Review article

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Epilepsy and anxiety: epidemiology, classification, aetiology, and treatment

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ABSTRACT – Anxiety in epilepsy has recently become a focus of interest for a number of reasons. Epidemiological studies have established that anxiety disorders are twice as common in patients with epilepsy compared to the general population, while in referral centres their prevalence is even higher. In addition, it has been recently appreciated that anxiety exerts a significant negative impact on the quality of life of patients with epilepsy of any age. With regard to the pathogenesis of anxiety in epilepsy, a number of theories have been put forward including those based on psychodynamics, learning-cognition, and neurobiology. From a clinical point of view, anxiety may occur as a comorbid disorder with epilepsy or be directly linked with epilepsy as a preictal, ictal, postictal or interictal phenomenon. The treatment of anxiety in patients with epilepsy requires a comprehensive, multidisciplinary, clinical assessment. Regarding pharmacological therapies, it should be recognised that some drugs prescribed for anxiety disorders are associated with a high risk of seizures, whereas some antiepileptic drugs possess anxiolytic properties that could be of use in the management of epileptic patients with anxiety. The correct diagnosis and successful treatment of anxiety is expected to have significant benefits for the quality of life of epileptic patients.

Key words: anxiety, epilepsy, panic attacks, antiepileptic drugs

Psychiatric disorders in epilepsy have received, over the years, considerable attention both from a clinical and research point of view. Depression, for instance, has been consistently shown to exert a significant negative impact on the health-related quality of life in patients with epilepsy, and a number of therapeutic strategies have been proposed in order to prevent and reverse these negative effects (Kanner, 2009). Anxiety, quite paradoxically, has been much less emphasized despite the fact that a large number of anxiogenic factors are present in the everyday life of patients with epilepsy. The unpredictable occurrence of seizures, the risk of physical injury or even death, the ever present social stigma and the profound effects it can have on social identity and discrimination, and the possible increased financial, marital, and emotional difficulties, synergistically interact to create

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anxiety and negatively affect the quality of everyday life of people who have epilepsy as well as their families (Valeta, 2005; Valeta, 2010).

Recently, the issue of anxiety has become the focus of attention in epilepsy research. The present article reviews current knowledge on the epidemiology, classification, pathophysiology, and diagnostic and therapeutic approach of anxiety disorders in patients with epilepsy and highlights recent advances in this rapidly evolving field.

Epidemiology

A number of epidemiological studies indicate that anxiety disorders are twice as common in people with epilepsy than in the general population. In a recent Canadian study (Tellez-Zenteno *et al*., 2007), which used contemporary diagnostic criteria for psychopathology based on the DSM-IV classification, the lifetime prevalence of anxiety in subjects aged >15 years was 22.8% in patients with epilepsy versus 11.2% in the control group. These data were derived from a population study, however, in specialist centres the incidence of anxiety is even higher. For instance, Jones and coworkers (Jones *et al*., 2005) conducted a study in five epileptological centres in the United States to assess psychiatric morbidity in adult patients with chronic epilepsy and detected anxiety disorders in 30.4%. For epilepsy surgery candidates aged ≥15 years, the prevalence rate of anxiety was particularly high, reaching 48% in the study by Reuber *et al*. (2004).

Brandt *et al*. (2010) examined the prevalence of specific subtypes of anxiety disorders in adult patients with refractory focal epilepsy by administering the Structured Clinical Interview for DSM-IV Axis I disorders. The prevalence of social phobia was 7.2%, specific phobia 6.2%, panic disorder 5.1%, and generalised anxiety disorder 3.1%. In the general population, the prevalence rates of the respective diagnoses were significantly lower: 1.24% for social phobia, 4.8% for specific phobia, 1.1% for panic disorder, and 1.2% for generalised anxiety disorder. Obsessive-compulsive disorder (OCD), which is also included within the class of anxiety disorders, is encountered with increased frequency amongst epileptic subjects, particularly with the temporal lobe epilepsy subtype, with prevalence rates in adult patients of up to 11% (Kaplan, 2011; de Oliveira *et al*., 2010). Finally, Pinquart and Shen (2011) performed a meta-analysis of 332 studies comparing levels of anxiety in children suffering from chronic illness with healthy peers and population norms, and concluded that children with epilepsy are at high risk for developing anxiety symptoms.

Overall, these data indicate that anxiety is one of the most common psychiatric disorders in epilepsy and underscore the significance of identifying this important comorbidity in everyday clinical practice (Brandt *et al*., 2010; Desai *et al*., 2010; de Oliveira *et al*., 2010).

The pathogenesis of anxiety in epilepsy

An issue of particular interest is the pathogenesis of anxiety in patients with epilepsy. A number of theories have been put forward to address this issue including a neurobiological theory, a learning and cognitive-behavioural theory, and a psychodynamic theory.

The neurobiological theory

This theory integrates neurochemical and neuroanatomical data to provide an explanation for the increased prevalence of anxiety in patients with epilepsy.

The neurochemical aspect of the neurobiological theory primarily implicates the inhibitory neurotransmitter GABA. A popular theory regarding anxiety disorders is that they result from defective GABAergic inhibition in the CNS. For instance, patients with panic disorder have decreased binding of flumazenil to benzodiazepine receptors in specific brain areas which reflects down-regulation of these receptors (Malizia *et al*., 1998). Interestingly, a similar reduction in flumazenil binding to benzodiazepine receptors has been described in the temporal lobe of patients with hippocampal sclerosis (Koepp *et al*., 1997) and this common biochemical defect may possibly underlie the pathogenesis of anxiety in patients with epilepsy. Similar associations have also been described with the serotonergic and noradrenergic systems.

From a neuroanatomical point of view, the most important structure for understanding the neurobiology of anxiety is the amygdaloid nucleus (Gorman *et al*., 2000). This key structure is traditionally divided into three groups of nuclei: an olfactory group, with connections to the hippocampus, piriform cortex and olfactory bulb; a centromedial group, with connections to extensive areas of the brain stem; and a basolateral group, with strong reciprocal connections to the somatosensory and motor cortex. These three groups of nuclei integrate interoceptive and exteroceptive stimuli, process the data, and then distribute them to multiple efferent systems that mediate the multiple autonomical, affective, cognitive, and endocrinological components of the anxiety response. There are many lines of evidence, both experimental and clinical, indicating that the amygdala, and the central nucleus in particular, is primarily responsible for mediating fear and anxiety related to epilepsy.

At an experimental level, kindling of the basolateral nucleus of the right amygdala results in the

development of limbic complex partial seizures, but simultaneously induces anxiogenic behavioural effects (*i.e.* reduced cage exploration and increased immobility) (Helfer *et al*., 1996). On the basis of these data, it may be hypothesized that recurrent stimulation of the amygdala during the course of temporal lobe seizures may cause increased irritability of this region interictally, which will become clinically manifested as an anxiety disorder.

At the clinical level, Lanteaume *et al*. (2007) have shown that direct electrical stimulation of the amygdala, particularly on the right, induces negative emotions, such as fear, anxiety, and sadness. In contrast, stimulation of the left amygdala induces either pleasant or unpleasant emotions. Therefore, these functional data indicate that the human amygdala is the anatomical substrate of a functionally asymmetric network that is directly involved in the pathogenesis of fear and anxiety.

From a morphometric point of view, however, recent volumetric magnetic resonance imaging (MRI) studies provided contradictory results. For instance, Satishchandra *et al*. (2003) reported an association between right amygdala hypetrophy and anxiety in patients with chronic epilepsy, whereas van Elst *et al*. (2009) observed a negative correlation between right amygdala volume and the number of psychopathological features of the dysphoric disorder of epilepsy, including anxiety. In order to reconcile these apparently conflicting results, the latter authors proposed a dimensional approach based on the assumption that amygdala volume status reflects the dominant mode of emotional information processing. According to this hypothesis, a hyperstable mode of emotional processing, expressed with phobic anxiety and other related features, is associated with enlarged amygdala volumes, whereas emotional instability, expressed with psychotic anxiety, irritability, and aggression is correlated with amygdala volume loss.

The amygdaloid nucleus and its interconnections with the striatum have been also implicated in the pathogenesis of OCD (Kaplan, 2011). Clinical observations suggest that dysfunction along the frontal-thalamic-pallidal-striatal-anterior, cingulate-frontal circuits may underlie the emergence of rituals and repetitive behaviours in patients with epilepsy.

The psychodynamic theory

The psychodynamic approach is based on the significant role that scientists and theorists have ascribed to psychological factors in the generation of seizures. Stress and anxiety are both accepted by current neurological thinking as precipitatory factors in the production of seizures (Betts, 1981). Freud's psychoanalytic theory sees anxiety as a reaction to a situation of danger. The ego, in order to protect itself from the instinctive forces of the id, creates symptoms to avoid the dangerous situation, the presence of which has been signalled by the generation of anxiety. In psychodynamic work, unconscious conflicts, which cannot be mastered psychically, create anxiety and stress that may predispose to seizures. It is important in clinical work to distinguish between pure organic epileptic seizures, psychologically produced epileptic seizures, and non-epileptic seizures (Valeta, 2009).

Classification and clinical correlates

The proper classification of anxiety disorders in epilepsy has been a matter of debate. The two established classificatory systems in psychiatry, the DSM-IV and the ICD-10, contain a multitude of different categories of anxiety. For instance, the DSM-IV system includes, under the rubric of anxiety disorders, the subcategories of generalised anxiety disorder, panic disorder with or without agoraphobia, OCD, posttraumatic stress disorder and phobias, and anxiety arising as a direct physiological consequence of a medical disease process. In clinical practice, however, this classification approach may not be easily applicable to the epilepsy field for a number of reasons. First, while there is ample empirical evidence that the psychiatric disorders of epilepsy are clinically distinct from psychopathology in other clinical settings, they are not recognised as such in either classificatory system. The second reason is that the operational rules of these systems mandate that the psychiatric disorders of epilepsy are subsumed under the specific category "anxiety disorders due to a general medical condition" and this may be neither appropriate nor accurate (Krishnamoorthy and Reghu, 2008). Finally, it is well-known that a common source of anxiety in patients with epilepsy, that is the fear of becoming injured during a seizure, may not be disproportionate to the event but still impair the patient's quality of life. This fear cannot be subsumed under any recognised DSM-IV category, including the diagnosis of generalised anxiety disorder, which according to the DSM-IV system requires symptoms disproportionate to the actual source of worry.

In 2007, the Commission on Psychobiology of Epilepsy of the ILAE proposed a classification scheme that differs from previous ones in various aspects (Krishnamoorthy *et al*., 2007). This classification begins by differentiating comorbid psychiatric disorders from epilepsy-specific disorders. Thereby, it is emphasized that people with epilepsy can suffer, like anyone else in the general population, from various psychiatric disorders that may be unrelated to epilepsy *per se*. These comorbid disorders include anxiety and pho-

bias and can be properly classified using the ICD-10 and DSM-IV. With this distinction, it becomes clear that the ILAE classification does not compete with the established classification systems in psychiatry but rather focuses on the epilepsy-specific disturbances. The latter are then classified, based on their relationship to ictus, into periictal and interictal disorders. Anxiety is present in both categories and this is a particularly useful distinction from a clinical point of view (*cf. Clinical Phenomenology and differential diagnosis*).

Anxiety in patients with epilepsy is associated with a number of medicosocial variables including the co-existence of depression, adverse effects of antiepileptic drugs, female gender, lower educational attainment, and unemployment status (Mensah *et al*., 2007). The association of anxiety with depression is of particular importance, due to its high prevalence and significant therapeutic ramifications as the response to psychiatric treatment in these cases is less favourable compared to when anxiety or depression occurs alone. This association is embodied in the concept of Interictal Dysphoric Disorder (IDD), initially put forward by Blumer (1984). IDD is characterised by a constellation of labile depressive symptoms (depressive mood, anergia, pain, and insomnia), labile affective symptoms (fear and anxiety), and symptoms considered specific for epilepsy (*i.e*. paroxysmal irritability and euphoric moods). In order to reach the diagnosis of IDD proper, the patients' symptoms should be differentiated from the periictal dysphoric symptoms that frequently occur in the postictal state (Mula *et al*., 2010). It should be noted that although the concept, as well as certain core features, of IDD were thought to be specific to epilepsy, it has been recently shown that this entity occurs in other neurological conditions as well (Mula *et al*., 2008).

Anxiety occurs with increased frequency in epileptic patients with comorbid psychogenic non-epileptic seizures (PNES). This combination of PNES with epilepsy, sometimes called "mixed PNES", can be further subdivided into three subgroups (Magaudda *et al*., 2011) with anxiety disorders being a prominent feature in two of them. The first subgroup is characterised by drug-resistant epilepsies, comorbid anxiety or depressive disorders, and normal cognition. In these patients, PNES are thought to occur as a direct consequence of epilepsy-related problems *per se*. The second subgroup includes patients with intellectual disability, whereas the third subgroup is characterised by epilepsy, normal cognition, comorbid cluster B personality disorders and anxiety disorders, and history of psychic trauma. In the latter cases, the psychic trauma is considered to be the prime aetiology of PNES.

Finally, it is worth mentioning that patients with PNES exhibit prevalence rates of anxiety comparable to patients with drug-resistant epilepsy or mixed PNES, with one notable exception. The prevalence of posttraumatic stress disorder is significantly increased in PNES patients compared to the general population or patients with intractable seizures (Fiszman and Kanner, 2010).

Clinical assessment

It is generally agreed upon that anxiety, in common with depression, is under-diagnosed and undertreated in epileptic patients. In order to optimise the detection and treatment of anxiety in epilepsy, it is essential for treating physicians to employ a screening instrument in everyday clinical practice. For a critical review on this issue, as well as a thorough discussion of future research directions on anxiety in epilepsy, the reader is referred to the recent review by Hamid *et al*. (2011).

A non-exhaustive list of screening tools for anxiety that are commonly used in adult patients includes the following:

a) *State-Trait Anxiety Scale* (STAI) (Spielberger, 1983). This is a self-report questionnaire consisting of two different forms, each comprising 20 items. The first (STAI-S) measures various subjective and somatic manifestations of anxiety at a given moment. In contrast, the second (STAI-T) refers to relatively stable individual differences in proneness to anxiety as a personality trait.

b) *Goldberg's Depression and Anxiety Scales* (Goldberg *et al*., 1988). A scale comprising nine questions designed to be administered by non-specialists in psychiatry, in order to assess mood and anxiety over the previous month.

c) *Hospital Anxiety and Depression Scale (HADS)* (Zigmond and Snaith, 1983). This widely used scale comprises an anxiety and a depression subscale and was developed to investigate various dimensions of mood in patients with medical comorbidities. The anxiety subscale (HADS-A) assesses features of a generalised anxiety state, such as restlessness, panic attacks, and anxious thoughts and mood, whereas the depression subscale (HADS-D) identifies a state of lost interest and reduced pleasure. Each subscale includes seven items and has a total score ranging from 0 to 21 with higher scores reflecting poorer psychological well-being. On both subscales, a score of 0-7 is considered normal whereas scores >8 represent levels of pathological anxiety and depression. A composite score (the total of HADS-A and HADS-D) has also been advocated as a general measure of psychological distress within the context of medical illness.

d) *Beck's Anxiety Inventory (BAI)* (Beck and Steer, 1990). A self-report scale comprising 21 items, each

one of which corresponds to a common symptom of anxiety. The patient indicates on a 4-point scale the degree to which he may have experienced these symptoms over the previous week, producing a total score that can range from 0 to 63.

e) *Hamilton Anxiety Rating Scale (HAM-A or HARS)* (Hamilton, 1959). This scale comprises 14 items which assess, on the basis of an interview, somatic and psychic manifestations of anxiety.

f) *Symptoms Check List (SCL-90-R)* (Derogatis, 2006). This is a self-report symptom inventory, comprising 90 items, for the assessment of psychological symptoms and psychological distress. It takes approximately 12-15 minutes to administer and yields 9 scores along primary symptom domains which include somatization, obsessive compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.

g) *GAD-7* (Spitzer *et al*., 2006). In this recently introduced self-report questionnaire, the patient indicates whether he has been bothered by anxiety-related problems over the past two weeks by answering seven questions on a 4-point scale (total score: 21). GAD-7 has been extensively investigated in generalised anxiety disorder and emerged as an excellent severity measure of anxiety enabling the identification of anxiety and comorbid depression as distinct dimensions. It is brief and completed entirely by the patient him/herself. It is therefore appropriate for busy epilepsy outpatient clinics and appears as a promising screening tool for patients with epilepsy (Fraser *et al*., 2011).

Clinical phenomenology and differential diagnosis

The difference between anxiety that is comorbid and aetiologically unrelated to epilepsy and anxiety that is directly linked to epilepsy is a useful distinction, crystallized in the recent Classification Proposal of the ILAE (Krishnamoorthy *et al*., 2007). The latter is divided into periictal anxiety, which is related to the seizure itself, and interictal anxiety, which is independent of seizures. Periictal anxiety can precede the seizure (preictal), occur during a seizure itself (ictal), or follow the seizure (postictal).

Preictal anxiety is the most difficult to distinguish and describe precisely. According to recent studies, its pathophysiology is possibly related to EEG changes occurring in the preictal states (Petitmengin *et al*., 2006). Electrophysiologically, these states are characterised by a loss of synchrony between EEG channels connected to the epileptic focus, and this phenomenon has two consequences. Firstly, the isolation of the epileptic focus from ongoing large scale dynamics in the rest of the cortex facilitates locally the epileptic recruitment of adjacent neurons which culminates in seizure occurrence. Secondly, at the same time, the loss of connectivity results in the clinical symptomatology of the prodromal phase which is mainly negative in nature but can include anxiety symptoms as well. From a clinical point of view, identifying prodromal anxiety symptoms is a challenging task since the facilitating factors for the occurrence of seizures frequently include distress, anxiousness, and irritation that are feelings which overlap with the prodromal anxiety symptoms of these patients.

Ictal anxiety, on the other hand, is a relatively well understood clinical phenomenon that occurs as an aura in up to 15% of patients with partial seizures. In the typical scenario, anxiety and fear are related to temporal lobe epilepsy affecting the amygdala, particularly on the right side, but may occur in frontal lobe epilepsy as well. The question naturally arises as to what is the symptomatogenic zone of ictal anxiety. Biraben *et al*. (2001) addressed this issue by performing SEEG recordings in four patients with intense ictal fear as the sole seizure manifestation and concluded that the epileptic discharge in these cases interferes with a complex information processing network that includes orbitofrontal, prefrontal, anterior cingulate, and limbic temporal cortices. Interestingly, this study provided direct SEEG evidence that involvement of the amygdala is not always necessary for the generation of ictal fear. This observation is compatible with current evidence that the neurobiological substrate of anxiety corresponds to a network rather than a single structure with variable involvement of network components according to the type of anxiety disorder (Hartley and Phelps, 2010).

The differential diagnosis of ictal anxiety is primarily panic attacks but these two entities are not always easy to distinguish (Beyenburg *et al*., 2005; Deutsch *et al*., 2009; Vazquez and Devinsky, 2003; Schondienst and Reuber, 2008) (*table 1*). In general, long-lasting anxiety symptoms (>2 minutes), precipitated by stressful external events, more likely represent panic attacks. The occurrence of episodes during night sleep can be particularly useful in that respect. Ictal fear wakes the patient up in the midst of an otherwise peaceful sleep, whereas nocturnal panic attacks always occur in a state of wakefulness. The optimal method for the diagnosis of ictal anxiety is video-EEG monitoring (although a relatively high rate of false negative results may occur with scalp recordings) and additional evidence may also be obtained with appropriate MRI studies.

Postictal anxiety is unrelated to epileptic discharges and may represent the psychiatric equivalent of the well-known phenomenon of Todd's paresis. Kanner *et al*. (2004) recently summarised the postictal psychiatric changes of 100 patients with refractory partial epilepsy and identified anxiety as the most frequent

Table 1. Ictal anxiety *versus* panic attacks: differential diagnosis (modified from Beyenburg *et al*. [2005] and Vazquez and Devinsky [2003]).

	Ictal anxiety	Panic attacks
Duration	0.5-2 min	5-10 min
LOC	May progress to impairment	Alert
Anticipatory anxiety	Can occur but not common	Very common
Déjà vu, hallucinations	>5%	Very rare
Automatisms	Common with progression to CPS	Very rare
Interictal EEG	Often abnormal	Usually normal
Ictal EEG	Usually abnormal	Usually normal
Temporal lobe MRI	Often abnormal	Usually normal

CPS: complex partial seizure; MRI: magnetic resonance imaging.

postictal disturbance, occurring in 45% of cases. Postictal anxiety included worry, agoraphobic symptoms, and panic feelings and the median duration of these symptoms was 24 hours but could last up to ten days or more. Anxiety in the postictal period frequently co-occurs with depressive symptoms representing either an exacerbation of interictal depression or the expression of depressive symptomatology restricted to the postictal phase. (Kanner *et al*., 2010).

Interictal anxiety is certainly the most common form of anxiety in epilepsy, occurring in up to 66% of epileptic patients. It is most frequent among patients with partial epilepsies related to limbic foci, but may also occur amongst patients with generalised epilepsies. The pathogenesis of interictal anxiety is multifactorial and involves both psychological and neurobiological factors (Johnson *et al*., 2004). The psychological factors include the so-called "seizure phobia", which occurs in 20-30% of patients but other issues are also significant, such as the fear of memory impairment, seizure-related trauma, and consequences regarding social environment and work. The neurobiological factors are complex but are possibly related to the kindling phenomenon, as previously discussed.

The differentiation between interictal anxiety and phobias specific to epilepsy, and comorbid anxiety and phobias, is a matter of importance in clinical practice and a key feature of the ILAE classification of Neuropsychiatric Disorders in Epilepsy (Krishnamoorthy *et al*., 2007). Interictal anxiety tends to occur intermittently or, less often, continuously with periods of exacerbations and may co-exist with other affective-somatomoform (dysphoric) symptoms (irritability, depressive moods, anergia, insomnia, atypical pains, and euphoric moods). The specific phobic fears of epilepsy, such as fear of seizures, agoraphobia, and social phobia, may occur either alone or in the context of the Interictal Dysphoric Disorder. In contrast to comorbid phobias, these specific fears are linked to issues related to epilepsy (for instance, the fear and avoidance of a situation reflects the fear of a seizure being provoked in that situation) (Krishnamoorthy *et al*., 2007).

Interictal anxiety exerts a powerful negative impact on the quality of life for people with epilepsy, perhaps even more than seizures themselves. A number of studies (Johnson *et al*., 2004; Cramer *et al*., 2005) have clearly shown that poor health-related quality of life is significantly associated with increased symptoms of interictal anxiety and depression. Interestingly, in these studies, psychiatric symptoms accounted for more variance in health-related quality of life than demographic and seizure-related variables. These data emphasize the significance of psychiatric disturbances for people with epilepsy and highlight the importance of diagnosing and effectively treating these disorders.

The management of anxiety in epilepsy

Anxiety in patients with epilepsy is a multifaceted problem and its management requires a multidisciplinary approach. Beyenburg *et al*. (2005) outlined a comprehensive and clinically useful algorithm which is based on the close collaboration between epileptologists, psychologists, and neuropsychiatrists. First of all, improvement of seizure control by appropriate measures has been recently shown to reduce anxiety levels and result in improved quality of life (Sancho *et al*., 2010) and therefore every effort should be made towards a more efficient control of the patient's epilepsy. Epilepsy surgery appears to have

a beneficial effect as the majority of relevant studies show a reduction in the levels of anxiety postsurgery (Spencer *et al*., 2003; Cankurtaran *et al*., 2005; Devinsky *et al*., 2005; Meldolesi *et al*., 2007; Pintor *et al*., 2007). On the other hand, continued seizures postsurgery are associated with increased anxiety and deterioration in psychiatric status after surgery (Reuber *et al*., 2004; Macrodimitris *et al*., 2011a).

Regarding the pharmacological treatment of anxiety in epilepsy, there are two important issues to consider. The first relates to the optimal treatment of the psychiatric symptomatology. Benzodiazepines are obviously an attractive choice due to their potent antiepileptic and anti-anxiety properties. However, they should be either completely avoided or used for short-term periods only (up to four weeks) due to the danger of dependence and the potential of withdrawal seizures (Gaitatzis *et al*., 2004). Alternatively, one might use buspirone (a partial agonist of serotonin 1a receptors) or, preferably, selective serotonin reuptake inhibitors (SSRIs) (Harden *et al*., 2007). The latter, are the drug of choice because of their effectiveness in primary anxiety disorders, their advantageous side-effect profile, their small effect on neuronal excitability, and their favourable pharmacokinetic properties with a low potential for drug-drug interactions. It should be noted that the propensity of SSRIs for pharmacokinetic interactions is not uniform. For instance, paroxetine inhibits, to a moderate degree, CyP 3A4 (thus affecting the metabolism of carbamazepine, tiagabine, and zonisamide), venlafaxine weakly inhibits 2C19 (phenytoin, phenobarbital) and CyP 3A4, whereas escitaloram does not affect any CyP450 isoenzymes (Harden *et al*., 2007). A recent study highlighted the fact that psychiatric disorders in epilepsy are under-treated with appropriate psychotropic medication possibly due to an overstated fear of causing seizure exacerbation (Henning and Nakken, 2010). Drugs that are commonly used for the treatment of anxiety can be classified in a high-risk, medium-risk or low-risk group, associated with a risk of inducing or exacerbating seizures in more than 5%, 0.5-5%; and <0.5% cases, respectively (Beyenburg *et al*., 2005). The high-risk group includes high-dose chloropromazine, the medium-risk group includes olanzapine, quetiapine, buproprion, and high-dose clomipramine, whereas the low-risk group includes risperidone, imipramine, SSRIs, venlafaxine, and mirtazapine. It is clear, therefore, that appropriately chosen psychotropic drugs can be relatively safely used in epileptic patients with psychiatric comorbidity including anxiety disorders.

The second issue regards the AED of choice in patients with epilepsy and anxiety. Although there are currently no randomised controlled trials specifically addressing this issue, it would be reasonable to prescribe an appropriate AED with anxiolytic potential. For instance, pregabalin, and to a lesser extent gabapentin, are effective in anxiety disorders and pregabalin is in fact licensed for the treatment of generalised anxiety disorder (Mula *et al*., 2007). A recent study of 98 adult patients with refractory partial epilepsy indicated that pregabalin add-on treatment results in significant reduction in anxiety levels (mean reduction in Hospital Anxiety and Depression Scale scores of 1.68 units; 95% CI: -2.60 to -0.76) (Tsounis *et al*., 2011). Other drugs, such as vigabatrin, tiagabine, and valproate may also possess anxiolytic properties whereas the anti-anxiety effects of carbamazepine and oxcarbazepine are supported by anecdotal reports (Beyenburg *et al*., 2005). On the other hand, clinicians should be aware about the possibility of aggravating anxiety symptomatology when prescribing certain AEDs to patients with epilepsy (*i.e*. lamotrigine, felbamate, and levetiracetam) (Brodtkorb and Mula, 2006).

Psychological treatments include anxiety management through relaxation therapy, components of cognitive therapy, aiming to address worrying behavioural challenges, and arts therapies to overcome resistance and enhance concentration, independence, courage, and capacity to survive (Valeta, 2009). With regard to Cognitive behavioural therapy (CBT), a recent study (Macrodimitris *et al*., 2011b) applied group CBT in 18 epileptic patients with comorbid depression and/or anxiety and observed significant improvements in depression, anxiety, negative automatic thoughts, and cognitive therapy knowledge and skills. The intervention was well accepted, as indicated by low drop-out rates, and emerged as a promising form of treatment for anxiety and depression in patients with epilepsy.

Conclusion

It is now well established that anxiety is commonly encountered in epilepsy and is frequently underdiagnosed and under-treated. Its clinical significance cannot be overemphasized as psychiatric comorbidities in general, and anxiety in particular, can profoundly erode health-related quality of life and constitute a major concern in patients with epilepsy (Choi *et al*., 2010). Prompt recognition and effective management of these disorders should be considered a priority in modern epilepsy care. □

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