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# Major depression, anxiety disorder and suicidality in epilepsy: What should neurologists do?☆

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ABSTRACT

Four to five patients with epilepsy (PWE) can suffer from Major Depressive episodes (MDE). Comorbid anxiety disorders (AD) frequently occur together with MDE. Failure to treat MDE can negatively affect several aspects of their life as well as the management of the epilepsy. Often, suicidal ideation is among its symptoms, which need to be addressed without delay to prevent suicidal attempts or a completed suicide. Unfortunately, access to health care professionals is very limited and, in many communities, non-existent. Accordingly, it falls upon the treating neurologist to begin a pharmacologic trial with psychotropic drugs. The purpose of this manuscript is to provide neurologists with very useful strategies on how to screen and identify MDEs with and without AD in the outpatient clinic and how to select the appropiate psychotropic drugs. Using an illustrative case, we discuss its differential diagnosis, particularly the recognition of iatrogenic episodes, and demonstrate the selection and mode of use of commonly used antidepressant in PWE. Finally, we provide a guide on how the neurologist can assess the suicidal risk of a patient that endorses suicidal ideation and the steps that need to be taken to minimize the risk of suicidal behavior.

## 1. Introduction

Population-based studies have found a 30 % lifetime prevalence rate of mood disorders in patients with epilepsy (PWE), typically presenting as major depressive disorders (MDD), and less frequently as bipolar disorders or dysthymia [1]. The diagnosis of MDD can include one or more major depressive episodes (MDE), while bipolar disorders are diagnosed when MDEs and manic and /or hypomanic episodes are identified in the same patient [2]. Dysthymia is the least frequent and presents with persistent symptoms of depression of at least two years duration but of lesser severity than the other two [2]. Their cause is multifactorial, including genetic, neurobiological, and psychosocial factors [3]. Suicidal ideation and behavior are frequent symptoms of MDEs, which may potentially result in completed suicide [4]. For example, PWE without identified psychiatric comorbidities have a two-fold higher risk of committing suicide, while in those with a mood disorder, the risk is 32-fold higher [5]. The prevalence rates of MDE have been reported to range from 15 % to 25 % [3,6]. [1] Yet, anxiety disorders (AD) occur together with MDE in a significant percentage of PWE, as shown in population-based studies and case series [7–9]. Thus, the existence of AD must be investigated in any PWE with a MDE (and vice-versa) as their comprehensive treatment is necessary to achieve symptom remission of both conditions.

Unfortunately, availability of mental health care providers is very often limited or non-existent and neurologists are faced with the dilemma of starting treatment with psychotropic medication, as failure to treat comorbid MDE and AD can not only worsen the suicidality risk but can also negatively impact the treatment of the seizure disorder. For example, iatrogenic events caused by antiseizure medications (ASMs) are more likely to occur in the presence of untreated comorbid MDE and AD, presenting with medical, neurologic and psychiatric symptomatology [9]. In addition, they can interfere with drug compliance [10], resulting in breakthrough seizures. Premature mortality caused by suicide or accidental death are also serious psychiatric complications resulting from untreated MDE [11]. Furthermore, compared to seizure frequency and severity, depressive and anxiety symptoms are stronger predictors of poor quality of life in patients suffering from treatment-resistant epilepsy [12]. Finally, all these factors call for a higher used of services increasing medical costs to patients, families and society [10].

Contrary to common belief, MDEs and ADs in PWE are not only a complication of the epilepsy, as in a significant number of patients both

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conditions precede the onset of epilepsy [11,12]. Furthermore, in several prospective population-based studies, PWE were found to have a two-fold higher risk of developing MDE and AD, while patients with primary MDE and AD were found to have a 2 to 2.5 risk of developing epilepsy [7,13,14]. This complex relation has been considered to reflect a bidirectional relation between epilepsy and these two psychiatric comorbidities that is likely explained by common pathogenic mechanisms operant in all three conditions [15].

Clearly, neurologists cannot and should not delay treatment of comorbid MDEs (with or without ADs) once they have been identified. The aim of this manuscript is to provide pragmatic strategies for their screening, identification and psychopharmacologic treatment that can be implemented in outpatient neurology / epilepsy clinics. In addition, it reviews practical steps that neurologists can follow in evaluating suicidality symptoms and specifically to estimate the risk for active suicidal ideation and behavior. Furthermore, it is intended to highlight the circumstances that require immediate referral to a mental health provider.

## 2. Illustrative case

The patient is a 35 years-old woman with a fifteen-years history of a focal epilepsy of left frontal lobe origin that started three months after a traumatic brain injury and presented with focal to bilateral tonic-clonic seizures. She had no relevant past medical or surgical history. She was started on levetiracetam, which resulted in remission of the seizures but had to be discontinued because of the development of a MDE consisting of anhedonia, sadness, feelings of hopelessness, marked irritability and poor frustration tolerance, insomnia and passive suicidal ideation; these symptoms remitted following levetiracetam's discontinuation. She was switched to carbamazepine and remained seizure-free for three years, after which she experienced the recurrence of focal impaired awareness hyper motor seizures in her sleep every two to three weeks, for which clobazam was added. The carbamazepine was switched to oxcarbazepine as she was planning to get pregnant, and she has remained seizure-free on the combination of oxcarbazepine (dose 1800 mg /day) and clobazam (15 mg /day).

In a follow-up visit eight months ago, the patient reported recurrence of her psychiatric symptomatology for the previous two months, which has worsened in severity in seven of the four weeks preceding her evaluation. She reports feeling sad and unable to find any pleasure in her activities most of the time, having to push herself to do anything with her family and being unable to focus on her work. She again reported feeling hopeless, helpless, crying easily without any cause, early night insomnia and middle of the night awakening, loss of sexual drive and loss of appetite, which had led to a weight loss of 10 lbs. since the start of her symptoms. She noticed a diurnal variation in the severity of her symptoms with a worsening in the afternoon and evening hours. In addition, she reported that in the previous six weeks and without any reason she started to worry about her work and the well-being of family members; she also became very restless, which further worsened her ability to concentrate and fall asleep. She also started to get recurrent headaches, described as holocephalic pressure-like pain. In the previous week, she started to experience passive suicidal ideation ("It would be OK with me if I did not wake-up in the morning"), and on one occasion two nights before her evaluation she contemplated taking an overdose of her ASMs. When asked what kept her from acting on her suicidal thoughts, she indicated that she could never kill herself because she had a family to take care of and indicated that she had a good source of support she could reach to in case of recurrence of active suicidal ideation.

On the day of her evaluation, she completed the Neurologic Depressive Disorders Inventory in Epilepsy Scale (NDDI-E) and the Generalized Anxiety Disorder-7 (GAD-7) which yielded total scores of 22 [16] and 15 [17], respectively, suggestive of a MDE and GAD. She denied any previous personal psychiatric history other than the MDE she experienced during the trial with levetiracetam and occasional *peri*-menstrual symptoms of irritability and unexplained sadness lasting one to two days. She did indicate, however, that her mother was diagnosed with mixed depression and anxiety disorders and her maternal grandfather had committed suicide.

She underwent blood work that included complete hemogram, chemistry panel and thyroid function tests, which were reported to be normal. She was started on 50 mg /day of sertraline, and the dose which was increased by 50 mg on a weekly bases with the intention to target 200 mg /day by the fourth week. In addition, given her GAD symptoms and the fact that selective serotonin reuptake inhibitors (SSRIs) can cause anxiety symptoms in the first two weeks, 1 mg / day of clonazepam was added for a period of 4 to 6 weeks with the plan to taper-it down and discontinue over 4 weeks. However, by the third week, she reported a significant improvement of her depression and anxiety symptoms, and she was kept on 150 mg /day of sertraline the clonazepam was tapered over three weeks. She became totally asymptomatic by the sixth week.

By eight weeks on sertraline, she started to complain of cramps in the legs. A repeat chemistry panel revealed that her serum sodium concentration had dropped from 132 mEq/l to 127 mEq/l. She was instructed to start salt tablets of 1 g three times /day with food, limit her fluid ingestion and switch to liquids with electrolytes, which resulted in remission of the cramps; a repeat BMP revealed that her serum sodium concentrations increased to 133 mEq/L. Given that the hyponatremia was attributed to the addition of the sertraline and /or a pharmacodynamic interaction between oxcarbazepine and sertraline, (the serum sodium was in the low range before the start of sertraline) the oxcarbazepine was switched to lamotrigine, which has antidepressant and mood stabilizing properties to a target dose of 200 mg /day [18]. On this regimen, she has remained seizure-free, euthymic and free of anxiety symptoms for six months, for which the sertraline was tapered down and discontinued, and she has had no recurrence of her MDE or AD also attributed to the lamotrigine monotherapy regimen.

## 3. Discussion

### 3.1. Diagnosis

This patient suffered from a typical MDE, which was associated with a GAD based on the diagnostic criteria listed in the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition [2]. While she endorsed all the symptoms of a MDE, the diagnosis would have been established with five of the symptoms she reported in addition to a low mood and anhedonia for a period of at least two weeks. In addition, her symptoms met DSM-5 diagnostic criteria of GAD [2].

Today, neurologists can easily screen for MDE in PWE in outpatient clinics with the self-rating instrument NDDIE [16], a six-item scale that investigates the existence of pivotal symptoms for the prior two weeks, which are rated in a 4-point Likert scale. It takes patients two to three minutes to complete, and it can be given while the patient is waiting to be seen. A diagnosis of MDE can be suspected with a total score $> 15$ with close to a 90 % sensitivity and specificity for MDE. This instrument has been validated in most languages and is the recommended screening instrument for MDE in PWE by the International league Against Epilepsy. Of note, lower cut-off scores have been reported to be associated with a possible diagnosis of MDE, such as in the Spanish version in which a score of $> 13$ could be used [19]. Accordingly, the interpretation of the significant cut-off score depends of the version used.

Other screening instruments have been used to identify patients with possible depressive episodes such as the Patient Health Questionnaire-9 (PHQ-9), which is a self-rating instrument widely used in many practices [20]. It consists of nine items scored on a Likert scale from 0 (never) to 3 (nearly every day). This scale generates a severity of the depression symptoms (none (0–4), mild (5–9), moderate (10–14), moderately severe (15–19) and severe (20–27).

Screening for GAD can be easily achieved with the GAD-7 self-rating

screening instrument, which is widely used in medical practices and has been validated in several languages [17]. It consists of seven items rated on a Lickert scale. A cut-off score > 10 suggests a diagnosis of GAD. Furthermore, the Epilepsy Anxiety Survey Instrument (EASI) is an instrument recently developed to screen anxiety disorders in specifically in PWE [21]. It has a short version and is now available in several languages.

### 3.2. Differential diagnosis

A MDE can also be the expression of a bipolar disorder, when occurring in patients who have experienced hypomanic and /or manic episodes. Hypomanic symptoms have been reported in up to 12 % of PWE [22] and hypomanic episodes include symptoms of expansive or elated mood with /or without irritability and increased energy, racing thoughts and pressured speech, insomnia and excessive pleasurable activities lasting for 4 days [2]. A diagnosis of manic episodes must be considered when psychotic symptoms are identified including grandiose delusions and hallucinations, aggressive behavior that can disrupt significantly the patient's activities and last at least seven days [2]. This diagnosis was ruled-out, as the patient denied any current and /or past symptoms suggestive of these episodes. Of note, a history of hypomanic and /or manic episodes must be investigated in any patient found to have a MDE because the treatment would require using a mood stabilizing drug to prevent their spontaneous recurrence or manic / hypomanic episodes triggered by antidepressant medications [23] (see below). The diagnosis of bipolar disorders is often delayed in patients with MDEs, as patients fail to report hypomanic episodes. A possible diagnosis of bipolar disorder can be suspected if there is a family history of bipolar disorder and /or hypomanic / manic episodes were triggered by antidepressant drugs. While neurologists can initiate pharmacotherapy of a MDE in PWE with suspected history of bipolar disorder, they must ensure that they are on an ASM with mood stabilizing properties (e.g., carbamazepine, oxcarbazepine, lamotrigine, valproic acid) or on an atypical antipsychotic drug used in this type of mood disorder (e.g., aripiprazole) [24]. However, they cannot and should not treat this type of mood disorder beyond the start of pharmacotherapy and patients must be referred to psychiatrists.

In PWE, MDE can also occur in patients with other types of mood disorder, such as the Interictal Dysphoric Disorder, which has been reported in up to 30 % of depressed people with chronic epilepsy [25,26]. It represents an atypical mood disorder which is not included in the DSM-5 or ICD-10 classifications and has a pleomorphic presentation that include depression symptoms, brief euphoric moods, irritability, anxiety, paranoia, and a variety of somatoform symptoms (e.g., atypical pain). It has a chronic course with intermixed asymptomatic periods. Fortunately, this mood disorder responds to the same pharmacologic regimen used in MDE [26]. While it was originally associated only with PWE it has been recently identified in patients with migraines [27].

Finally, MDE can occasionally occur together and /or intermixed with a chronic mood disorder known as dysthymia, today referred as "Persistent Depressive Disorder", which has a lower prevalence (3 %). It consists of "a chronically depressed mood for most of the day, for more days than not, for at least 2 years with at least two of the following 10 symptoms: changes in appetite, sleep disturbance, fatigue, low self-esteem, poor concentration, difficulty making decisions or feelings of hopelessness" [2]. Patients are diagnosed with "double depression" when MDE occur in the presence of Persistent Depressive Disorder. The pharmacologic treatment for this type of mood disorder is the same for MDE, but pharmacotherapy may require a longer duration.

The GAD can often be associated with other types of AD, including panic attacks with and without agoraphobia and social phobia. None of these were identified in our patient.

Patients with chronic, pharmaco-resistant epilepsy and a history of MDE and /or ADs can also experience *postictal* depression and anxiety symptoms (including suicidality). These symptoms typically occur within a few hours to up to three days from the time of the seizure. In one case series of 100 such patients, 43 reported postictal depression symptoms, 13 of whom also endorsed suicidal ideation, and 45 anxiety symptoms with a median duration ranging from 6 to 24 h. These symptoms occurred after > 50 % of seizures in the previous three months [20]. These symptoms may occur even if the interictal MDE or AD are in remission and may not respond to psychotropic medications with antidepressant drugs. In such cases, cognitive behavior therapy is very effective in teaching patients how to cope with these symptoms [28].

### 3.3. Latrogenic factors

In this patient, the first MDE was an iatrogenic event, caused by the administration of levetiracetam that remitted upon its discontinuation. This case illustrates the following pivotal concepts that neurologists must always consider about iatrogenic MDE in PWE: – The patient had a family psychiatric history in first degree relatives which is a risk factor for iatrogenic MDE (and other psychiatric symptoms) when started on ASMs that can cause psychiatric symptoms such as levetiracetam, phenobarbital, topiramate, zonisamide and perampanel [29–32]. Accordingly, these ASMs should not be considered as an initial choice without having investigated the patients' personal and family psychiatric history. Of note, such history can also herald the potential development of spontaneous MDEs and may also explain the patient's perimenstrual dysphoric episodes.

In patients with personal and family psychiatric histories, iatrogenic psychiatric adverse events can also be triggered by the discontinuation of ASMs with mood stabilizing (carbamazepine, oxcarbazepine, lamotrigine, valproic acid), antidepressant (lamotrigine) and anxiolytic (gabapentin, pregabalin, benzodiazepines) properties, by unmasking a mood and /or anxiety disorder that may have been kept in remission by these drugs [33]. Of note, the patient did not experience an AD when she was treated with levetiracetam, even though she had a family history and developed a GAD later.

### 3.4. Common comorbid psychiatric disorders

This case clearly illustrates the co-occurrence of MDE with anxiety disorders, which in our patient consisted of GAD. However, as already stated, panic disorder, agoraphobia and anticipatory anxiety of seizures are relatively frequent in PWE and need to be identified, as their treatment must be incorporated with that of the MDE [1,3,7,33]. This topic is reviewed in detail in the articles devoted to the treatment of anxiety disorders in this issue.

### 3.5. Suicidality

The patient experienced passive suicidal ideation as part of her MDE, and a few weeks after the onset of the GAD. It evolved into active suicidal ideation, that included a short-lived suicidal plan but never evolved to suicidal behavior (e.g., attempt). Suicidality is clearly the most serious symptom as it can lead to a completed suicide and neurologists need to be able to assess the risk for suicide attempts in any patient with suicidal ideation. In fact, screening for suicidal ideation and behavior must be carried out in every PWE as they have a 2-fold increased risk of suicide even in the absence of comorbid identified psychiatric comorbidity [4]. As indicated above, this risk goes up by 32 and 12- fold in the presence of a MDE and AD, respectively [5]. In addition, our patient suicidal ideation illustrates how AD can worsen the risk of suicidality associated with MDE. Screening for suicidality can (and should) be carried-out at every visit with the following self-report screening instruments: Item 4 of the NDDIE ('I would be better off dead'), which has an excellent discrimination and specificity [16,33]. Item 9 of the Beck Depression Inventory-II is another option, which distinguishes between passive and active suicidal ideation [34] or item 9

of the PHQ-9 [20]. Of note, a prior suicide attempt is a risk factor for future suicide attempts and should be always investigated. Asking patients with suicidal ideation "what is keeping you from acting on your suicidal thoughts?" can allow the neurologist to understand their frame of mind and estimate the risk for an imminent attempt. For example, our patient's explanation that having a family she needs to care for would keep her from attempting to take an overdose suggests a lower risk. Finally, in addition to MDE and ADs, screening for the other common psychiatric comorbidities associated with suicidality and epilepsy is necessary (e.g., drug and alcohol abuse) and psychosocial precipitating events (see below) [4].

An iatrogenic cause of suicidality by ASMs has been the source of great concern among clinicians since the Food and Drug Administration (FDA) required that the package inserts include a black box warning of an increased risk of suicidal ideation and behavior associated with these drugs [35]. Yet, the FDA's data on which these warnings were based had serious methodologic problems that raised serious questions about their validity [36]. Yet, as in the case of iatrogenic risk of a MDE and AD, the ASMs with negative psychotropic properties can cause suicidal ideation and behavior, particularly in people with a prior and /or family psychiatric history. In such cases, the prescription of these ASMs should be carried out with great caution, and individuals and family members should be educated on these potential iatrogenic adverse events.

As in the case of MDE and AD, suicidality and epilepsy also have a bidirectional relation whereby patients with epilepsy have an increased risk of developing suicidality and vice-versa, which can also be explained by common pathogenic mechanisms [37].

## 4. Treatment of MDE in epilepsy

### 4.1. Pharmacological treatment of MDE in epilepsy

In PWE, the first step in the treatment of MDE is to rule-out an iatrogenic cause, which requires a change of the ASM. The pharmacologic treatment of MDE with and without concurrent AD follows the same strategies applied in the treatment of primary MDE, as there are no large multicenter randomized controlled trials [38]. Yet, there is evidence that MDE in PWE has a better response to pharmacotherapy and cognitive behavior therapy (CBT) than primary MDE. This was shown in a randomized controlled study that compared the safety and efficacy of sertraline vs. CBT in 140 PWE suffering from MDE; both treatments yielded a symptoms remission in nearly 60 % of patients [39]. In contrast, symptom remission in primary MDE is typically achieved in about a third of people after the first trial [40]. Other authors have reported similar findings in open trials with TCAs and SSRIs [26,41]. This is an important concept as the achievement of total symptom remission is the aim of the treatment of any MDE and AD, lest their recurrence is likely to occur [16]. In 2021, the Task Force of the International League Against Epilepsy (ILAE) Commission on Psychiatry, the ILAE Executive and the International Bureau for Epilepsy (IBE) recommended the use of SSRIs as a first-line pharmacotherapy [42]. Persistence of symptoms should lead to a trial with a serotonin-norepinephrine reuptake inhibitor (SNRI). Of note, these drugs yield a therapeutic effect in common AD and hence both conditions when present can be treated with the same psychotropic drug. Persistent symptoms of depression following trials at optimal doses of an SSRI and SNRI suggest that the patient is suffering from a treatment-resistant depression and should be referred to a psychiatrist for treatment. Antidepressant treatment should be maintained for at least six months following remission from a first depressive episode. Still, it should be prolonged to nine months in people with a history of previous episodes. It should continue even longer in severe depression or cases of residual symptomatology until such symptoms have subsided. Citalopram, escitalopram and sertraline are the SSRIs of choice in PWE, while venlafaxine is the option for an SNRI [43]. None of these drugs have an impact on the metabolism of ASMs, while phenobarbital and phenytoin can increase the metabolism of the three SSRIs and may require a dose adjustment. Their initial and maximal dose and titration rates are summarized in the table below (Table 1).

### 4.2. Pharmacological treatment of concurrent AD and MDE in epilepsy

The psychotropic drugs used in the pharmacologic treatment of ADs include the antidepressant drugs of the SSRIs and SNRI and when these are not available, certain TCAs can be prescribed. [38,43] Nonetheless, since antidepressant drugs can be anxiogenic during the initial two to four weeks, it is recommended to treat the patient with a benzodiazepine (clonazepam 0.5 mg – 1 mg HS) for the first four to six weeks and then taper down and discontinue. The benzodiazepine will yield a therapeutic effect on the anxiety symptoms.

### 4.3. Adverse events resulting from concomitant use of ASMs and commonly used psychotropic drugs

Hyponatremia caused by SSRIs and SNRIs go often unrecognized by non-psychiatrists. This iatrogenic effect is more likely to occur when these drugs are prescribed in PWE taking carbamazepine, oxcarbazepine and eslicarbazepine, which are also known to cause hyponatremia [44]. A potential pharmacodynamic interaction and /or additive effect should be anticipated for which basic metabolic panels should be obtained on a regular basis. In addition, SSRIs can enhance the risk of osteopenia / osteoporosis caused by ASMs with enzyme-inducing properties [45]. Lastly, sexual adverse events are reported in 20 % to 30 % of people taking SSRIs and SNRIs and can worsen the libido and sexual dysfunction associated with epilepsy and some ASMs [38,43]. There is no evidence that SSRIs or SNRIs have proconvulsant properties as demonstrated in a study that compared the incidence of seizures between subjects randomized to placebo and these antidepressant drugs in people with primary mood and anxiety disorders who participated in multicenter randomized double-blind-placebo controlled trials of SSRIs, SNRIs, Tricyclic antidepressants (TCAs) [46]. The authors found that the occurrence of seizures was significantly less frequent among individuals randomized to these antidepressants than to placebo. Clomipramine was the only TCA associated with a higher incidence of seizures than placebo. In fact, potential anticonvulsant effects of SSRIs, SNRIs and TCAs have been suggested in animal models of epilepsy and open trials in PWE [15]. Still, this effect has yet to be established in double-blind placebo-controlled trials in epilepsy.

### 4.4. Psychotherapy

In a recent report, the ILAE Task Force on the medical treatment of depression in PWE suggested the consideration of psychotherpies as the first line treatment of AD as well as for mild to moderate depression in the general population [42]. Today, CBT is the most frequently recommended type of therapy and has been found to be effective for the treatment of MDE as weel. For example, as shown in the study by Gilliam et al., cited above [39] CBT was as effective (close to 60 %) in achieving remission of MDE as sertraline. Other studies have confirmed the efficacy of CBT [47,48]. It consists of 16 to 20 weekly sessions administered by health care professionals, specifically in this technique. Finally, psychotherapy should also be considered together with psychopharmacotherapy in patients with a chronic mood disorder with or without anxiety, as the two treatment modalities complement each other.

## 5. Suicidality: what is the role of the neurologist?

### 5.1. What neurologists should consider

Immediate attention must be paid to PWE with suicidality symptoms as 30 % may implement a plan [49]. In contrast to MDE, neurologists cannot be expected to treat PWE with suicidal ideation and /or behavior

**Table 1**
Efficacy of selected SSRIs and SNRI and titration schedules.

| Antidepressant | MDE | Panic disorder | Generalized anxiety | Starting dose mg/day | Titration | Maximal dose mg/day |
|---|---|---|---|---|---|---|
| **SSRIs** | | | | | | |
| **Sertraline** | + | + | + | **25–50** | 25 mg – 50 mg q week | **200** |
| **Citalopram** | + | + | + | **10–20** | 10–20 mg q 2 weeks | **40** |
| **Escitalopram** | + | + | + | **5–10** | 5–10 mg q/ 2 weeks | **20** |
| **SNRI** | | | | | | |
| **Venlafaxine ER or IR** | + | + | + | **37.5–75** | 37.5–75 mg q weeks | **ER: 225 IR: 375** |

**ER** = Extended release
**IR** = Immediate release.

and a referral to mental health professionals should be started at the time of the recognition of suicidality symptoms. Precipitating factors for suicidality symptoms should be investigated including the development of any new or exacerbations of psychiatric comorbidities, or having suffered recent loss (e.g, employment, family member, partner, etc.) or exposure to or persistence of an abusive relationship. As indicated above, understanding what has kept the patient from acting on the suicidal ideation can assist the neurologist in establishing the risk for suicide attempts. Immediate psychiatry referral is required for patients with active suicidal ideation, and referral to a psychiatric emergency room for hospital admission should be recommended for patients with a plan or who have exhibited suicide behavior and those with recent suicide attempts or high-risk activity [4]. As illustrated in our patient, the comorbid occurrence of an AD is likely to worsen the risk of suicidality, and its treatment needs to be part of the comprehensive management.

In PWE and a history of suicidality, treating the seizure disorder with ASMs with mood stabilizing properties and avoiding those with negative psychotropic effects is of the essence. In addition, pharmacologic treatments can be initiated by the neurologist targeting a comorbid MDE with or without ADs with the use of SSRIs or SNRIs and a short course of a benzodiazepine as indicated above. Neurologists, however, should not manage patients with suicidality and bipolar disorders or comorbid interictal psychotic disorder.

Suicidal ideation and behavior can occur as part of a post-ictal psychotic episode, for which neurologists may be called to start pharmacotherapy. This topic is reviewed in the article by Fischl and Perucca in this issue.

## 6. Conclusions

In an ideal world, people with epilepsy with psychiatric comorbidity should be referred to a mental health professional who would undertake the optimum care tailored to their individual psychiatric history and work with the neurologist to ensure a comprehensive treatment. Unfortunately, access to psychiatric care is often limited, and it frequently falls upon the neurologist to provide pharmacotherapy for their MDE with or without ADs, which often may be present at the time of the initial evaluation of the seizure disorder. Given the relatively high prevalence of MDE in PWE, patients need to be screened for this type of mood disorder at every visit with the NDDI-E, which also screen for suicidal ideation and with the GAD-7 which screens for GAD. The early recognition of a mood disorder has a direct bearing on the selection of the ASMs and a timely treatment can prevent the negative impact on the management of the seizure disorder and facilitate the remission of psychiatric symptomatology. Neurologists can be expected to treat MDE, dysthymia and their comorbid anxiety disorders. They are not expected to manage bipolar disorders, people with suicidal ideation and behavior and MDEs with psychotic features.

## Ethical statement

The authors acknowledge that they have followed all the ethical rules and standards of the journal Epilepsy& Behavior Reports.

## CRediT authorship contribution statement

**Andres M. Kanner:** Project administration, Investigation, Formal analysis, Data curation, Conceptualization.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Andres M. Kanner has received honoraria from Xenon Laboratories for participation in an advisory board and from the Epilepsy Foundation of America for serving as Co-Editor-in-Chief of its publication Epilepsy.com.

## References


[1] Tellez-Zenteno JF, Patten SB, Jetté N, et al. Psychiatric comorbidity in epilepsy: a population-based analysis. Epilepsia 2007 Dec;48(12):2336–44.
[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition – Text Revision DSM-V-TR, 2022.
[3] Mula M, Kanner AM, Jett´e N, et al. Psychiatric comorbidities in people with epilepsy. Neurol: Clin Pract 2021;11:e112–20.
[4] Kanner AM. Suicidality in patients with epilepsy: why should neurologists care? Front Integr Neurosci 2022;16:898547.
[5] Christensen J, Vestergaard M, Mortensen PB, et al. Epilepsy and risk of suicide: a population-based case–control study. *Lancet Neurol* 2007;6:693–8.
[6] Scott AJ, Sharpe L, Hunt C, et al. Anxiety and depressive disorders in people with epilepsy: a meta-analysis. Epilepsia 2017;58:973–82.
[7] Kanner AM, Saporta AS, Kim DH, et al. Mood and anxiety disorders and suicidality in patients with newly diagnosed focal epilepsy: an analysis of a complex comorbidity. Neurology 2023 Mar 14;100(11):e1123–34.
[8] Kanner AM, Barry JJ, Gilliam F, Hermann B, Meador KJ. Depressive and anxiety disorders in epilepsy: do they differ in their potential to worsen common antiepileptic drug-related adverse events? Epilepsia 2012;53(6):1104–8.
[9] Nogueira MH, Yasuda CL, Coan AC, Kanner AM, Cendes F. Concurrent mood and anxiety disorders are associated with pharmacoresistant seizures in patients with MTLE. Epilepsia 2017 Jul;58(7):1268–76.
[10] Cramer JA, Blum D, Reed M, Fanning K. Epilepsy Impact Project Group. The influence of comorbid depression on quality of life for people with epilepsy. Epilepsy Behav 2003 Oct;4(5):515–21.
[11] Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. Lancet 2013 Nov 16;382(9905):1646–54.
[12] Gilliam F, Kuzniecky R, Faught E, et al. Patient-validated content of epilepsy-specific quality-of-life measurement. Epilepsia 1997;38(2):233–6.
[13] Josephson CB, Lowerison M, Vallerand I, Sajobi TT, Patten S, Jette N, et al. Association of Depression and Treated Depression With Epilepsy and Seizure Outcomes: A Multicohort Analysis. JAMA Neurol 2017 May 1;74(5):533–9. https://doi.org/10.1001/jamaneurol.2016.5042.
[14] Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. *Ann Neurol* 2012; 72(2):184–91. https://doi.org/10.1002/ana.23601.
[15] Kanner AM, Mazarati A, Koepp M. Biomarkers of epileptogenesis: psychiatric comorbidities (?). Neurotherapeutics 2014 Apr;11(2):358–72.
[16] Gilliam FG, Barry JJ, Hermann BP, et al. Rapid detection of major depression in epilepsy: a multicenter study. *Lancet Neurol* 2006;5:399–405.

[17] Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166(10):1092–7.
[18] Goldberg JF, Bowden CL, Calabrese JR, et al. Six-month prospective life charting of mood symptoms with lamotrigine monotherapy versus placebo in rapid cycling bipolar disorder. Biol Psychiatry 2008 Jan 1;63(1):125–30.
[19] Di Capua D, Garcia-Garcia ME, Reig-Ferrer A, Fuentes-Ferrer M, Toledano R, Gil-Nagel A, et al. Validation of the Spanish version of the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E). Epilepsy Behav 2012 Aug;24(4):493–6.
[20] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med 2001;16(9):606–13.
[21] Micoulaud-Franchi JA, Kotwas I, Arthuis M, et al. Screening for epilepsy-specific anxiety symptoms: French validation of the EASI. Epilepsy Behav 2022;128:108585.
[22] Ettinger AB, Reed ML, Goldberg JF, Hirschfeld RMA. Prevalence of bipolar symptoms in epilepsy vs other chronic health disorders. Neurology 2005;65(4):535–40.
[23] Charney DS, Berman RM, Miller HL. Treatment of depression. In: Schatzberg AF, Nemeroff CB, eds. Textbook of Psychopharmacology, Second Edition. American Psychiatric Association Press; Washing- ton, DC, pp. 705–732; 1998.
[24] Kraepelin E. *Psychiatrie*. 7. Auflage. Liepzig: JA Barth; 1903.
[25] Blumer D, Zielinski J. Pharmacologic treatment of psychiatric disorders associated with epilepsy. *J Epilepsy* 1988;1:135–50.
[26] Mula M, Jauch R, Cavanna A, et al. Interictal dysphoric disorder and peri ictal dysphoric symptoms in patients with epilepsy. Epilepsia 2010 Jul;51(7):1139–45.
[27] Kanner AM, Soto A, Gross-Kanner H. Prevalence and clinical characteristics of postictal psychiatric symptoms in partial epilepsy. *Neurology* 2004;62:708–13.
[28] Josephson CB, Engbers JDT, Jette N, et al. Prediction Tools for Psychiatric Adverse Effects After Levetiracetam Prescription. JAMA Neurol 2019 Apr 1;76(4):440–6.
[29] Kanner AM, Patten A, Ettinger AB, et al. Does a psychiatric history play a role in the development of psychiatric adverse events to perampanel… and to placebo? Epilepsy Behav 2021;25(12):108380.
[30] Brent DA, Crumrine PK, Varma RR, Allan M, Allman C. Phenobarbital treatment and major depressive disorder in children with epilepsy. *Pediatrics* 1987;80:909–17.
[31] Mula M, Hesdorffer DC, Trimble M, Sander JW. The role of titration schedule of topiramate for the development of depression in patients with epilepsy. *Epilepsia* 2009;50(5):1072–6.
[32] Kanner AM. Management of psychiatric and neurological comorbidities in epilepsy. Nature Reviews Neurol 2016 Feb;(12)2: 106-16.
[33] Mula M, McGonigal A, Micoulaud-Franchi J-A, May TW, Labudda K, Brandt C. Validation of rapid suicidality screening in epilepsy using the NDDIE. *Epilepsia* 2016;57:949–55.
[34] Beck AT. The Beck Depression Inventory-II. San Antonio, TX: THE PSYCHOLOGICAL CORPORATION Harcourt Brace & Company; 1996.
[35] U.S. Food and Drug Administration: Center for Drug Evaluation and Research. Information for healthcare professionals: suicidality and antiepileptic drugs [online] http://www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm.
[36] Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: fire or false alarm? Epilepsia 2009;50(5):978–86.
[37] Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: A bidirectional association. *Ann Neurol* 2012;72:184–91.
[38] Mula M. The pharmacological management of psychiatric comorbidities in patients with epilepsy. Pharmacol Res 2016;107:147–53.
[39] Gilliam FG, Black KJ, Carter J, et al. A trial of sertraline or cognitive behavior therapy for depression in epilepsy. Ann Neurol 2019 Oct;86(4):552–60.
[40] Sinyor M, Schaffer A, Levitt A. The sequenced alternatives to relieve depression (STAR*D) trial: a review. Can J Psychiatry 2010;55(3):126–35.
[41] Ribot R, Ouyang B, Kanner AM. The impact of antidepressants on seizure frequency and depressive and anxiety disorders of patients with epilepsy: Is it worth investigating? Epilepsy Behav 2017 May;70(Pt A):5–9.
[42] Mula M, Brodie MJ, de Toffol B, et al. ILAE clinical practice recommendations for the medical treatment of depression in adults with epilepsy. Epilepsia 2022 Feb;63(2):316–34.
[43] Kanner, AM. Most antidepressant drugs are safe for patients with epilepsy at therapeutic doses: A review of the evidence. Epilepsy & Behavior, Volume 61, 282 – 286.
[44] Letmaier M, Painold AM, Holl AK, et al. Hyponatraemia during psychopharmacological treatment: results of a drug surveillance programme. Int J Neuropsychopharmacol 2012 Jul;15(6):739–48.
[45] Rizzoli R, Cooper C, Reginster JY, Abrahamsen B, Adachi JD, Brandi ML, et al. Antidepressant medications and osteoporosis. Bone 2012 Sep;51(3):606–13.
[46] Alper K, Schwartz KA, Kolts RL, et al. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry 2007;62:345–54.
[47] Michaelis R, Tang V, Goldstein LH, et al. Psychological treatments for adults and children with epilepsy: evidence-based recommendations by the International League Against Epilepsy Psychology Task Force. *Epilepsia* 2018;59:1282–302.
[48] McLaughlin DP, McFarland K. A randomized trial of a group based cognitive behavior therapy program for older adults with epilepsy: the impact on seizure frequency, depression and psychosocial well-being. J Behav Med 2011;34(3):201–7.
[49] Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ. Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. Epilepsy Behav 2003 Oct;4(Suppl 3):S31–8.