

Review

Anxiety in patients with epilepsy: Systematic review and suggestions for clinical management

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Abstract

Up to 50 or 60% of patients with chronic epilepsy have various mood disorders including depression and anxiety. Whereas the relationship between epilepsy and depression has received much attention, less is known about anxiety disorders. It is now recognized that anxiety can have a profound influence on the quality of life of patients with epilepsy. The relationship between anxiety disorders and epilepsy is complex. It is necessary to distinguish between different manifestations of anxiety disorder: ictal, postictal, and interictal anxiety. Preexisting vulnerability factors, neurobiological factors, iatrogenic influences (antiepileptic drugs, epilepsy surgery), and psychosocial factors are all likely to play a role, but with considerable individual differences. Despite the high prevalence of anxiety disorders in patients with epilepsy, there are no systematic treatment studies or evidence-based guidelines for best treatment practice. Nevertheless, a practical approach based on the temporal relationship between anxiety and epileptic seizures allows clinicians to consider appropriate treatment strategies to reduce the psychiatric comorbidity in patients with epilepsy.

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1. Introduction

Psychiatric aspects of epilepsy have been extensively reviewed in the past [1–7]. Several large studies have shown that the rate of mood disorder is higher in patients with epilepsy than in those with other chronic medical conditions such as diabetes and asthma [8]. Most of the attention has been focused on depression, despite the fact that anxiety may actually be more common and equally disabling [6,9–11]. As early as 1971, Currie and colleagues documented a 19% point prevalence of anxiety disorder, compared with an 11% point

prevalence of depressive disorder, in patients with temporal lobe epilepsy [12]. A more recent study looking for psychopathology using a standardized diagnostic interview in inpatients with all types of epilepsy obtained similar results: The 1-year prevalence of anxiety disorders was 25%, and that of mood disorders, 19% [13]. However, in some secondary care and specialist settings, the prevalence of anxiety disorder may exceed 50% [9,14].

Several recent studies have attempted to examine the relative contribution of anxiety symptoms to reduced health-related quality of life (HRQOL) in patients with epilepsy. In a study from Korea, anxiety was the most significant predictor of reduced HRQOL, explaining 27% of the variance compared with 12% for depression

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and 3% for seizure frequency [15]. Johnson and colleagues also examined the relative contribution of depression and anxiety to HRQOL in patients with temporal lobe epilepsy [16]. Depression and anxiety were independently associated with reduced HRQOL, and psychiatric comorbidity explained more variance in HRQOL than did combined groups of clinical seizure or demographic variables.

2. Epidemiology and phenomenology of anxiety syndromes in epilepsy

The DSM-IV [17] distinguishes between 11 different types of anxiety disorder, but most are excluded when a significant explanatory medical condition is present. No groups have attempted to delineate the special features (if any) of anxiety occurring in epilepsy, an approach that has been successful in depression [18]. It is therefore unclear if current diagnostic instruments for anxiety perform adequately in this population. In addition, most studies have not considered subtypes of anxiety disorder or the setting of the sample (primary or secondary care). Nevertheless, self-report rating scales suggest elevated levels of anxiety, panic attacks, panic disorder, generalized anxiety, and obsessive–compulsive symptoms in epilepsy patients compared with healthy controls [19–21]. There is little information on the prevalence of anxiety symptoms in community-based populations of patients with epilepsy. In one large study based on diagnoses in primary care records, the rate of anxiety disorders was 11% in 5834 people who had epilepsy, compared with 5.6% in 831,163 without epilepsy. Obsessive–compulsive disorder was rare, present in only 0.4% of cases, although this represented a relative risk of 2.5 [22].

2.1. Generalized anxiety disorder and epilepsy

The cardinal symptom of generalized anxiety disorder (GAD) is a disabling and persistent worry that is free-floating and present much of the time for at least 6 months. Associated somatic or vegetative symptoms such as increased fatigue, insomnia, difficulty with concentration, and sleep problems are common [17]. It is always important to inquire about the theme of the patient's concerns in GAD, and this is particularly the case in the context of physical disease. Considerable anxiety occurs in relation to investigations for any serious physical disease, and this is heightened in disorders such as epilepsy where diagnostic delays are common [23]. After diagnosis, GAD may continue if there is fear of future seizures, fear of disease progression, or fear of specific complications [15]. Many clinicians would define a fear of possible future health complaints as health anxiety or hypochondriasis, but boundaries are unclear in

those with definite physical disease [24]. Nevertheless, a persistent fear of seizures contributes directly to impaired HRQOL ratings above and beyond the effect of depression in epilepsy [25].

2.2. Panic attacks and panic disorder

Panic attacks are defined by sudden and severe paroxysmal episodes of anxiety of typically sudden onset and short duration, often with no clear external precipitant. A frequency of more than one attack per week for a period of at least 1 month is sufficient for a diagnosis of panic disorder [17]. Patients with epilepsy have panic attacks up to six times more frequently than control populations with a point prevalence of 15–30% [6,11,19,26]. In a small retrospective study, Mintzer and Lopez recently found that 4 of 12 patients (33%) had panic disorder comorbid with ictal anxiety symptoms [26]. Two patients had other anxiety disorders and eight (66%) had comorbid depression. Other authors found a 5–21% prevalence of panic disorder in patients with epilepsy [13,19], compared with 3.5% in the general population [27]. The differential diagnosis of panic attacks and seizures can be difficult. Of all the types of anxiety disorder, panic is the type most likely to be generated directly by a seizure—so-called “ictal fear” (see below and Table 1).

2.3. Phobia

Phobias are characterized by fear of specific situations or confinement of the anxiety to the feared domain. Specific fears in epilepsy overlap with GAD, the distinction being made on the degree to which the person can relax in a nonthreatening environment. Common phobias in epilepsy are fear of seizures or accidents occurring out of the house, leading to a variant of agoraphobia, or fear of social embarrassment, leading to a variant of social phobia [28]. Agoraphobia and social phobia in the context of physical disease should probably be considered distinct from primary phobias.

2.4. Obsessive–compulsive disorder

The hallmarks of obsessive–compulsive disorder (OCD) are recurrent intrusive and unpleasant thoughts often allied with compulsive actions. One study examining the prevalence of obsessional symptoms using two self-report measures in patients with temporal lobe epilepsy obtained scores in the clinical range in 22% of the patient group and 2.5% of healthy controls [21]. There are also some case reports of epilepsy and comorbid OCD [29–32]. Further, obsessive thoughts can occasionally be part of an epileptic aura in temporal lobe seizures in the form of “forced thinking” [6,11].

Table 1
Differential diagnosis of panic attacks versus focal epileptic seizure

	Primary panic attack	Focal seizure with ictal fear
Consciousness	Alert	Alert but may progress to impaired
Duration	5–10 min	0.5–2 min
Déjà vu, hallucinations	Very rare	>5%
Automatisms	Very infrequent	Common with progression to complex partial seizures
Agoraphobia	Common	Not unless comorbid interictal anxiety
Depressive symptoms	Common, severity associated	Not uncommon, severity not associated
Anticipatory anxiety	Very common	Can occur but not common
Interictal EEG	Normal	Often abnormal
Ictal EEG	Normal	Usually abnormal
MRI of temporal structures	Usually normal	Often abnormal ^a

Source. Modified with permission, from Vazquez and Devinsky [11].

^a Explicit search for hippocampal sclerosis or other discrete amygdala lesion with appropriate MRI.

3. Pathophysiology of anxiety in epilepsy

3.1. Risk factors for anxiety

Seizure frequency has been linked with severity of anxiety in some [33] but not all studies [15]. This does not necessarily imply ictal fear, but rather that as the burden of epilepsy increases, so does the anxiety. Yet clinically, the degree of anxiety is dissociated from seizure frequency in that it is the individual's *perception* of danger (e.g., of falling or dying) that is critical. Age and gender have a relatively subtle effect: for example, first-onset epilepsy in late life may be linked with higher levels of anxiety [34]. The risk of anxiety disorders appears to be higher in focal (especially temporal lobe) than in generalized epilepsies [6,10,11,20], but they are also seen in patients with frontal lobe epilepsy as well as primary or generalized seizures [20,35]. Several groups have found a link with the left temporal lobe but this is not entirely consistent in the literature [40]. The highest rates of psychiatric comorbidity (including anxiety) are reported in patients with chronic refractory seizure disorders [1,3,11,36–38]. In these disorders, psychiatric variables are strong predictors of poor quality of life [39]. One important factor linked to both depression and anxiety is perceived stigma [41,42]. This is critical because high rates of perceived stigma itself are present in about half of those with epilepsy and are highest in younger age groups [34,43].

3.2. Neurobiological mechanisms

The theory of a common pathophysiological mechanism of anxiety attacks and epilepsy is based on the observation that epileptic activity in certain areas of the brain directly causes paroxysmal anxiety, usually in the form of panic [44–49]. The amygdala seems to be a particularly important structure for the production of anxiety symptoms and epileptic discharges in temporal lobe epilepsy. The amygdala is responsible for

processing and relaying emotional stimuli from multiple sources to limbic and other cortical structures, basal ganglia, hypothalamus, and brain stem. The amygdala is therefore central to the generation of affective, autonomic, cognitive, and endocrine components of the clinical symptom “anxiety” [44–49]. Studies based on stimulation and lesioning support the importance of the amygdala for the production of anxiety symptoms. Electrical stimulation of the amygdala in humans, for instance, causes anxiety states, déjà vu phenomena, hallucinations, and disturbances of autonomic functions [50]. Selective bilateral destruction of the amygdala leads to impaired processing of fearful faces and decreased aggression [51]. However, ictal fear is not only a feature of temporal lobe seizures with involvement of the amygdala, but is also associated with seizures arising in the anterior cingulate or orbitofrontal cortex or other limbic structures [52]. In vivo structural and functional magnetic resonance imaging (MRI) studies confirm the association of abnormalities of the amygdala and anxiety or panic disorders [47,53,54]. More than 50% of patients with MRI-confirmed amygdala atrophy on the same side as the seizure focus have some form of ictal fear [55]. Patients with temporal lobe epilepsy and ictal anxiety symptoms have been found to have a reduced amygdala volume [53]. The central role of GABA_A receptors and other neurotransmitter systems (especially serotonin, dopamine, noradrenaline) in both epilepsy and anxiety is a further pathophysiological similarity between the two disorders [45,56,57].

γ -Aminobutyric acid (GABA) is the most important inhibitory transmitter in the central nervous system. Recent evidence suggests that the abnormal functioning of GABA_A receptors could be of great importance in the pathophysiology of epilepsy and anxiety disorders [44,57]. This hypothesis is supported by the observation that some substances, including the GABAergic antiepileptic drugs gabapentin, vigabatrin, tiagabine, valproate, and pregabalin [58–65], as well as barbiturates, benzodiazepines, and neuroactive steroids, have antiep-

ileptic as well as anxiolytic properties [56]. These pharmacological properties are either mediated through the interaction of drugs with the GABA_A receptor (for instance, by allosteric modulation in the case of benzodiazepines or neuroactive steroids), through agonism at the GABA binding site, or through an increase in endogenous GABA. Vigabatrin, for instance, inhibits GABA transaminase, whereas tiagabine is a selective inhibitor of GABA reuptake, thereby increasing the effects of GABA. The exact effect of the antiepileptic drugs gabapentin, pregabalin, and valproate on GABAergic neurotransmission remains unclear, but these drugs can increase GABA concentrations in certain brain regions [58–65].

4. Clinical differential diagnosis

It is useful to distinguish between epilepsy-related ictal, postictal, and interictal anxiety symptoms and “comorbid anxiety” unrelated to epilepsy:

- Anxiety as an *ictal* phenomenon (for instance, as an isolated aura or simple partial seizure causing the patient to experience fear/panic, especially from temporal lobe epilepsy with involvement of the amygdala)
- Anxiety as a *postictal* phenomenon (for instance, soon after recovery from a fit, often in association with clouding of consciousness or reduced orientation)
- Anxiety as an *interictal* phenomenon with a possible indirect relationship to epilepsy (for instance, as an adjustment reaction, a seizure phobia, a side effect of anticonvulsant medication, or a consequence of epilepsy surgery).

4.1. Anxiety as an ictal symptom

Ictal anxiety is most often experienced by patients with simple focal seizures of temporal lobe origin, but has also been reported with extratemporal epilepsies. Ictal anxiety is reported by at least 20% of patients when they are specifically questioned [6,10,11]. It is unclear whether the risk is greater when the seizure focus is in the right temporal lobe or left temporal lobe (see below). Although ictal anxiety and interictal anxiety generally are produced by different mechanisms, there is overlap in the occurrence of the two disorders [66]. One reason for this could be that some patients with presumed interictal anxiety actually experience subclinical seizures. The manifestation of ictal anxiety is characteristically isolated fear or panic, sometimes in association with other features of temporal lobe seizures, such as depersonalization and *déjà vu*, as well as other psychological, psy-

chopathological, and autonomic phenomena. The causation of anxiety symptoms by ictal epileptic discharges (in the sense of a simple partial seizure or aura) is most clear when anxiety occurs in a highly repetitive manner shortly (seconds or minutes) before a classic complex partial seizure [11]. The relationship to epileptic discharges is less clear when anxiety occurs more than a few minutes beforehand and is not stereotyped. The pathophysiological underpinnings of this longer pre-ictal or prodromal phase, which can be characterized by irritability, emotional lability, depression, and increased aggression, remain unclear [6].

If an epileptic cause of anxiety symptoms is suspected, physicians should question patients carefully about the timing of the anxiety symptoms and note other paroxysmal events suggestive of epilepsy (Fig. 1). Anxiety symptoms of long duration and those that are linked to clear external precipitants are unlikely to be seizure related. Nocturnal panic attacks can be a useful distinguishing feature. Patients with primary panic disorder experience nocturnal panic attacks any time during the night, occurring in a state of wakefulness and with symptoms identical to those of their daytime panic attacks. Patients with ictal fear also frequently describe nocturnal panic, but in this case the panic wakes them from an otherwise peaceful sleep [67]. Fear associated with nonepileptic panic attacks can present like ictal fear with hyperventilation, tachycardia, sweating, gastrointestinal symptoms (especially nausea), paresthesias, and other autonomic symptoms [68]. Ictal anxiety disorders are often misdiagnosed, even when they occur in the presence of other features of temporal lobe epilepsy (Table 1). Sazgar et al. [69] described five patients with epilepsy misdiagnosed as having panic attacks in the past. All of these patients had structural lesions in the right temporal lobe. Occasionally, the opposite mistake occurs and patients with primary panic disorder are misdiagnosed with focal epileptic seizures [70]. The gold standard for the exact diagnosis of ictal fear is video recording of attacks with simultaneous EEG. Clinicians should also look hard for abnormalities in the mesial temporal lobe or other limbic structures on MRI scans.

4.2. Anxiety as a postictal symptom

Postictal anxiety occurs in the period shortly after a seizure and is not thought to be a direct manifestation of epileptic discharges in the brain. Anxiety is often associated with postictal dysphoria or depression [2,37]. Postictal dysphoric states can last days but typically are much shorter. Occasionally, pure anxiety is seen after a seizure, but this is less common than the combination of mood symptoms [36]. Kanner et al. [37] recently examined the prevalence and clinical phenomenology of postictal psychiatric symptoms in a prospective study in patients with refractory focal

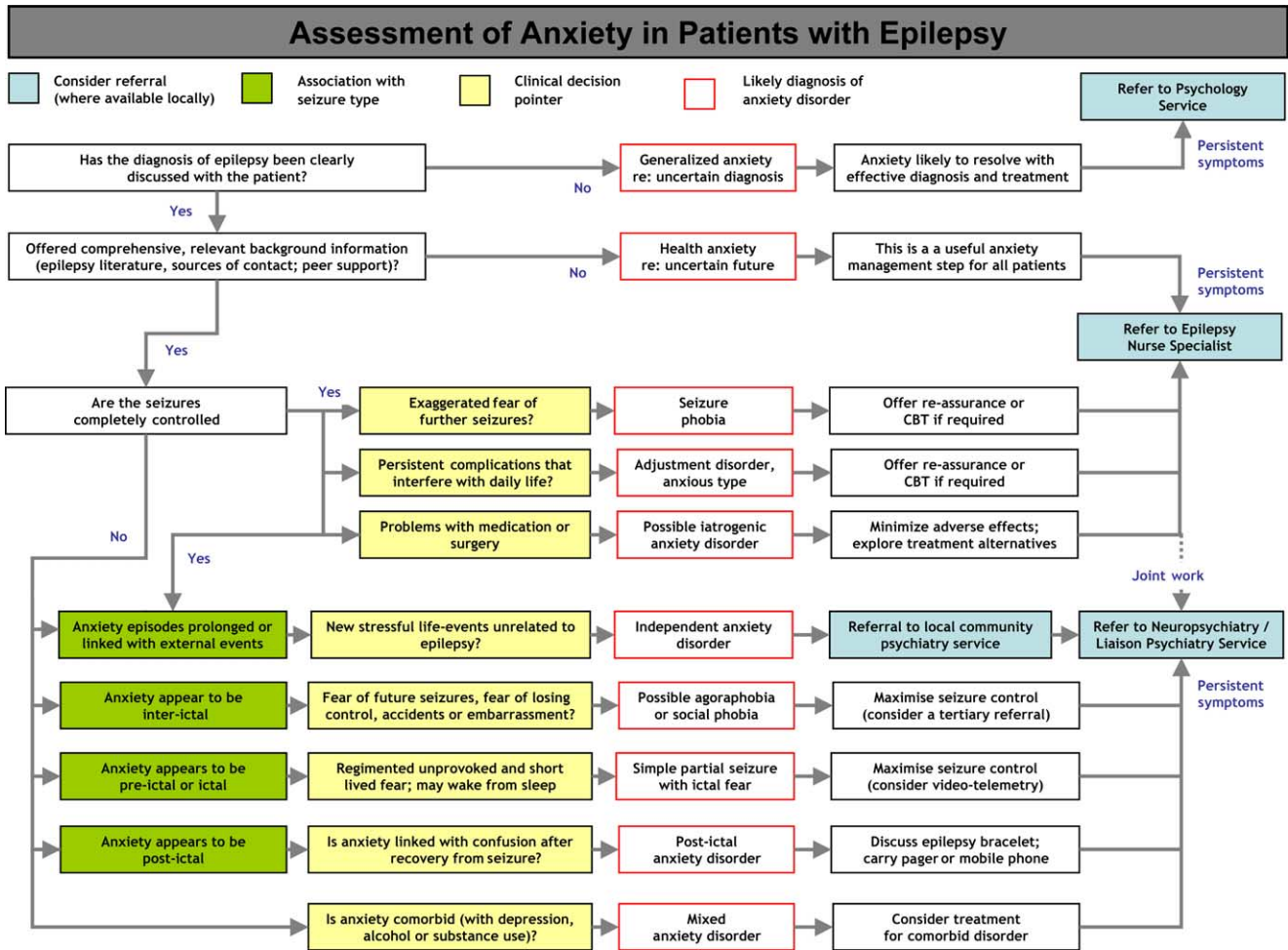


Fig. 1. A clinical guide to the assessment of anxiety in patients with epilepsy. CBT, Cognitive-behavioral therapy.

epilepsies. In the first 72 hours after a seizure, 45 of 100 patients had anxiety symptoms, although they were combined with depressive symptoms in most cases. There was a correlation between the severity of interictal psychiatric symptoms and the severity of postictal symptoms [37]. Postictal depression and other psychiatric symptoms are particularly common in medically refractory and prolonged seizures [1–3,11,36,37].

4.3. Anxiety as an interictal symptom

Although *interictal* anxiety is common, the phenomenology of this condition has not been well described. One reason for this is that the diagnostic distinction of interictal anxiety from independent comorbid anxiety disorder is difficult when anxiety symptoms are not closely seizure-related (Fig. 1) [6,10,11]. Interictal anxiety is again not thought to represent the direct manifestation of abnormal electrical discharges, but intriguingly appears to be most common in patients with limbic epilepsies [35,71]. Experimental studies suggest that *kindling* mechanisms could be responsible for the

development of interictal anxiety. That is, recurrent epileptic stimulation of the amygdala could give rise to an increased irritability in this region of the brain [72]. More likely, interictal anxiety represents a combination of psychological worries about the disorder and its complications. Common concerns focus on the risk of seizure-related injury or brain damage, memory impairment, the prognosis of the seizure disorder, and issues related to work and employment [5,73].

Anxiety symptoms may have a significant implication for quality of life because patients with anxiety disorders typically overestimate the risks associated with situations triggering their anxiety and underestimate their ability to manage their anxiety [10]. The result can be a disabling combination of anticipatory anxiety about seizures in unfamiliar situations, leading to avoidance and isolation. If asked directly, about 20–30% of patients endorse a specific fear of seizures (“seizure phobia”) [28]. However, when asked about maladaptive avoidance, the rates of people reporting fear of leaving the house and anticipatory anxiety are even higher [74]. Fears are often learned from significant others.

For example, children with epilepsy may become anxious by observing the reaction of their parents [75]

5. Anxiety symptoms and epilepsy surgery

The prevalence of anxiety disorders in candidates for epilepsy surgery has been reported to be between 10 and 30% [76,77]. Most studies suggest that if surgery for epilepsy is successful, then quality of life is improved [78]. This is usually reflected in an improvement in mood, but some patients develop new-onset mood disorders [79]. Anxiety may persist in the first year after surgery, despite an improvement in depression [80,81]. However, in the long term, anxiety levels generally decrease if seizures remit [82]. Risk factors for postoperative anxiety include persistence of seizures, previous (preoperative) psychiatric complaints, and new complications such as

memory deficits [81,83–85]. Kulaksizoglu et al. [32] reported the postoperative manifestation of OCD in two of five patients with refractory temporal lobe epilepsy and preoperative evidence of obsessive personality traits. In view of the high prevalence of anxiety and other psychiatric disorders and the poor standard of psychiatric diagnosis and management in patients with refractory epilepsy, some authors have argued that a detailed psychiatric assessment of patients should be considered as integral to the epilepsy surgery workup as neuropsychological testing or the recording of seizures by video EEG [86].

6. Anxiety symptoms and antiepileptic drugs

There is a complex relationship between anxiety symptoms and the medical therapy of epilepsy (see

Table 2
Positive and negative psychotropic effects of antiepileptic drugs^a

Substance	GABAergic mode of action ^b	Antiglutamatergic mode of action	Negative effects	Positive effects
Barbiturates	++	–	Sedation, depression, cognitive impairment	Anxiolytic, hypnotic
Benzodiazepines	+++	–	Confusion, irritability, depression, cognitive impairment	Anxiolytic, hypnotic, minor antimanic and antidepressant effects
Carbamazepine (CBZ)	+	+	Depression, sexual dysfunction, manic episodes, irritability, somnolence	Antimanic, moderate antidepressant effect, anxiolytic in animal models
Ethosuximide	–	–	Sedation, anxiety, behavioral abnormalities, psychoses	
Felbamate	+	++	Apathy, depression, agitation, psychoses, irritability, anxiety and panic	Activating, increased attention and concentration
Gabapentin	–	–	Sedation, somnolence	Anxiolytic, “mood stabilizer,” no cognitive impairment
Lamotrigine	–	++	Irritability, additive toxic effects in combination therapy with CBZ, insomnia	“Mood stabilizer,” positive psychotropic effects, anxiolytic in animal models
Levetiracetam	?	?	Irritability, reversible psychosis (including anxiety), somnolence	Anxiolytic effects in animal experiments
Oxcarbazepine	?	+	Somnolence	Less cognitive impairment than with CBZ
Phenytoin	–	–	Sedation, confusion (including anxiety), depression	
Pregabalin	–	–	Sedation, somnolence	Anxiolytic, no impairment
Tiagabine	+++	–	Sedation, psychoses (very rare), depression	Anxiolytic
Topiramate	+	++	Sedation, psychoses, anxiety, cognitive dysfunction	“Mood stabilizer”
Valproate	+	+	Sedation, somnolence, depression (very rare)	Antimanic, moderate antidepressant effects, anxiolytic
Vigabatrin	+++	–	Sedation, psychoses (including anxiety), depression	Anxiolytic?
Zonisamide	+	–	Somnolence, agitation, psychoses (including anxiety), depression	“Mood stabilizer”?

Source. Modified from Refs.[87,105].

^a The list of anxiolytic antiepileptic drugs includes barbiturates and benzodiazepines, which should be considered only after careful consideration of the risk of adverse effects and the development of tolerance.

^b Effects: –, none; +, minor; ++, clear; +++, major; ?, questionable.

Table 2). Antiepileptic drugs (AEDs) can exacerbate anxiety or have beneficial mood-stabilizing and anxiolytic effects. Several AEDs (valproate, tiagabine, gabapentin, and pregabalin) have been used in trials for the treatment of anxiety disorders with variable success [59–65]. It remains unclear why some AEDs increase anxiety in some patients with epilepsy. There is some evidence that a history of psychiatric disorder increases the vulnerability to psychiatric side effects of AEDs [6]. Ketter et al. [87] formulated the hypothesis that substances with predominantly glutamatergic mechanisms of action cause “activation” (leading to such effects as weight loss, increase in anxiety, improvement of depressive symptoms), whereas AEDs that enhance GABAergic neurotransmission (like barbiturates, benzodiazepines, valproate, tiagabine, and vigabatrin) cause sedation, cognitive slowing, weight gain, and alleviation of anxiety [87]. Unfortunately, this approximate division of AEDs into those with sedating and those with “activating” properties is too simplistic from a clinical point of view. Vigabatrin, for instance, is an incontrovertibly GABAergic substance, but causes anxiety in some patients. AEDs clearly have several relevant mechanisms of action and probably others that are not yet known. In general, the anxiolytic and mood-stabilizing potential of AEDs is more powerful than their anxiogenic effects. In line with this observation, anxiety symptoms are sometimes seen when AEDs are discontinued [88].

7. Therapy of anxiety disorders in patients with epilepsy

7.1. Basic information and support

An essential component of treatment for any patient and his or her carer(s) must include an adequate explanation of the condition, pointers to further information, and provision of further support [89,90]. The degree of information requested will vary considerably between patients. One reason for the need to consider this as mandatory is that perceived needs are often underestimated by staff [91]. The role of several of these elements, particularly “psychoeducation,” is finally being examined in randomized trials [92,93]. Such interventions can be performed in community, clinic, or group settings [94]. The availability of a nurse specialist in epilepsy care can be an enormous benefit in this area [95–97].

7.2. Advanced counselling and psychotherapy

For patients who need more than basic information, support, and reassurance, more advanced psychological interventions are useful [98,99]. In fact, cognitive-behavioral therapy (CBT) can provide physical as well as psychological benefits, including, perhaps surprisingly, a reduction in seizure frequency [100,101]. Further, CBT

can work even if seizure frequency cannot be reduced [102]. Psychotherapeutic strategies can be combined with pharmacological treatments, but successful treatment may require close collaboration between epileptologist and psychotherapist.

7.3. Medication options

The most important substances for the medical therapy of anxiety disorders are antidepressants including selective serotonin reuptake inhibitors (SSRIs), serotonin–noradrenaline reuptake inhibitors, tricyclic antidepressants, reversible monoamine oxidase inhibitors (MAOIs), as well as buspirone and benzodiazepines [98,103]. To date there are no controlled studies of the medical therapy of anxiety disorders in patients with epilepsy. The main concern using psychotropics is the risk of inducing or exacerbating seizures. This has been extensively studied (Table 3).

In terms of specific antidepressant drugs, some reports suggest that MAOIs may be anticonvulsant, although they can cause myoclonic jerks and there are reports of hypertensive crises associated with the combined use of carbamazepine and MAO inhibitors [6,98]. Serotonin does not appear to be crucial in the pathophysiology of seizures, and hence SSRIs do not significantly alter the seizure threshold. Reboxetine also appears to be well tolerated. Seizures have been reported with amoxapine, maprotiline, and most tricyclic antidepressants. Carbamazepine is structurally related to tricyclic antidepressants, and it has been suggested that tricyclic antidepressants may have anticonvulsant effects in low but not high doses [104]. Risk is considerably increased in toxic quantities [104]. Practically, SSRIs are often the drug of choice because of their advantageous side effect profile, their relatively small effect on neuronal excitability, and their favorable pharmacokinetic properties with a low potential for drug–drug interac-

Table 3
Risk of seizures with drugs prescribed for anxiety disorders

Drug	Approximate risk (%)
High risk (5% or higher risk of seizure)	
Chlorpromazine (high dose)	9
Medium risk (0.5% or higher risk of seizure)	
Olanzapine	1
Quetiapine	1
Bupropion	0.5
Clomipramine (high dose)	1
Low risk (0.5% or lower risk of seizure)	
Risperidone	0.3
Imipramine	0.5
SSRIs	0.1
Venlafaxine	0.3
Mirtazepine	0.05

Source. Refs. [6,98,103,104].

tions [6,7,11,98] The effectiveness of different SSRIs in patients with primary anxiety disorders (without epilepsy) is well documented. Benzodiazepines (e.g., clonazepam, alprazolam) are also very effective in anxiety disorders and clearly anticonvulsant, but still carry a risk of dependence in the long term [6,7,11,98]. Buspirone, a partial agonist at the serotonin 1A receptor, lowers the seizure threshold in animal experiments [6], but (like the β -blocker propranolol) is considered relatively safe in patients with epilepsy [98].

7.4. Antiepileptic drugs with anxiolytic effects

There is currently no good evidence from randomized studies of possible anxiolytic effects of AEDs in patients with epilepsy. However, one may consider choosing an AED with anxiolytic potential in a patient with epilepsy who also has symptoms of an anxiety disorder if this AED is suitable for his or her particular type of epilepsy (see Table 2). GABAergic drugs, in particular, can reduce anxiety in animal experiments and in clinical practice; this “side effect” can therefore be put to good therapeutic use [59–65]. The GABA analogs gabapentin and pregabalin, for instance, have proven effects in anxiety disorders and focal epilepsies [59–65,105]. The precise mode of action of these two AEDs is not fully understood, although it has been shown that gabapentin and pregabalin bind selectively to the $\alpha_2\delta$ subunit of voltage-gated calcium channels [58,62]. Both molecules do not interact with GABA_A or GABA_B receptors, but do increase the concentration in some brain regions and rate of synthesis of GABA and, thereby, decrease glutamate concentration indirectly. They also modulate other neurotransmitter systems including the noradrenergic, dopaminergic and serotonergic systems [58,62]. Vigabatrin, a GABA transaminase inhibitor, and tiagabine, a GABA reuptake inhibitor [65,105], as well as valproate [61], have anxiolytic properties. The possible positive effect of other AEDs like carbamazepine and oxcarbazepine on anxiety symptoms has only been reported anecdotally [31,98].

7.5. Pharmacokinetic interactions between anxiolytic and antiepileptic drugs

A discussion of the medical treatment of anxiety symptoms in patients with epilepsy has to take account of possible pharmacokinetic interactions between antiepileptic and psychotropic drugs. The metabolism of many drugs is dependent on hepatic monooxygenases, which contain hemoproteins of the cytochrome P450 type. This is a complex and inducible enzyme system with many different isoenzymes (CYPs). More than 30 different CYPs have been identified in humans so far. Psychotropic drugs are metabolized mainly by four isoenzymes (CYP 1A2, 3A4, 2C, and 2D6) [106]. In princi-

ple, almost all antidepressant drugs interact with different cytochrome P450 enzymes, which can lead to interactions, especially with enzyme-inducing and enzyme-inhibiting antiepileptic drugs. Often, however, the clinical effect is hardly relevant. Enzyme-inducing substances (for instance, carbamazepine, phenytoin, phenobarbital) cause a reduction in serum concentrations of hepatically metabolized comedication, whereas valproate (an enzyme inhibitor) can increase antidepressant concentrations [6,106,107]. Because of these interactions it may be preferable to use antidepressant drugs with one of the newer antiepileptic drugs, because most of these agents have more favorable pharmacokinetic properties so that the risk of interactions is low or nil. Gabapentin, levetiracetam, and pregabalin, in particular, do not cause any clinically relevant pharmacokinetic interactions [105].

8. Conclusion

The prevalence of anxiety symptoms is higher in patients with epilepsy than in the general population or in patients with several chronic medical disorders, suggesting a special relationship. Detailed descriptions of the prevalence of anxiety disorders in patients with well-controlled epilepsy versus treatment-refractory epilepsy or those with a history of status epilepticus are not currently available. The psychopathology of anxiety occurring in different phases of epilepsy is beginning to be understood, although many questions remain. One classic manifestation of temporal lobe seizures is ictal fear, but interictal anxiety and other rational worries are more common. Fundamental concerns such as fear of accidents, fear of losing control, and fear of social embarrassment are often not volunteered by patients and demand specific inquiry. The influence of sociocultural factors and stigma must also be considered. The detection of anxiety should raise questions about comorbid depression and possible substance misuse. Appropriate management must be based on a comprehensive history, which will help formulate the subtype of anxiety disorder and its relationship to the seizure disorder. In difficult cases video EEG monitoring is recommended. Clinicians must also bear in mind possible iatrogenic effects of medical or surgical epilepsy treatment.

Anxiety disorders often go unrecognized and untreated in both primary and secondary care [108,109]. It should be no surprise that this is also the case in neurological settings. Given the great prevalence of the whole spectrum of anxiety disorders in neurological patients, particularly those with epilepsy, neurologists must incorporate the essentials of diagnosis and management into routine clinical practice. For difficult cases, close work with psychology, liaison psychiatry, or neuropsychiatry is certain to be an advantage.

A variety of strategies are now available to manage anxiety in patients with epilepsy but one cornerstone of good management remains optimal seizure control. Without this, complete treatment of anxiety is likely to be difficult for any specialist. The first step in management is nondrug interventions. Here the input of clinical nurse specialists and psychology can be particularly valuable. More research is needed about the effects of more advanced treatments, including cognitive-behavioral therapy and other psychological and pharmacological interventions, in patients with epilepsy. However, much evidence demonstrates that pharmacological treatments for anxiety can be prescribed safely even in patients with continuing seizures. Although there have been no routine clinical trials of the treatment of anxiety disorders in epilepsy this should not discourage health professionals from assessing and treating anxiety symptoms that significantly impact the quality of life of patients with epilepsy.

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