Neuropsychiatric issues in patients with epilepsy: focus on depression

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 illness in epilepsy, but emerging evidence is providing a more complete and clearer elucidation of the problem. 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 quality of life than does seizure rate. In fact, depression is second only to medication toxicity as the clinical factor that explains the greatest variance in quality of life. Only a small number of studies have investigated the plausible neurobiological mechanisms of depression in epilepsy, but preliminary data suggest that underlying brain dysfunction may be a more important predictor than vocational or social disability. Furthermore, specific aspects of hippocampal dysfunction may be a causal factor in the genesis and maintenance of depression in temporal-lobe epilepsy. Current treatment recommendations for depression in epilepsy are similar to those for otherwise neurologically normal depressed patients, emphasizing the role of serotonin reuptake inhibitors, 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, are expected to become available in the near future.

KEYWORDS: depression ■ quality of life ■ seizures ■ serotonin reuptake inhibitors ■ temporal-lobe epilepsy

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Epilepsy is often a chronic condition that may be associated with several other neurological disorders; stroke, migraine and psychiatric disorders are the most frequent comorbid disorders in patients with epilepsy (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 incidence and prevalence rates of psychiatric comorbidities vary widely among studies; from 12 to 41%. This variation is largely caused by methodological differences among the studies; selection bias, population under study, diagnostic methods used, and number of antiepileptic drugs (AEDs) and their dosages are some of the confounding factors that could have an effect 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, anxiety disorders, mood disorders (diagnostic and statistical manual of mental 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]. In this article, we will focus on the comorbidity of depression and epilepsy. We will review the available information regarding the etiologies of depression in epilepsy as well as the current recommendations for management. We attempt to offer areas for further research in order to alleviate the burden of depression in persons with epilepsy.

Prevalence of depression in epilepsy

Based on the available 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.* used the Hamilton Depression Rating Scale in 175 consecutive patients in an outpatient epilepsy clinic, finding that 55% met the criteria for depression [11]. In a well-designed community-based study that used the Hospital Anxiety and Depression Scale, Jacoby *et al.* observed that 21% of 168 patients with recurrent seizures were depressed; whereas, only 9% of controlled patients had significant symptoms of depression [12]. On the other hand,

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in a primary care setting, O'Donoghue *et al.* used the same scale to demonstrate that, in a group of 155 patients in the UK, 33% with recurrent seizures and 6% of those in remission had probable depression [13]. Finally, a recent study by Seminario *et al.,* using the Patient Health Questionnaire nine-item depression scale (PHQ-9), found that 30% of their patients attending a specialized epilepsy clinic scored in the depressed range [14]. In fact, although different methodologies have been used in various studies, depression is consistently found to be 3–10-times more prevalent in association with uncontrolled epilepsy than in the general population. The findings from 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 examined the implication of depression on health-related quality of life (QOL) in PWE. Ettinger *et al.* recently utilized the household panel maintained by the National Family Opinion to study depression and QOL in persons with epilepsy, asthma and healthy controls [2]. 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 (37%), than 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 in the epilepsy group as compared with the asthma group. In another cross-sectional study, Beghi *et al.* compared depression severity across disease states in a recent study of epilepsy, Type I diabetes mellitus and community controls [15]. A total of 55 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 a less severe form of epilepsy similar to the study of Ettinger *et al.* [2]. A total of 34% 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. The studies demonstrated that depression is the most powerful predictor of health-related QOL, even after controlling for seizure frequency, severity and other psychosocial variables [16–20].

Furthermore, several studies have demonstrated the increased incidence of suicide in patients with depression and epilepsy. In a review of 11 studies, Harris and Barraclough found the overall suicide rate to be five-times higher in PWE, as compared with patients who have depression alone [21]. Moreover, patients with complex partial seizures of temporal-lobe origin and depression were at 25-times greater risk for suicidality compared with patients with depression. In a review of the literature, Jones *et al.* identified a lifetime average suicide rate of 12% in people with epilepsy compared with 1.1–1.2% in the general population [6].

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.* found that patients with untreated depression used significantly more health resources of all types, independent of seizure type or duration [22]. Likewise, 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.

Finally, recent data suggest that 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.* found that a prior history of depression is associated with at least 2.5-times increased risk of not responding to AEDs over 5 years of follow-up [23]. On the other hand, the presence of depression prior to epilepsy surgery may also serve as an independent marker for worse postsurgical outcome following anterior temporal lobectomy, as demonstrated by a study by Kanner *et al.* that included 100 patients with a mean follow-up of 4 years [24]. These studies raise the question as to whether depression can be considered as a marker for 'difficult-to-control' epilepsy.

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 it is no longer acceptable or valid. Instead, several emerging data have explored other multifactorial etiologies of depression in epilepsy. These include underlying genetic, neurochemical, anatomical, neurologic and iatrogenic factors.

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 PWE. More than half of these patients have been reported to have family histories of psychiatric illness, usually mood disorders [25]. Moreover, PWE and major depression appear to be unipolar and to have a genetic predisposition comparable to that of primary or idiopathic affective disorders [26]. In addition, animal studies have suggested that depression in PWE is the product of interaction between environmental factors, for example social isolation and genetic predisposition. A recent work by Koh *et al.* has demonstrated a significant downregulation of the serotonin receptor gene following kainic acid-induced seizures [27]. In this study, rats expressed depressive-like behavior when they were put in an isolated environment, whereas they did not develop depression when they were provided with an enriched environment.

Role of neurotransmitters

It appears that epilepsy and depression may share common pathogenic mechanisms involving decreased serotonergic, noradrenergic, dopaminergic and GABAergic activities. Furthermore, the decreased activity of these neurotransmitters has been shown to facilitate the kindling process of seizure foci and to exacerbate seizure frequency and severity in some animal models [28]. 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* [29]. As a matter of fact, several imaging studies, utilizing interictal PET using different ligands, have consistently demonstrated some degree of decreased 5HT1A binding in the mesial structures, raphe nuclei, thalamus and cingulate gyrus [30–32]. In a study of 45 patients with temporal-lobe epilepsy (TLE), Theodore *et al.* demonstrated an inverse correlation between increased severity of symptoms of depression identified on the Beck depression inventory (BDI) and 5HT1A receptor binding at the ipsilateral hippocampus to the seizure focus, and, to a lesser degree, at the contralateral hippocampus and midbrain raphe [33]. These changes in 5HT1A receptor binding are quite similar to those identified in the PET studies of patients with primary major depressive disorders. To further support these shared pathogenic mechanisms, three case–control population-based studies have demonstrated that a history of depression was associated with several-fold increased risk for developing new-onset epilepsy among cases than among controls [34–36]. This bidirectional relationship does not necessarily suggest causality in that depression causes epilepsy or *vice versa*. Rather, it may indicate the existence of common pathogenic mechanisms, operant in both conditions that facilitate the development of one disorder in the presence of the other. Interestingly enough, many centuries ago, Hippocrates (400 BC) 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" [37]. Galen (200 AD) had further reconfirmed the organic cause of depression [37].

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 both 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 cortex, 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 [38]. 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, which is a hallmark of mesial TLE, is a common finding in patients with depression and, according to some studies, correlates with both the severity and duration of the depressive state [39]. Furthermore, Quiske *et al.* examined the association of MRI-defined mesial-temporal sclerosis (MTS) BDI scores in

60 patients with TLE [40]. Mean depression scores were significantly higher in patients with MTS, independent of the lateralization of MTS. The investigators described depression as a good indicator of MTS, but not *vice versa*. Moreover, a study by Gilliam *et al.* has shown a correlation of the degree of magnetic resonance spectroscopic abnormalities in the ipsilateral hippocampus in patients with TLE and the severity of depression as measured by BDI [41]. In addition, some studies suggest that the presence of hippocampal atrophy/sclerosis is a risk factor for developing depression in PWE when treatment is initiated with certain AEDs, such as topiramate and levetiracetam [42–43].

Role of neurological/seizure factors

Seizure type has been shown to correlate with depression. The latter is more common in patients with complex partial seizures, particularly those of temporal-lobe origin. 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 [44]. Furthermore, a recent work by Shamim *et al.* suggests that patients with right TLE are more likely to have depression and left MTS, compared with left TLE as measured by BDI sores [45].

Role of iatrogenic factors

Among the most important factors contributing to the risk for depression in people with epilepsy are those associated with medication. A number of drugs and drug classes have been implicated in the etiology of depression, including some AEDs, such as barbiturates, levetiracetam, viagabtrin and topiramate, which are clearly associated with behavioral changes and depression [42,43]. Other investigators have related depression to the rapid withdrawal of an AED with mood-stabilizing properties, such as carbamazepine, oxcarbazepine and lamotrigine [46]. Another, uncommon but well-documented, example is the occurrence of *de novo* depression following anterior temporal lobectomy. Interestingly, this risk occurs independently of postsurgical outcome. This paradoxical 'iatrogenic' cause of psychopathology among PWE includes the phenomenon of 'alternative or reciprocal psychosis'. In this phenomenon, the psychosis is better when seizures are poorly controlled, while psychosis becomes worse when seizures are better controlled [47]. On the other hand, a recent study demonstrated a significant improvement in depression and anxiety in patients with refractory epilepsy following epilepsy surgery, especially in those who became seizure-free [48].

Clinical manifestations

Depressive symptoms can present according to the temporal relation to the seizure's 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 subsyndromic depressive episodes 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 led Blumer to coin the term 'interictal dysphoric disorder' (IDD) to refer to this type of depression in epilepsy, which is characterized by eight key symptoms that are grouped into three major categories: labile depressive symptoms (depressed mood, anergia, pain and insomnia), labile affective symptoms (panic-like symptoms and anxiety), and symptoms of paroxysmal irritability and unstable euphoric moods) [49]. 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 [25]. However, the distinction between true IDD and perictal depressive symptom (PDS) is still a matter of debate in the literature. Some authorities in the field believe that making this distinction has implications, not only for diagnosis but, more importantly, for prognosis and for treatment approaches [50]. In fact, in the previously cited study by Mula *et al.*, of 142 adults with epilepsy in tertiary referral centers, the two groups were clearly distinguished, with prevalence rates of 9.8% for the IDD group and 12% for the PDS group. In that study, the diagnosis of PDS was made by the occurrence of at least three symptoms of at least 'moderate' or 'severe' severity, and causing 'moderate' or 'severe' distress (i.e., Blumer's criteria for IDD), referred by the subject as habitually related only to seizures. Furthermore, there was no difference in the two groups in reference to seizure type, seizure frequency, AED regimen (mood stabilizers

vs not on any mood stabilizers) and combination of AEDs. However, in the IDD group, the IDD inventory labile affective symptoms scores strongly correlated with the age of seizure onset and the duration of epilepsy [49].

Screening for depression

Despite its high frequency and great impact on QOL and care for PWE, depressive symptoms remain 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 [25]. 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 *et al.* found that 80% of clinicians do not routinely screen for depression in PWE [51]. This suggests that, in a busy neurology practice, where the major focus is seizure control, it is likely that symptoms of depression will be missed.

Several tools have been used to screen for depression in PWE; most of which are time consuming in a busy clinic setting. Recently, a six-item questionnaire has been developed and validated to screen for depression, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E); it takes less than 3 min to fill out at the office, and has a sensitivity and specificity of 90 and 81%, respectively [52]. A score of 14 and higher is suggestive of the possibility of a major depressive disorder and can serve as a signal to carry out a more in-depth evaluation. Clearly, the use of this and other screening instruments for psychiatric research on epilepsy must be followed by structured psychiatric interviews designed to establish a DSM-IV (text revision) diagnosis, which would permit regular rescreening to yield meaningful data on changes in severity of symptomatology.

Treatment options

A significant percentage of PWE and depression are under-recognized and untreated. Reasons for this include a lack of appreciation for the impact of depression on QOL and the fear that seizures might be exacerbated by antidepressants. Despite the consistent finding that depression occurs in a high proportion of people with epilepsy and has a significant impact on their lives, this condition remains underdiagnosed and undertreated. The treatment of these patients has been largely 'empirical', 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 double-blind, placebo-controlled study published to date that included 42 adult patients with a confirmed diagnosis of epilepsy. 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. Obviously, the small sample size limits the ability to draw meaningful conclusions [53].

Before starting a patient on antidepressant drug therapy, it is important to differentiate between IDD and PDS symptoms. Seizure control is the main goal for the management of affective manifestations related to seizures (i.e., PDS), whereas specific psychiatric treatments (e.g., psychopharmacologic or psychotherapeutic interventions) are needed for IDD, especially because symptoms are chronic and unremitting in a third of cases [50]. In addition, every effort should be made to rule out the following potential causes for a depressive episode:

- The depressive episode followed the discontinuation of an AED with mood-stabilizing properties, such as carbamazepine, valproic acid or lamotrigine [46]. In such a case, reintroduction of that AED or of another mood-stabilizing agent may be sufficient to reach a euthymic state;
- The depressive episode followed the introduction or dose increment of an AED with known negative psychotropic properties, such as phenobarbital, topiramate or vigabatrin. In such cases, lowering of the dose or discontinuation of the culprit AED should result in symptom remission.

In general, the delay in initiating treatment in PWE stems from the unfounded belief that antidepressants worsen or trigger seizures. By contrast, modern antidepressant drugs, such as selective serotonin reuptake inhibitors (SSRIs), might actually decrease the risk of seizures rather than increasing it – see later. However, some other antidepressant drugs, particularly in higher doses, might be associated with an increased seizure risk. In a study at the Rush Epilepsy Center, Kanner *et al.* reported definite seizure exacerbation in only one of 100 patients

treated with sertraline; in another five patients the causality of the transient increase in seizure frequency attributable to this antidepressant drug was rated as probable but not definite [54]. It should be noted that even AEDs can sometimes exacerbate seizures. If any drug is found to be associated with a definite increase in seizures then the situation should be reviewed. Bupropion, maprotiline and amoxapine are the antidepressant drugs with the strongest proconvulsant properties, and should be avoided in epileptic patients [55]. Current recommendations for the treatment of depression in PWE are SSRIs or cognitive therapy [56]. SSRIs are generally considered safe and well tolerated, keeping in mind that all of the currently available SSRIs, except for citalopram and escitalopram, inhibit one or more of the hepatic cytochrome P450 isoenzymes – an enzyme system involved in the metabolism of the 'old' AEDs (carbamazepine, phenytoin and phenobarbital). In addition, it is well established that sertraline raises lamotrigine levels [57,58].

One recent and very reassuring article suggests a possible 'protective' effect of SSRIs, and serotonin and epinephrine reuptake inhibitors in depressed patients. In the study, Alper *et al.* compared the incidence of seizures between depressed patients who were randomized with placebo and SSRIs, serotonin and epinephrine reuptake inhibitors, and the α2 antagonist mirtazapine, in the course of regulatory studies submitted to the US FDA [59]. 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, indicating that the seizure risk was significantly less for those treated with SSRIs compared with placebo. Other options for treatment include cognitive, interpersonal and behavioral therapy, and, in severe cases, electroconvulsive therapy can be considered safely in PWE who do not respond to appropriate antidepressant therapy [60].

A randomized trial of an SSRI and cognitive behavior therapy in depressed patients without other neurological disorders demonstrated greater efficacy with combined therapy compared with either one alone [61]. A similar trial, randomizing 140 PWE to either sertraline or cognitive behavior therapy for 16 weeks, has been recently completed [62]. At the end of the trial, no significant difference in outcome for depressive symptom remission was observed in the two arms. Moreover, patients in whom depressive symptoms remitted had a significant improvement in QOL, independent of other epilepsy-related factors. Similar to the study of Alper *et al.* [59], no worsening of seizures was observed in patients who were randomized to sertraline. This finding adds further support to the previously cited reports on the safety of SSRIs in PWE.

In addition, in selected cases, one may consider an AED that has antidepressant and/or mood-stabilizing properties to treat both conditions with a single agent. Alternatively, vagal-nerve stimulation might be considered because it has been found to improve symptoms of depression, independent of the degree of seizure control, in addition to the fact that it has well-established antiepileptic activity [63].

AEDs & the risk of suicidality

In January 2008, the FDA issued an alert regarding the association between suicidality, (defined as suicidal ideation), suicidal attempts and completed suicides, and AEDs based on the results of a meta-analysis that included data from 199 randomized clinical trials of 11 AEDs [101]. The meta-analysis encompassed a total of 43,892 patients who were treated for epilepsy, psychiatric disorders and various pain disorders. The FDA concluded that, with 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).

However, a detailed evaluation of this meta-analysis questioned the validity of its findings owing to several methodologic problems [64]. Furthermore, this risk is insignificant if compared with the average lifetime incidence of suicidality in PWE attending epilepsy clinics [6]. This view has been endorsed by the American Epilepsy Society consensus statement [102].

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.* concluded that AEDs, as a class, are not associated with an increased risk of suicidality in patients with bipolar disorders [65]. On the other hand, a recent study by Patorno *et al.*

found a significantly higher risk of suicidality and violent deaths with certain AEDs, such as lamotrignine, oxcarbazepine, gabapentin and tigabine. Unlike the finding from the FDA meta-analysis, topiramate was not associated with that risk [67].

We can conclude that several AEDs, but not all, as suggested by the FDA warning, might be associated with psychiatric adverse events, which can lead to suicidal ideation and behavior, keeping in mind that the rate of completed suicide and suicidal attempts are, fortunately, rare. On the other hand, given the relatively high prevalence of both comorbid mood and anxiety disorders in PWE [68], as well as increased suicidal risk [5], clinicians should, as previously discussed, screen patients for these conditions independently of whether AEDs have any influence on suicidal risk. Specifically, clinicians should be extremely alert to this high risk in patients with a current and/or past psychiatric history [69].

Conclusion

Epidemiological studies should 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. Since depression is common in people with epilepsy, there is a strong argument for early screening for this condition, because early and effective treatment should decrease the duration of the depression, increase the patients' compliance with AEDs and, consequently, increase QOL.

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Executive summary

Impact of depression on patients with epilepsy

- It is important for physicians to be aware of the impact of depression in patients with epilepsy (PWE) so that the current high rates of underdiagnosis and undertreatment can be decreased.
- The presence of depression in PWE may underlie a severe form of epilepsy.
- The association of depression and severe epilepsy requires increased healthcare resources.
- The suicide rate is much higher in PWE than in the general population and appears to be particularly high in those with temporal-lobe epilepsy.

Making the diagnosis

- Despite high prevalence, depression remains underdiagnosed.
- Rapid and early recognition of depression in PWE is cost effective and should be promoted and adopted by all physicians caring for these patients.
- Interictal depression is the most frequently recognized type of depression in PWE. However, 30–40% of presentations are atypical.
- A new screening tool, Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), which takes less than 3 min to complete, has been validated with a high specificity and sensitivity.

Etiologies

- Depression and epilepsy share the same pathogenic mechanisms, as demonstrated by several neuroanatomical and neurofunctional studies, and animal models.
- Abnormal serotonin affinity or binding, among other neurotransmitters, is operant in both conditions.
- A bidirectional relationship is well established in several case–control population-based studies.
- PWE may have a different pathophysiology than patients without this comorbid condition.

Treatment options

- Treatment should be initiated promptly once iatrogenic causes are excluded.
- Selective serotonin reuptake inhibitors should be considered as first choice. They are safe and well tolerated. Other options are also available.

Future perspective

- Genetic testing may help identify patients at risk of developing depression. Whether social support and environmental intervention at that stage would protect these patients from developing depressive symptoms will require further research.
- New neuroimaging techniques are expected to differentiate PWE and depressive symptoms from patients without depression at the time of diagnosis so that early and effective therapy can be offered and initiated.
- Further research should focus on making a clear distinction between perictal depressive symptoms and major depression. Furthermore, prospective and longitudinal studies are needed to measure the effect of either entities, that is, perictal depressive symptoms and interictal dysphoric disorder, on health-related quality of life, in order to develop specific treatment modalities.
- Randomized controlled trials to assess the efficacy of various antidepressant options are overdue.
- Randomized controlled trials are urgently needed to assess the effect of immediate verses delayed treatment on seizure response, compliance rate and overall quality of life.

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