

Depressive Disorders in Patients with Epilepsy: Underdiagnosed and Appropriately Managed?

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Rec date: Jan 23, 2015; Acc date: Feb 12, 2015; Pub date: Feb 16, 2015

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Abstract

Epilepsy is a complex disorder that is commonly associated with additional brain dysfunction, social isolation, and vocational difficulty. Each of these factors may contribute to the increased prevalence of psychiatric disorders in epilepsy. Yet, epidemiological data suggest that depression is the most prevalent disorders among all psychiatric illness in epilepsy. Likewise, several emerging data have explored several multifactorial etiologies of depression in epilepsy. These include underlying genetic, neurochemical, anatomical, neurologic, and iatrogenic factors. Furthermore, clinical investigations have consistently demonstrated that depression has a large impact on subjective health status. In patients with recurrent seizures, depression appears to have a stronger association with QOL than does seizure rates. Unfortunately, however, a significant proportion of patients with epilepsy and depression are not diagnosed nor offered the appropriate treatment. Current treatment recommendations for depression in epilepsy are similar to those for otherwise neurologically normal depressed patients, emphasizing the role of SSRI, but certain antidepressants should be used with caution. Ongoing studies are attempting to define optimal treatment strategies, and more definitive data to guide clinical management is expected to become available in the near future.

Keywords: Depression; Seizures; Temporal Lobe Epilepsy (TLE); Quality of Life (QOL); Serotonin Reuptake Inhibitors (SSRIs)

Abbreviations:

AED: Antiepileptic Drugs; BDI: Beck Depression Inventory; MTS: Mesial Temporal Sclerosis; NDDI-E: Neurological Disorders Depression Inventory for Epilepsy; PHQ-9: Patient Health Questionnaire nine-item depression scale; PWE: Patients with Epilepsy; QOL: Quality of Life; SSRIs: Serotonin Reuptake Inhibitors; SNRI: Serotonin and Epinephrine Reuptake Inhibitors; TLE: Temporal Lobe Epilepsy; TCA: Tricyclic Antidepressant

Introduction

Epilepsy is a chronic condition that may be associated with several other neurological disorders; stroke, migraine, and psychiatric disorders are the most frequent comorbid disorders in PWE. The term comorbidity is used to describe greater than coincidental association of two or more conditions in the same individual [1].

Epilepsy has been associated with increased risk of psychiatric disorders. Although the incidence and prevalence rates of psychiatric comorbidities vary widely among studies from 12%–41%, this variation is largely due to methodological differences among the studies; selection bias for the population under study, diagnostic methods used, AED numbers and dosages are some of the confounding factors that could have an impact on the prevalence rates [2-5] Epilepsy has also been associated with increased risk of suicide, even after adjustments for various factors known to pose a risk for suicide in the general population [6-9].

The most frequent psychiatric diagnoses reported in people with epilepsy include psychoses, neuroses, mood disorders (DSM-IV axis I

disorders), personality disorders (DSM-IV axis II disorders), and behavioral problems. Among these, mood disorders are the most frequent psychiatric comorbidity in PWE with a prevalence of depression estimated between 11% and 60% in patients with recurrent seizures [10,11]. Indeed, it is well established that one of every three PWE will experience a depressive disorder in the course of their life, often associated with anxiety symptoms or a full blown anxiety disorder.

Worldwide Prevalence of Depression in Epilepsy

Based on the available worldwide epidemiological studies, the prevalence of depression ranges from 11 to 60% in patients with recurrent seizures and from 3 to 9% in patients with well-controlled seizures. Mendez et al. [11] used the Hamilton Depression Rating Scale in 175 consecutive patients in an outpatient epilepsy clinic, concluding that 55% met criteria for depression. In a community-based study that used the Hospital Anxiety and Depression Scale, Jacoby et al. [12] observed, in a well-designed survey, that 21% of 168 patients with recurrent seizures were depressed; whereas, only 9% of controlled patients had significant symptoms of depression. On the other hand, in a primary care setting, O'Donoghue et al. [13] used the same scale to demonstrate that, out of a group of 155 patients in the United Kingdom, 33% with recurrent seizures and 6% of those in remission had probable depression. Similarly, a study by Seyal et al. [14] using PHQ-9 found that 30% of their patients attending a specialized epilepsy clinic at the University of California at Davis, USA have scored in the depressed range. Likewise, a recently submitted work in UAE has drawn similar conclusions [15] In fact, despite several methodological variability among various studies, depression is consistently found to be up to 10 times more prevalent in association with uncontrolled epilepsy than in the general population. Finally, a recently published meta-analysis of all well designed studies of

depression in PWE concluded that the risk of depression increases several folds in patients with epilepsy, when compared to the general population [16]. The findings from all these studies underscore the importance of depression in epilepsy and the need to effectively screen and treat depressive disorders.

Impact of Depression on Health Related Status

Several studies have studied the implication of depression on health related quality of life in PWE. Ettinger et al. [2] has utilized the household panel maintained by the National Family Opinion to study depression and QOL in persons with epilepsy, asthma, and healthy controls. The response rate for the survey was approximately 50% in each group, with a total of 1532 responses. PWE were significantly more likely to score in the depressed range on the Center for Epidemiological Studies Depression Scale (CES-D) (37%), than were those with asthma (28%) or healthy subjects (12%). Although nearly half of the group with epilepsy had not had a seizure during the past year, suggesting that the sample represented the less severe aspect of the spectrum of epilepsy, the mean scores on the Short Form-36 scales for role limitations, emotional wellbeing, and social wellbeing were significantly worse than the asthma group. On the other hand, none of the scales was lower for asthma. In another cross sectional study, Beghi et al. [17], compared depression severity across disease states in a study of epilepsy, type I diabetes mellitus, and community controls. Fifty-five patients with idiopathic or cryptogenic epilepsy were compared with age and sex matched subjects with type I diabetes or persons donating blood in the local medical clinic. Epilepsy subjects with any structural brain abnormality were excluded from the study, and only 37% reported a seizure within the past year, reflecting less form of severe epilepsy, similar to, the study of Ettinger et al. [2] Thirty-four percent of epilepsy patients scored in the depressed range compared with 27% of type I diabetes patients and 7% of blood donors.

The Importance of Identifying Depression in PWE

The impact of depression on QOL in PWE has been well described in five studies involving patients with pharmacoresistant epilepsy. They demonstrated that depression is the most powerful predictor of health related quality of life, even after controlling for seizure frequency, severity, and other psychosocial variables [18-22]. Furthermore, a recent study has found that mood disorders are strongly and, independently, associated with worse QOL after epilepsy surgery [23]. On the other hand, several studies have demonstrated the increased incidence of suicide in patients with depression and epilepsy. In a review of 11 studies, Harris and Barrowclough [24] have estimated 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. [6] identified a lifetime average suicide rate of 12% in people with epilepsy compared to 1.1% to 1.2% in the general population.

Moreover, other studies have clearly shown that depression in people with epilepsy has significantly increased the healthcare costs associated with the management of the seizure disorder. Cramer et al. [25] found that patients with untreated depression used significantly more health resources of all types, independent of seizure type or latency. Likewise, 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.

Additionally, and more importantly perhaps, depression in PWE might be a marker of "bad" epilepsy. A well designed study suggests that the presence of depression in PWE may predict a failure to respond to pharmacotherapy with AEDs in patients with newly diagnosed epilepsy. Of a cohort of 890 patients with newly diagnosed epilepsy, Hitiris et al. [26] found that a prior history of depression is associated with at least 2.5 times risk of not responding to AEDs over 5 years of follow up. Likewise, the presence of depression prior to epilepsy surgery, may also serve as an independent marker for worse postsurgical outcome following anterior temporal lobectomy (ATL), as shown by the study of Kanner et al that included 100 patients with a mean follow up of 4 years [27]. These studies could support the hypothetical believe that depression can be considered as a marker for "difficult to control" epilepsy.

Finally, and on a separate note, it is worth mentioning that epilepsy may have an extensive impact on patients' physical, psychological, and social functioning (i.e., QOL). QOL in PWE is affected by several components, one of which is related to comorbid mood disorder, where high rates of anxiety, depression, and low self-esteem have been reported among these patients. Furthermore, they are more likely to be under- or unemployed, to be at great risk of educational achievements, and face restrictions on driving and social stigma, and, for women, they are at fear of lower rates of marriage and having children. Other factors to be addressed in PWE are broad; seizure control status, burden of AEDs in relation to dosages and numbers, other chronic comorbidity conditions that may negatively and, independently, affect the QOL in these patients and would also affect the choice of AED therapy.

Etiologies of Depression in Epilepsy

The perception that depression is a "normal" response to having a chronic condition such as, epilepsy has long been held, by both patients and physicians, but is no longer acceptable or valid. Instead, several emerging data have explored other multifactorial etiologies of depression in epilepsy. These include genetic, neurochemical, anatomical, neurologic, and iatrogenic factors.

The role of genetics

The role of genetics in the etiology of depression in epilepsy is suggested by the fact that a family history of depression is quite common among depressed patients with epilepsy. More than half of these patients have been reported to have family histories of psychiatric illness, usually mood disorders [28].

The role of neurotransmitters

It appears that epilepsy and depression may share common pathogenic mechanisms involving decreased serotonergic, noradrenergic, dopaminergic, and GABAergic activity, which has been shown to take part in the kindling process of seizure foci, exacerbating seizure frequency in some animal models [29]. Studies of neurotransmitter activity in both epilepsy and depression suggest that the occurrence of one disorder may facilitate the development of the other, and vice versa [30]. As a matter of fact, several imaging studies utilizing interictal PET using different ligands, have consistently shown some degree of decreased 5-HT_{1A} binding in the mesial structures, raphe nuclei, thalamus, and cingulate gyrus [31-33]. In a

study of 45 patients with TLE, Theodore et al demonstrated an inverse correlation between increased severity of symptoms of depression identified on the BDI and 5HT_{1A} receptor binding at the ipsilateral hippocampus to the seizure focus and to a lesser degree at the contralateral hippocampus and midbrain raphe [34]. These changes in 5 HT_{1A} receptor binding are quite similar to those identified in PET studies of patients with primary major depressive disorders (MDDs). To further support this shared pathogenic mechanisms, three case-control population based studies have shown that a history of depression was associated with several fold increased risk for developing new onset epilepsy among cases than among controls [35-37]. More recently, a population-based case-control study from Stockholm with new onset unprovoked seizures assessed the risk of developing unprovoked epileptic seizures before and after hospitalization for a psychiatric diagnosis. The age-adjusted odds ratio for unprovoked seizures was 2.5 after a hospital discharge diagnosis for depression, 2.7 for bipolar disorder, 2.3 for psychosis, 2.7 for anxiety disorders, and 2.6 for suicide attempts [38].

Although the data from all these case-controlled suggest a bidirectional relationship among depression and epilepsy, it does not necessarily, however, suggest that depression causes epilepsy or vice versa. Rather, it may support the point towards the existence of common pathogenic mechanisms operant in both conditions which facilitate the development of one disorder in the presence of the other. Interestingly, many centuries ago, Hippocrates 400 BC had suggested this type of bidirectional relationship when he 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". Galen at 200 AD had further reconfirmed the organic cause of depression [39].

Neuroanatomical factors

Changes in common brain structures have been identified in patients with primary major depressive and bipolar disorders and in PWE, including atrophy of temporal- and frontal-lobes. These changes have been identified with the use of high-resolution MRI and volumetric measurements of the amygdala, hippocampus, entorhinal cortex, temporal, lateral neocortex, as well as of the prefrontal, orbitofrontal, and mesial-frontal cortex, and to a lesser degree, of the thalamic nuclei and basal ganglia [40]. It is, therefore, not surprising that PWE whose seizure foci are in temporal and frontal lobes have a higher prevalence of depression. Furthermore, hippocampal atrophy/sclerosis (HS) which is a hallmark of mesial temporal lobe epilepsy is a common finding in patients with depression and, according to some studies, correlate with both the severity and duration of the depressive state [41]. Furthermore, Quiske et al. [42] examined the association of MTS on MRI with BDI scores in 60 patients with TLE. Mean depression scores were significantly higher in patients with MTS, independent of the lateralization of MTS. The investigators suggested depression as "a good indicator of MTS, but not vice versa." Moreover, a study by Gilliam has shown a correlation of the degree of MR spectroscopic abnormalities in the ipsilateral hippocampus in patients with TLE and the severity of depression as measured by BDI [43]. In addition, additional studies suggest that the presence of HS is a risk factor for developing depression in PWE when treatment is initiated with AEDs with depressive properties, such as topiramate, and levetiracetam [44,45].

The role of seizure related factors

Seizure types have been shown, in some studies, to correlate with depression. Depression is more commonly encountered in patients with complex partial seizures, particularly those of temporal lobe origin [15]. Others have looked at the possibility that depression might be associated with laterality of seizure focus. Most studies have found that depression is more common in those with left-sided foci [46]. Furthermore, a recent work by Theodore et al suggests that depression, when measured by BDI scores, is more likely to occur in patients with right TLE and left MTS, as compared with, left TLE without depression [47].

The role of iatrogenic factors (drug related)

Among the most important factors contributing to the risk for depression in PWE are those associated with medication side effects. A number of drugs and drug classes have been implicated in the etiology of depression, including some AEDs, such as barbiturates, levetiracetam, vigabatrin, and topiramate. These drugs and, especially in patients susceptible to psychiatric illness, (e.g., history of a prior psychiatric illness and/or family psychiatric illness) can be clearly associated with behavioral changes and depression [45]. Other investigators have related depression to the rapid withdrawal of an AED with mood stabilizing properties, such as, carbamazepine, oxcarbazepine, and lamotrigine [48]. Likewise, and as an example of drug related depression, the addition of AEDs with enzyme-inducing AEDs (e.g., phenobarbital, primidone, phenytoin, carbamazepine, high-dose topiramate, and oxcarbazepine) in patients taking antidepressant drugs that had yielded a remission of a depressive episode. The increased clearance of the antidepressant drug results in lower serum concentration and potential loss of efficacy. Another, uncommon, but well documented example is the occurrence of de novo depression following ATL. Interestingly, this risk occurs independently of postsurgical outcome [49].

Geschwind syndrome and TLE

As an example of the close relationship between psychiatric issues and epilepsy, Geschwind and Waxman were the first to describe a specific set of personality alterations in PWE which was later called Geschwind syndrome [50]. This syndrome has been described in patients with TLE and is characterized by sexual behavioral disorders, hyperreligiosity, hypergraphia, and viscosity. The existence of this syndrome, as a specific personality disorder, in PWE is not accepted unanimously and has led to considerable debate [51,52]. The evidence for its existence is largely empirical, and following Benson [53]. The strongest support so far stems from the many clinicians who have described and attempted to manage patients with epilepsy and these personality features. It has also been described in a subgroup of patients with TLE with bilateral hippocampal atrophy [54]. Its occurrence, however, in patients with unilateral hippocampal atrophy is very questionable.

Clinical manifestations

Depressive symptoms can present according to the temporal relation to the seizures occurrence into *ictal* (the depressive symptoms are a clinical manifestation of the seizure, a rare form of depression in PWE), *periictal* (symptoms precede and/or follow the seizure occurrence), and *interictal* (symptoms occur independently of the seizure occurrence). Interictal depression is the most frequently

“recognized” type of mood disorder and can present differently among PWE. Major depression, bipolar disorder, dysthymic disorder, and minor depression are all well described in PWE. Nevertheless, a significant percentage of patients present an atypical clinical picture that fails to meet any of the DSM Axis I categories, which lead Blumer to coin the term “interictal dysphoric disorder” to refer to this type of depression in epilepsy with its prolonged and interrupted depression free course that is often associated with anhedonia, hopelessness, helplessness, anergia, pain, and insomnia [55]. In a study by Kanner et al, symptoms of depression mimicked dysthymic disorders in 69 of 97 consecutive patients (70%); the interrupted nature of these symptoms accounted for the failure to meet DSM-IV criteria of dysthymic disorder [29].

The underlying etiology of this interrupted course is not well explained. Conceivably, it is possible that breakthrough seizures in PWE might interrupt the course of depression and improve the depressive symptoms episodically and hence the interrupted course of the disease [56]. On the other hand, the phenomenon of “forced normalization” may also explain in part the interrupted nature of the disease. This phenomenon consists of the appearance of psychiatric disorders associated with the cessation of epileptic seizures [57]. Having said that, the relationship between depression and epilepsy is far from being that simple. Indeed, a recent study showed, in contrast to the forced normalization concept, a significant improvement in depression and anxiety symptoms in patients with refractory epilepsy following epilepsy surgery, especially in those who became seizure-free [49].

Screening for depression

Despite its high frequency and great impact on the QOL and care for PWE, depression remains undertreated and unrecognized in a significant number of PWE. 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 [24]. While the clinical manifestations of depression in people with epilepsy can be atypical, the most frequent cause for this underdiagnosis is the failure of clinicians to inquire about the symptoms, and for patients and families to report them, assuming that it is quite normal to have them in the setting of this chronic disease. In a survey of neurologists, Gilliam found that 80% do not routinely screen for depression in patients with epilepsy [58]. This last figure suggests that in any busy neurology practice, where the major focus is seizure control, it is very likely that symptoms of depression may be easily missed.

Several tools have been used to screen for depression in PWE; some of which are time consuming in a busy clinic setting. A 6-item questionnaire referred to as NDDI-E has been developed and validated to screen for depression. It takes less than 3 minutes to fill out at the office and has a sensitivity and specificity of 90%, 81%, respectively [59]. A score of 14 and higher is suggestive of the possibility of a major depressive disorder and can serve as an alarming sign to carry out a more in-depth evaluation. A recent study enrolled 266 PWE at a specialized neurologic epilepsy service in London and compared verbal self-report and visual analog (VAS) screening methods for depression. These included two generic depression scales (Hospital Anxiety and Depression Scale [HADS], BDI-II, one epilepsy specific scale [NDDI-E]) and one new visual-analog scale (Emotional Thermometers [ET]). The authors conclude that the six-item NDDI-E or seven-item HADS-D should be considered if a conventional scale is

preferred and that the revised ET4 be considered if a visual-analog method is required [60]. Clearly, the use of these 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. In support of using these instruments, a recently well designed study evaluated the accuracy of, and the operating characteristics of PHQ-9 for depression screening in PWE and concluded that PHQ-9 is an efficient and nonproprietary depression screening instrument with excellent accuracy validated for use in PWE [61].

AEDs and suicidal risk

To highlight the seriousness and complexities of psychiatric problems associated with AED use, a recent meta-analysis has linked AED use with increased suicide risk [62]. The meta-analysis encompassed a total of 43,892 patients who were treated for epilepsy, psychiatric disorders and various pain disorders. The FDA concluded and based on that meta-analysis that, with the exposure to AEDs, the risk for suicidality was increased by a statistically significant 1.80 fold. Suicidality occurred in 4.3 per 1000 patients treated with AEDs in the active arm, compared with 2.2 per 1000 patients in the comparison arm. The use of AEDs was associated with a higher risk for suicidality in PWE (odds ratio: 3.53; 95% CI: 1.28–12.10) than in patients with psychiatric disorders (odds ratio: 1.51; 95% CI: 0.95–2.45) or other disorders (odds ratio: 1.87; 95% CI: 0.81–4.76). Despite the aforementioned caveats for linking AED use to any psychopathology, and the methodological issues associated with the meta-analysis [63], a detailed evaluation questioned the validity of its findings owing to several methodological problems [64]. Furthermore, this risk is insignificant if, compared with the average lifetime incidence of suicidality, in PWE attending epilepsy clinics [6]. As a matter of fact, and since the FDA warning, at least three large studies have attempted to clarify whether AEDs are associated with an increased suicidal risk [65–67]. The data from these studies yielded contradictory results. A study by Gibbons et al. in patients with bipolar disorders taking AEDs, concluded that AEDs, as a class, are not associated with an increased risk of suicidality [65]. On the other hand, a study by Paterno et al. found a significantly higher risk of suicidality and violent deaths with certain AEDs, such as lamotrigine, oxcarbazepine, gabapentin and tigabine. Unlike the finding from the FDA meta-analysis, topiramate was not associated with that risk [67]. Based on all the above reviews and studies, we can propose that several AEDs, but not all, as suggested by the FDA warning, might be associated with psychiatric adverse events, which may lead to suicidal ideation and behavior, keeping in mind that the rates of completed suicide and suicidal attempts are, fortunately, rare. It is worth mentioning, however, that given the relatively high prevalence of comorbid mood and anxiety disorders in PWE [8], as well as the increased suicidal risk in PWE [5], clinicians should be alerted to screen patients for both conditions, independently of whether, AEDs have any influence on suicidal risk. Specifically, clinicians should be extremely alert to the high risk in patients with a current and/or past psychiatric history [6].

Treatment options

Despite its relatively high prevalence and significant impact on management, the treatment of depression in PWE remains an, “unexplored territory.” Indeed, a significant percentage of PWE and depression are under-recognized and under-treated. One reason for

this includes the fear that seizures are exacerbated by antidepressants. To that extent, the treatment of these patients has been, for all intents and purposes, empiric, based on the untested assumption “that patients with depression and epilepsy should respond to antidepressant drugs in the same manner as depressed nonepileptic patients.” In fact, there has only been one small double-blind, placebo-controlled study published till recently that included 42 patients. It compared the efficacy of mianserin, amitriptyline, and placebo to treat major depression in PWE in three treatment arms. At the end of 6 weeks of treatment, no significant differences in outcome were observed between the groups. It is very clear that the small sample size of that trial limits the draw of any meaningful conclusions [68].

Similarly, and in a very recently published Cochrane review on this topic, further confirms the limitations of the evidence on the efficacy of antidepressants in treating depressive symptoms associated with epilepsy. As a matter of fact, in that systematic review, only one small RCT have met the inclusion criteria and demonstrated a statistically significant effect of venlafaxine on depressive symptoms. The authors have urgently, and, correctly so, called for further comparative clinical trials of antidepressants and psychotherapy in large cohorts of patients with epilepsy and depression [69]. On that note, and to further show the complexity of this matter, it is of equal importance to keep in mind that in patients with depression, but without any other comorbid condition, a meta-analysis performed by NICE of all the placebo controlled trials of SSRI did not find any clinically significant difference between placebo and SSRIs arms [70].

Treatment strategies

Before starting a patient on antidepressant drug therapy, it is important to realize that AEDs have a range of beneficial and adverse psychotropic effects. Some AEDs can be effective as treatments for mania and bipolar depression and as mood stabilizers in bipolar and schizoaffective disorders on one hand, and may in some patients on the other hand, cause depressive symptoms [71]. Obviously, establishing the causal role of any particular AED in regard to an affective symptom is quite complex, as it may be confounded by the type of epilepsy, other co-occurring medication exposures, pre-existing psychopathology, cognitive deficits, the impact on seizure activity (e.g. a marked reduction in seizures may have either beneficial or it may carry adverse effects on mood) and the pharmacokinetic effects. Furthermore, the characterization of psychological symptoms is often poor; for example, many studies record ‘agitation’ and ‘irritability’, ill-defined symptoms that may stem from anxiety or other causes; similarly, ‘apathy’ or ‘tiredness’ may stem from depression or other causes. Therefore, and as previously discussed in the section of “iatrogenic causes of depression”, it is widely recommended to rule out the following potential causes for depression before treatment with antidepressant is initiated 1) the depressive episode followed the discontinuation of an AED with mood stabilizing properties, such as carbamazepine, valproic acid, or lamotrigine, especially in patients with a past and/or a family psychiatric history, as these AEDs may be keeping an underlying mood disorder in remission [48]. In such a case, reintroduction of that AED or of another mood-stabilizing agent may be sufficient to reach a euthymic state and 2) the depressive episode followed the introduction or dose increment of an AED with known negative psychotropic properties, such as Phenobarbital, topiramate, vigabatrin, and levetiracetam. Depressive episodes in these cases may be dose-related, with some (e.g., barbiturates, benzodiazepines). In such cases, lowering the dose of AED, without compromising seizure control, if possible, may result in symptom

remission. On the other hand, depression may occur de novo in patients taking levetiracetam, regardless of the dose, the patient is taking, i.e. lowering the dose of the drug may not result in symptoms remission. In these patients, discontinuation of the medication or, in case levetiracetam was the most effective AED for that patient, the addition of an antidepressant should be considered. Other AEDs, however, such as topiramate can cause depression as result of rapid titration of the medication [72]. In such cases, slowing of the titration rate of the culprit AED may result in symptom remission. However, if an AED to be discontinued, it is important to remember that expert consensus has proposed a preferred approach to transitional alternative monotherapy, recommending that an existing baseline AED be tapered only after a presumably efficacious dose of the new adjunctive AED is reached. Initially, the patient’s current baseline AED should be held at its current dose to limit breakthrough seizures, while the new adjunctive AED is titrated to a presumably effective protective target dose, followed by taper and withdrawal of the baseline AED. The rationale for this measured approach is that abruptly stopping an existing baseline AED increases the risk of breakthrough seizures, while introducing a new adjunctive AED too rapidly can cause an excess of adverse effects.

Pharmacotherapy in PWE

Among the six families of antidepressant drugs, most of the published data in PWE include open trials with SSRIs, SNRIs, and TCAs and the norepinephrine and dopamine reuptake blocker (e.g., bupropion), which is one of the antidepressant drugs that is not recommended in these patients because of a proconvulsant effect in nonepileptic patients. SSRI are the most widely used classes of antidepressant medications to treat depression in PWE. Other options include SNRI, and, in selected patients, TCAs. In general, the delay of initiating treatment in PWE stems from the belief that antidepressants worsen or trigger seizures.

Do antidepressant drugs cause or worsen seizures?

Notably, and in contrary to that idea, the actual risk of antidepressant drugs causing or worsening of seizures in PWE is small and should not deter the start of therapy. In a study at the Rush Epilepsy Center, sertraline was found to definitely worsen seizures in only 1 out of 100 patients [73]. In another five patients, a transient increase in seizure frequency was attributed to this antidepressant drug with a probable but not definite causality. On that note, surveyed primary care physicians, neurologists, and psychiatrists chosen from the Ohio State Medical Board registry on the topics of depression in epilepsy, seizures with antidepressant use, have identified fear of increased seizure frequency with antidepressant use as a significant barrier to treatment. There was a clear inverse relationship between the estimated risk of antidepressant-induced seizures and comfort treating depression in epilepsy ($P=0.02$), with 52% of primary care physicians identifying this as a reason for not treating depression in this population. The author called for further education of community physicians and neurologists regarding the importance of treating depression in PWE [74]. On the other hand, bupropion, maprotiline, and amoxapine are the antidepressant drugs with the strongest proconvulsant properties and should be avoided in patients with epilepsy [75].

Furthermore, a recent and very reassuring paper suggests a possible “protective” effect of SSRIs and SNRI in depressed patients: In that study, Alper et al. [76] compared the incidence of seizures between

depressed patients randomized to placebo and SSRIs, SNRIs and the α_2 antagonist mirtazapine in the course of regulatory studies submitted to the FDA. The seizure frequency among patients randomized to placebo was 1501.5 seizures/100,000 years, while that of patients randomized to the antidepressants was 534.8 seizures/100,000 years. Moreover, and contrary to the widespread misbelief, some investigators have suggested that SSRIs, possibly through its increase extracellular 5-HT, inhibits both focal and generalized seizures in several animal models of generalized epilepsy and focal epilepsy [77,78].

Choice of antidepressant drug

Clinicians must factor in several variables in the process of choosing a first antidepressant drug among the most commonly used classes SSRIs, SNRIs, and TCAs. The choice of drugs should be individualized according to many variables. Potential pharmacokinetic interactions, patient's age and sex, adverse effect profile of the medication, other comorbid psychiatric and non-psychiatric conditions are among the most important variables that determine the choice of antidepressants.

Pharmacokinetic interactions with concurrent AEDs or any other concurrent medication in patients with other comorbid chronic disease states are among the first important variables that should be considered when choosing a drug or a class of drugs. For example, several drugs of the SSRI family are inhibitors of one or more cytochrome P450 (CYP) isoenzymes; [79] while, citalopram and escitalopram, from that family have a very mild inhibitory effects. This effect becomes extremely important if a patient is using a drug that is metabolized by these enzymes. In addition, it is important to realize that in settings where higher SSRI doses are used, or perhaps in elderly patients who may have reduced clearance of both phenytoin and the SSRI, the potential for a clinically meaningful interaction may be increased. Likewise, several case reports have suggested that SSRIs such as fluoxetine and sertraline have caused increased phenytoin and carbamazepine serum concentrations [80] On the other hand, and unlike the SSRI family, venlafaxine and duloxetine from the SNRI family are unlikely to cause significant interactions with currently available AEDs.

Furthermore, it is worth reporting that most SSRIs, SNRIs, and TCAs are substrates for one or more of the CYP isoenzymes [81], comedication with an enzyme inducing AED is expected to increase their systemic clearance resulting in lower serum concentrations. This effect has been demonstrated in antidepressants, such as, sertraline, paroxetine, citalopram, as well as in most TCAs, requiring an adjustment of their dose (by 25–30%) to avert recurrence of psychiatric symptoms. In contrast to the enzyme-inducing drugs, the AED sodium valproate can inhibit certain CYP (2C9) and UDP-glucuronyltransferase enzymes, and may cause significant increases (50–60%) in serum concentrations of antidepressants such as amitriptyline or nortriptyline [80].

Finally, the potential for cardiac arrhythmias mediated by a sodium channel blocking effect of high serum concentrations of TCAs needs to be factored in the choice of antidepressant drugs in PWE, given the increased risk of sudden death in PWE. Similarly, the anticholinergic effects of these medications that cause dry mouth, constipation, urinary hesitation/retention, blurred vision, tachycardia, exacerbation of narrow angle glaucoma, problems with memory, and confusion; while, blockade of the α_1 adrenoreceptor has been associated with postural hypotension, dizziness, and reflex tachycardia, and can potentiate the effects of antihypertensive drugs. All these negative

adverse effects can be quite problematic in patients with diabetes, for example, with its associated widespread neuropathy.

On a separate note, adverse effects of SSRIs and SNRIs have to be considered prior to initiation of treatment. They have been reported in about 20–30% of patients with primary mood disorders and include anxiety and agitation during the acute phase of treatment, gastrointestinal symptoms (i.e., nausea, abdominal cramping, and diarrhea), and changes in appetite and weight, sexual disturbances, and rarely involuntary movements. Furthermore, SSRIs can compound on a weight gain caused by other AEDs such as valproic acid, gabapentin, pregabalin, and carbamazepine. Among the SNRIs, hypertension is a potential adverse event identified in patients taking venlafaxine, but not duloxetine [82]. Therefore, blood pressures need to be monitored closely and venlafaxine and duloxetine should be used with great caution among patients with a risk or with existing hypertension. This should be an important point to consider, especially in certain part of the world, such as the Gulf region, for example, where chronic conditions such as hypertension, diabetes, and dyslipidemia are quite prevalent [83]. Duloxetine should be used with great care in patients with a history of liver disease and should be avoided in those with glaucoma.

All SSRIs and SNRIs can cause sexual disturbances, although the effect is less frequent with the latter. Accordingly, it is essential for clinicians to investigate the existence of sexual disturbances before starting an SSRI, as these are relatively common among PWE, either, as a direct consequence of the seizure disorder, as an adverse event in response to an AED, or a combination of the two factors, or can be related to other chronic disease states such as diabetes. On that note, citalopram and escitalopram and the SNRIs have been reported to have a lower incidence of sexual adverse events.

Several population-based studies have suggested that SSRIs can cause osteopenia and/or osteoporosis. It is well established that bone disease is quite prevalent in woman with epilepsy either as, a direct effect of the AED, mainly with an enzyme-inducing AEDs that affects the metabolism of vitamin D [84]. This issue becomes of paramount importance in a setting of low vitamin D, especially in certain part of the world, where low vitamin D is quite prevalent among their women population, which is the case in our Gulf region [85].

Nonpharmacological therapy

Other options for treatment include cognitive, interpersonal and behavioral therapy, and, in severe cases, electroconvulsive therapy (ECT) can be considered safely in PWE who do not respond to appropriate antidepressant therapy [86]. A randomized trial of an SSRI and cognitive behavior therapy (CBT) in depressed patients without other neurological disorders demonstrated greater efficacy with combined therapy compared to either one alone [87]. A similar trial design for PWE randomizing 140 PWE to either sertraline or CBT for 16 weeks has been recently completed. At the end of the trial, no significant difference in outcome for depressive symptoms remission was observed in the two arms. Moreover, patients whom their depressive symptoms remit had significant improvement in QOL independent of other epilepsy related factors. Similar to the study of Alper et al, no worsening of seizures were observed in patients randomized to sertraline [88].

Finally, in selected cases, one may consider an AED that has an antidepressant and or a mood stabilizing properties to treat both conditions with a single agent. Alternatively, vagal nerve stimulator

(VNS), which has a unique mechanism of action that would explain its antiepileptic and antidepressant properties, can also be considered in selected cases [89].

Recommendations

Worldwide epidemiological studies conquer the high occurrence of depression in people with epilepsy, and the great negative impact this comorbidity has, on these patients at multiple domains. These alerting figures should call on all physicians caring for these patients to screen early for this condition, because early and effective treatment is expected to decrease the duration of depression, increase the patients' compliance with AEDs and, consequently, improve their overall QOL.

Final thoughts

Future epidemiological studies should aim to address the unanswered question of the risk factors to develop depression in epilepsy patients and the impact of such association on selecting the most optimal treatment strategies. To date, there have been no clinical studies that have investigated whether antidepressant treatment has any disease-modifying effects on the epilepsy itself (as opposed to anti-seizure or pro-seizure effects). Undertaking such a study would be logistically difficult, requiring long-term treatment and follow-up, and appropriately matched placebo-treated controls. This planned study needs to address the various manifestation of epilepsy progression, such as seizure frequency, AED resistance, neuropsychiatric and neurocognitive deficits and structural brain changes.

Additionally, future studies need to investigate the effects of chronic SSRI exposure, studying the effects on seizures at clinically relevant time points including prior to seizure onset, at onset and, at the chronic stages. That trial should investigate the effects of antidepressant use on mediators of epileptogenesis and how this phenomenon can be altered with antidepressant treatment.

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