for individual, family, or group therapy.

As with the general population, antidepressants may be used for mild depression in PWE, but psychotherapy also serves an important role and may be preferred as the sole treatment in some patients. Antidepressants are recommended as first-line therapy for those PWE with moderate to severe depression; psychotherapy again may be warranted if psychosocial issues are important or relevant. The combination of psychotherapy and medication seems to be synergistic in the treatment of depression.

Figure 2 shows a proposed algorithm for using pharmacotherapy to treat unipolar depression in PWE. The algorithm is based on available clinical studies treating PWE and comorbid depression. First-line therapy is an SSRI or an SNRI but, as reported by Blumer and Zielinski, low to moderate dosages of tricyclic antidepressants (TCAs) also may be used.97 If a patient shows partial response, augmentation strategies may be used. If there is a lack of response, a different SSRI, SNRI, or a TCA can be tried. Barring success with that type of therapy, combinations of antidepressants may be effective, but the only evidence in this population is from Blumer who combined TCAs and SSRIs.40 As with all drug combinations, drug interactions must be assessed, especially between fluoxetine, paroxetine and, to a lesser extent, sertraline, when used with TCAs.2 Electroconvulsive therapy is reserved for patients who do not respond to medication and can be used in PWE.41,42 The Sidebar (see “Some Important Drug Interactions Between Antidepressants and Antiepileptic Drugs”) lists some important drug interactions between commonly used antidepressants and AEDs.43

**Figure 2. Proposed Algorithm for Treating Depression in Adult Patients with Unipolar Depression**

<table>
<thead>
<tr>
<th>Stage 1: Monotherapy</th>
<th>Stage 2: Monotherapy</th>
</tr>
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<tbody>
<tr>
<td>SSRIs or venlafaxine</td>
<td>SSRIs, TCAs, venlafaxine, or mirtazapine</td>
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</table>

**Stage 3: Monotherapy**

- SSRI, TCA, venlafaxine, or mirtazapine from a class other than that used in stage 1 or 2; OR
- Combined Antidepressants
  - TCA + SSRI, TCA + venlafaxine or mirtazapine

**Stage 4: Combined Antidepressants**

- TCA + SSRI, TCA + venlafaxine or mirtazapine

**Stage 5: ECT**

ECT = electroconvulsive therapy; SSRI = serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

Adapted with permission from Crismon et al. J Clin Psychiatry. 1999;60:142-156.41
An important challenge in treating depression, in the general population and in PWE, is the goal of treating to remission. Many clinical studies cite success rates of more than 50% improvement on a depression rating scale. For patients with moderate or severe depressive symptoms, even a 50% improvement still leaves the patient partially disabled by the depression. Paykel et al showed clearly that residual depressive symptoms, even a 50% improvement still leaves the patient partially disabled by the depression. Thus, the goal, which is attainable, is to treat to remission if possible.

CONCLUSIONS

Depression and anxiety, as defined disorders or presenting as a spectrum of symptoms, in PWE are more common than was previously thought and have significant detrimental effects on the patient’s well-being—physical and psychological. Mood and anxiety disorders do not appear to be strictly reactions to this chronic illness. Research into the underlying mechanisms is critical as the relationship between epilepsy and psychiatric disorders unfolds. Meanwhile, clinicians can make screening for depression or anxiety a higher priority in the management of PWE. Once diagnosed, treatment approaches may be similar to those approaches for treating depression in the general population, with complete symptom remission as the treatment goal.

REFERENCES