COMORBID DEPRESSIVE DISORDERS IN EPILEPSY

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Case Presentation

A 27-year-old woman presented to the emergency room after having witnessed generalized tonic clonic seizure while asleep. Birth and development were normal. She had suffered a single febrile seizure at 13 months of age, but had no other seizure risk factors. She was otherwise well except for a history of depression for which she was taking sertraline. Depressive symptoms had been well controlled over the past 3 months, but she had been under increased stress working to finish a doctoral thesis. Neurological examination was normal. Magnetic resonance imaging (MRI) showed modest asymmetry of the hippocampi, slightly smaller on the right, but no abnormal signal and well-preserved laminar anatomy. An electroencephalogram was negative. She was discharged from the emergency room with no treatment. Three weeks later, the patient's boyfriend witnessed an episode of behavioral arrest with lip smacking and swallowing automatisms lasting 45 seconds, after which the patient was confused for 20–30 minutes. The next morning she and her boyfriend kept a previously scheduled appointment with a neurologist.

Introduction

Depression is the most common comorbid psychiatric disorder in patients with epilepsy,[1] yet it remains underrecognized and undertreated. Population-based studies have established that one in three patients with epilepsy will have experienced a depressive episode in the course of their life.[1] While depression in people with epilepsy is typically considered to be a consequence of the seizure disorder, data have demonstrated a bidirectional relation between the two conditions. Thus, not only are people with epilepsy at greater risk for developing a depressive disorder, but people with a history of depression have a 3- to 7-fold higher risk for developing epilepsy.[2-4] Furthermore, in one of these studies,[4] a prior history of suicidality was associated with a 5-fold increased risk for developing epilepsy. Such bidirectional relationships suggest that common pathogenic mechanisms are operant in both conditions, with the presence of one disorder potentially facilitating the development of the other.

Comorbid Depressive Disorders

Early recognition and treatment of comorbid depressive disorders are of the essence given that they impact the life of the patient with epilepsy at several levels.

Increased Suicidality Risk

Patients with epilepsy, without any comorbid condition have a 2-fold higher risk for committing suicide. In the presence of a mood disorder, the risk increases by 32-fold.[5]

Negative Impact on Quality of Life

Five studies demonstrated that depression is the most powerful predictor of health-related reduction in quality of life in people with pharmacoresistant epilepsy, even after controlling for seizure frequency, severity, and other psychosocial variables.[6-9] In one study, however, depression was significantly associated with poor quality of life scores on the 89-item Quality of Life in Epilepsy Inventory, independent of seizure type; however, in one study the investigators found that seizure freedom for the last 3 months improved the quality of life ratings.[10]

Impact on Costs and Use of Medical Services

Depression in people with epilepsy significantly increases the healthcare costs associated with the management of the seizure disorder. One study found that patients with untreated depression used significantly more health resources of all types, independent of seizure type.[11] Furthermore, mild to moderate depression was associated with a 2-fold increase in medical visits compared with nondepressed controls, while severe depression was associated with a 4-fold increase. The presence and severity of depression was a predictor of lower disability scores, irrespective of the duration of the seizure disorder.

Impact on Control of Seizures

Recent studies have suggested that a lifetime history of depression is predictive of a poorer response to pharmacologic and surgical treatment of the seizure disorder. Indeed, in one study of 780 patients with new-onset epilepsy followed for a period of 5 years, a lifetime history of depression was associated with a 2-fold higher risk for developing pharmacoresistant epilepsy.[12] Likewise, in a study of 100 consecutive patients with pharmacoresistant temporal lobe epilepsy, who underwent an anterior temporal lobectomy, a lifetime history of depression was predictive of a failure to reach seizure freedom after surgery.[13] Whether early and successful treatment of the depressive disorder prevents those risks is yet to be established. Such risks may be an expression of the bidirectional relation between depressive disorders and epilepsy, alluded to previously, explained by common pathogenic mechanisms. These mechanisms include abnormal central nervous system activity of several neurotransmitters, particularly serotonin (5-hydroxytryptamine, 5-HT), norepinephrine, dopamine, γ-aminobutyric acid, and glutamate; and hyperactive hypothalamic–pituitary–adrenal axis, which in turn can also explain common structural

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and functional abnormalities such as the atrophy of temporal and frontal lobe structures (identified by high-resolution MRI and volumetric measurements), in the amygdala, hippocampus, entorhinal cortex, temporal lateral neocortex, prefrontal, orbitofrontal, and mesial frontal cortex, and to a lesser degree, of the thalamic nuclei and basal ganglia, and functional abnormalities (identified by positron emission tomography in temporal and frontal lobes, consisting of decreased 5-HT1A binding in the mesial temporal structures, raphe nuclei, thalamus, and cingulate gyrus.[14-18]

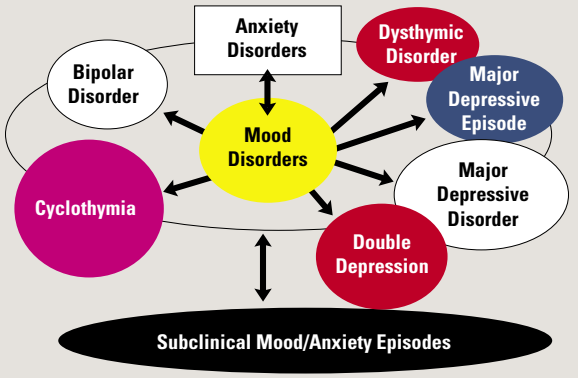
Depressive Disorders are a Heterogeneous Condition

Depressive disorders in patients with epilepsy can mimic the primary mood disorders described in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision.[19] Yet, in a significant number of patients, the depressive episodes may not meet any of the *DSM-IV-TR* criteria (Slide 1). Kraepelin[20] and then Bleuler[21] were the first authors to describe the unique pattern of symptoms in depressive episodes of people with epilepsy consisting of prominent irritability intermixed with euphoric mood, fear, and symptoms of anxiety, as well as anergia, pain, and insomnia. Blumer and colleagues[22] coined the term "interictal dysphoric disorder" to refer to this type of depression in epilepsy, and described the chronic course of the disorder as having recurrent symptom-free periods and responding well to low doses of antidepressant medication.

Peri-ictal depressive episodes are among the unique clinical expressions of this psychiatric comorbidity in people with epilepsy. Preictal symptoms or episodes typically present as a dysphoric mood that precedes a seizure by several hours to days[23]; they become more accentuated during the 24 hours prior to the seizure and may remit postictally or persist for a few days after the seizure.

Postictal symptoms occur typically after seizures, though frequently a symptom-free period of 1–5 days exists between the seizure and onset of psychiatric symptoms. In a study of 100 consecutive patients with refractory epilepsy, Kanner and colleagues[24] investigated the presence of postictal psychiatric symptoms during the last 3 months and occurring after >50% of seizures. Forty-three patients experienced a median of five postictal symptoms of depression with a median duration of 24 hours (Slide 2).[24] Twenty-five patients had a history of mood disorder and 11 of anxiety disorder. In addition, postictal suicidal ideation was identified in 13 patients; 10 of the 13 patients (77%) had a history of either major depression or bipolar disorder—the association was highly significant. Among the 43 patients with postictal depression, 27 (63%) had concurrent anxiety and seven reported postictal psychotic symptoms.

SLIDE 1
Depression is a Heterogeneous Disorder[1]



Comorbid Anxiety Symptoms in Depression

In patients with and without epilepsy, depressive episodes are frequently associated with comorbid symptoms of anxiety or full-blown anxiety disorders, with rates ranging between 50% and 80% in patients with primary mood disorders.[25,26] In a study of 174 patients with epilepsy from five epilepsy centers, 73% of patients with a history of depression also met *DSM-IV* criteria for an anxiety disorder.[25] Recognition of comorbid symptoms of anxiety is of the essence as they may worsen the quality of life of depressed patients and significantly increase their risk for suicide.[26] Thus, evaluation of mood disorders must include investigation of comorbid symptoms of anxiety and vice versa.

Treatment of Depressive Disorders in Patients With Epilepsy

The choice of antiepileptic drugs (AEDs) in patients with epilepsy and depressive disorders must follow the same parameters followed in patients without epilepsy (eg, depending on the type of epileptic seizure and syndrome, comorbid medical conditions, concomitant medications, gender, and age) with some caveats.

The choice should give priority to AEDs with positive psychotropic properties. They include AEDs with mood-stabilizing properties such as carbamazepine, oxcarbazepine, and lamotrigine. Valproic acid is another AED with mood-stabilizing properties and is not advised in women of childbearing age because of the serious teratogenic effects and the negative impact on the cognitive development of the child exposed to this AED in utero. In patients in whom it is the only AED that can control seizures, doses below 1,000 mg/day or serum concentrations below 50 mg/l have been associated with a lower risk. Gabapentin and pregabalin are two AEDs with anxiolytic properties.

Lamotrigine has been found to yield antidepressant effects in patients with bipolar major depressive episodes, and antidepressant effects have been also suggested in two trials in patients with epilepsy.[27-29] Carbamazepine and oxcarbazepine tend to be used for their mood-stabilizing properties, but not as antidepressant agents.

SLIDE 2
Postictal Symptoms of Depression[24]

Postictal Symptom	***Frequency (N=100)***	***Duration (Range, Hours)***
Poor frustration	36	24 (0.5-108)
Anhedonia	33	24 (0.1-148)
Hopelessness	25	24 (1.0-108)
Helplessness	31	24 (1.0-108)
Crying bouts	26	6 (0.1-108)
Suicidal ideation	13	24 (1.0-240)
Irritability	30	24 (0.5-108)
Guilt	23	24 (0.1-240)
Self-deprecation	27	24 (1.0-120)

Any postictal symptom of depression, n=43 patients; Median number of symptoms: 5 (range: 2-9)

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Caution should be exerted when discontinuing these AEDs, as it can result in recurrence of mood and anxiety disorders that may have been in remission because of these agents. Certain AEDs with negative psychotropic properties should be used with great caution or avoided if possible in patients with a lifetime or family history of mood and anxiety disorders. These include, in particular, the barbiturates phenobarbital and primidone, and topiramate, zonisamide, levetiracetam, and vigabatrin. Indeed, several studies have shown that psychiatric adverse events are likely to occur in patients at risk, that is, those with a prior history or a family history.

Treatment of Depressive Disorders

The treatment of depressive disorders includes the use of antidepressant drugs with or without cognitive behavior therapy (CBT) or CBT alone. To date there is only one controlled study that has compared the efficacy of sertraline, a selective serotonin reuptake inhibitor (SSRI) with CBT in patients with major depressive disorder and epilepsy. Both treatment modalities yielded the same efficacy, with 60% of patients in each arm showing remission of symptoms [Gilliam et al, data presented at the 61st Annual Meeting of the American Academy of Neurology, Seattle, WA].

There is a consensus that SSRIs are safe and effective agents in the treatment of depressive disorders in patients with epilepsy. The choice of the SSRI depends on the presence of comorbid anxiety disorders/symptoms. The aim of therapy is total remission of symptoms as residual symptomatology is associated with an increased risk for recurrence of major depressive episodes.[30,31] If a trial at optimal doses of an SSRI fails to achieve that goal, a trial of a serotonin-norepinephrine reuptake inhibitor (SNRI) (either venlafaxine or duloxetine) should be considered. Both of these agents have also the advantage of having anxiolytic properties. Persistence of symptoms after two optimal trials, one with an SSRI and one with an SNRI, suggests that this patient may be suffering from a resistant form of depression and should therefore be managed by a psychiatrist.

Do AEDs Increase the Suicidal Risk of Patients With Epilepsy?

In January of 2008, the United States Food and Drug Adminstration issued an alert regarding the association between suicidality and AEDs, based on results of a meta-analysis that included data from 199 randomized clinical trials of 11 AEDs: carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide.[6] The meta-analysis encompassed studies for the use of these AEDs in epilepsy, psychiatric disorders, and pain. The FDA concluded that there was a statistically significant 1.80-fold increased risk for suicidality with exposure to AEDs. Suicidality occurred in 4.3 per 1,000 patients treated with AEDs in the active arm compared with 2.2 per 1,000 patients in the comparison arm. Of all the suicidality reported, suicidal ideation accounted for 67.6%, preparatory acts for 2.8%, attempts for 26.8%, and completed suicide for 2.8%. AEDs were associated with a greater risk for suicidality with epilepsy (OR, 3.53; 95% CI: 1.28-12.10) than with psychiatric disorders (OR, 1.51; 95% CI: 0.95-2.45) or other disorders (OR, 1.87; 95% CI: 0.81-4.76).

Yet, the validity of the results of this meta-analysis recently has been questioned because of methodological problems.[32] The assessment of suicidality was based on "spontaneous" reports of patients and not gathered in a systematic prospective manner; the FDA associated the increased risk for suicide with all AEDs, despite the fact that statistical significance was found in only 2 (ie, topiramate and lamotrigine) of the 11 AEDs studied. Furthermore, inclusion of three additional studies of lamotrigine resulted in the loss of statistical significance for this AED. Two other AEDs, valproic acid and carbamazepine, actually yielded a "small protective effect." The FDA's decision to present the risk as involving all AEDs stemmed from a concern that singling out specific AEDs might only change prescribing practices, rather than emphasize the suicide risk. Clearly, their reasoning is not scientifically based. Most epilepsy trials (92%) include patients on adjunctive therapy (compared with 14% of psychiatric trials and 15% of other medical trials). It is unclear whether the higher suicidality rates in the epilepsy trials were due to drug interactions, given the high proportion of epilepsy trials designed with polytherapy, or whether they potentially were due to the low suicidality risk associated with carbamazepine and valproate—both drugs are protective for suicidality and are the most common comparison drugs in these trials. Suicidal behavior was greater in certain geographic regions. For example, the odds ratio of suicidality was 1.38 (95% CI: 0.9-2.13) in North American studies and 4.53 (95% CI: 1.86-13.18) in studies done elsewhere. Such differences strongly suggest serious methodological errors in data gathering.

In the opinion of various professional societies, including the American Epilepsy Society, The American Neurological Association, as well as lay societies, including the Epilepsy Foundation of America, the results of this meta-analysis must be considered with great caution at this time. We cannot exclude the possibility that certain AEDs (but not all) can facilitate the development of psychiatric adverse events that can potentially facilitate suicidal ideation and behavior in patients predisposed to suffer from psychiatric comorbidities, such as patients with a prior personal or family psychiatric history. Thus, screening for depression, anxiety, and suicide risk should be part of the evaluation of all patients, given the high prevalence of depressive and anxiety disorders in epilepsy. Furthermore, the inclusion of the FDA warning in the package insert of all AEDs (indicating that patients must be screened for psychiatric conditions that can predispose patients to develop suicidal ideation and behavior before starting an AED and during the course of its treatment) poses potential medicolegal liabilities if clinicians fail to screen for comorbid depressive disorders. The three most frequent risk factors associated with suicidality include current or past history of mood and anxiety disorders; family psychiatric history of mood disorders, particularly of suicidal behavior; and past suicidal attempts.

The task force on Psychiatric Aspects of Epilepsy of the American Epilepsy Society has recommended the use of the following instruments to screen patients for current major depressive episodes and suicidal ideation. These include a 6-item, self-rating questionnaire called the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), which was developed to identify major depressive episodes, specifically for people with epilepsy.[33] None of its items can be confounded with adverse events of AEDs or cognitive symptoms associated with the seizure disorder or the underlying neurological insult that caused the epilepsy. The NDDI-E takes <3 minutes to complete; a score >15 is suggestive of a major depressive episode and serves as a red-flag referral to a psychiatrist for further evaluation. Suicidal ideation can be screened with the item nine of the Beck Depression Inventory–II (BDI-II).

Since depressive and anxiety disorders occur together frequently, it is worth screening for generalized anxiety disor-

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der (GAD). The Patient Health Questionnaire, GAD-7, can be extremely helpful.[34] It is a 7-item, self-rating instrument that takes 3 minutes to administer; a score of >10 is suggestive of a GAD.

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QUESTION-AND-ANSWER SESSION

Q: Given limited time available, especially at follow-up, how do you suggest that neurologists efficiently offer screening and interpretation of multiple inventories during a time-limited appointment?

Dr. Kanner: The Neurological Disorders Depression Inventory for Epilepsy and the Patient Health Qusetionnaire, generalized anxiety disorder-7, are two self-rating instruments that take patients 5 minutes to complete while they are waiting to see their doctor. A total score of the NDDI-E >15 is suggestive of a major depressive episode, while a total score of the GAD-7 >10 is suggestive of a GAD. These scores are very helpful in establishing whether the treatment started on prior visits has yielded the desired effect.

Q: Because psychiatric resources may be difficult to access in some areas, to what extent are neurologists obligated to become experts at the selection, administration, and monitoring of selective serotonin reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor treatment?

Dr. Kanner: Most neurologists are familiar with the use of SSRIs and SNRIs as they are often used for the treatment of various pain disorders. Nonetheless, given that comorbid depression and anxiety disorders are seen in up to 25% to 30% of patients with most neurologic disorders, neurologists should become familiar with the basic principles in treating the most common types of depression and anxiety disorders. However, if patients have been tried on two trials, one on an SSRI and a second on an SNRI (or vice versa) at optimal doses and the patient continues to be symptomatic, a referral to a psychiatrist is indicated, as it is likely that this patient may be suffering from a pharmacoresistant disorder. In addition, neurologists should not treat suicidal or psychotic patients and should not initiate treatment in bipolar patients.

Q: Aside from offering screening, how do you recommend that neurologists counsel patients about suicide warnings they will encounter in package inserts provided by pharmacists? Is it possible some patients may be discouraged from adhering to important treatment programs?

Dr. Kanner: Patients must be made aware that epilepsy is associated with an increased risk for depressive and anxiety disorders and that suicidal ideation and behavior may be associated with these comorbid psychiatric disorders. Patients should understand that certain antiepileptic drugs like phenobarbital, zonisamide, topiramate, and levetiracetam can bring to the surface psychiatric symptoms in patients who have a predisposition for psychiatric disorders, which include a past and/or family psychiatric history. Suicidal ideation and behavior may be part of the psychiatric symptoms. Having said that, patients need to understand that these side effects are reversible and patients should alert their physicians, should they start noticing any of these symptoms. Patients must also be made aware of the life-threatening risks associated with stopping or refusing to take their AEDs. Finally, neurologists must explain to patients that professional societies are questioning the validity of all the Unoted States Food and Drug Adminsitration findings. This concern, however, should not stop clinicians from monitoring patients' psychiatric status.

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