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Psychiatric issues in epilepsy: The complex relation of mood, anxiety disorders, and epilepsy

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ABSTRACT

The comorbid psychiatric disorders in patients with epilepsy have been neglected for a long time. And yet, epidemiological studies have demonstrated a relatively high prevalence of mood, anxiety, and attention deficit hyperactivity disorders. Furthermore, the relation between psychiatric disorders and epilepsy is complex, as illustrated by the relation between mood disorders and epilepsy. The aim of this article is to summarize the most relevant data on the complex relation between mood disorders and epilepsy, which extends to anxiety disorders and which can be explained by the existence of common pathogenic mechanisms shared by these three conditions. The significance of such a relation is not only theoretical, but has a marked impact on the response to pharmacological and surgical treatment of seizure disorders.

1. Introduction

Up until the 19th century, many cultures considered epilepsy to be the expression of a "mental" disorder. Such misconceptions persisted up to the 20th century, and people with epilepsy (PWE) continued to suffer from multiple forms of discrimination at all levels (i.e., academically, professionally, and socially). Ignoring the existence of comorbid psychiatric disorders in epilepsy became one of the "accepted" ways of fighting the stigma associated with this disease and, in this manner, minimized the possibility of any potential relation between epilepsy and mental illness. Not surprisingly then, comorbid mood, anxiety, and attention deficit disorders go unrecognized and untreated in large number of patients.

Yet, as epidemiological studies have demonstrated, not only are psychiatric comorbidities relatively frequent in PWE, but the relation between psychiatric disorders and epilepsy is complex. For example, in a recent population-based Canadian study, Tellez-Zenteno et al. demonstrated that "PWE were more likely than individuals without epilepsy to report lifetime anxiety disorders or suicidal thoughts with odds ratio of 2.4 (95% CI = 1.5–3.8) and 2.2 (1.4–3.3), respectively" [1]. In a review of the literature, Pellock concluded that "psychiatric and behavioral comorbidities are believed to affect approximately 40–50% of children and adolescents with epilepsy" [2]. Among all psychiatric comorbidities, mood disorders exemplify the complex relations between epilepsy and psychiatric comorbidities. The purpose of this article is to summarize the known relations between the mood disorders and epilepsy and to illustrate how such relations can impact the pharmacological and surgical treatment of seizures.

2. Is it the chicken or the egg?

The idea that depressive disorders are a consequence of the epilepsy has been the conventional conceptualization of the relation between the two conditions. Yet, 24 centuries ago, Hippocrates wrote: "Melancholics ordinarily become epileptics, and epileptics melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy" [3]. In this statement, Hippocrates suggests that just as epilepsy is a risk factor for depression, depression may be a risk factor for epilepsy. In other words, he was describing a "bidirectional relation" between depression and epilepsy. Although the increased risk that PWE have of developing depression was illustrated in the study by Tellez-Zenteno [1], three population-based, case–control studies of patients with newly diagnosed adult-onset epilepsy suggest that a history of depression increases the risk of developing epilepsy and provide evidence in support of Hippocrates' observations [4–6]. In the first study, carried out in Sweden, depression was found to be seven times more common among patients with new-onset epilepsy, *preceding the seizure disorder*, than among age- and sex-matched controls [4]. When analyses were restricted to cases with a "localized onset" seizure, depression was 17 times more common among cases than among controls. The second study included all adults aged 55 years

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and older at the time of the onset of their epilepsy living in Olmstead County, MN, USA; in this study, the investigators found that a diagnosis of depression *preceding the time of their first seizure* was 3.7 times more frequent among cases than among controls after adjusting for medical therapies for depression [5]. As in the previous study, this increased risk was greater among cases with partial-onset seizures. The same authors investigated the role of specific symptoms of depression in predicting the development of unprovoked seizures or epilepsy in an Icelandic population-based study of 324 children and adults, aged 10 years and older, with a first unprovoked seizure or newly diagnosed epilepsy and 647 controls (see study for which this commentary was written) [6]. They found that major depression was associated with a 1.7-fold increased risk for developing epilepsy and a history of attempted suicide was 5.1-fold more common among cases than among controls.

In another population-based study, Austin et al. compared the behavior profiles of 224 children with new-onset seizures (aged 4–14) and 159 siblings (aged 4–18) using the diagnostic instrument Child Behavior Checklist (CBCL) [7]. Data were obtained at baseline and at 6, 12, and 24 months. During the 2-year period, 163 (73%) children had at least one additional seizure. On average, all children with new-onset epilepsy had higher CBCL scores, indicative of psychopathology across all times when experiencing recurrent seizures than when not experiencing recurrent seizures. In addition, these investigators identified higher rates found in 32% of these children than in the siblings in the 6 months *preceding* the first recognized seizure. The psychopathology included symptoms of mood and anxiety disorders, attention disturbances, thought disorders and somatic complaints [8]. In recent years other studies, have confirmed these observations. In a study of 53 children and adolescents with new-onset epilepsy and 50 age- and gender-matched controls, 45% of the children with new-onset epilepsy had already exhibited a psychiatric disorder presenting as mood, anxiety, or attention deficit hyperactivity disorder (according to DSMIV-TR diagnostic criteria) at the time of the diagnosis of epilepsy [9].

Likewise, recent studies have suggested that psychiatric pathology could be a "risk factor" for the development of unprovoked nonfebrile seizures and epilepsy in children. For example, McAfee et al. conducted a retrospective cohort study of 133,440 pediatric patients (aged 6–17) without history of seizures or prior use of anticonvulsant medications [10]. The data source for this study was a research database containing pharmacy and medical claims for members of a large United States-based managed care organization. The incidence rate of seizures among children without psychiatric diagnoses was 149 per 100,000 person-years (95% CI = 122–180), whereas that among children with psychiatric diagnoses other than attention deficit hyperactivity disorder was 513 per 100,000 person-years (95% CI = 273–878).

The higher risk of epileptic seizures in patients with mood disorders was also suggested in a study by Alper et al., who reviewed data from Food and Drug Administration Phase II and III clinical regulatory trials of several selective serotonin reuptake inhibitors (SSRIs), the serotonin–norepinephrine reuptake inhibitor (SNRI) venlafaxine, and the α2-antagonist mirtazapine [11]. They compared seizure incidence among active drug and placebo groups in these clinical trials and the published rates of unprovoked seizures in the general population. The incidence of seizures was significantly lower among patients assigned to antidepressants than among those taking placebo (standardized incidence ratio = 0.48; 95% CI = 0.36–0.61). In both patients assigned to antidepressants and placebo, the seizure incidence was greater than the published incidence of unprovoked seizures in community nonpatient samples. These data support the increased risk of depressed patients for the development of unprovoked seizures and epilepsy alluded to above, and suggest a possible protective effect of SSRIs and SNRIs (see below). The bidirectional relation between mood disorders and epilepsy may be explained by the presence of common pathogenic mechanisms operant in both disorders. This hypothesis is discussed in great detail below.

Table 1
Efficacy of SSRIs and SNRIs in primary depression and anxiety disorders.

Antidepressant drug	Depression	Panic disorder	Generalized anxiety	Starting dose	Maximal dose
Paroxetine[a]	+	+	+	10	60
Sertraline[a]	+	+		25	200
Fluoxetine[a]	+	+		10	80
Citalopram[a]	+			10	60
Escitalopram[a]	+	+	+	5	30
Venlafaxine[b]	+	+	+	37.5	300

[a] SSRI.
[b] SNRI: the SSRI fluvoxamine and the SNRIs mirtazapine and duloxetine were not included in this table because of the lack of data in PWE.

3. Mood and anxiety disorders: two faces of the same coin?

In patients with and without epilepsy, mood and anxiety disorders tend to occur together with a very high frequency. Hence, no evaluation of a mood disorder is complete unless a careful investigation of comorbid symptoms of anxiety (or actual anxiety disorders) is carried out and vice versa. By the same token, the two disorders are today managed with the same pharmacological regimens, as shown in Table 1.

Thus, in a meta-analysis of studies that investigated comorbidity between *primary* depression and anxiety disorders, Dobson and Cheung concluded that among patients with a depressive disorder, a mean of 67% (range: 42–100%) also experienced anxiety disorders concurrently or in their lifetime; conversely, in patients with anxiety disorders, a mean of 40% (range: 17–65%) also had depression [12]. Furthermore, comorbid occurrence of primary social phobia and both major depression and dysthymia of up to 70% has been reported [13].

The co-occurrence of the disorders has a significant impact on the achievement of symptom remission of *both* disorders. For example, in a study carried out in a general medical clinic setting, 880 patients were screened for depression and 112 patients (13%) were found to have a depressive disorder. Comorbid symptoms of anxiety of moderate severity were identified in 67% of depressed patients. After a follow-up period of 1 year during which symptoms of depression and anxiety were monitored at five time points, depressed patients who improved showed a significant decrease in severity of comorbid symptoms of anxiety, whereas depressed patients who worsened showed a significant increase in their anxiety index; the decrease in the anxiety index of patients in the no-change group was not statistically significant [14]. In PWE, comorbid anxiety and depressive disorders are also a common occurrence. In a study of 199 patients with epilepsy from five epilepsy centers, 73% of patients with a history of depression also met DSM-IV criteria for an anxiety disorder [15].

Of note, mood and anxiety disorders share as well common pathogenic mechanisms, and by the same token, common pathogenic mechanisms can be identified between anxiety disorders and epilepsy.

4. The impact of mood and anxiety disorders in PWE

Mood and anxiety disorders have significant negative impacts on the patients' quality of life and are the strongest risk factors for increased suicidality seen in PWE; furthermore, they interfere