

Depression and Epilepsy: A New Perspective on Two Closely Related Disorders

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Depression is the most frequent psychiatric comorbidity in epilepsy. Yet, it remains under-recognized and untreated in a significant number of patients. It may mimic primary depressive disorders, but in a significant percentage of patients, depression presents with atypical pleomorphic characteristics. The use of screening self-rating scales may help to identify depressive episodes in patients with epilepsy, but a diagnosis cannot be established by the sole use of these instruments without an additional, in-depth evaluation. Timely recognition and treatment of depression is of the essence in epilepsy patients, as its persistence is an independent predictor of poor quality of life, increased suicidal risk, greater use of health services, and higher medical costs not related to the psychiatric treatment. Neurologists will often find themselves in the position of being the only health care provider available to initiate treatment. Accordingly, they should be well trained to provide psychopharmacologic treatment for major depressive episodes, dysthymic disorders, and minor depression. However, patients with suicidal ideation, psychotic symptoms, or bipolar disorders should be referred immediately to the care of a psychiatrist.

Depression is the most common comorbid psychiatric disorder in patients with epilepsy (1), yet it remains under-recognized and under-treated. Wiegartz et al. found that 43% of 76 patients with epilepsy had a major depressive disorder (MDD) and that 38% of patients with lifetime histories of MDD never had been referred for treatment, while 68% of the patients with a minor depression were untreated (2). In a study of 97 children and adults with epilepsy and a depressive disorder

severe enough to warrant pharmacotherapy, Kanner et al. determined that 63% of patients with spontaneous depression and 54% of patients with an iatrogenic depression were symptomatic for more than 1 year before treatment was initiated (3). Ettinger et al. identified symptoms of depression in 26% of 44 children with epilepsy—all were undiagnosed and untreated (4).

While the clinical manifestations of depression in people with epilepsy can be atypical, the most frequent cause for the under-recognition is the failure of clinicians to inquire about it and of patients or families to report it. In a survey of neurologists, Gilliam found that 80% do not routinely screen for depression in patients with epilepsy (5). It is common for clinicians to presume that evaluation and management of comorbid psychiatric disorders in epilepsy patients are the responsibility of psychiatrists, which in practicality is unrealistic, given the limited (and often nonexistent) availability of psychiatric services. The purpose of this review is to highlight the heterogeneous nature of depression in epilepsy patients and to elucidate the role of the epileptologist in the management of depression in these patients.

Identifying Depression in Patients with Epilepsy

Depressive disorders in patients with epilepsy can mimic the primary mood disorders described in the fourth edition (text-revised) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), which classifies depressive disorders into four types: MDD, dysthymic disorder, minor depression, and depressive disorder not otherwise specified (6). The differences between MDD and dysthymic disorder is based largely on severity, persistence, and chronicity, with symptoms in both disorders sharing common features, such as depressed mood, anhedonia, worthlessness, guilt, decreased ability to concentrate, recurrent thoughts of death, and neurovegetative symptoms (i.e., weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue). A diagnosis of MDD is considered in patients with recurrent major depressive episodes that last at least 2 weeks and consist either of a depressed mood or anhedonia, plus four of the other symptoms listed above. In a recent study of 174 patients with epilepsy from five tertiary epilepsy centers, Jones et al. found the rate of DSM-IV-TR MDD to be 17.2% (7). In contrast, dysthymic disorder is more chronic but less intense, with symptoms persisting on most days for at least 2 years. Minor depression is a category that is similar to MDD in duration but encompasses two to five of the symptoms noted above.

Bipolar disorders also afflict epilepsy patients but with a lower frequency than the depressive disorders described. The DSM-IV-TR also includes bipolar disorders in the family of mood disorders; bipolar disorders are of two types depending on the occurrence of manic (type I) or hypomanic (type II) episodes in addition to major depressive episodes. Manic episodes require a distinct period of abnormally and persistently elevated mood of sufficient severity to cause marked impairment in social functioning and lasting at least 1 week. The diagnosis of hypomanic episodes requires a distinct period of persistently elevated mood that is observable as a disturbance by others and lasts at least 4 days. In addition to bipolar disorders, DSM-IV-TR lists the diagnosis of cyclothymic disorder, which should be considered in the presence of recurrent hypomanic and minor depressive episodes that last for at least 2 years. Cyclothymic disorder may occur with epilepsy, but its exact prevalence has yet to be established. In addition, up to 50% of mood disorders identified in patients with epilepsy present with atypical clinical characteristics that fail to meet any of the DSM-IV-TR criteria.

In patients with epilepsy, depressive, manic, and hypomanic episodes are categorized according to their temporal relation with seizure occurrence into peri-ictal (i.e., symptoms that precede, follow, or are the expression of the ictal activity) or interictal episodes (i.e., occur independently of seizure). The degree to which peri-ictal symptoms contribute to the overall clinical semiology of depression in epilepsy patients remains unknown, as large studies characterizing their clinical manifestations have not been performed. Interictal depressive episodes are the most frequently recognized and can be identical to those described in primary mood disorders or may present with atypical clinical semiology.

Atypical Expressions of Depression in Epilepsy

The atypical presentation of depressive disorders in people with epilepsy has been recognized for a long time. Using DSM-III-R criteria, Mendez et al. studied the clinical semiology of 175 patients with epilepsy; 22% of 96 patients with a depressive episode were classified as having atypical depression (8). Kraepelin (9) and then Bleuler (10) were the first authors to describe a pleomorphic pattern of symptoms that included affective symptoms consisting of prominent irritability intermixed with euphoric mood, fear, and symptoms of anxiety, as well as anergia, pain, and insomnia. Gastaut (11) confirmed Kraepelin and Bleuler's observations, leading Blumer to coin the term "interictal dysphoric disorder" to refer to this type of depression in epilepsy (12). Blumer described the chronic course of the disorder as having recurrent symptom-free periods and as responding well to low doses of antidepressant medication.

Other investigators have been impressed as well by the pleomorphic presentation of depressive disorders in epilepsy.

For example, among 97 consecutive patients with refractory epilepsy and depressive episodes severe enough to merit pharmacotherapy, Kanner et al. found that 28 (29%) met DSM-IV criteria for MDD (3). The remaining 69 patients (71%) failed to meet criteria for any of the DSM-IV categories and presented with a clinical picture consisting of anhedonia (with or without hopelessness), fatigue, anxiety, irritability, poor frustration tolerance, and mood lability with bouts of crying. Some patients also reported changes in appetite and sleep patterns and problems with concentration. Most symptoms presented with a waxing and waning course, with repeated, interspersed symptom-free periods of 1 to several days duration. The semiology most resembled a dysthymic disorder, but the intermittent recurrence of symptom-free periods precluded DSM criteria for this condition. Kanner and colleagues referred to this form of depression as "dysthymic-like disorder of epilepsy." In a separate study of 199 consecutive patients with epilepsy, 132 (64%) failed to meet any DSM-IV-TR axis I diagnosis with two structured psychiatric interviews (i.e., the Structural Clinical Interview for DSM-IV Axis I [SCID] and the MINI-International Neuropsychiatric Interview [MINI]); yet, using the self-rating instruments Beck Depression Inventory and the Center of Epidemiologic Studies-Depression, 32 patients (16%) were identified with symptoms of depression of mild-to-moderate severity (13). Furthermore, of the 32 patients, symptoms of anxiety were identified in 31, irritability in 32, physical symptoms in 24, and increased energy in 18 patients. The patients' ratings of quality of life revealed a significant negative impact on their quality of life compared with asymptomatic patients. The depressive episode identified in these 32 patients reflect a "subsyndromic" type of mood disorders, which psychiatrists are also recognizing in nonepilepsy patients as a cause of poor quality of life.

Peri-ictal Episodes and Symptoms of Depression

Peri-ictal clusters of symptoms and episodes, which usually last from a few hours to a few days, may occur. It is possible that peri-ictal symptoms to some degree account for the atypical manifestations of the depressive disorders in patients with epilepsy. Pre-ictal symptoms or episodes typically present as a dysphoric mood that precedes a seizure by several hours to days (14); it becomes more accentuated during the 24 hours prior to the seizure and remits postictally or persists for a few days after the seizure. Postictal symptoms can be elusive, as symptom-free periods of 1 to 5 days can exist between the seizure and onset of psychiatric symptoms. In a study of 100 consecutive patients with refractory epilepsy, Kanner et al. investigated the prevalence rate and clinical characteristics of postictal psychiatric symptoms during a 3-month period. Forty-three patients experienced on a regular basis a median of 5 postictal symptoms of depression with a median duration of 24 hours (15).

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 7 reported postictal psychotic symptoms.

Comorbid Anxiety Symptoms in Depression

A frequent comorbidity of mood and anxiety disorders has been identified in patients with and without epilepsy, with rates ranging between 50% and 80% in patients with primary mood disorders. Similar observations have been made in patients with epilepsy and depression. 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 (7). Recognition of comorbid symptoms of anxiety is of the essence, as they may worsened the quality of life of depressed patients and significantly increase their risk of suicide (16). Thus, evaluation of mood disorders must include investigation of comorbid symptoms of anxiety and vice versa.

Impact of the Bidirectional Relationship Between Depression and Epilepsy

That epilepsy is a risk factor for depression is no longer questioned. Similarly, data from three population-based control studies indicate that people with a history of depression have a 4- to 7-fold higher risk of developing epilepsy (17–19); in one of these studies, a prior history of suicidality was associated with a 5-fold increased risk of developing epilepsy (19). The bidirectional relationship does not imply causality but rather suggests that common pathogenic mechanisms are operant in both conditions, with the presence of one disorder potentially facilitating the development of the other.

A review of this topic previously published in *Epilepsy Currents* (20) listed the following pathogenic mechanisms shared by depression and epilepsy:

- Abnormal CNS activity of several neurotransmitters, particularly serotonin (5-hydroxytryptamine, 5-HT), norepinephrine, dopamine, GABA, and glutamate.
- Structural changes, presenting as atrophy of temporal- and frontal-lobe structures (identified by high-resolution MRI and volumetric measurements), in the amygdala, hippocampus, entorhinal cortex, temporal lateral neocortex, as well as in the prefrontal, orbitofrontal, and mesial-frontal cortex, and to a lesser degree, of the thalamic nuclei and basal ganglia.
- Functional abnormalities (identified by positron emission tomography [PET] and single-photon emission

computed tomography [SPECT]) in temporal and frontal lobes, consisting of decreased 5-HT_{1A} binding in the mesial structures, raphe nuclei, thalamus, and cingulate gyrus.

- Abnormal function of the hypothalamic–pituitary–adrenal axis.

The previous review focused on the theory that the pathogenic mechanisms that are common to both depression and epilepsy may explain their bidirectional relationship. So, can any of the MDD pathogenic mechanisms worsen the course of a comorbid seizure disorder? There are data that support this hypothesis. In a study of 890 patients with new onset epilepsy, Mohanraj and Brodie found that individuals with a history of psychiatric disorders were more than three times *less likely* to be seizure-free with antiepileptic drugs (median follow-up period was 79 months) than patients without a history of psychiatric disorders (21). Similarly, among 121 patients who underwent a temporal lobectomy, Anhoury et al. reported a worse post-surgical seizure outcome for patients with a psychiatric history compared with those without a psychiatric history (22).

Given that depression (along with anxiety) is one of the most frequent psychiatric comorbidities in epilepsy, can depression predict a worse postsurgical outcome for patients who undergo a temporal lobectomy? In a study of 90 patients who had a temporal lobectomy and were followed for a mean period of 6.5 ± 3.3 years, Kanner et al. investigated the role of a lifetime history of depression as a predictor of postsurgical seizure outcome (23). Using a multivariate logistic regression model, the investigators evaluated the covariates of a lifetime history of depression, cause of temporal lobe epilepsy (i.e., mesial temporal sclerosis, lesional, or idiopathic), duration of seizure disorder, and occurrence of generalized tonic–clonic seizures. They found that a lifetime history of depression was the sole predictor of persistent auras in the absence of disabling seizures, while the cause of the temporal lobe epilepsy and a lifetime history of depression were both significant predictors of failure to achieve freedom from disabling seizures. The data in these three studies raise the question of whether a history of depression may be a marker of a more severe form of epilepsy.

How to Recognize Depressive Disorders in the Neurology Clinic

Clearly, depression in epilepsy *is not* a homogeneous condition. How can a neurologist identify a depressive disorder in patients with epilepsy? First, inquiring about anhedonia, that is, the inability to find pleasure in most activities, is an excellent predictor of the presence of depression. Second, the use of self-rating screening instruments is typically revealing.

A six-item screening instrument, the neurological disorders depression inventory for epilepsy (NDDI-E), recently was

validated to screen for major depressive episodes in patients with epilepsy (24). This instrument has the advantage of being constructed specifically to minimize confounding factors that plague other instruments, such as adverse events related to antiepileptic drugs or cognitive problems associated with epilepsy. Completion of the instrument takes less than 3 minutes. A score of 14 or higher is suggestive of a major depressive episode and indicates that a more in-depth evaluation is necessary. Other self-rating screening instruments developed to identify symptoms of depression in the general population, such as the Beck Depression Inventory-II and the Center of Epidemiologic Studies-Depression, are valid instruments to screen symptoms of depression in patients with epilepsy (25). It should be emphasized that these instruments are *not diagnostic* of MDDs or other mood disorders; follow-up with an in-depth evaluation is necessary. Once the diagnosis of a mood disorder has been established by psychiatric evaluation, the self-rating screening instruments can be given at every visit to measure changes in symptom severity or document symptom remission.

The Use of Screening Instruments in Research: A Cautionary Note!

One of the most frequent methodological errors in research studies on depression and epilepsy is the sole reliance on screening instruments to diagnose depressive disorders. Investigators who support the exclusive use of screening instruments commonly argue that they identify conditions, such as major depression, with a high degree of sensitivity and specificity. Thus, proponents of the sole use of these scales might reason, "if a patient has a score of >30 on the BDI-II, what can it be, other than a major depressive episode?" While this statement is probably correct, a major depressive episode may be the expression of various types of mood disorders, each requiring a different prognosis and treatment strategy. If a major depressive episode is the patient's first, there is a 50% risk of experiencing additional episodes. If the depression is one of multiple episodes, a diagnosis of MDD is suggested, which would require that the patient remain on prophylactic treatment. Alternately, a major depressive episode may occur as part of bipolar disorder, which implies a worse prognosis for symptom remission, a greater risk of suicide than MDDs, and requires very cautious use of antidepressant medication. A depressive episode may take place as part of a double depression, which consists of recurrent major depressive episodes during a dysthymic disorder.

Clearly, the use of screening instruments for psychiatric research on epilepsy must be followed by structured psychiatric interviews designed to establish a DSM-IV-TR diagnoses, which would permit regular rescreening to yield meaningful data on changes in severity of symptomatology.

Why Should Neurologists Identify Depression in Epilepsy?

Failing to treat and identify depressive disorders in people with epilepsy has serious consequences at several levels:

1. *Increased suicidality risk.* Depression in patients with epilepsy is associated with a significantly higher suicide rate than in the general population. In a review of 11 studies, Harris and Barrowclough (26) found the overall suicide rate in people with epilepsy to be five times higher than in the general population and 25 times greater for patients with complex partial seizures of temporal lobe origin. In a review of the literature, Jones et al. (27) identified a lifetime average suicide rate of 12% in people with epilepsy compared to 1.1% to 1.2% in the general population. Similarly, Kanner et al. identified a 13% prevalence of habitual postictal suicidal ideation among 100 patients with refractory epilepsy (15).
2. *Negative impact on quality of life.* Five studies involving pharmaco-resistant epilepsy patients demonstrated that depression is the most powerful predictor of health-related reduction in quality of life, even after controlling for seizure frequency, severity, and other psychosocial variables (28–32). Cramer et al. determined that depression was significantly associated with poor quality-of-life scores on the Quality of Life in Epilepsy Inventory-89, independent of seizure type; however, the investigators found that seizure-freedom for the last 3 months improved the quality-of-life ratings (32).
3. *Impact on costs and use of medical services.* Depression in people with epilepsy significantly increases the health-care costs associated with the management of the seizure disorder. Cramer et al. found that patients with untreated depression used significantly more health resources of all types, independent of seizure type or latency (33). Furthermore, mild-to-moderate depression was associated with a two-fold increase in medical visits compared with nondepressed controls, while severe depression was associated with a four-fold increase. The presence and severity of depression was a predictor of lower disability scores, irrespective of the duration of the seizure disorder.

What Is the Neurologist's Role in the Management of Depression in Epilepsy?

Access to health care for patients with comorbid psychiatric disorders is hampered by economic factors, as insurance coverage frequently does not include psychiatric services or offers only a limited number of visits per year. Thus, it is not unusual for neurologists to be the only source of treatment for patients with

comorbid depression. When left untreated, MDD may last for 6 to 24 months in 90% to 95% of cases, while the remaining 5% to 10% patients could have symptoms persist for more than 2 years. With pharmacotherapy, patients can experience a 50% reduction of symptoms during the first 8 weeks. Yet, the goal of therapy is to achieve a complete symptom-free state, also referred to as remission. Approximately 50% of patients will reach remission within the first 6 months and about 66% within 2 years of the start of pharmacotherapy. Failure to enter remission is predictive of recurrence of future major depressive episodes. Approximately 15% to 20% of patients will fail to respond to any antidepressant trial (34). The variables predictive of relapse include multiple prior episodes, severe or long-lasting episodes, episodes with psychotic or bipolar features, and incomplete recovery between two consecutive episodes. Neurologists will benefit from knowing how to initiate pharmacotherapy for major, dysthymic, and minor depressive episodes, but should refer to the patient to a psychiatrist for the following:

- A depressive episode associated with suicidal ideation.
- MDD with psychotic features. Approximately 25% of MDDs can present with psychotic features. In such cases, pharmacotherapy has to include antipsychotic and antidepressant drugs, and at times, electroshock therapy is considered. Furthermore, the presence of psychotic symptomatology significantly increases suicidal risk.
- Any major depressive or dysthymic episode that has failed to respond to a prior trial of selective serotonin reuptake inhibitors and/or serotonin–norepinephrine reuptake inhibitors at optimal doses.
- Bipolar disorder, as the management is fret with significantly lower therapeutic success and associated with potentially serious complications that are beyond the therapeutic skills of neurologists. The use of antidepressant medication for a bipolar disorder can facilitate the development of manic and hypomanic episodes or of a rapid cycling bipolar disorder (i.e., four or more depressive, manic, or hypomanic episodes in a 12-month period). The American Psychiatric Association guidelines for the treatment of acute depression in bipolar disease advise against an initial use of antidepressant drugs (35). Furthermore, a bipolar disorder can begin with recurrent major depressive episodes before the first manic or hypomanic episode occurs. Accordingly, before prescribing antidepressant medication for a major depressive, dysthymic, or minor depressive disorders, neurologists will need to inquire about a history of manic or hypomanic episodes as well as of a family history of bipolar disease and refer positively identified patients to a psychiatrist for management.

Concluding Remarks

Depression in epilepsy is a heterogeneous disorder often with atypical manifestations. Its recognition and timely treatment are of the essence to avert the multiple complications that directly result from the depressive disorder, including the possibility of worsening the seizure disorder.

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