DEVELOPMENTS IN DEPRESSION IN EPILEPSY: SCREENING, DIAGNOSIS AND TREATMENT

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Summary

Introduction: Depression is one of the most frequent comorbidities in epilepsy affecting between 17% and 22% of patients but it is still underdiagnosed and undertreated.

Areas covered: This paper discusses recent advances about screening, diagnosis and treatment of depression in epilepsy taking into account the heterogeneity of clinical scenarios where depression can occur.

Expert opinion: A number of screening instruments are now validated for adults with epilepsy and their psychometric properties are discussed but the NDDIE is the most practical and cost-effective. Challenges in diagnosing depression in epilepsy are discussed including reasons for the atypical features of mood disorders in epilepsy. Psychological treatments and/or SSRIs are indicated but the level of evidence is still low. Even if there is no reason to hypothesis that internationally accepted guidelines of treatment of depression outside epilepsy may not be valid, rigorous studies are needed in order to have proper outcome measures. Epilepsy centers should have well-defined care pathways for depression in order to provide access to mental health support when needed.

Key words: epilepsy, depression, antiepileptic drugs, interictal dysphoric disorder, NDDI-E, BDI, screening, diagnosis, treatment, antidepressant drugs

1. INTRODUCTION

Depression is one of the most frequent psychiatric comorbidity in epilepsy and the strong links with epilepsy have attracted the interest of physicians for centuries [1]. Cross-sectional epidemiological studies show a uniformly increased prevalence of depression with prevalence rates similar to those of the general population among seizure free patients [2], but ranging between 17% and 22% in unselected populations [3], up to 55% in people with drug-resistant epilepsy [4]. Over time, it became apparent that these two conditions have a bidirectional relationship [5,6] and this seems to be based on quite solid neurobiological underpinnings apart from the obvious psychosocial reasons. In fact, neuroimaging studies of depression outside epilepsy have shown a number of neuroanatomical changes which largely overlap with those seen in patients with temporal lobe epilepsy [7] including a 10 to 20% bilateral decrement in the hippocampal volumes [8], decreased cortical thickness in the frontal lobes and decreased glial/neuronal cell density in the cingulate gyrus, rostral and caudal orbitofrontal cortex and dorsal prefrontal cortex [9,10].

Further, studies in animal models of epilepsy or depression have shown a number of neurochemical and anatomical changes which can be responsible for both conditions including low serotonin levels [11] [12] [13], the reduction in CA3 neuronal cells in the dentate gyrus [14] and the acceleration of the kindling process under high cortisol levels [15].

Finally, a number of studies are now pointing out that depression is a prognostic marker in epilepsy as it is associated not only with poor quality of life [16] but also with antiepileptic drug-resistance [17,18], increased seizure severity [19], increased side effects of antiepileptic drugs [20], increased risk of accident and injuries [21], poor outcome after epilepsy surgery [22] and increased mortality [23].

Despite the evident academic interest in this subject, depression is still underdiagnosed and undertreated in epilepsy unless it is severe enough to cause major problems or disability. This can be due to many reasons including the patients' reluctance to volunteer spontaneously mental health issues, a lack of a specific training of neurologists to recognize and manage psychiatric comorbidities, lack of time in busy clinics and the need to focus on seizures and side effects.

This is a narrative review about current knowledge in the clinical management of depression in epilepsy from screening to diagnosis and treatment. References have been identified through Medline/PubMed searches until September 2018 using the terms "epilepsy" AND "depression". Additional publications (e.g. books or book chapters) were hand searched if relevant for the discussion.

2. SCREENING FOR DEPRESSION IN EPILEPSY

In 2004, Gilliam et al. reported that only 7% of US neurologists routinely screen patients with epilepsy for depression [24]. In 2011, an international consensus statement on the management of neuropsychiatric comorbidities of epilepsy recommended periodic screening for depression in all patients at least once a year [25]. A more recent survey of the Task Force on Education of the International League Against Epilepsy (ILAE) report that around 50% of child and adult epileptologists routinely screen their patients for psychiatric disorders [26]. Although these figures are probably quite optimistic, surely reflect the increasing awareness of the epilepsy community on this subject.

Every clinician is probably familiar with the concept of depression and the existence of specific diagnostic criteria for what is defined as Major Depressive Episode and Major Depressive Disorder in the current version of the Diagnostic and Statistical Manual of Mental

Disorders (DSM-5). Symptoms of depression can be broadly grouped into emotional, neurovegetative and cognitive symptoms, but because they can commonly occur in other psychiatric and medical conditions, the definition of depression as a disorder is based on these symptoms forming a syndrome causing a functional impairment [27].

Many depression-screening tools have been developed to be used in primary and secondary care settings in the general population and they have shown to be effective [28]. In the case of epilepsy, screening and diagnosing depression is obviously more complex than in the general population because people with epilepsy can develop depressive symptoms in different clinical contexts such as peri-ictal phenomena or as a consequence of the epilepsy treatment [29]. For all these reasons, it is possible that many of these well-known screening instruments are not valid in people with epilepsy. A recent study systematically has reviewed the literature about the validity of screening tools for depression in epilepsy [30]. The validity of 16 screening tools was assessed against seven reference standards and the authors concluded that the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E) [31] is probably the most practical for a variety of settings because it is freely available in the public domain, it has been already validated in a number of languages and it is easy to score. Still, the NDDI-E is the only depression-screening instrument specifically developed for people with epilepsy; it showed a specificity of 90%, a sensitivity of 81% and showed to be valid also against the Adverse Event Profile [31], representing quite an advantage. More recently, the NDDI-E has also been validated as a suicidality screening tool showing a sensitivity of 84% and a specificity of 91% [32].

In this systematic review of depression screening tools [30], the authors also evaluated different cut off scores for all identified tools showing that in many cases, the diagnostic threshold is different from the one adopted in the general population. For example, for the Beck Depression Inventory II (BDI-II) the usually adopted cut off score is 10 while in the

epilepsy population seems to be 15 while for the PHQ-9 the usual cut off score is 5 while in the epilepsy population is 10 (Table 1). This is probably due to the already mentioned atypical features of depression in epilepsy and the occurrence of depressive symptoms in a variety of clinical contexts as it will be discussed in the subsequent section. However, in general terms, it is important to point out that the ideal tool depends on many different reasons, including not only the psychometric properties of the individual screening instrument, but also on the clinical setting and resource availability. For example, the NDDIE has been validated to screen for a major depressive episode not to rate or quantify depressive symptoms or to monitor for example response to antidepressant treatment. On the contrary, the Hamilton Depression Rating Scale (HDRS) is often used in clinical trials of depression outside epilepsy and the validation of the HDRS in the epilepsy population [33] will provide outcome data which can be compared to those in the general population.

If literature on adults is at an advanced stage, that on children is still more than scant [34]. A 12-item, self-report screening tool for patients age 12-17 years, named NDDI-E-Youth, has been validated in epilepsy [35] but there are no studies specifically investigating psychometric properties of screening instruments for depression in children with epilepsy. This partially reflects current practice about screening for depression among children in the general population. The American Academy of Child and Adolescence Psychiatry published a comprehensive document for the assessment and treatment of depression in children and adolescents [36] and the main recommendation is to use checklist of symptoms present in the DSM or ICD but did not recommend any specific screening tool. Among children in general, depression has a prevalence of 2% which is far lower than that of anxiety disorders, ranging between 6% and 20%; in addition, it is comorbid with other mental health issues in up to 90% of cases. It seems, thus, evident that, in the general population, depression among children

tends to occur in the context of quite obvious, but at the same time complex, mental health problems easily requiring medical attention. However, the clinical setting is completely different for children with epilepsy. A population-based study among children and adolescents with active epilepsy age 5-15 showed prevalence rates for depression up to 7% but this was already diagnosed in only 1% of patients [37]. It is, therefore, evident that studies aimed at developing and validating depression screening tolls for children with epilepsy are needed.

As previously mentioned, anxiety is far more common among children than depression. The American Academy of Child and Adolescence Psychiatry has pointed out the importance of routine screening for anxiety among children in the general population [38]. In fact, only a minority of children with an anxiety disorders go into remission during adulthood and around 30% of those in remission develop a more serious psychiatric condition during adulthood; around 50% of adults with depression had an anxiety disorder during child [38]. A number of screening tools are available to screen for anxiety in children and their use in epilepsy has been discussed [39].

3. THE DIAGNOSIS OF DEPRESSION IN EPILEPSY

Major classificatory systems such as ICD and DSM are widely used to diagnose major depressive disorder within hospital and community settings. Many authors have pointed out that the phenomenology of depression in epilepsy may sometimes be atypical, not reflecting diagnostic criteria adopted by major classificatory systems such as the DSM [40–42]. As already mentioned, this can be due to a number of reasons, including peri-ictal symptoms and the effect of the epilepsy treatment such as AEDs or epilepsy surgery. For these reasons, the first step in the diagnosis and management of depression in epilepsy is to

dissect out the various potential contributors to the final clinical presentation, as different contributing factors need to be approached in parallel and require different treatments including psychotherapy, counseling, antidepressant drugs or changes in the antiepileptic drug (AEDs) treatment.

3.1 Peri-ictal depressive symptoms

The practicality of classifying psychiatric symptoms according to their temporal relation to seizure occurrence (peri-ictal/para-ictal symptoms vs. interictal symptoms) is well established [29] (Table 2).

The occurrence of mood changes preceding a seizure is well-known to patients and clinicians, and these changes are usually described as irritability or dysphoria rather than depressed mood, preceding by hours to days a tonic clonic seizure [43]. A cross sectional study reported that up to 30% of patients report pre-ictal mood changes [44] but otherwise the exact prevalence of this phenomenon is still unknown as well as its neurobiology.

Depressed mood as a focal seizure has been occasionally reported and, according to some authors, is reported by 1% of patients with temporal lobe epilepsy [45]. It is usually described as an intense, out of the context, anhedonia, with feelings of guilt and/or suicidal ideation, lasting from a few seconds to minutes with preserved awareness. Ictal fear or ictal panic is definitely more frequent than ictal depression and it has a strong localizing and lateralizing value for the non-dominant amygdala [46] [47].

Post-ictal depression and post-ictal worsening of depressive symptoms are also reported and probably better documented than other peri-ictal depressive symptoms. A cross-sectional study from a monitoring unit has shown that up to 18% of patients can report depressive symptoms lasting more than 24 hours [48] and similar figures have been shown by another

cross-sectional study using a structured questionnaire [42]. Contrapolar mood changes such as manic/hypomanic symptoms have been also reported post-ictally by a similar proportion of patients (i.e. 22%) but are often associated with psychotic symptoms [48]. Post-ictal mania has a stronger localizing value than post-ictal depression and it has been associated with frontal EEG discharges and non-dominant hemisphere involvement [49].

3.2 Treatment-related depression

That depression may be a treatment-emergent adverse event of AED is now established and this is seen more frequently in people with epilepsy than in other conditions where these drugs are widely used such as pain, migraine, movement disorders or primary psychiatric disorders [50]. AED-related depression was initially associated with long-term exposure to barbiturates but became evident, over time, that many different compounds can be associated with depression as a treatment-emergent adverse event, especially topiramate, vigabatrin, perampanel and levetiracetam [51]. This has obviously revived the concept of forced normalization, the phenomenon which describes the sudden switching off of seizures in people with intractable epilepsy who then develop an alternative psychiatric syndrome, very often a psychotic disorder, but depressive symptoms are also described [52]. It has been reported that up to 8% of patients with drug-resistant epilepsy develop treatment-emergent psychiatric adverse events regardless of the mechanism of action of the individual AED and this is mainly driven by the underlying psychiatric comorbidity, representing the fertile ground on which these paradoxical reactions develop [53].

The rapidity of the titration rate of the AED is another relevant variable. In fact, even if it is true that some compounds seem to be more frequently associated with behavioral problems than others [51,54,55], it is also established that the rapidity of the titration can significantly increase the likelihood to develop treatment-emergent psychiatric problems [56,57]. For

example, a retrospective study in a large cohort of consecutive patients treated with topiramate has shown that while a previous history of depression is associated with a 3.5-times increased risk of developing depression as a treatment-emergent adverse event, the use of a rapid titration schedule in someone with a previous history of depression is associated with a 23-times increased risk [58].

Finally, it is important to bear in mind the possibility of mood symptoms occurring after discontinuation of a mood stabilizing agent such as carbamazepine, oxcarbazepine or valproate, which may have masked a mood disorder in comorbidity. Although this possibility has a clear theoretical ground, data on this subject are still limited.

Depression is also a well-known complication of epilepsy surgery and all patients are usually counseled that up to 30% of them can develop transitory depressive symptoms within the first three months after epilepsy surgery [59,60]. Some authors pointed out that the phenomenology of post-surgical depression is usually different from that of interictal depression with the former being more severe, and more frequently associated with clear anhedonic features than inter-ictal depression, which tends to have dysthymic/dysphoric features [60]. Still, some patients, after surgery, may present with a physical and mental asthenia which goes along with avoidance of or withdrawal from social interactions [61].

3.3 Inter-ictal depression and its diagnosis

Historically, both Kraepelin and Bleuler reported that patients with epilepsy can develop a unique mood disorder characterized by a pleomorphic pattern of depressive symptoms intermixed with euphoric moods, irritability, fear and anxiety as well as anergia, pain and insomnia [62]. In modern times, this formulation has been rejuvenated by Blumer who coined the term Inter-ictal Dysphoric Disorder (IDD) to refer to a somatoform-

depressive disorder claimed to be typical of patients with epilepsy [63]. Subsequent studies pointed out that such a condition can be diagnosed in up to 12% of patients but it is not specific of epilepsy as it can be diagnosed also in other neurological disorders, such as migraine [42]. However, these studies and observations clearly pointed out that interictal depression is not simply characterized by chronic dysthymic-like features but many patients with epilepsy present also mood instability and dysphoric symptoms.

In addition, studies investigating the phenomenology of inter-ictal depression have also shown that depression is highly comorbid with anxiety disorders [42,64] and this point, along with peri-ictal symptoms, the effect of AEDs on mood and the mood instability largely account for the atypical features of depression in epilepsy [65].

Given the complexities in the phenomenology of inter-ictal depression, it is easy to understand that structured clinical interviews shaped on DSM or ICD criteria may not be always valid. For this reason, some authors tried to develop clinical instruments tailored on these atypical manifestations. An adapted version of the Structured Clinical Interview for DSM Axis I (SCID-I), named SCID-E, has been suggested [66], and a specific epilepsy questionnaire to be used with the Mini International Neuropsychiatric Interview (MINI), named the Epilepsy Addendum for Psychiatric Assessment, has also been described [67]. Although occasionally used for research purpose, the relative benefits of these various instruments in clinical practice is still matter of debate.

A couple of questionnaires for the assessment of IDD symptoms are also available, mainly for research purposes. The Seizure Questionnaire [68] investigates the eight key symptoms of the IDD as theorized by Blumer. Patient and next of kin answer the questionnaire jointly and the examiner reviews the answers. Another questionnaire, again developed research purposes, named the Interictal Dysphoric Disorder Inventory, is available [42]. The reliability and utility of these questionnaires has been debated. The pleomorphic nature of the IDD itself

along with the issue of peri-ictal symptoms make the development of an epilepsy-specific clinical instrument quite challenging.

4. TREATMENT OF DEPRESSION IN EPILEPSY

Screening for depression should always be linked to well-defined and effective care pathways [69]. In general terms, data on treatment of depression in epilepsy is still limited and relies heavily on individual clinical experience [70]. Two documents, an International Consensus Statement and a US consensus paper have issued a number of recommendations [25,71].

4.1 Psychological treatments

According to the National Institute for Clinical Excellence (NICE), psychological therapies represent first line treatment for mild to moderate depression in both the general population [72] and in subjects with a chronic health problem [73]. Data in people with epilepsy are still limited but systematic reviews and meta-analysis have shown that psychological therapies are associated with a significant improvement in quality of life [74,75] and a recent document from the ILAE Psychology Task Force confirmed that psychotherapeutic interventions are recommended in patients with epilepsy and mild to moderate depression, even if the level of evidence is still moderate and further studies are needed [76].

4.2 Antidepressants

Data on the pharmacological treatment of depression in epilepsy is limited. A Cochrane Review on this subject highlighted that the level of evidence is still low due to the

poor quality of available studies [77]. In fact, there are only two randomized controlled trials for depression in epilepsy, the first, published more than 30 years ago, comparing nomifensine, amitriptyline and placebo [78] and the second investigating the antidepressant effect of a traditional Chinese medicine remedy, Xylaria Nigripes, as compared to placebo [79]. Both studies are significantly underpowered as the first study involved only 45 patients while the second one 104. The first study reports response rates in the region of 43% for amitriptyline and 79% for nomifensine and significantly higher than placebo while the second reports a significant reduction in mean HDRS scores but none of them provide response rates or remission rates. In addition, nomifensine is no longer available in many countries as it was withdrawn from the US, Canadian and UK markets. Apart from these few controlled trials, there are many open studies mostly of Selective Serotonin Reuptake Inhibitors (SSRIs) in relatively small unselected samples of people with different epileptic syndromes: sertraline [41,80], citalopram [81–83], fluoxetine [80], reboxetine [83] and mirtazapine [83]. One study is of particular interest as it is the only one in children and adolescents [80]. In general terms, all these studies seem to suggest that SSRIs (Table 3), sertraline and citalopram in particular, are safe and effective, but the level of evidence is low and the reported response rates are quite heterogeneous and ranging from 24% [82] to 97% [80]. The variability in response rates can be due to many reasons such as the heterogeneity of participants (from newly diagnosed epilepsy to drug-resistant epilepsy) and pharmacokinetic interactions, especially the effect of inducers [70].

4.3 Antiepileptic drugs

Some AEDs are currently licensed not only for the treatment of epilepsy but also for mood and anxiety disorders. For example, lamotrigine is licensed for the maintenance treatment of depression in bipolar disorder type II [84] and pregabalin in generalized anxiety

disorder [85], with studies suggesting also some potential in depression [86]. However, evidence in epilepsy is very limited and most studies focus on quality of life measures rather than on depression. Only a few studies investigated the antidepressant effect of AEDs in people with epilepsy, three with lamotrigine and one with oxcarbazepine.

Regarding the three studies with lamotrigine, the first one is a randomized, double-blind, placebo-controlled study, involving 70 individuals with epilepsy and depression [87]. However, this is a secondary analysis of an efficacy study [88] and remission rates are not provided. The other two studies are a US multicenter open label studies in an unselected population of 158 people with epilepsy (50% with generalized epilepsies) [89]. Clinical response rates, as measured with the BDI, range between 51% and 71% but again remission rates are not reported. The second paper is a sub-analysis of the same study in people older than 50 years, showing similar results [90].

A single open label study investigates the antidepressant effect of oxcarbazepine in 40 patients with focal epilepsy and depression [91]. Patients have been assessed with a number of clinical instruments including the BDI, HDRS and the Cornell Dysthymia Rating Scale (CDRS). The authors report a significant reduction in all depressive scores. A remission rate of 13% as measured with the CDRS is provided but remission rates with usually used outcome scales, such the HDRS or the BDI, are not provided.

4.4 Interactions between antidepressant and antiepileptic drugs

AEDs have a different potential for pharmacokinetic interactions. Among first generation of AEDs, carbamazepine, phenytoin and barbiturates are inducers of several drug-metabolizing enzymes including the CYP and the UGT systems, while valproate is a well-known inhibitor [70,92]. Among second generation AEDs, oxcarbazepine is a weak inducer,

while topiramate has some inducing properties at doses higher than 200 mg per day [92]. Third generation AEDs, have a better pharmacokinetic profile with a low propensity for pharmacokinetic interactions. Conversely, the majority of antidepressants have a complex metabolism and some of them may inhibit some metabolic pathways [92].

In general terms, the clearance of almost all antidepressants is increased by AEDs with inducing properties with a reduction in blood levels of about 25% for all SSRIs, mirtazapine and venlafaxine [70][92]. However, there is no clear evidence that these interactions are clinically relevant with the exception of bupropion whose clearance can be increased by up to 90% when carbamazepine is introduced [70].

SSRIs, especially fluoxetine and fluvoxamine, are inhibitors of the CYP2C9 and may potentially interact with phenytoin and, to a lesser extent, with valproate [70] while other more recent antidepressants seem to have a low potential for pharmacokinetic interactions.

4.5 Seizure worsening

Historically, antidepressants have been linked to epileptic seizures as a treatment emergent adverse event and epileptic seizures are still listed in the information leaflet of all antidepressants. However, this was based on an *a priori* assumption rather than on any clinical evidence [70]. In fact, a meta-analysis of FDA data clearly showed that the occurrence of seizures during treatment with antidepressants is not different from that with placebo [93]. An exception been for clomipramine at high doses (>150 mg), maprotiline, bupropion immediate release formulation [70]. These findings have been recently confirmed by a systematic review on this subject [94].

The issue of drug-related seizures is quite complex and it is not only confined to psychotropic medications. Regarding the risk of seizures during treatment with antidepressants outside

epilepsy, given the recent epidemiological data on the bidirectional relationship, it is clearly evident that the reported prevalence of epileptic seizures in patients with mood disorders is even lower than the expected one, suggesting that antidepressant drugs reduce the risk of seizures in patients with depression [70]. Obviously, it is still unknown whether these data can be transferred to patients with epilepsy and whether some epileptic syndromes are more at risk than others but data about seizure frequency from studies mentioned in section 4.2 do not support any increased risk of seizure deterioration.

5. EXPERT OPINION

Although the relationship between epilepsy and depression has been established for a long time, clinical research into this area became systematic only in the last 15 years. Data on validity of screening tools in adults with epilepsy has identified the NDDI-E as a valid and cost-effective clinical instrument to be used in routine clinical care to screen for major depressive episode. Other clinical instruments have been validated in adults with epilepsy and they may be used in different clinical settings and depending on the aim of the evaluation. For example, the HRSD is often use in clinical trials of antidepressants while the BDI may be useful to monitor or identify specific depressive symptoms.

Conversely, data on children is almost non-existent and further studies are needed.

Studies looking at the phenomenology of depression in epilepsy have clearly pointed out that a variable, but not negligible, proportion of patients develop depressive disorders which do not fulfill criteria adopted by internationally accepted classificatory systems such as the DSM. This seems to be due to the high comorbidity rates with anxiety disorders and the variety of clinical scenarios where depressive symptoms can occur, from side effects of AEDs, to peri-ictal symptoms or as a complication of epilepsy surgery.

Regarding the treatment of depression, majority of studies have an open design and they have been conducted in small samples of patients with quite heterogeneous epilepsy syndromes. Overall, these studies support SSRIs, citalopram and sertraline in particular, as reasonably safe and effective. However, the available evidence on the efficacy of treatment of depression in epilepsy is still quite low. In general terms, there is no reason to hypothesize that internationally accepted guidelines for the treatment of depression in the general population may not be valid in epilepsy and the available open studies seem to support that. However, it is quite astonishing that very basic outcome measures like response, remission and recovery rates for depression in epilepsy are still unavailable.

Given the complexities in the diagnosis and management of depression in epilepsy, epilepsy centers should have well-defined care pathways involving health care professionals in other disciplines, including psychiatrists, clinical psychologists, neuropsychologists and social workers, to ensure that people with epilepsy receive the best management.

6. FIVE-YEAR VIEW

A number of areas will probably expand in the next 5 years. Research in children with epilepsy is urgently needed not only in terms of clinical instruments to be used in routine clinical care but also in terms of phenomenology and therapeutic strategies.

Rigorous controlled studies on the treatment of depression in epilepsy are needed for both adults and children in order to obtain informative outcome measures and develop evidence-based treatment strategies.

Internationally guidelines for the management of epilepsy will need to take comorbidities into account, especially depression, including not only the need to adequately counsel all patients with epilepsy about the increased risk of depression but also on the potential consequences

such as the increased risk of drug-resistance, morbidity and mortality. Finally, studies on the impact of the treatment of depression on the long-term outcome of epilepsy will be needed. In fact, it is still unknown whether a prompt and effective treatment of depression in epilepsy leads to a better outcome in terms of seizure control, morbidity and mortality.

7. ARTICLE HIGHLIGHTS

- A number of clinical instruments have been validated in adults with epilepsy and psychometric properties are available.
- The NDDI-E showed to be the most practical screening tool because it is freely available in the public domain, it has been already validated in a number of languages and it is easy to score but different clinical settings may require different clinical instruments.
- Data on screening tolls in children is still almost non-existent and studies are urgently needed
- A non-negligible proportion of patients with epilepsy develop a depressive syndrome not in keeping with internationally accepted classificatory systems.
- The atypical features of depression in epilepsy are due to the high comorbidity rates with anxiety disorders and the different clinical scenarios where depressive symptoms can occur such as peri-ictal symptoms and as side effect of AEDs.
- Evidence on the treatment of depression in epilepsy is still based on low quality data
- Even if there is no reason to hypothesis that internationally accepted guidelines of treatment of depression outside epilepsy may not be valid, rigorous treatment studies are needed in order to have proper outcome measures.
- Despite seizures are mentioned as a potential adverse event of antidepressants, the evidence, in the general population, is entirely against that assumption showing no increased risk as compared to placebo. Studies in people with epilepsy are needed.

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Table 1. Depression-screening tools validated in adults with epilepsy and psychometric properties (modified from [23]).

Tool	Cut off	Sensitivity	Specificity	PPV	NPV
BDI-II	15	89%	81%	56%	97%
HADS-D	8	77%	85%	64%	98%
HRSD-17	6	94%	80%	46%	99%
NDDIE-E	15	80%	86%	59%	96%
PHQ-9	10	83%	80%	46%	96%

BDI: Beck Depression Inventory; HADS-D: Hospital Anxiety and Depression Scale – Depression Subscale; HRSD-17: Hamilton Rating Scale for Depression 17-item version; NDDIE-E: Neurological Disorders Depression Inventory for Epilepsy; PHQ-9: Patient Health Questionnaire 9

Table 2. Peri-ictal depressive symptoms.

Relationship with seizures	Duration	Clinical features
Pre-ictal symptoms	24 – 48 hours	Dysphoria, insomnia, irritability
Ictal symptoms	Minutes	Out of the context, stereotyped, intense anhedonia, feeling guilty/suicidal
Post-ictal symptoms	<24 hours	Deterioration of pre-existing depressive symptoms, anxiety, suicidal thoughts, psychotic symptoms
Para-ictal symptoms	Days/weeks	Depressed mood and psychotic symptoms in the context of sudden seizure control

Table 3. Antidepressant drugs.

Selective Serotonin Reuptake Inhibitors
Citalopram
Sertraline
Fluoxetine
Fluvoxamine
Paroxetine
Escitalopram
Selective Serotonin Noradrenaline Reuptake Inhibitors
Venlafaxine
Duloxetine
Tricyclic Antidepressants
Imipramine
Clomipramine
Amitritpyline
Nortriptyline
Other antidepressants
Moclobemide
Phenelzine
Agomelatine
Mirtazapine
Trazodone
Vortioxetine