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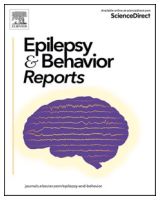

Should neurologists treat common psychiatric comorbidities in patients with epilepsy?

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ABSTRACT

Psychiatric comorbidities are common and highly impactful among people with epilepsy, yet they are under-recognized and undertreated due to challenges including shortage of specialty mental health providers and lack of neurologist education to enable management by neurologists. The purpose of this special issue is to address these gaps by providing a practical resource for neurologists to safely manage comorbidities via pharmacotherapy for common comorbidities. In this introductory article, we summarize key categories of psychiatric problems in epilepsy and a broad overview of management strategies. These include reactive psychiatric symptoms, interictal psychiatric disorders, *peri*-ictal psychiatric episodes, and iatrogenic causes of psychiatric symptoms. Reactive psychiatric symptoms can be addressed via epilepsy education and neurologist acknowledgement of the loss of predictability inherent in epilepsy. Interictal psychiatric disorders can be identified via standardized screening instruments and managed using evidence-based pharmacotherapy with a similar approach to the general population. Peri-ictal psychiatric episodes have a consistent temporal relation to seizure occurrence and are primarily managed via prevention through seizure treatment. Patients with personal or family history of psychiatric disorders are at particular risk for iatrogenic psychiatric effects; neurologists should take care in treatment selection among these individuals and be ready to respond to manage iatrogenic effects if they arise. Management of specific psychiatric conditions are addressed in more depth in topic-focused articles throughout the remainder of the special issue.

1. Introduction

Population-based studies have established that one in three people with epilepsy (PWE) experience a psychiatric disorder in the course of their life, with mood disorders, anxiety disorders and Attention Deficit Hyperactivity Disorder (ADHD) being the most frequently reported [1]. Their negative impact extends beyond the psychosocial aspects of life, as psychiatric disorders increase the risk of premature death [2], interfere with seizure management and worsen the course of the epilepsy [3]. Yet, despite their high prevalence and negative impact on the lives of PWE at multiple levels, psychiatric comorbidities go untreated in a majority of patients [4]. Limited or no access to mental health professionals or patients' reluctance to seek specialty mental health care have been the more common reasons given to explain this phenomenon [5–7]. Accordingly, *should neurologists treat some of the common psychiatric comorbidities in patients with epilepsy (PWE)*?

The purpose of this Special Issue is to provide neurologists and any clinician treating PWE with a very pragmatic resource that can be used to identify:

(i) which of the common psychiatric comorbidities are amenable to psychopharmacologic therapies, that could be prescribed by epilepsy clinicians.
(ii) which psychotropic drugs are the most appropriate to treat common psychiatric comorbidities.
(iii) which (if any) pharmacodynamic and pharmacokinetic interactions between psychotropic and concomitant antiseizure medications (ASMs) should be anticipated.
(iv) Which psychopathology is an expression of iatrogenic or *peri*-ictal phenomena.

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2. What type of psychiatric symptoms?

Psychiatric symptoms in PWE can be the expression of several pathologic processes, which must be accurately identified as their treatment differs significantly. These include:

(i) A reactive process to adverse events.
(ii) An interictal psychiatric disorder.
(iii) A *peri*-ictal episode.
(iv) An iatrogenic process.

a) A reactive process to an adverse experience.

Stressful situations can often result in the development of anxiety and /or depressive episodes which typically remit after a few weeks and are referred as adjustment reactions. Yet, a prior personal and /or family psychiatric history can increase their risk of occurrence and should always be investigated, as it can herald a longer course or a recurrence of prior psychiatric comorbidity.

Facing the diagnosis of epilepsy is an inevitable stressful experience that all PWE and their family must cope with. Adjustments in their daily activities (e.g., giving up driving privileges and / or having to limit certain work-related responsibilities) have been the most frequent cited cause of stress; yet, "the loss of predictability" is in fact the most significant stressor that PWE and their family members have to face, as they cannot be given 100 % assurances that seizures will not recur. Learning to accept this fact it is a fundamental step in coping with a diagnosis of epilepsy.

While clinicians usually explain the seizure precautions that PWE have to follow, they do not always make sure that patients and family members have understood what epilepsy and seizures are and do not take the time to assess the impact of this diagnosis at cognitive and emotional levels. Furthermore, they almost never prepare them on how to cope with the "loss of predictability" and the fears and misconceptions associated with the diagnosis of epilepsy.

Consequently, it is not unusual for patients (and their family members) to experience an adjustment reaction following the diagnosis of epilepsy with symptoms of anxiety and / or depression, often resulting in family conflicts. To minimize such adjustment reaction, clinicians do not need to be mental health providers. Addressing the issues raised above can go a long way in helping patients and family members adjust and cope with the above cited problems. Statements like "*you just suffered a loss of predictability in your life when you had the first seizure*" will help patients and family members become aware "at a conscious level" of the source of the conflicts they may be experiencing. In addition, patients and family members may be given the option of joining support groups, often available in local Epilepsy Foundation or other advocacy group chapters, or referred to an epilepsy nurse educator, if available.

Why should neurologists care? A persistent adjustment reaction to the diagnosis of epilepsy may transition into a chronic type of anxiety disorder known as Anticipatory Anxiety of Seizures, which can result in dysfunctional avoidant behaviors that significantly interfere with the patient's daily activities [8]. It may also lead patients to use denial as a coping mechanism and stopping the ASMs (see article by Hingray et al in this issue).

Interictal vs *peri*-ictal psychiatric episodes:

Psychiatric comorbidities are separated according to their temporal relation to seizure occurrence [9]. Interictal episodes are those that occur independently of seizures and are the most frequently recognized. Peri-ictal episodes are temporally related to seizures, either because they precede them (pre-ictal), or because they are the expression of the seizure (ictal) or follow them (postictal). Unfortunately, *peri*-ictal psychiatric episodes are more often than not unrecognized and / or misdiagnosed as interictal episodes, yet *peri*-ictal psychiatric episodes are managed primarily via seizure treatment/prevention, rather than mental health focused approaches typical for interictal psychiatric disorders. Thus, identifying *peri*-ictal psychiatric episodes by epilepsy clinicians and subsequent focus on seizure management to prevent these episodes are the key actions to manage *peri*-ictal psychiatric symptoms.

b) Interictal psychiatric comorbidities.

As stated above, one of every three PWE will experience a psychiatric comorbidity in the course of their life [1]. These psychiatric disorders often precede the onset of epilepsy and herald an increased risk of developing epilepsy. Indeed, epilepsy and most psychiatric comorbidities have a complex bidirectional relation, whereby patients with a primary psychiatric disorder (mood, anxiety, ADHD and psychotic disorders) have an increased risk of developing epilepsy, while epilepsy also increases the risk of developing these psychiatric disorders [10]. The bidirectional relation has been attributed to the existence of common pathogenic mechanisms operant in both disorders.

The prevalence of comorbid mood, anxiety, ADHD and psychotic interictal disorders is higher in PWE than in the general population. Among these, the following are common psychiatric comorbidities amenable to pharmacotherapy that can be prescribed by neurologists and are reviewed in great detail in the different articles of this issue:

(i) Mood disorders:
  - Major depressive episodes (MDE) and major depressive disorder (MDD).
  - Dysthymia
(ii) Anxiety disorders:
  - Generalized anxiety disorder (GAD)
  - Panic disorder (PD)
  - Anticipatory Anxiety of Seizures (AAS)
  - Separation Anxiety (in children)
(iii) ADHD
  - Predominantly inattentive subtype
  - Predominantly hyperactive / impulsive subtype
  - Combined presentation subtype
(iv) Psychotic Disorder
  - Interictal psychosis.

NOTE: While neurologists cannot be expected to treat psychotic disorders, they need to be able to initiate psychopharmacologic treatment and stabilize the psychotic episode under a mental health professional is available to take over the care of these patients.

The efficacy of psychotropic drugs in the treatment of comorbid psychiatric disorders has not been established in double-blind-placebo-controlled trials in PWE. Accordingly, their management follows the protocols follows in patients without epilepsy [11].

Screening for major depressive episodes, anxiety disorders and ADHD can be easily performed by neurologists in their outpatient office with the use of self-rating screening instruments, which take less than 5 min to complete. These instruments are reviewed in detail in the different articles dedicated to each of these comorbidities, and general principles focused on anxiety and depression are reviewed in the article by Conner et al. in this issue.

Contrary to frequent misconceptions, most psychotropic drugs used to treat these comorbidities are safe and do not cause seizures when prescribed at therapeutic doses. Thus, selective serotonin reuptake inhibitors like sertraline, citalopram and escitalopram or serotonin norepinephrine reuptake inhibitors such as venlafaxine and duloxetine are safe and effective in the management of major depressive episodes, dysthymia, GAD and panic disorder [12]. CNS stimulants like methylphenidate are not only safe and effective in the treatment of ADHD but appears to decrease the frequency of seizures in PWE and ADHD [13,14]. Finally, risperidone or aripiprazole are safe and effective options to stabilize a de-novo psychotic episode. The type of psychotropic drug appropriate for these psychiatric comorbidities are reviewed in detail in their respective articles in this issue.

c) Peri-Ictal Psychiatric Symptoms and Episodes.

Psychiatric symptoms of depression, anxiety, behavioral disturbance, and psychosis can be the expression of *peri*-ictal episodes. With

the exception of postictal psychotic episodes, their actual prevalence is yet to be established because of the lack of investigation in clinical practice and research studies.

- *Pre-ictal episodes* can be suspected when patients and /or family members report symptoms of mood lability, irritability, poor frustration tolerance and impulsive behavior up to 3 days before a seizure, with a worsening of their severity as they approach the time of the seizure [15]. These episodes are stereotypic within patients and while no treatment is available, the use of rescue medication could be potentially considered to prevent a seizure, but no data are available at this time on this strategy.
- *Ictal psychiatric episodes* are the expression of focal aware seizures presenting with symptoms of panic, depression, or euphoria as the most frequent ictal psychiatric symptoms (in that order), while ictal psychotic symptoms are relatively rare. Of note, ASMs may be more effective in yielding remission of focal to bilateral tonic-clonic seizures or focal unaware seizures than these focal aware seizures.
- *Ictal panic* should be suspected when sudden symptoms of panic / fear begin in the absence of any trigger in wakefulness or out of sleep with a short duration (less than 60 s), with other associated symptoms suggesting mesial temporal structure involvement (e.g., deja-vu, palpitations, epigastric discomfort, nausea, derealization) and stereotypic in their presentation. These episodes are very frequently misdiagnosed (and treated) as panic attacks, but a careful history can clearly distinguish the two, as interictal panic attacks are longer in duration (5 to 30 min), have an intense sensation of "impending doom" and are not stereotypic. Of note, patients with ictal fear have an increased risk of suffering from interictal panic disorder and anticipatory anxiety of seizures [8,16], and their accurate recognition is of the essence to provide the correct treatment.
- *Ictal depression* presents as stereotypic paroxysmal episodes of sadness, anhedonia, crying and suicidal ideation of short duration (30 s to 2 min) [17]. Interictal mood disorders may also occur in the same patients.
- *Postictal Psychiatric Symptoms and Episodes:*

Postictal psychiatric symptoms can be the expression of immediate or delayed postictal states. The psychiatric episode during the immediate postictal period occurs in the setting of a confusional state and consist of agitation and restlessness, which may be often triggered by attempts to restrain the patient who is trying to stand-up or walk or may occur spontaneously. Walking with the patient until the confusional state remits is sufficient to avoid further aggressive behavior. However, intranasal administration of benzodiazepines at the end of a seizure may mitigate the agitation in patients known to habitually experience spontaneous postictal agitation.

Symptoms / episodes of depression, anxiety, or psychosis typically occur during the delayed postictal period, which begins between 8 h and up to 7 days following a seizure (or cluster of seizures) [9]. Such symptoms can last between several hours to several days and rarely several weeks.

Postictal psychiatric symptoms or episodes typically occur in patients with chronic and treatment-resistant epilepsy. For example, Kanner et al., (2004) conducted a systematic investigated of the prevalence and type of postictal psychiatric symptoms among 100 consecutive PWE. Symptoms had to occur after > 50 % of seizures in the previous 3 months [9]. Forty-three patients endorsed postictal symptoms of depression (13 including suicidal ideation), 45 symptoms of anxiety and seven psychotic symptoms with a median duration of 24 h. Of note, some of these patients also experienced interictal psychiatric disorders (which may have been in remission with or without psychotropic medications). In fact, the use of antidepressants do not prevent the occurrence of postictal symptoms of depression and anxiety. On the other hand, low doses of antipsychotic drugs (aripiprazole, risperidone) or benzodiazepines may be effective for postictal psychotic symptomatology.

Postictal psychotic episodes have to be considered a psychiatric emergency as patients can often display suicidal and homicidal ideation and behavior or become very aggressive to others. Contrary to interictal psychotic episodes, neurologists must be able to treat postictal psychotic episodes and be familiar with the strategies to start immediate psychopharmacologic treatment that can often prevent their evolution to more severe episodes.

Why should neurologists care?

Untreated psychiatric comorbid disorders can affect the lives of PWE at several levels.

a) Impact on the epilepsy:
   - A history of mood disorder preceding the onset of epilepsy is associated with a higher risk of treatment-resistant epilepsy, which could result from a worse tolerance and adherence with ASMs and /or common neurobiological pathogenic mechanisms operant in both disorders.

b) Psychiatric and psychosocial implications:
   - PWE have an increased risk of premature death by suicide and accidents [18].
   - Psychiatric comorbidities contribute to a poor quality of life, often to a greater degree than the actual seizures [19–21].
   - Increase in the use of medical services and costs to the patient, family, and society [22].

d) Iatrogenic episodes:

Iatrogenic psychiatric symptoms are a very common cause of psychopathology in PWE. While any ASM can cause these adverse events, they are significantly more likely to occur when ASMs with negative psychotropic properties are prescribed in patients at risk for psychiatric comorbidities, which include PWE with a past or current psychiatric history and /or family psychiatric history, including mood, anxiety disorders, ADHD, psychosis, alcohol and drug abuse and personality disorders [23,24]. The ASMs with negative psychotropic properties that are often the cause of iatrogenic psychiatric symptoms include: levetiracetam, topiramate, zonisamide, perampanel, vigabatrin, phenobarbital, primidone and ethosuximide [25,26]. Among these ASMs, levetiracetam, which is the most frequently prescribed drug for epilepsy in North America and Europe today accounts for the highest frequency of psychiatric adverse events, which require its discontinuation in up to 25 % to 30 % of patients.

Iatrogenic psychopathology can also result from the discontinuation of ASMs that have mood stabilizing (carbamazepine, oxcarbazepine, valproic acid, lamotrigine), antidepressant (lamotrigine) and anxiolytic (gabapentin, pregabalin, benzodiazepines, valproic acid) properties in patients with a mood and /or anxiety disorder in which these ASMs had yielded a therapeutic effect [27].

In addition, iatrogenic psychopathology can be triggered by epilepsy surgery, including temporal lobectomy and /or laser ablation of mesial temporal structures, presenting as a major depressive and /or anxiety disorder beginning within the first three months and remit by 6 to 12 months after the surgical procedure, or after treatment with antidepressant medications. Suicidal ideation and attempts have been also reported. While these iatrogenic events can occur in any patient, it is those with a prior psychiatric history who are at greater risk. Post-surgical de-novo psychotic episodes have been reported in 3 % to 5 % of temporal lobectomies, while manic and /or hypomanic episodes can occur in the immediate post-surgical weeks.

These data clearly indicate that iatrogenic psychiatric adverse events can be prevented or at least minimized if clinicians take the time to investigate the PWE's past, current, and family psychiatric histories. Such data can guide the appropriate selection of the ASM that can yield a therapeutic effect for the seizure disorder and a comorbid psychiatric condition or at least prevent the recurrence of psychiatric comorbidities, by avoiding the use of ASMs with negative psychotropic properties or

taking care in the discontinuation of ASMs with positive psychotropic properties.

Prevention of post-surgical psychiatric complications can be achieved by the education of patients and family members in recognizing the psychiatric symptoms which can lead to an early introduction (or reintroduction) of the appropriate psychotropic drug, and potential attention to psychiatric stabilization preoperatively.

3. Conclusions

Psychiatric comorbidities are frequent in PWE and their treatment is essential to ensure a comprehensive management of the seizure disorder. Yet, psychiatric comorbidities remain untreated with serious consequences to their life at several levels. This special issue provides clinicians treating any PWE with pragmatic tools that can be applied in the recognition and management of common psychiatric comorbidities that neurologists can treat.

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: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization. **Heidi M. Munger Clary:** Writing – review & editing, Writing – original draft, Methodology, 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.

Dr. Heidi Munger Cleary Author Munger Clary received consulting fees for being a Topic Editor for DynaMed, contributing to educational materials for Prova Inc., and honoraria from the J. Kiffin Penry Epilepsy Programs. She receives research funding for studies related to anxiety and depression screener delivery in routine care and for research examining evidence-based integrated care delivery implementation from the NIH (R03TR004251), US Congressionally Directed Medical Research Programs (CDMRP) (W81XWH2210630), and the Duke Endowment that are ethics committee-approved and peer-reviewed to address any potential bias. She also receives research funding from the National Science Foundation for work related to mental health comorbidities in childhood absence epilepsy that is ethics committee-approved, and peer reviewed to address any potential bias. She has received research funding from the Susanne Marcus Collins Foundation for research related to anxiety, insomnia, and stress in a variety of samples not involving epilepsy and Eysz, Inc, for work unrelated to the present manuscript. Dr. Munger Clary received partial travel reimbursement from the International League Against Epilepsy to attend the International Epilepsy Conference in Dublin and received a Per Diem Speaker Payment to present on the topic of Managing Anxiety in Epilepsy.

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