Current Psychiatry Reports (2019) 21: 40
https://doi.org/10.1007/s11920-019-1029-9

ANXIETY DISORDERS (A PELISSOLO, SECTION EDITOR)

The Relationship Between Epilepsy and Anxiety Disorders

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Published online: 29 April 2019

Abstract

Purpose of Review The current review aims at providing an overview of relevant aspects of anxiety symptoms and anxiety disorders (AD) in adults patients with epilepsy (PWE).

Recent Findings Firstly, the appropriate diagnosis of type of anxiety symptoms and AD in PWE will be presented. Anxiety symptoms are often peri-ictal and classified in relation to their temporal occurrence to seizures. Anxiety symptoms are of three types: preictal (preceding a seizure), ictal (presenting as part of the seizure symptoms and signs), and postictal (occurring within 72 h of a seizure). AD are diagnosed in the interictal period and occur independently of seizures. Four specific AD in PWE can be objectified: anticipatory anxiety of epileptic seizures (AAS), seizure phobia, epileptic social phobia, and epileptic panic disorder. Secondly, the bidirectional pathophysiological relationship between anxiety and epilepsy will be described. Anxiety is a trigger for seizures in some patients, and the notion of stress and arousal is essential to understand the relationship between anxiety and seizure. Moreover, seizures arising from the limbic network especially involving amygdala, which may express fear-related semiology, provide insight into the pathophysiology of AD comorbidities. Thirdly, the methods of screening for AD and anxiety symptoms will be detailed. Fourthly, the pharmacological and psychobehavioral management of anxiety symptoms and AD in PWE will be presented. Arousal-based approaches for preictal and ictal symptoms and anxiety-based approaches for postictal and interictal symptoms will be presented.

Summary Despite lack of evidence-based approaches, it is recognized that management of epilepsy is not only about controlling seizures, but also depends heavily on detecting, correctly diagnosing, and appropriately managing anxiety symptoms and AD comorbidities, in order to maximize quality of life. Improving self-control and self-efficacy is of fundamental importance in the management of PWE. Further rigorously designed studies focusing on anxiety symptoms and AD are essential to improve the overall care of PWE.

Keywords Epilepsy · Anxiety · Psychiatric comorbidity · Psychiatric symptoms · Seizure control · Perceived self-control · Quality of life

This article is part of the Topical Collection on *Anxiety Disorders*

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Introduction

Psychiatric comorbidities are 2 to 3 times more frequent in patients with epilepsy (PWE) than the general population [1]. Despite increasing recognition of psychiatric comorbidity in epilepsy, most research has focused on depressive or psychotic disorders. Anxiety symptoms and disorders (AD) have been described as the "forgotten" psychiatric comorbidity in PWE [2]. The importance of identifying and treating anxiety symptoms and AD comorbidities in PWE has been increasingly recognized in the literature, but in the clinical setting, anxiety remains under-recognized and under-treated [3]. This may be because AD are very heterogeneous compared with depressive disorder [4]; neurologists also seem more attuned to detecting and treating mood disorders than AD [5•].

AD have long been considered as the second most frequent psychiatric comorbidity after depressive disorder, but in fact in PWE are more prevalent than depressive disorder [5•, 6, 7,

8••]. In adult PWE, prevalence estimates for AD range from 11 to 50% [8••]. Use of varying tools, and varying definition of anxiety symptoms or AD, may explain discrepancies in incidence and prevalence [4, 8••]. Existing studies show heterogeneous methodology, in particular between studies using psychometric instruments evaluating severity of anxiety symptoms (using validated scales), and studies identifying presence or absence of a specific diagnostic condition (AD) using criterion-based structured interview. For simplification, it can be remembered that at least 28% of PWE present AD [5•, 6, 7]. Recent results suggest no difference in rates of AD for refractory versus well-controlled epilepsy [6]. Many outcomes are significantly impacted by anxiety symptoms or AD in epilepsy. In one study, anxiety symptomatology was the most significant predictor of reduced quality of life, explaining 27% of the variance compared with 12% for depression and 3% for seizure frequency [9]. Presence of anxiety symptoms in PWE is also associated with increased suicide risk [2], higher seizure frequency, and poorer seizure control outcome with antiepileptic drugs or after epilepsy surgery [10••]. Factors most consistently associated with anxiety symptoms and AD include female gender, depression, and unemployment. Data on relationship between anxiety and epilepsy localization, lateralization, and type have been contradictory [3, 5•]. Importantly, anxiety does not only result from the direct impact of epilepsy on psychosocial well-being, but may also precede onset of epilepsy; in one study, incidence was significantly increased in 3 years before epilepsy onset and the first 2 years after epilepsy onset [11].

The current review aims at providing an overview of relevant aspects of anxiety symptoms and AD in epilepsy. Firstly, the appropriate diagnosis of type of anxiety symptoms and AD in PWE will be presented. Secondly, the bidirectional pathophysiological relationship between anxiety and epilepsy will be described. Thirdly, the methods of screening will be detailed. Fourthly, the pharmacological and psychobehavioral management of anxiety symptoms and AD in PWE will be presented.

Clinical Aspects of Anxiety Symptoms and Disorders in Epilepsy

In PWE, psychiatric symptoms and disorders are classified as peri-ictal or interictal, in relation to their temporal occurrence to seizures. Peri-ictal anxiety symptoms are of three types: preictal (preceding a seizure), ictal (presenting as part of the seizure symptoms and signs), and postictal (occurring within 72 h of a seizure). Interictal anxiety symptoms occur independently of seizures, and AD can be present during this period. Iatrogenic anxiety disorders may also exist in PWE, due to pharmacologic effects and/or surgical treatment. All types of symptoms can co-occur in the same individual [3] (Table 1 and Figs. 1 and 2).

Peri-ictal Anxiety Symptoms

Preictal

Preictal anxiety symptoms can occur a few hours or days before a seizure; indeed, some patients or their relatives can predict impending seizure occurrence by this characteristic emotional disturbance [12]. It is also described that hyperventilation in the context of anxiety occurring during panic attacks or psychogenic non-epileptic seizures can trigger an epileptic seizure. It may be difficult to distinguish anxiety directly linked to changes in preictal symptoms, from that occurring in the context of a stressful event that could also act as a seizure trigger.

Table 1 Types of anxiety symptoms and disorders in patients with epilepsy

Ictal period	Categories	Anxiety symptoms or disorders
Peri-ictal	Preictal Anxiety occurring 1 to 3 days before a seizure	
	Ictal Anxiety that is part of seizure semiology	Ictal fear Subjective anxious experience of seizure
	Postictal Anxiety starting or worsening within 3 days after the seizure	
Interictal	Classical anxiety disorders Meeting the criteria Classification of DSM-5	Generalized anxiety disorder (GAD) Obsessive–compulsive disorder Panic disorder Agoraphobia Social phobia
	Specific anxiety disorder to epilepsy	Anticipatory seizure anxiety Seizure phobia Epileptic social phobia Epileptic panic disorder
Iatrogenic	Addition of an AED with negative anxiety properties	Lamotrigine Levetiracetam Perampanel Topiramate Zonisamide
	Withdrawal of an AED with anxiolytic properties	Pregabalin Benzodiazepines Gabapentin Valproic acid
	Reduced levels of ongoing psychotropic drugs caused by the addition of an enzyme-inducing AED	Addition of phenytoin, carbamazepine, phenobarbital to existing SSRI
	Postsurgical	All anxiety disorders possible Intermittent increasing anxiety

AED, antiepileptic drug; *DSM-5*, Diagnostic and Statistical Manual-5

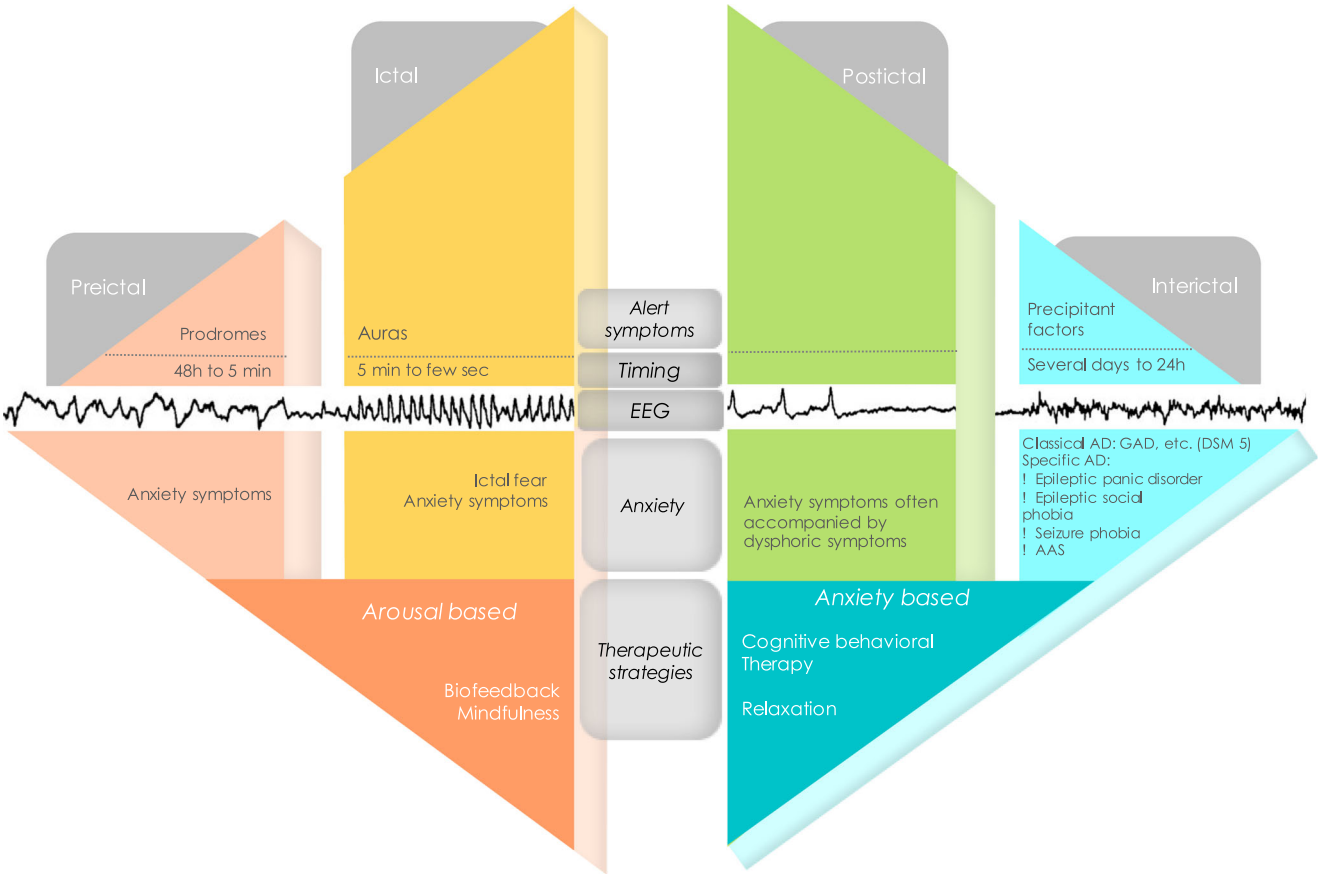

Fig. 1 The relationship between anxiety and epilepsy

Ictal

Anxiety symptoms during the ictal period may be referred to as "ictal panic" and may be difficult to distinguish from a classic panic attack. Diagnostic errors may readily occur: it is not infrequent for simple partial seizures of mesial temporal lobe origin presenting as panic or anxiety episodes to be untreated until the patient develops a secondarily generalized tonic-clonic seizure [13]. Ictal panic or fear constitutes the most frequent type of simple partial seizures, presenting primarily with psychiatric symptoms and corresponding to 60% of all psychiatric auras [13]. As will be further discussed in the

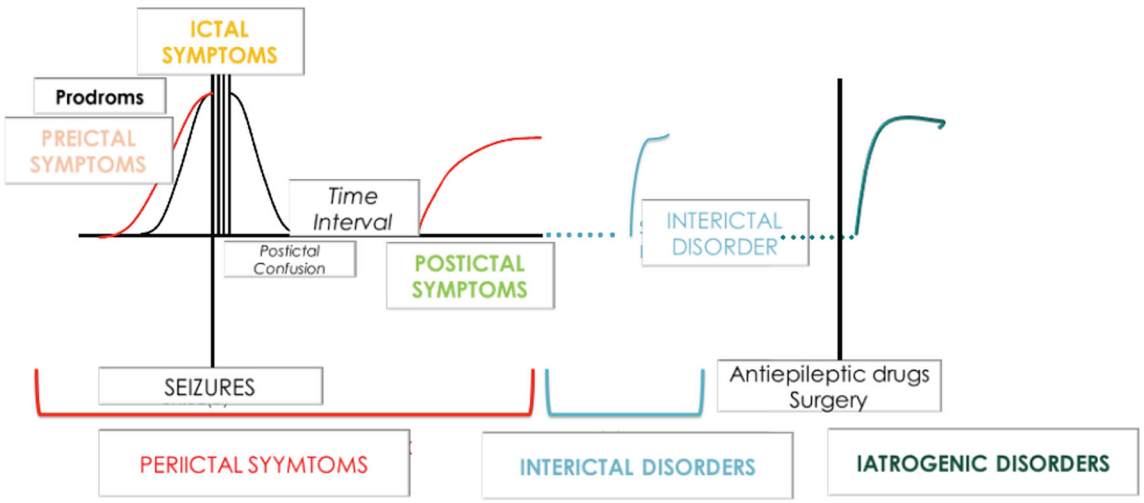

Fig. 2 View of classification of psychiatric symptoms and disorders in epilepsy

subsequent section on pathophysiology of anxiety, focal seizures without impairment of awareness, of limbic origin, may present as isolated fear or panic. More commonly, other features of temporal lobe seizures are also present, such as déjà vu, epigastric rising sensation, or olfactory hallucinations. If ictal (i.e., if directly caused by epileptic discharge within limbic structures), the anxiety will occur in a paroxysmal, stereotyped manner lasting for seconds to minutes, and may evolve to a focal seizure with impaired awareness [4]. Features most consistent with panic attack are described in Table 1.

Beside this specific ictal fear directly caused by epileptic discharge, 40% patients with drug-resistant focal epilepsy present other anxiety symptoms, which may be poorly characterized: the subjective anxious experience related to having a seizure. This separate entity incorporates a feeling of imminent death, fear of doing something incongruous while in an altered state due to the seizure, fear of being in danger, and fear of what other people may think during an actual seizure [13]. These can be justified fears in most cases, appropriate to the actual risk of seizure-related problems for many PWE.

Postictal

Anxiety symptoms are the most frequent emotional symptoms during the postictal period (defined as the 72 h following a seizure or cluster of seizures) [14]. These typically occur within 6–24 h after seizure offset. Postictal anxiety can manifest as anxiety, panic, agoraphobia, or compulsive symptoms and is often accompanied by other dysphoric symptoms such as depression [15, 16]. For example, 39% of patients reported postictal symptoms of agoraphobia [14].

Interictal Anxiety Disorder

Classical Anxiety Disorder

All classical AD may occur in PWE. However, even if AD respond to classic criteria of mental disorder classification (e.g., Diagnostic and Statistical Manual of mental disorders—DSM-5), PWE may display unique characteristics when compared with the general population. Generalized anxiety disorder (GAD) is frequent but the anxious thoughts and worries are often centered on the epilepsy and its consequences. The risk of presenting agoraphobia disorder with or without panic disorder is more frequent in PWE compared with the general population [6], argued to be a result of avoidance due to fear of having seizures and/or accidents outside the home. Interictal dysphoric disorder (Blumer syndrome), defined as the association of affective and anxious dimensions, is considered as a mood disorder, and as such will not be discussed here; for review [17, 18].

Specific Interictal Anxiety Disorder in PWE

We will focus here on specific AD not described in classical psychiatric classifications, which are. They are also insufficiently described by the International League Against Epilepsy (ILAE) classification [19], and thus we will propose here a new classification of specific interictal AD in PWE. In our opinion, these syndromes exhibit sufficiently specific features to be considered different from AD as described in classical psychiatric classifications. Correct diagnosis of these seems to us essential to optimize management and maximize quality of life. The ILAE recognizes fear of seizures, social phobia, agoraphobia, and behavior avoidance linked to the fear [19]. We propose distinguishing between (Table 2):

i. Anticipatory anxiety of epileptic seizures (AAS): anticipatory and excessive fear of having a seizure. In a recent study [20•], it was shown that AAS occurs in 53% of subjects with drug-resistant focal epilepsy, with no link between AAS and the localization or severity of seizures but an association with shorter epilepsy duration. Patients with AAS had significantly poorer quality of life compared with patients without AAS.
ii. Seizure phobia: excessive fears about seizures. This fear is associated with intense cognition and avoidance behavior concerning specific circumstances, places, or situations where seizures have already occurred or where they might occur (e.g., lack of sleep, missed dose of antiepileptic drug) that may interfere with normal life (e.g., obsessive attention to sleep quality and timing of drug doses). Seizure phobia and AAS can be considered as closed entities and can overlap. AAS can be diagnosed without seizure phobia. However, seizure phobia is classically associated with AAS. Further studies are thus needed to determine if the distinction between these two entities is clinically accurate or perhaps represents a continuum of the same phenomenon.
iii. Epileptic social phobia: excessive fear of being seen by others specifically during a seizure that interferes with normal life.
iv. Epileptic panic disorder: a specific panic disorder associated with agoraphobia. Classically, a diagnosis of panic disorder is based on the experience of recurrent, unexpected panic attacks, in which at least 1 attack is followed by a 1-month period during which the individual worries about having additional attacks, and/or changes behavior in a maladaptive way (e.g., avoiding situations that may provoke panic feelings). Many patients with drug-resistant focal epilepsy who have strong anticipatory seizure anxiety may develop recurring paroxysmal anxiety, who interpret anxiety symptoms as being like the beginning of a seizure. While these are mostly actual panic attacks, distinction

Table 2 Proposition of reliable question to diagnose specific anxiety disorder in patients with epilepsy

Specific interictal anxiety disorder	Suggested questions for diagnostic enquiry	Suggested evaluation of symptom severity
Anticipatory seizure anxiety	Are you afraid of having an epileptic seizure? Are you constantly worried about the possibility of having a seizure? Do you feel persistently preoccupied or concerned about your seizures and their possible consequences?	How would you rate this worry or fear of having a seizure on a scale of 0–10, 10 being the maximum level of worry or fear? Do you think that this fear, anxiety causes significant distress or impairment in your social, work, and/or family life, and/or that it reduces your quality of life?
Seizure phobia	When you think about your seizures do you feel terrified? Do you tend to avoid going to places where you have previously had an epileptic seizure? Are you extremely strict in avoiding anything that might increase the risk of a seizure? (For example, are you able to sometimes take your anti-seizure medication 15 min later than usual, have 1–2 h less sleep than usual, or to drink a small amount of alcohol?)	How would you rate your attempts to avoid having a seizure on a scale of 0–10, 10 being the maximum level of avoidance? Do you think that this need for avoidance causes significant distress or impairment in your social, work, and/or family life, or that it reduces your quality of life?
Epileptic social phobia	Do you find it frightening to imagine having a seizure in front of other people, especially strangers? Are you constantly worried about what other people would think about you if you had a seizure? Do you think that people who see your seizure would be likely to have a negative, judgmental opinion of you? Would having a seizure in front of other people feel humiliating or embarrassing? Do you tend to avoid situations in which other people might see you having a seizure?	How would you rate this fear of other people's view of your seizure on a scale of 0–10, 10 being the maximum level of fear? How would you rate this fear of other people's view of your seizure on a scale of 0–10 if the person watching was as follows: 1. a stranger 2. someone you know slightly 3. someone close to you? Do you think that this fear of other people's view of your seizures causes significant distress or impairment in your social, work, and/or family life, or that it reduces your quality of life?
Epileptic panic disorder	Do you sometimes have sudden (which interrupt your activity) overwhelming anxiety or panic attacks, with symptoms such as the following? 1. Palpitations or accelerated heart rate 2. Sweating 3. Trembling or shaking 4. Sensations of shortness of breath or smothering 5. Feelings of choking or of a tight ball in your throat 6. Chest pain or discomfort 7. Nausea or abdominal discomfort, rising sensation in your stomach 8. Feeling dizzy, unsteady, light-headed, or faint 9. Chills or hot flushes 10. Numbness or tingling sensations 11. Derealization (feelings of unreality) or depersonalization (being detached from oneself). 12. Fear of losing control 13. Fear of dying Do you think that these symptoms represent a seizure or a panic attack? Is it sometimes difficult for you and/or your family and/or your doctor to distinguish between your anxiety/panic attacks and your epileptic seizures? Do you have persistent concern or worry about these kinds of attack or their consequences? Are you worried on a daily basis about having seizures and/or panic attacks?	How often do you have panic attacks? How would you rate your fear about of having a seizure or a panic attack on a scale of 0–10, 10 being the maximum level of fear? Do you think that this fear of other people's view of your seizures causes significant distress or impairment in your social, work, and/or family life, or that it reduces your quality of life?
Avoidance behavior	Agoraphobic criteria: Because of your epilepsy and the risk of having a seizure, do you tend to avoid any of the following situations? 1. Using public transportation (e.g., buses, metros, buses, trains, ships, planes). 2. Being in open spaces (e.g., parking lots, shopping centers, bridges). 3. Being in enclosed places (e.g., shops, theaters, cinemas). 4. Standing in line or being in a crowd.	Do you think that avoidance of certain situations causes significant distress or impairment in your social, work, and/or family life, or that it reduces your quality of life? NB without taking into account situations that have been specifically forbidden by your doctor, such as driving or high-risk sports

Table 2 (continued)

Specific interictal anxiety disorder	Suggested questions for diagnostic enquiry	Suggested evaluation of symptom severity
	5. Being outside of the home alone. Can you manage to cope with these types of situations if someone else is with you? Other avoidance criteria: Do you avoid certain household or personal activities because of the risk of having a seizure? For example, having a shower or a bath, cooking, ironing? Do you tend to avoid taking the stairs, or remaining in a standing position, because of the risk of falling during a seizure? If yes, which?	

between panic attack and focal seizure is not easy, especially in temporal epilepsy Table 3**.** Not only the patient but also caregivers and doctors may have difficulty distinguishing these episodes. Patients show anxious anticipation of both the epileptic seizure and panic attack. This mixed anticipatory anxiety is associated with agoraphobia, resulting in a very disabling combination.

All these interictal AD can lead to avoidance behavior that can interfere with life.

Note that posttraumatic stress disorder (PTSD) can be associated with epilepsy. Indeed, some patients with epilepsy can experience their seizures as traumatic, either physically (e.g., injuries, accidents) and/or psychologically (e.g., fear of dying or of serious injury). Thus, the occurrence of postepileptic seizures PTSD has been described [21]. This particularly interesting dimension is the subject of a current research. Further studies are also needed concerning the relationship of seizure phobia with this traumatic dimension. However, PTSD is not in the anxiety disorders section of the DSM-5, but in the trauma- and stressor-related disorders, and as such will not be discussed in detail here; for review [21].

Iatrogenic Disorders

Pharmacological Anxiety Symptoms

Iatrogenic symptoms of anxiety related to pharmacologic treatment may include the following:

i. Addition of AED with potential negative psychotropic properties (barbiturates, felbamate, levetiracetam, topiramate, zonisamide, vigabatrin, clobazam, and perampanel);
ii. Withdrawal of AED with mood-stabilizing effects (carbamazepine, oxcarbazepine, valproic acid, and lamotrigine) or anxiolytic properties (benzodiazepines, gabapentin, pregabalin, valproic acid);
iii. Reduced levels of current anxiolytic drugs caused by addition of enzyme-inducing AED (e.g., addition of phenytoin, carbamazepine, phenobarbital, primidone, rufinamide to ongoing fluoxetine treatment).

Particular caution must be exercised with certain commonly prescribed AED that may produce or exacerbate anxiety, e.g., levetiracetam, perampanel, and lamotrigine.

Postsurgical Anxiety Disorders

Following cerebral surgery for intractable epilepsy, de novo or worsening AD may occur. There may at least a transient increase in anxiety postoperatively [22]. Patients with previous anxiety and mood disorders are more susceptible to postoperative anxiety. In patients with temporal epilepsy, preoperative fear auras showed greater risk of postsurgical anxiety disorders despite seizure freedom [22]. An association between left temporal lobe resection and the development of de novo postoperative anxiety is possible. There is conflicting evidence as to whether postoperative anxiety is influenced by seizure outcome [23].

Pathophysiological Aspects

Anxiety, Stress, Arousal, and Epilepsy

There is a complex relation between epilepsy, seizures, and anxiety [16], and it is helpful to consider this in terms of timescale. The medical disorder of epilepsy should be considered over a long time-scale (months-years-decades), with regard to the pathophysiological changes leading up to onset of the condition ("epileptogenesis"), and long-term fluctuations and consequences of the disorder (e.g., periods of seizure worsening, associated features such as psychiatric comorbidity and cognitive impairment). On the other hand, seizures,

Table 3 Differential diagnosis of panic attacks versus focal epileptic seizure

	Ictal fear	Panic attack
Duration	0, 5–2 min	5–15 min
Consciousness	No initial impairment but may progress to impaired	No impairment
Anticipatory anxiety	Can occur	Very frequent
Agoraphobia	Can occur	Frequent
Déjà vu, hallucinations	> 5%	Very rare
Automatisms	Common with progression to complex partial seizures	Very infrequent
Salivation	Increased	Decreased
Occurrence	Diurnal/nights	Almost diurnal
Ictal EEG	Usually abnormal	Normal
Interictal EEG	Often abnormal	Normal
MRI of mesial temporal structures	May be abnormal	Usually normal
Antidepressant treatment	Not efficacious	Usually efficacious
Anti-epileptic drug	Usually efficacious	Rarely efficacious

which are the principal symptoms of epilepsy, should be considered over a shorter time-scale (seconds, minutes, hours), with regard to the clinical expression of the seizure and also factors that may trigger seizures.

Epileptogenesis can arise from diverse causes but tends to be multifactorial, and anxiety may play an important role in some [24]. This involves both individual background factors (e.g., exposure to early life stress) and environmental factors (e.g., acute exposure to a stressful event), in keeping with the allostatic load model [25], which has been particularly characterized through animal studies. Clinically, it has been noted that onset of epilepsy may be triggered by a stressful life event [26], and such observations reinforce the notion of close and likely bidirectional relations between epilepsy, stress, anxiety symptoms, and AD [2].

As well as this bidirectional link between AD and epilepsy, anxiety symptoms have a similar bidirectional link to epileptic seizures: the seizure may trigger anxiety symptoms, while conversely, anxiety may trigger a seizure. Anxiety sensitivity (risk of seizures being triggered by stressful events) has been observed in temporal lobe epilepsy (TLE) and is associated with abnormal emotional processing with bias towards negatively valenced emotion [27]. Thus, anxiety and epilepsy are linked across multiple time-scales, at both etiopathological (epileptogenesis) and symptomatic (seizure) levels.

Anxiety as a trigger of seizures is related to the notion of stress and arousal. Studies measuring electrodermal responses can contribute interesting data in this respect. Electrodermal response reflects the action of sympathetic autonomic nerves on eccrine sweat glands and is a sensitive indicator of involuntary and voluntary induced changes in arousal, associated with emotion, attention, and physical activity [28]. Electrodermal response can be increased not only by stress, but also by arousal, for example preparation of intellectual activity [29]. Electrodermal response is related to the amplitude of the contingent negative variation (an event-related potential considered to relate to a slow cortical potential (SCP)), an index of cortical excitation. CNV is increased during states of reduced sympathetic activity measured peripherally with electrodermal response, i.e., electrodermal activity is inversely related to cortical excitation as measures by CNV [30]. In the immediate preictal period, CNV can reflect diminution of arousal associated with increased cortical excitation [31]. It could therefore be hypothesized that seizure onset may be associated with reduction of arousal [32]. This is indeed the basis for neurofeedback targeting SCP and for skin conductance biofeedback as adjunctive treatment for epilepsy, which aims to increase arousal [33]. It is known that the thalamus plays an important role in generation of the CNV [34] and that different cortical regions (i.e., orbitofrontal and prefrontal cortex, anterior cingulate cortex, right insula, and right parietal cortex) which have direct projections in the thalamus are involved in regulation of electrodermal response [35]. However, further studies are warranted to better understand the relationship between stress as a seizure trigger, arousal, and seizure onset.

Epilepsy Networks as a Model for Investigating the Pathophysiological Basis of Anxiety

Epilepsy is considered to be a network disease [36] and may arise from any cortical area. Limbic structures, including amygdala, hippocampus, insula, and prefrontal cortex, are among the most commonly involved regions in focal epilepsies. Temporal lobe epilepsies in particular appear to have a stronger association with anxiety symptoms and AD than other focal epilepsies [5•]. Neurophysiological data, including intracerebral EEG, as well as other neurophysiological methods (magnetoencephalography) and structural and functional neuroimaging (e.g., magnetic

resonance imaging, positron emission tomography) in subjects presenting both epilepsy and anxiety symptoms or AD represent an interesting means of investigating pathophysiological substrates of these psychiatric comorbidities. It has been shown for example that direct electrical stimulation of amygdala (both right and left) during stereoelectroencephalography (SEEG) recording of patients undergoing presurgical evaluation for pharmacoresistant epilepsy can induce emotional responses including anxiety and fear, associated with altered electrodermal response [37].

Moreover, ictal anxiety and fear (that is, epileptic seizures manifesting as feelings and/or behavioral expression of fear and often challenging to distinguish from panic attacks, as described earlier in this chapter) have been very clearly linked to epileptic electrical activity in temporal or fronto-temporal limbic networks [38•], including data from intracerebral SEEG studies showing abnormal synchronization between limbic structures at the onset of ictal fearful behavior [39].

This close relation with limbic network alterations, especially involving amygdala, seems particularly relevant when thinking about the pathophysiology of interictal AD comorbidities in epilepsy. Studies of prefrontal epilepsy have shown association between interictal psychiatric disturbance (antisocial behavior) and subclinical epileptic activity within ventromedial prefrontal networks, with improvement of interictal psychiatric profile following successful epilepsy surgery [40]. To date, no equivalent data have implicated low-grade interictal epileptic activity (for example, within amygdala or connected limbic structures) in the pathogenesis of interictal anxiety, but this represents an interesting possibility for future investigation. Recent studies of resting state connectivity in patients with focal epilepsies, based on both SEEG [41] and MRI [42] studies, converge to show network changes that reach beyond the epileptogenic zone of initial seizure organization. In particular, a common feature across focal epilepsies of various localizations is abnormality of salience network connectivity [42], which may be of relevance in terms of understanding the bias towards negatively valenced stimuli in some patients with anxiety states. While recognizing the potential pitfalls of resting state data [43], this observation provides an interesting avenue for further pathophysiological studies of AD in the context of epilepsy, since future work could help refine epilepsy phenotypes (i.e., those with and without associated specific anxiety disorders) and correlate MRI findings with clinical, PET, and SEEG data in a multi-modal approach [37], with both scientific and clinical implications.

Screening for Anxiety in Patients with Epilepsy

Anxiety Disorder Screening

The most commonly used screening instrument is the Generalized Anxiety Disorder 7 (GAD-7), validated to detect GAD in PWE [44•]. This is a reliable, practicable screening instrument based on a self-reported questionnaire similar to the NDDI-E (the Neurological Disorders Depression Inventory for Epilepsy validated for screening for depression in PWE) [45]. The GAD-7 is particularly well suited as a screening tool in PWE since it contains no somatic items that might be confused with symptoms related to epilepsy or AED and provides complementary information to the NDDI-E [44•]. It is a shorter questionnaire than classical self-reported screening questionnaires for GAD, which helps to optimize its use. It has been translated into and validated in Korean, Chinese, Spanish, and French [45, 46]; translation and validation in other languages have been promoted by the ILAE in order to make the GAD-7 a worldwide instrument similar to the NDDI-E [44•]. While the GAD-7 presents high acceptability, cognitive deficits and/or a language barrier in some PWE can make even relatively short questionnaires challenging to complete, for which reasons an ultra-short version was recently validated in PWE [47].

No specific screening instrument yet exists for peri-ictal anxiety symptoms (preictal, ictal, and postictal), specific interictal disorders (anticipatory seizure anxiety, seizure phobia, epileptic social phobia, epileptic panic disorder) or iatrogenic AD. We propose in Table 2 a list of questions that can help diagnose interictal AD.

Screening for Anxiety Symptoms

Some other psychometric tools can help evaluate anxiety symptoms and patients' spontaneous control strategies and can be used before and after psychobehavioral management to assess therapeutic impact. Tools such as the Social Readjustment Rating Scale (SRRS) (which evaluates stressful events) or the Perceived Stress Scale (PSS) (which evaluates stress and anxiety perception) can assess the impact of anxiety on the epilepsy and quality of life. Evaluation of perceived self-control over the epilepsy and anxiety through the Self-Control Schedule (SCS) or the Multidimensional Health Locus of Control Scale (MHLCS) may point to methods that could increase the sense of control. Scales investigating coping strategies, such as Emotion Regulation Profile-Revised (ERP-R) or the dispositional Resilience Scale–15 (DSR-15), highlight spontaneous adjustment strategies and strengths of the person, which can direct psychobehavioral management. For a review see [48]:.

Management of Anxiety in Patients with Epilepsy

Pharmacological Management

AD (in particular GAD) must be appropriately treated in PWE as for patients without epilepsy, with the caveat that medications should be chosen with a view to avoiding adverse effects on seizure control or drug interactions with existing therapy; for example, selective serotonin reuptake inhibitors (SSRI) are

preferred over tricyclic antidepressants. For review, see [49••]:. The use of SSRI or NDRI can be recommended in PWE. Hyponatremia should be carefully screened for. Lowering of seizure threshold is clearly recognized for tricyclic antidepressants, as well as clomipramine, maprotiline, amoxapine, and bupropion, which should be avoided.

Psychobehavioral Management

Anxiety symptoms and AD should be appropriately managed according to their temporal relation to seizures, especially for certain disorders such as seizure-specific phobia. Anticipation is possible for patients who identify alert symptoms (auras, prodromes, and triggering factors) [50•]. Despite low predictive value, patients can use these symptoms to anticipate seizures and develop preventive or control strategies [51].

- Preventive strategies consist of preparing for immediate consequences of the seizure (sitting or lying down, alerting someone).
- Control strategies may concern seizure prevention by adopting a healthy lifestyle (e.g., stress management, sleep patterns), or control of the seizure when it occurs.

This latter type of strategy, according to patients' reports, typically consists of intensely focusing attention on something else, of relaxing, thinking positively, or adopting a neutral emotional state [50•, 51]. Some patients also use breathing techniques. The ability to voluntarily control seizures is linked to the concept of perceived self-control (PSC)—the belief that one's own capacities and actions can influence one's environment, situation, or a desired result [52]. This is constructed from the concepts of self-efficacy (the perception of the subject's own capacities to perform an action or achieve a goal [53]) and locus of control (LOC), an a priori assessment of what determines the success or failure of an action based on self (internal LOC) or external factors (external LOC). In epilepsy, high internal LOC is associated with greater perceived self-control over seizures and better-controlled seizures [54], whereas patients whose LOC is external tend to have poorer seizure control [55]. PWE with high perceived self-control [54] and internal LOC [56] are less subject to anxiety. The main objective of psychobehavioral interventions is to restore a sense of control over seizures [57]. Considering the variety of anxious symptoms depending on peri-ictal period, psychobehavioral management must be adapted to the appropriate time window.

Preictal and Ictal Periods: Arousal-Based Approaches

Among alert symptoms, auras represent seizure onset (ictal), may be related to objective EEG abnormalities and help signal seizure onset. They may be experienced by 45–65% of people with focal epilepsy [58] and are characterized by symptoms that are specific to the individual, including neurocognitive changes (déjà vu), emotional changes (anxiety, fear), sensory changes (somatosensory, olfactory, gustatory, auditory, or visual), or viscero-autonomic features (e.g., epigastric sensation, thoracic oppression, and tachycardia), depending on the type of epileptic discharge and the anatomical localization of seizure onset. Prodromes on the other hand are preictal, unaccompanied by objective EEG changes [59] and are recognized by between 6.9 and 39% of PWE [60–62]. These are heterogeneous between patients and are characterized by diverse clinical features including behavioral changes, cognitive disorders, mood changes, fatigue, sleep disorders, headaches, gastrointestinal symptoms, changes in appetite, and altered voice [61, 62]. Therapeutic approaches targeting preictal and ictal periods are mainly of relevance to patients experiencing these alert symptoms, since they can identify when to apply control strategies they have learned during (interictal) training sessions.

Psychobehavioral management, such as aura interruption and systematic desensitization, focuses on seizure control in preictal and ictal periods. They are based on operant conditioning, which can be traced back to 1970s, relying on the principle of reward/punishment in response to absence/occurrence of seizures [63] and are mainly based on shifting attention when alert symptoms are recognized [64]; however, efficacy is not well established [65]. Derived from operant conditioning approaches using positive physiologic reinforcement, neurofeedback and biofeedback methods are non-invasive bio-behavioral technique providing control strategies to regulate physiological activity, aimed at reducing acute anxiety and/or seizures. Applied to epilepsy, neurofeedback targeting SCP [33] and skin conductance (SC) biofeedback have shown clinical value in reduction of seizures and psychiatric comorbidity [66, 67]. Neurophysiological mechanisms are unknown. Available data indicate lack of change in electrodermal responses to emotions after biofeedback sessions [66], as well as lack of correlation between anxiety symptoms and functional connectivity of the brain regions involved in SC activity (i.e., right amygdala and cortex orbito-frontal and frontal pole) [68]. It has been suggested that improvement in anxiety symptoms could be related to suppression of attentional biases towards threat [69], a cognitive mechanism known to be involved in the onset and maintenance of anxiety disorders [70]. This could potentially be related to changes in salience networks as suggested above. We hypothesize that biofeedback, which requires development of personal strategies, could increase perceived self-control and control, which could contribute to reduced depressive and anxiety symptoms in PWE.

Another interesting approach to target anxiety disorders in preictal and ictal periods is mindfulness [71]. Theoretically, meditative practices could enhance neuronal hypersynchrony and thus represent potential risk of triggering epileptic seizures

[72]. However, this risk remains poorly characterized and clinical evidence suggests the opposite [73–75]. A recent study showed improved self-efficacy and mastery (a concept close to perceived self-control) after mindfulness-based treatment [76••]: after 6 months, patients reported better control over their lives despite the fact that they were more aware of their disease, since awareness served as an empowering incentive towards self-care. In addition, patients realized that this could only be achieved through personal work and not through medication or even the advice of a clinician. These results show the relevance of therapeutic approaches in improving perceived control in patients. A word of caution here: some patients are not capable, for different reasons, of implementing such strategies, or may implement them without clinical improvement; they should not be made to feel that they have "failed" in any way.

Postictal and Interictal: Anxiety-Based Approaches

Subjective identification of at least one potential triggering factor affecting the likelihood of seizure onset has been reported by 60 to 70% of patients [77, 78], anxiety, stress [79], and stressful events [80]are being the most frequent. Moreover, patients who reported seizure precipitants tended to have higher levels of anxiety [81]. This anxiety added disability to their condition: the fear of seizure can be worse than seizures themselves. A simple diagnostic question like: "Are you afraid of having an epileptic seizure?" could lead to changing the treatment and the quality of life of patients with epilepsy, highlighting the importance of early intervention and preventive approaches after screening for AAS. Moreover, high anxiety could act as a precipitant factor through alterations related to the impact of stress hormones on neuronal excitability and thus seizure susceptibility [82].

In the interictal period, it is appropriate to manage triggering factors of seizures and also interictal AD: GAD and other classical AD, but also specific AD in PWE, notably anticipatory seizure anxiety, seizure phobia, epileptic social phobia, and epileptic panic disorder as mentioned above (Table 1**)**. In particular, AAS should be actively treated in the same way as other anxiety disorders, with selective serotonin reuptake inhibitors (SSRIs) and certain antiepileptic drugs with anxiolytic properties (such as pregabalin), combined with cognitive behavioral therapy (CBT). The goal is to intervene upstream to reduce the risk of seizure occurrence and also to act on the associated AD comorbidities. Studies have investigated CBT programs especially designed for the management of epilepsy in individual [83] or group [84–86] sessions. However, their efficacy in PWE is debatable [87]. Relaxation methods have not yet been studied in detail, but may help reduce seizure frequency [88–90], probably through effects on stress reduction [91].

Summary and Conclusion

Anxiety symptoms and anxiety disorders are very frequent comorbidities in PWE that impact strongly upon epileptic and functional outcomes. Peri-ictal anxiety symptoms may be preictal (i.e., preceding a seizure, which can serve as alert symptoms for PWE), ictal (called "ictal panic" that should be differentiated from classical panic attacks), or postictal (frequently accompanied with dysphoric symptoms). Interictal AD correspond to classical AD psychiatric disorders such as GAD, but also specific AD in PWE that are not classified in current psychiatric nosography. These specific interictal AD are as follows: anticipatory seizure anxiety, seizure phobia, epileptic social phobia, and epileptic panic disorder. GAD can be usefully screened for with a validated questionnaire, the GAD-7. However, detecting peri-ictal anxiety symptoms and specific AD in PWE is rendered more difficult by current lack of validated screening tools. These are needed to further investigate bidirectional relationships between anxiety symptoms, AD, and epilepsy. Better psychopathological understanding will be crucial for the development of psychobehavioral treatments. Indeed, despite lack of evidence-based approaches, it is recognized that management of epilepsy is not only about controlling seizures, but also depends heavily on detecting, correctly diagnosing, and appropriately managing any psychiatric comorbidities, in order to maximize quality of life. Improving self-control and self-efficacy is of main importance in the management of epilepsy and despite limited evidence, the psychobehavioral approaches presented above are recommended. Further rigorously designed studies focusing on anxiety symptoms and AD are essential to improve the overall care of PWE.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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