

NEUROPSYCHIATRIC DISORDERS IN EPILEPSY: PRACTICAL STRATEGIES FOR THEIR IDENTIFICATION AND MANAGEMENT

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Psychiatric comorbidities are relatively frequent in people with epilepsy (PWE), as they can be identified in 25% to 50% of patients, which include depression, anxiety, attention deficit and psychotic disorders, as well personality disorders. In addition, psychiatric symptomatology can be classified according to its temporal relation with the occurrence of seizures into pre-ictal, ictal, postictal and interictal. Often, these psychiatric phenomena can occur during interictal periods and worsen in severity in the pre-ictal or postictal periods. Finally, psychiatric symptoms can be the expression of spontaneous psychiatric disorders or of an iatrogenic process, following the administration of antiepileptic drugs (AEDs) with negative psychotropic properties, the discontinuation of AEDs with positive psychotropic properties in patients susceptible to suffer from psychiatric disease.

Depressive and anxiety disorders are the most frequent psychiatric comorbidities in PWE with lifetime prevalence rates of 35% and affect adult as well as pediatric patients. In children, however, Attention Deficit Hyperactivity Disorders are the most frequently identified. Of note depressive and anxiety disorders often occur together, while in children with ADHD, comorbid depressive and anxiety disorders are not rare.

Psychiatric Disorder	Prevalence	
	Epilepsy	General Population
Depression	11 - 80%	3.3%: Dysthymia 4.9 – 17%: Major Depression
Psychosis	2 – 9.1%	1%: Schizophrenia 0.2%: Schizophreniform Disorder
Generalized Anxiety Disorders	15 – 25%	5.1 – 7.2%
Panic Disorder	4.9 – 21%	0.5 – 3%
ADHD	12 – 37%	4 – 12%

For a long time, psychiatric comorbidities were considered to be a complication of the seizure disorder, as higher prevalence rates are found in patients with poorly controlled epilepsy. Yet, several population-based studies have shown evidence of a bidirectional relationship between epilepsy and several psychiatric disorders including depression, anxiety, ADHD and psychotic disorders (Hesdorffer et al., 2012). In other words, not only are PWE at greater risk of developing psychiatric disorders, but patients with primary psychiatric disorders are at greater risk of developing epilepsy. For example, patients with a history of major depressive disorders or suicidality (independent of a major depressive disorder) have a four to seven greater risk of developing epilepsy (Forsgren & Nystrom, 1990; Hesdorffer, et al 2000;and 2006). In addition, children with a history of ADHD of the Inattentive type have a 3.7 fold higher risk of developing epilepsy (Hesdorffer et al., 2004).

Why should neurologists care?

While it is a recognized fact that psychiatric comorbidities are a serious problem in PWE, clinicians' reaction is "shouldn't psychiatrists be taking care of these conditions?". This can be expected in an ideal world. However, access to psychiatrists and mental health professionals is extremely limited,

even in developed countries and consequently, psychiatric comorbidities go unrecognized and untreated. Thus, it falls upon the treating neurologist to provide pharmacologic treatment in the appropriate psychiatric conditions (see below). Furthermore, psychiatric comorbidities have a negative impact on the treatment of the seizure disorder and increase the mortality risk of PWE. Thus, the reasons that neurologists should care to recognize these psychiatric comorbidities and ensure that they are treated include:

1. *Psychiatric disorders are associated with a worse response to treatment of the seizure disorder*

Two studies have shown that a history of depression and/or the presence of symptoms of depression at the time of diagnosis of epilepsy can be associated with a higher risk of pharmacoresistance to AEDs [Hitiris et al., 2007; Petrovski et al., 2010]. Furthermore, a lifetime history of depression has been found to be associated with a worse postsurgical seizure outcome following an antero-temporal lobectomy in patients with treatment-resistant TLE who underwent an antero-temporal lobectomy. For example, in one study, Kanner et al. found a lifetime history of depression in only 12% of patients who became free of auras and disabling seizures in contrast to 79% of patients with persistent disabling seizures [Kanner et al., 2009]. Others have replicated these data (Cleary et al, 2012, Guarneri et al., 2009; Anhoury et al., 2000).

2. *Impact on tolerance to AEDs*

Psychiatric disorders have been found to worsen the tolerance of AEDs. For example, several studies have shown that the presence of depressive symptoms has a negative impact on the severity of adverse events (AEs) to AEDs in PWE (Cramer et al., 2003; Ettinger et al., 2004). Likewise, more recent studies found a negative effect of major depressive episodes, sub-syndromic forms of depression and anxiety disorders (according to DSM-IV-TR criteria) on Adverse events (Perucca et al., 2011; Kanner et al., 2011).

3. *Increased mortality risk.*

Suicide is the most serious complication of psychiatric disorders in patients with and without epilepsy. In a population-based study conducted in Denmark, Christiansen et al., found that PWE without any psychosocial problems had a two-fold higher risk of committing suicide; this risk increased by 32-fold in the presence of a mood disorder, 12-fold in the presence of an anxiety disorder and schizophreniform disorder [Christensen et al., 2007]. In a more recent population based study from Sweden, psychiatric comorbidity, in particular depression and substance abuse was associated with external causes of mortality in PWE, which accounted for 16% of all deaths in these patients.

4. *Impact on quality of life*

The negative impact of psychiatric disorders on the quality of life of PWE has been well established. For example, eight studies involving patients with treatment-resistant epilepsy demonstrated that depressive and/or anxiety disorders are the most powerful predictors of poor quality of life, even after controlling for seizure frequency, severity, and other psychosocial variables (Perrine et al, 1995; Gilliam et al., 2002; Cramer et al, 2003; Boylan et al, 2004; Loring et al, 2004; Johnson et al, 2004; Tracy et al, 2007; Kanner et al., 2010). In addition, depressive disorders in PWE significantly increase the healthcare costs associated with the management of the seizure disorder, as shown by Cramer et al., who found that patients with untreated depression used significantly more health resources of all types, independent of seizure type or latency (Cramer et al., 2004). Furthermore, mild-to-moderate depression was associated with a two-fold increase in medical visits compared with non-depressed 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.

5. *Psychiatric disorders can provide data on the location of ictal foci*

Several attempts have been made to associate an epileptogenic zone with specific psychiatric comorbidities. Peri-ictal psychiatric events have been helpful in providing data on the location of epileptogenic zone. For example, ictal panic or ictal fear has been closely associated with mesial-

temporal seizure foci [Kanner, 2009]. Postictal psychotic episodes (PIPE) have been associated with bilateral independent interictal (Kanner et al., 1996; Devinsky et al., 1995; Savard et al., 1991; Umbricht et al., 1991) and ictal foci (Kanner et al., Devinsky et al., 1995, Umbricht et al., 1991, Kanner & Ostrovskaya, 2008).

What psychiatric comorbidities should be identified by neurologists?

As stated above, in adults with epilepsy, depressive and anxiety disorders are the more frequent psychiatric comorbidities. Depressive and anxiety disorders are two families of psychiatric disorders, each constituted by several categorical entities. Furthermore, each of these conditions may often have pleomorphic clinical manifestations and atypical presentations, particularly in the setting of neurologic disorders. While “non-psychiatrists” cannot be expected to recognize all of the subtypes of these conditions, neurologists can screen for the existence of current “symptoms” of depression and anxiety, which can alert to the presence of the more frequent severe forms of depression (.e.g., major depressive episode) and the most frequent type of anxiety disorders (e.g., generalized anxiety disorder). To that end, clinicians can use self-rating screening instruments. These include:

- (i) The Beck Depression Inventory-II, developed to identify current symptoms of depression in the course of the last two weeks, has been validated for PWE [31] and provides a measure of symptom severity (ranging from mild to severe).
- (ii) The Neurologic Depression Disorders Inventory for Epilepsy [NDDI-E] [32], a self-rating instrument developed specifically for PWE to screen for major depressive episodes (MDE). The NDDI-E is a six item and the GAD-7 a seven item instrument, respectively. A total score >15 of the NDDI-E is suggestive of a current MDE.
- (iii) The Patient’s Health Questionnaire-Generalized Anxiety Disorder- 7 (GAD-7) is a self-rating instrument used widely in medicine to screen for Generalized Anxiety Disorders (GAD) [33]. A total score >10 in the GAD-7 suggests the presence of a GAD.

Patients can complete both self-rating scales in less than 6 minutes while waiting to see their neurologist. While these two screening instruments do not establish a diagnosis of MDE or GAD, their sensitivity and specificity is high enough to ensure that most symptomatic patients are identified.

In addition to the above, neurologists should be able to recognize panic disorders and distinguish them from ictal panic, one of the most frequent type of simple partial seizure of mesial temporal origin (Vasquez & Devinsky). Furthermore, neurologists must recognize postictal psychotic episodes, which tend to occur in up to 7% of PWE undergoing video-EEG monitoring studies (Kanner et al., 1996).

Some general principles in addressing psychiatric aspects of epilepsy:

The evaluation of any type of psychopathology in PWE must be approached with the following questions in mind.

- 1) Is this psychiatric disturbance temporally related to the occurrence of seizures? (e.g., peri-ictal and /or interictal)
- 2) Is the onset of psychiatric symptoms associated with the remission of seizures? (e.g., forced normalization phenomena).
- 3) Are the psychiatric symptoms the result of the introduction of an antiepileptic drug (AED) with potential negative psychotropic properties, or did they appear after discontinuation of an AED with positive psychotropic properties (mood stabilizing, antidepressant and anxiolytic properties)?
- 4) Do the symptoms meet diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), or the International Classification of Diseases (ICD) or do these symptoms present as an atypical disorder?
- 5) What is the treatment for the psychiatric disorder? If pharmacotherapy is required, how do psychotropic drugs interact with AEDs and what is the impact of psychotropic drugs on the seizure threshold?

What should be the role of the neurologist in the identification and management of psychiatric comorbidities?

Based on the above, neurologists should be expected to identify PWE with MDE, GAD, panic disorder and postictal psychotic episodes. In addition, treatment of these conditions should be started and /or carried out by the treating neurologists if there is limited access to a psychiatrist. On the other hand, neurologists should not be expected to prescribe psychotropic drugs in all types of depressive, anxiety disorders or psychotic disorders. In fact, they should restrict their pharmacologic intervention to PWE with MDE, dysthymia, GAD and panic disorder. Furthermore, neurologists should not treat patients with MDE who are suicidal, who suffer from treatment-resistant MDE (that is those who have persistent symptoms despite two trials with an antidepressant drug at optimal doses) and those with an MDE that is part of a bipolar disorder. The existence of a bipolar disorder should be suspected in patients with a history of a first MDE before the ages of 16, a history of previous spontaneous and / or iatrogenic hypomanic episode, triggered with antidepressant drugs, and / or a family history of bipolar disorder (three questions that any neurologist can easily incorporate in the evaluation of a PWE). Such patients should be referred to the care of psychiatrists.

Pharmacologic treatment of depressive and anxiety disorders include the use of SSRIs and SNRIs. In fact, most of these drugs are effective in the treatment of most MDE and anxiety disorders (treatment protocols will be discussed in the course). Furthermore, these drugs are very safe in PWE and do not lower the seizure threshold (Kanner et al., 2000). The following table summarizes the use of SSRIs in depressive and anxiety disorders that can be used in PWE.

Table Efficacy of SSRIs and SNRIs in primary depression and anxiety disorders

Antidepressant drug	Depression	Panic disorder	Generalized anxiety	Starting dose	Maximal dose
Paroxetine*	+	+	+	10	60
Sertraline*	+	+	+	25	200
Fluoxetine*	+	+	-	10	80
Citalopram*	+	+	+	10	60
Escitalopram*	+	+	+	5	30
Fluvoxamine	+	+	+	50	300
Venlafaxine^	+	+	+	37.5	300
Duloxetine	+	+	+	20	120

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