

## ***Anxiety disorders in people with epilepsy***

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## ***Abstract***

Anxiety disorders are frequent, though probably underdiagnosed comorbidities in epilepsy. Epilepsy and anxiety may share common neurobiological correlates as shown in animal models and suggested by studies demonstrating anxiety disorders before the manifestation of epilepsy. Comorbid anxiety disorders have a major impact on the affected patients' quality-of-life and may increase the risk for suicidality. Successful treatment of the epilepsy may alleviate anxiety symptoms. Treatment of anxiety is based on selective serotonin reuptake inhibitors, benzodiazepines (although only further choice) and psychotherapy. Specific AEDs (especially pregabalin) have been shown to have anxiolytic properties. This paper is aimed at reviewing anxiety disorders in patients with epilepsy discussing current scientific evidence about pathophysiology, clinical aspects and treatment strategies.

## ***Introduction***

Psychiatric diseases constitute important comorbidities of epilepsy. This is not only because of their high prevalence but also because of the impact they have on the affected individual's life. They also merit attention because of special implications for treatment and specific pathophysiological considerations. Whilst psychoses and depressive disorders have found attention since several years, it is only in recent years that anxiety disorders find the attention they deserve (Brandt, 2016). Anxiety disorders are even called the “forgotten comorbidity” (Kanner, 2011). The importance of this topic has also recently been underlined by the fact that a workgroup of the International League of Epilepsy has worked on a consensus paper concerning neuropsychiatric conditions in epilepsy, which also included anxiety (Kerr et al., 2011). The current paper aims at giving an overview of relevant aspects of anxiety disorders in epilepsy with a special focus on prevalence, the impact of an anxiety disorder on the affected individual's daily living, and aspects of treatment.

## ***Prevalence***

Whilst some studies did not find a high prevalence of obsessive compulsive disorder (OCD) in patients with epilepsy (PWE) (Brandt et al., 2010), others have highlighted high rates of OCD or obsessive-compulsive symptoms (OCS) (Monaco et al., 2005, Isaacs et al., 2004, Hamed et al., 2013). Such a discrepancy may be related to the wide spectrum of OCS in epilepsy representing a spectrum rather than an Axis I disorder.

Another study from the UK aimed at identifying not only the prevalence of anxiety disorders in people with epilepsy, but also risk factors associated with this comorbidity (Mensah et al., 2007). The diagnosis of anxiety was made when more than 11 points were reached in the hospital anxiety and depression Scale (HADS). The prevalence rate for anxiety was with 20.5% well within the range found in several other studies. It was associated with a current history of depression, perceived side effects, lower educational attainment, chronic ill health, female gender, and unemployment. In contrast to other studies, there was no association with the duration of epilepsy. State anxiety was significantly associated with symptomatic

focal epilepsy, and trait anxiety with high seizure frequency, symptomatic focal epilepsy and female gender in a study from Greece (Kimiskidis et al., 2007). The coexistence of another chronic disorder does not seem to have an influence on the presence of anxiety symptoms in PWE (Asadi-Pooya et al., 2007) although poorer general health has been found as a contributing factor to anxiety (Jacoby et al., 2015). Good social support is, however, protective (Jacoby et al., 2015). A recent review analyzed studies assessing risk factors for depression and anxiety in epilepsy patients (Gandy et al., 2012). All six studies assessing anxiety found one or more risk factors for the development of that comorbidity. A problem is, however, that the findings of these studies were not consistent to each other and that the identified risk factors generally only explained a certain amount of the variance. A statistically significant relationship has been found between anxiety and higher scores relating to powerful-others Health Locus-of-Control (HLOC; see also below: Impact/Quality-of-life) (Asadi-Pooya et al., 2007). The presence of anxiety (and also depressive) disorders worsened adverse events to antiepileptic drugs (Kanner et al., 2010). Increased levels of neuroticism have also been found to be a risk factor (Endermann and Zimmermann, 2009). Stigma (McCagh et al., 2009), higher escape-avoidance and decreased distancing (Goldstein et al., 2005) and increased use of wish-fulfilling fantasy (Thompson and Upton, 1992) predicted higher levels of anxiety. Generally, those studies have been criticized for their quality by the authors of the review (Gandy et al., 2012).

A study from Hong Kong found a higher prevalence of anxiety in patients with frontal lobe epilepsy than in those with generalized epilepsy (Tang et al., 2012). This would highlight pathophysiological considerations, as psychosocial factors should be similar in both groups of epilepsy syndromes. A limitation of that study might be that the authors combined idiopathic, cryptogenic and symptomatic forms of generalized epilepsies (GE). They included, for instance, patients who were diagnosed as having GE after stroke or infection or trauma. There was also a high proportion of cryptogenic GE. It would be of interest to see the results for idiopathic GE which might form a more homogeneous group.

Anxiety disorders are not only important comorbidities of epilepsy, but an anxiety

disorder may also precede the onset of epilepsy. According to a large register study, the incidence rate ratio for an anxiety disorder was significantly increased in the three years before epilepsy onset and in the first two years after (Hesdorffer et al., 2012). See the „neurobiological correlates“ section for implications of these epidemiological findings.

It is of importance, to differentiate anxiety symptoms from the diagnosis of an anxiety disorder. Postictal cognitive and psychiatric have been studied thoroughly using a questionnaire of 42 items answered by 114 patients with respect to a period of 72 hours after a seizure (Kanner et al., 2004). Anxiety was the most frequent postictal emotional symptom, experienced by 45 out of the 114 patients. This means that some patients deserve special attention during the first three days following a seizure because of emotional disturbances.

### ***Anxiety in childhood and adolescence***

Anxiety affects not only adult patients with epilepsy and exerts an impact on their quality-of-life, but this applies also to children and adolescents (Stevanovic et al., 2011). In children the rate of self-reported anxiety is higher than parent-reported showing the importance of relying on the children's self-assessment wherever possible (Reilly et al., 2015). Persons in the general population (not restricted to persons with epilepsy) with a diagnosis of anxiety disorder at age 26 have had an anxiety disorder during adolescence in many cases (Kim-Cohen et al., 2003). The importance of anxiety disorders in younger years has led the American Academy of Child and Adolescent Psychiatry to recommend that children and adolescents should be routinely screened for symptoms of anxiety (Connolly et al., 2007). Data in children with epilepsy are still limited and evidence is sparse. Further studies are urgently needed in order to understand whether specific epilepsy syndromes are associated with an increased risk of anxiety disorders.

### ***Neurobiological correlates***

Although numerous brain regions are likely to be involved, the amygdala and the hippocampus play a key role in the neurobiology of both epilepsy and anxiety. This strict association seems to be further supported by the existence of a bidirectional relationship between epilepsy and anxiety meaning that anxiety does not only follow epilepsy but that it may precede the onset of epilepsy by years (Hesdorffer et al., 2006), which is, by the way, also true for psychosis, depression and suicidality. One explanation for the bidirectional relationship between anxiety disorders and epilepsy may be in the role that serotonin plays for both diseases (Kanner, 2009). These findings are paralleled in a couple of animal studies listed below.

The amygdala is determinant in the experience of fear and its autonomic and endocrine response (through the output to the hypothalamus), while the amygdala output to periaqueductal gray is mainly implicated in avoidance behavior, also typical of fear responses (Stahl, 2003). Furthermore, the hippocampus is important in the re-experiencing of fear. Activation of fear circuits is a major hypothesis for explaining symptoms in anxiety disorders and the reduction of an excessive output from these neurons may theoretically improve the clinical picture (Stahl, 2003) (Rogawski and Löscher, 2004). Such a mechanism has a number of similarities with the excessive outburst typical of epileptic neurons, explaining the effects of antiepileptic agents (such as benzodiazepines; BDZs and antiepileptic drugs) in the treatment of anxiety (Mula et al., 2007). In fact, the potentiation of GABA-ergic inhibition and the modulation of calcium channels represent valuable anti-anxiety mechanisms (Stahl, 2003) (Mula et al., 2007).

Animal models of epilepsy also suggest a correlation with anxiety. Genetic absence rats of Strasbourg (GAERS), a genetic model of human generalized epilepsy, were tested using the elevated plus maze (EPM) and the open field arena (OF) tests. When compared to healthy controls, the GAERS rats showed increased levels of anxiety. An important finding is that the development of anxiety was already detectable before the onset of epilepsy. This is an especially important paper as it suggests a common pathophysiological basis of epilepsy

and anxiety rather than explaining anxiety as a secondary (neurodegenerative or psychosocial) consequence of epilepsy and seizures (Jones et al., 2008).

Anxiety-like behavior has been observed during the maturation phase in male Wistar rats in the pilocarpin model (Lopes et al., 2016). This finding supports the hypothesis that anxiety and epilepsy are associated on a pathophysiological level. Status epilepticus in early life caused an increase in anxiety-like behavior in male Wistar rats. Behavioral change could be prevented by administration of ketamine during the status (Loss et al., 2012).

Long-Evans rats with spontaneous spike-wave-discharges and normal (healthy) Wistar rats as controls were examined with two animal models of anxiety disorders: the open field (OF) and the elevated plus maze (EPM) tests. Long Evans rats interestingly showed a less anxious behavior, i.e. longer duration on the open arms of the EPM and in the center zone of the OF (Shaw et al., 2009). Their level of anxiousness was associated with spike-wave frequency and could be ameliorated by administration of ethosuximide.

Even subconvulsive doses of pilocarpine led to anxiety-like behavior in male Wistar rats (Duarte et al., 2013). These effects were assessed by the EPM, the elevated T-maze, the OF and the step-down avoidance task tests.

### ***Diagnosis/ diagnostic procedures/ differential diagnosis***

According to our knowledge, no screening instrument for the detection of anxiety disorders has been validated yet in people with epilepsy. An attempt was recently made but the authors themselves concluding that the psychometric properties of the tested instrument were not sufficient (Mbewe et al., 2013).

In clinical terms, the first step in the diagnosis of anxiety disorders in epilepsy comprises the analysis and identification of all elements that may contribute to psychiatric symptoms, such as psychosocial issues, adverse treatment effects or neurobiological factors directly related to the seizures or the epileptic disorder. In particular, patients with epilepsy may experience a number of psychiatric manifestations around the ictus that have to be clearly

differentiated from true psychiatric comorbidities. The practicability of classifying such symptoms according to their temporal relation to seizure occurrence (peri-ictal/para-ictal symptoms vs. interictal symptoms) is well established. Peri-ictal phenomena have been well described by Gowers (Gowers, 1881) and Jackson (Jackson, 1850) but also by Kraepelin (Kraepelin and Johnstone, 1912) and Bleuler (Bleuler, 1916). The differentiation between peri-ictal and interictal psychiatric symptoms has relevant implications in terms of prognosis and treatment. Such feelings are almost indistinguishable from interictal ones, apart from duration and close relation with seizure occurrence. It seems, therefore, important for clinicians to enquire about these phenomena, because they cannot be detected by rating scales or questionnaires (Mula et al., 2008). A case of a patient who had had a few generalized tonic-clonic seizures in his youth and subsequently developed an agoraphobia with panic disorder has been reported (Harter et al., 2000).

Ictal anxiety is frequent in right temporal lobe epilepsy (Guimond et al., 2008) and rare in extratemporal epilepsy (Oehl et al., 2012). It seems to be reported by 10%-15% patients with partial seizures (Gaitatzis et al., 2004), is more common in women than men (Chiesa et al., 2007, Toth et al., 2010) and seems to have a poor prognostic value for surgery (Feichtinger et al., 2001). Ictal anxiety can be differentiated through a careful history taking with special attention to the association between the duration of the attacks and the presence of accompanying non-paroxysmal symptoms of an anxiety disorder like avoidance behavior or the "circle of fear". Linguistic methods may be helpful in the differential diagnostic process (Schoendienst and Reuber, 2008).

## ***Impact***

### ***Quality-of-life***

Comorbid anxiety disorders or anxiety symptoms yield a negative impact on the subject's quality of life, especially within the context of a combined comorbidity of anxiety and depression (Kanner et al., 2010, Kwan et al., 2009). Trait anxiety seems to be more associated with poorer quality-of-life than state anxiety (Jacoby et al., 2015). Health locus of



control (HLOC) is a concept that concerns a person's beliefs regarding where control over his or her illness lies. Patients who attribute the control over their illness to so-called powerful others experience higher levels of anxiety (Asadi-Pooya et al., 2007). Self-perception of seizure precipitants also increased the anxiety level (Sperling et al., 2008). This is on first sight a bit surprising, as people who are able to name seizure precipitating factors might be able to exert control over their seizures. An explanation, however, may be that patients attribute seizures to irrelevant factors and thus experience anxiety. Anxiety (and also depression) is associated with the presence of adverse events (AE) to antiepileptic drugs (Gomez-Arias et al., 2012, Jacoby et al., 2015). This is actually a finding that may have a major impact on clinical practice: It can be speculated that it might be necessary in patients who report a high number or severity of AE to focus on a comorbid anxiety or mood disorder rather than merely on changing the antiepileptic drug regimen. The causal relationship may, however, also be the other way, i.e. that a higher rate of AEs might lead to a mood or anxiety disorder. Depression and anxiety have also been found to be negatively correlated with adherence to the antiepileptic drug regimens (Guo et al., 2015). The authors speculate that anxious patients have lower confidence and more difficulty remembering to take AEDs and following the prescriptions of doctors. In shed of the above-mentioned study (Gomez-Arias et al., 2012) it might also be possible that they experience more side-effects and thus are prone to be non-compliant. A high level of anxiety is also associated with perceived stigma in persons with newly diagnosed epilepsy (Lee et al., 2015). Anxiety also contributes to memory complaints in persons with epilepsy (Mula et al., 2016).

### ***Suicidality***

The presence of a comorbid anxiety disorder is according to a Danish study a risk factor for suicidality in people with epilepsy (Christensen et al., 2007). In the study population, the risk of completed suicides was increased 11.4-fold (rate ratio) for persons with epilepsy and anxiety disorder compared to people without epilepsy and without a psychiatric disorder. In a

study concerning psychiatric comorbidity and suicidal behavior in epilepsy, suicidal ideation was associated with a comorbidity of anxiety and depression in 71.4%, 62.5% when there was a comorbid depression alone and 54% when anxiety was the only comorbidity.

### ***Localization/ lateralization***

A clear lateralization could not be demonstrated for psychopathology (including anxiety) in epilepsy patients by several studies (Altshuler et al., 1990, Sperli et al., 2009) nor could a clear localization (temporal lobe versus extra-temporal lobe epilepsy) be shown (Swinkels et al., 2006).

### ***Anxiety pre and post epilepsy surgery***

The presence of anxiety predicts a worse seizure outcome after epilepsy surgery (Guarnieri et al., 2009, Kanner et al., 2009). Epilepsy surgery, vice versa, may improve pre-existing anxiety symptoms especially when seizure freedom could be achieved (Meldolesi et al., 2007, Devinsky et al., 2005, Cleary et al., 2013). Anxiety has been shown to decrease slowly indicating that it may have something to do with a gradual accommodation to the changes in life provoked by surgery (Meldolesi et al., 2007). This could also explain that another study showed reduced levels of depression but not anxiety 12 months after temporal lobe surgery (Reuber et al., 2004). According to a recent review, there may, however, be an at least intermittent increase in anxiety post-operatively (Cleary et al., 2013). A study showing that anxiety symptoms negatively correlated with the remnant hippocampal volume in left-sided temporal lobe resections has some weaknesses as it does not provide sufficient information on pre-operative psychiatric comorbidity or pre-operative brain imaging (Paparrigopoulos et al., 2008).

### ***Treatment***

Although several therapeutic approaches have been established and are being applied in different forms of anxiety disorders in general, there is a dearth of treatment studies in the

subgroup of epilepsy patients suffering also from anxiety (Mula, 2013b). Therefore, until nowadays, the general therapeutic principles have to be applied.

## ***Drugs***

Selective serotonin reuptake inhibitors (SSRI) are established in the treatment of several subsyndromes of anxiety disorder (Mula, 2013b). There is, however, a latency of 2-6 weeks (Bandelow et al., 2013) before they can show full efficacy. Benzodiazepines (BZD), mainly alprazolam, are advocated as treatment during that phase. As BZDs have also antiepileptic properties, treatment of both conditions with one drug should be possible. They are, however, only treatment option of further choice in epilepsy. Dal Pizzol et al found similar anxiety levels in patients with and without BZD administered for epilepsy (Pizzol et al., 2012). This may, however, be due to the fact that the anxiety levels were not examined before initiation of BZD so that there is no baseline examination. There is data for anxiolytic properties of AEDs with varying degrees of evidence. Strong evidence (at least one randomized controlled trial) has been demonstrated for pregabalin in social phobia and generalized anxiety disorder, lamotrigine in posttraumatic stress disorder, and gabapentin in social anxiety (Mula et al., 2007). This refers to the efficacy on anxiety disorders, not necessarily meaning comorbid anxiety disorders in persons with epilepsy. Pregabalin has been shown to reduce effectively symptoms of anxiety in patients with refractory focal epilepsy and comorbid anxiety disorder in an open, uncontrolled study (Brandt et al., 2013)..

Epilepsy patients treated with add-on levetiracetam (LEV) for their seizure disorder showed significantly less anxiety after LEV was added (Hagemann et al., 2013). This was, however, only true for the subgroup that had an improved seizure frequency and is thus not a specific anxiolytic effect of LEV. This finding is therefore in line with the above mentioned studies showing improvements of anxiety symptoms after successful epilepsy surgery. Anxiety has – among other psychiatric conditions – also been reported as a side effect of LEV (Mula et al., 2003).

## ***Psychotherapy***

Cognitive-behavioral therapy (CBT) has been shown to improve anxiety in patients with epilepsy (Macrodimitris et al., 2011). This was, however, a non-controlled study in a small group of patients. It has also to be discussed whether an approach with a standard manual is adequate or whether a specific program for people with epilepsy and anxiety symptoms should be designed. More or less the same limitations are present in a study with a computerized CBT in children with epilepsy and anxiety (Blocher et al., 2013).

### ***Alternative treatments***

Bright light therapy for symptoms of anxiety and depression in patients with focal epilepsy has been examined in a randomized controlled trial (Baxendale et al., 2013). There were significant improvements in the rates of depression and anxiety but there was no significant difference between the study group and the control group that had been treated with light of lower intensity. Interestingly, the authors do not draw the conclusion that bright light therapy had only a placebo effect but express the opinion that emotional symptoms in epilepsy need only lower intensities of light to be treated successfully.

### ***Perspectives***

First of all, it is beyond all scientific needs necessary to improve the diagnosis of anxiety disorders in epilepsy patients as currently probably many patients with this comorbidity go undiagnosed and thus untreated. Diagnostic tools for comorbid anxiety disorder in epilepsy, especially simple-to-use screening instruments, should be developed and tested (Hamid et al., 2011).

### ***Need for therapeutic options***

As mentioned above, it has to be discussed whether psychotherapeutic approaches using standard manuals are adequate for the treatment of anxiety in epilepsy patients or whether special concepts focusing on epilepsy-related anxiety are necessary.

### ***Do we need an own diagnostic entity?***

In our own research (Brandt et al., 2010) we got the impression that many people with epilepsy show relevant anxiety symptoms that did, however, not lead into the diagnosis of an anxiety disorder. It should be part of future research to elucidate whether a specific diagnostic category for anxiety in epilepsy patients is needed compared to the concept of Interictal Dysphoric Disorder (IDD) for affective symptoms (Mula, 2013a).

## **Conclusion**

Anxiety disorders are important comorbidities of epilepsy with special implications concerning diagnostic process, impact on the patients' lives and treatment. After being neglected for a long time, recent research has elucidated many aspects of this comorbidity. There is, however, still a major need for future research.

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