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Commentary

Is it time to train neurologists in the management of mood and anxiety disorders?

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1. Introduction

Depression and anxiety disorders are the most frequent psychiatric comorbidities in people with epilepsy (PWE), with lifetime prevalence rates estimated to range between 30 and 35% in population-based studies [1]. The need for their timely identification and treatment has been recognized for the last two decades. In fact, the National Institute of Neurological Disorders and Stroke (NINDS) has singled out psychiatric comorbid disorders as one of its benchmarks, while various aspects of mood and anxiety disorders in epilepsy have been the topic of major lectures and symposia at national and international scientific epilepsy congresses for the last ten years (e.g., American Epilepsy Society, European Epilepsy Congress, International Epilepsy Congress of the International League Against Epilepsy, Brain Mind and Epilepsy Congress). Yet, despite the wide recognition of the problems associated with these two conditions, they remain undiagnosed and untreated in a vast majority of these patients. Asato et al. address this problem head-on, as illustrated in their statement "*again and again it is pointed out that the comorbidities continue to be under-recognized and undertreated and that patients with epilepsy have significant unmet mental health needs. Nonetheless, there is no indication that this disappointing state of affairs will change anytime*" [2].

So where is the disconnect between the recognition of the high prevalence of psychiatric comorbidities and the lack of access to treatment? This commentary first discusses the reasons why neurologists should be prepared to recognize psychiatric comorbidities. It then reviews the obstacles in the management of these psychiatric comorbidities, examining why their treatment is not carried out by psychiatrists and/or mental health providers and the lack of patient access to these specialists. Finally, the question as to whether neurologists should be involved in the management of these conditions is addressed and, if so, why is this not happening.

2. Magnitude of the problem

Depressive and anxiety disorders have a direct *negative* impact on the management of the seizure disorder at various levels including the following: (i) response to pharmacotherapy with antiepileptic drugs (AEDs); (ii) tolerance to AEDs; (iii) postsurgical seizure outcome after epilepsy surgery; and (iv) mortality risks. Some of the evidence includes the following.

2.1. Worse response to the pharmacologic treatment of the seizure disorder

Two studies have suggested a worse response of the seizure disorder to pharmacotherapy with AEDs in patients with new onset epilepsy. In a prospective study of 138 patients, those with symptoms of depression and anxiety at the time of diagnosis of epilepsy were significantly less likely to be seizure-free at the one year follow-up evaluation [3]. The second study included 780 patients with new onset epilepsy; individuals with a history of psychiatric disorders, particularly depression, were twofold less likely to be seizure-free with AEDs after a median follow-up period of 79 months compared to patients without a psychiatric history [4].

2.2. Worse tolerance of antiepileptic drugs

Two studies have shown that PWE with MDEs endorsed more severe adverse events of AEDs [5,6]. Furthermore, one study [6] highlighted the point that the reported adverse events were "non-psychiatric". In addition, that study demonstrated that the worse tolerance was not limited to MDEs, but was of comparable magnitude in patients with less severe forms of depression such as subsyndromic depressive episodes and anxiety disorders. In addition, tolerance was worse among PWE who experienced comorbid MDEs and anxiety disorders [6].

Recognition of a history of mood disorder can anticipate the development of "potential psychiatric" adverse events with certain AEDs,

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including barbiturates, benzodiazepines, levetiracetam, topiramate, and zonisamide [7–9]. Indeed, a past psychiatric history and/or a family psychiatric history were associated with the development of depressive symptomatology after the start of these AEDs.

2.3. Worse response to the surgical treatment of the seizure disorder

Likewise, a lifetime history of psychiatric disorders and, in particular, depression has been associated with a worse postsurgical seizure outcome following an anterotemporal lobectomy. For example, in a study of 100 consecutive patients, only 12% of patients who reached complete seizure freedom after surgery (mean follow-up period of 8.3 ± 3.3 years) had a lifetime history of depression, while such history was identified in 67% of patients who had auras, but no complex partial and/or secondarily generalized tonic–clonic seizures, and in 79% of patients with persistent disabling seizures [10]. These data were confirmed in two other studies that included patients with mesial temporal sclerosis (MTS): in one study of 280 patients, those with a preoperative psychiatric diagnosis (38% of the entire cohort) were significantly less likely to remain seizure-free [11], while in the second study of 115 patients, a presurgical history of major depressive disorders was a risk factor for persistent postsurgical seizures [12].

2.4. Impact on mortality risk

A recent population-based study from Sweden found that mortality is 11-fold higher in PWE than controls [13]. Close to 16% of all deaths were attributed to external causes, which included death by suicide and accidents (in a motor vehicle, drug poisoning, falls, drowning, and assault, among others). In fact, PWE had a greater than threefold higher risk of premature death from these causes than the control groups. Furthermore, among PWE who died from external causes, comorbid psychiatric disorders were identified in 75.2%, the majority of which included depression and substance misuse. It is worth noticing that the lifetime prevalence of psychiatric disorders in PWE was 40.7% compared to 10.3% in controls. In a separate population-based study conducted in Denmark, the presence of mood disorders increased the risk of suicide by 32-fold [14].

2.5. Other

In addition to the above, the presence of depression and anxiety disorders has been shown to be a strong predictor of poor quality of life. Indeed, in PWE with treatment resistant epilepsy, several studies demonstrated that depressive and anxiety disorders are the most powerful predictors of poor quality of life, even after controlling for seizure frequency, severity, and other psychosocial variables [15–19]. Of note, comorbid depressive and anxiety disorders have a worse impact on the quality of life of PWE than the depressive or anxiety disorders occurring alone, particularly when a major depressive episode is comorbid with more than one anxiety disorder [15]. In addition, PWE with untreated depression were found to use significantly more health resources of all types, independent of seizure type or duration [20]. Mild-to-moderate depression was associated with a twofold increase in medical visits compared with nondepressed controls, while severe depression was associated with a fourfold increase.

Clearly, these data confirm the fact that neurologists can no longer ignore the need to recognize the existence of a past and/or current mood and anxiety disorder and ensure that they are properly treated. Furthermore, the observations made above are not limited to epilepsy. Indeed, depressive disorders have been found to impact, in a negative manner, the course of Parkinson's disease and dementia, accelerating their progression of motor and cognitive deficits in the former and accelerating the cognitive deterioration and need for transfer to nursing facilities in the latter (see reference [21] for additional details). In the case of stroke, poststroke depression is associated with worse recovery of motor and cognitive deficits and a lower likelihood to reacquiring activities of daily living. Thus, these observations are not limited to epileptologists!

3. Possible obstacles to treatment?

The obstacles and caveats that limit access to treatment of depression and anxiety disorders in PWE can be separated into several categories that are analyzed below.

3.1. Where have all the psychiatrists gone?

Should not psychiatrists be dealing with these issues? Unfortunately, access to psychiatrists is very limited. In the U.S.A., patients with medical insurance are covered for a limited number of visits with a psychiatrist. Those on governmental insurance (e.g., Medicaid, Medicare) are rarely treated by private practitioners and have to wait for a long time to be seen in hospital-based clinics staffed by psychiatry residents or local mental health centers. In other words, to see a psychiatrist without having to wait and/or get the proper treatment, patients need to pay out-of-pocket. At medical institutions (e.g., large medical centers, teaching hospitals), psychiatry departments will provide a psychiatrist to epilepsy centers to evaluate and treat their patients only if the epilepsy center contributes to the salary of the psychiatrist. In other words, "you want a psychiatrist… you have to pay for his/her time". The shortage of child psychiatrists is significantly worse, reaching critical proportions in most areas of the U.S.A. and the world.

Yet, if financial reasons were the only barrier to access to a psychiatrist, this would not be a problem in health-care systems that provide universal health care (e.g., Canada, Europe, and Israel). Unfortunately, treatment of comorbid depressive and/or anxiety disorders in PWE in these countries does not appear to be any better than that in the U.S.A. Thus, financial constraints do not explain the limited involvement of psychiatrists in the treatment of PWE.

Other explanations may include the following: (i) refusal of PWE to see a psychiatrist; (ii) limited understanding by psychiatrists of psychiatric comorbidities in epilepsy and persistent temerity to use psychotropic drugs in PWE (see below); and (iii) limited (or no) communication between neurologists and psychiatrists, which perpetuates the psychiatrists' misconceptions and reluctance to treat these patients. After all, the exposure of psychiatrists to the field of "all" neurology is limited to 4 weeks in medical school and eight weeks during the internship year of their residency training.

There has been a misconception held by practitioners of all disciplines, including neurologists and psychiatrists, that antidepressant drugs lower the seizure threshold and, hence, can worsen seizures in PWE. This misconception is reinforced by the listing of seizures as a possible "adverse event" in the package insert of all antidepressant drugs. Yet, there is a consensus today that seizures associated with antidepressant drugs occurred when used at very high doses (e.g., in overdoses). In fact, seizures have been associated with exposure to only four antidepressants at therapeutic doses: maprotiline, amoxapine, chlorimipramine, and bupropion [22]. With the exception of bupropion, these antidepressant drugs are hardly prescribed any more.

The antidepressant drugs of the selective serotonin-reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) have become the first line of pharmacotherapy for primary MDEs and anxiety disorders [23] and have been recommended in two consensus documents by experts for PWE [24,25]. Any proconvulsant effect of SSRIs and SNRIs has been put to rest in a study published in 2007 by Alper et al. who compared the incidence of seizures between patients randomized to placebo vs. an SSRI and the SNRI venlafaxine during multicenter-randomized placebo-controlled trials submitted to the FDA for regulatory purposes [26]. Subjects randomized to antidepressants were 52% less likely (69% less likely when excluding bupropion immediate release formulation) to develop seizures *compared to those*