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Panic disorder in epilepsy

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ABSTRACT

A 51-year-old woman showed structural epilepsy following an atypical, nontraumatic intracranial hemorrhage in the right frontal area. Despite successful seizure control with lamotrigine, she developed severe morning anxiety and panic attacks, leading to agoraphobia, social withdrawal, and psychogenic nonepileptic seizures. Neuropsychiatric and psychological assessments confirmed an anxiety disorder with no significant symptoms of depression. The patient received various psychopharmacological treatments with limited success. This case report illustrates that managing panic disorder in patients with structural epilepsy requires a comprehensive treatment approach that includes pharmacotherapy and psychotherapy. Differential diagnosis and accurate treatment are crucial because of the symptom overlap between panic attacks and *peri*-ictal fear. Screenings instruments such as the Panic and Agoraphobia Scale (PAS) can aid in assessing anxiety-related symptoms. First-line pharmacotherapy with selective serotonin reuptake inhibitors, especially sertraline, or venlafaxine can effectively reduce panic attacks and can be recommended in patients with epilepsy. Psychotherapy, particularly cognitive-behavioral therapy, is the treatment of choice. Referral to a psychiatrist is indicated when symptoms are severe or refractory to treatment.

1. Illustrative case

A 51-year-old woman developed structural epilepsy after an atypical, nontraumatic intracranial hemorrhage (ICH) situated in the right frontal area. The patient underwent a decompressive hemicraniectomy with hematoma evacuation and experienced subsequent focal to bilateral tonic-clonic seizures. She also developed physical disabilities, including paralysis of the left arm, which improved during rehabilitation. Electroencephalographic (EEG) monitoring showed a generalized slowing and right centro-temporo-parietal breach rhythm. No epileptiform discharges were detected.

Initial brain magnetic resonance imaging (MRI) confirmed the presence of the ICH. However, the patient subsequently avoided undergoing further MRI due to agoraphobic fears. Response to antiseizure medication (ASM) was as follows: Levetiracetam and lacosamide were discontinued due to side effects (irritability) and lack of efficacy. Under lamotrigine, the patient was seizure free. Initially, the patient's condition showed a positive course, allowing her to actively engage in daily activities, including driving a car, without perceiving any subjective limitations.

Approximately 11 months after ICH, the patient began experiencing severe morning anxiety characterized by body shaking, shortness of breath, and a sense of impending doom. These symptoms progressed to frequent panic attacks, leading to an emergency hospitalization due to chest pain and a fear of dying. The patient also developed agoraphobia (fear and avoidance of situations/places where escape might be difficult or help may not be available), social withdrawal, and psychogenic nonepileptic seizures.

Neuropsychiatric and psychological examinations confirmed the presence of an anxiety disorder and ruled out significant depressive symptoms. In addition to a clinical interview, the German versions of the Generalized Anxiety Disorder 7 (GAD-7, total value 17, "severe anxiety") [1,2], the Beck Anxiety Index (BAI, total value 11, "mild anxiety") [3,4], the Beck Depression Inventory (BDI-II, total value 12, "minimal depression") [5,6], and Neurological Disorders Depression Inventory in Epilepsy (NDDI-E, total value 13, "depression unlikely") [7,8], were administered. Various psychopharmacological treatments were attempted to manage the patient's affective symptoms. However, finding an effective treatment regimen proved challenging.

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2. Anxiety disorders

The prevalence of anxiety disorders is significantly higher in people with epilepsy (PWE) compared with the general population (20.2 % vs. 9.4 %) [9]. Anxiety disorders in epilepsy are associated with reduced quality of life [10], increased health care utilization [11], decreased social function, and a higher severity of epilepsy [12]. Moreover, it is important to highlight the association between anxiety and suicidal behavior in PWE (for a review, see Munger Clary [13]). Johnson et al. [14] summarized that anxiety-related symptoms are stronger predictors of health-related quality of life than seizure type/frequency or depressive symptoms.

In a prospective clinic-based survey [15], we demonstrated increased rates of anxiety disorders, particularly social phobia (7.2 % point prevalence), specific phobia (6.2 % point prevalence), and panic disorder (5.1 % point prevalence), in patients with refractory focal epilepsy when compared with the general population in Germany (4-week prevalence of 1.1 %). As seen in the review by Johnson et al. [14], the prevalence rates of panic disorder were 2 to 3 times higher among PWE compared to healthy controls. These results emphasize that panic disorder is more prevalent among PWE, warranting careful diagnosis and management [14,16].

2.1. Clinical signs and symptoms of panic disorder

Panic attacks are characterized by sudden intense fear and discomfort (for a review, see Craske and Barlow [17]), accompanied by somatic and cognitive reactions (Table 1). Panic attacks usually peak within a few minutes and can last up to 30 min [18]. In general, patients with panic attacks cannot identify an external trigger, such as a specific phobic object, and therefore report that the panic attack occur spontaneously. The presence of recurrent panic attacks may lead to a diagnosis of panic disorder, especially if there is persistent worry about experiencing future panic attacks and/or maladaptive behavioral changes—for example, avoidance behaviors (Table 1). Based on the recent International Classification of Disease 11th Revision (ICD-11), panic disorder and panic attacks can be coded separately when panic attacks do not meet the diagnostic criteria for panic disorder [19]. Of note, there is a significant overlap between panic disorder and agoraphobia [17], as seen in our case report. Agoraphobia is an anxiety disorder characterized by intense fear or panic attacks in situations where a person perceives the environment as dangerous without having support or means of escape [17]. Patients with agoraphobia often avoid unfamiliar situations like open areas, crowds, public transportation, shopping centers or places outside of their home.

Table 1
Diagnostic criteria of panic disorder in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5; adapted from [22]).

A. Recurrent unexpected panic attacks. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur:
Note: The abrupt surge can occur from a calm state or an anxious state.

- Palpitations, pounding heart, or accelerated heart rate.
- Sweating.
- Trembling or shaking.
- Sensations of shortness of breath or smothering.
- Feelings of choking.
- Chest pain or discomfort.
- Nausea or abdominal distress.
- Feeling dizzy, unsteady, light-headed, or faint.
- Chills or heat sensations.
- Paresthesia.
- Derealization/depersonalization.
- Fear of losing control or "going crazy."
- Fear of dying.

B. At least one of the attacks has been followed by 1 month (or more) of one or both of the following:
1. Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, "going crazy").
2. A significant maladaptive change in behavior related to the attacks (e.g., behaviors designed to avoid having panic attacks, such as avoidance of exercise or unfamiliar situations).

C. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism, cardiopulmonary disorders).

D. The disturbance is not better explained by another mental disorder (e.g., panic attacks do not occur only in response to feared social situations, as in social anxiety disorder; in response to circumscribed phobic objects or situations, as in specific phobia; in response to obsessions, as in obsessive–compulsive disorder; in response to reminders of traumatic events, as in posttraumatic stress disorder; or in response to separation from attachment figures, as in separation anxiety disorder).

2.2. Differential diagnosis considerations

Distinguishing between *peri*-ictal fear and panic attacks is crucial for an accurate diagnosis and appropriate treatment (for a review, see Kanner [20]). As outlined by Hingray et al. [21], anxiety symptoms can be classified as *peri*-ictal (preictal, ictal, postictal) and interictal (Table 2A), and these manifestations can occur in any combination. Ictal anxiety ("ictal panic") is commonly associated with focal aware seizures of the mesial temporal lobe and is sometimes not correctly diagnosed until patients develop focal to bilateral tonic-clonic and/or focal non-aware seizures [20]. By contrast, interictal panic disorder and anxiety disorders are not related to epilepsy. To differentiate ictal fear and interictal anxiety, focusing on central worries is useful for differential diagnosis. For example, panic attacks associated with panic disorder usually involve fear of an impending physical or mental catastrophe [22], whereas ictal events generally exhibit milder panic intensity without reaching the peak of a panic attacks. Additionally, ictal fear is sometimes described as less reality based [20]. As for the duration of anxiety, ictal panic is a short event (0.5 to 2 min) [21], whereas panic attacks last considerably longer (up to 30 min) [18]. Panic attacks typically develop during wakefulness, while ictal panic can occur in both awake and sleep states [23]. Ictal panic has also been associated with an increased risk of interictal panic disorder [20].

Moreover, anxiety disorders specific to epilepsy (Table 2B) should be considered, although they are not described in the current psychiatric classification systems [13,21]. Anticipatory anxiety of epileptic seizure [24] and seizure phobia are related entities [21] that encompass the anxiety of having a seizure and avoidance behavior of places or situations where seizure have already happened or where it potentially could occur. Individuals with epileptic social phobia experience persistent anxiety associated with being observed by other people during seizures and being judged negatively as a result [21].

Furthermore, it is essential to distinguish *peri*-ictal and interictal anxiety from other medical conditions like cardiac arrhythmias,

Table 2
Classification of the anxiety symptoms in people with epilepsy [13,20,21].

A	Peri-ictal anxiety	Interictal anxiety	B	Epilepsy-specific anxiety disorders
	▪ Preictal: anxiety symptoms up to 3 days before a seizure ▪ Ictal: anxiety symptoms as part of the semiology ▪ Postictal: anxiety symptoms over the 3 days after a seizure	Anxiety disorders • Panic disorder Agoraphobia • Social phobia • Specific phobia • … etc.		▪ Anxiety about epilepsy diagnosis ▪ Anticipatory anxiety of epileptic seizure ▪ Seizure phobia ▪ Epileptic social phobia ▪ Fear of side effects of ASM

alcohol/drug withdrawal, or hyperthyroidism [20].

2.3. The effect of iatrogenic processes on psychopathology.

Various anxiety-related symptoms may occur in relation to seizures, making a differential diagnosis necessary to avoid misdiagnosis and iatrogenic effects (for a review, see Mula [25]). The use of ASM with negative psychotropic characteristics (e.g., levetiracetam, zonisamide, and topiramate) or the discontinuation of ASM with mood-stabilizing properties (e.g. carbamazepine, gabapentin, lamotrigine, pregabalin and valproic acid) might induce symptoms of fear. In addition, some ASM have enzyme-inducing properties that can reduce the levels of psychoactive drugs and thus elicit states of anxiety [26].

2.4. Psychometric assessment of anxiety symptoms

There are several screening instruments to assess anxiety-related symptoms during the treatment course (for a review, see Rauh et al. [27]), some of which can be accessed free of charge online [28]. The Beck Anxiety Index (BAI) is a 21-item self-report scale measuring the severity of anxiety symptoms [29] and is commonly used to measure anxiety in PWE. The Hospital Anxiety and Depression Scale (HADS) is also used in a clinical context [30]. The Generalized Anxiety Disorder 7 (GAD-7, available online [31]) is a 7-item self-rating scale to identify anxiety disorders, particularly generalized anxiety disorder [2]. Although it is a well-validated and widely used screening tool for anxiety disorders in PWE [32], it may not be able to specifically detect panic disorder [33]. For PWE, the Epilepsy Anxiety Survey Instrument (EASI, available online [34]) and the shorter screening instrument brief EASI (brEASI) are useful to assess anxiety [35]. The brEASI demonstrated high sensitivity and specificity to detect anxiety disorders like panic disorder or agoraphobia. For a panic disorder oriented assessment, the Panic and Agoraphobia Scale (PAS) can be used as a screening tool [36]. This brief 13-item instrument (clinician and self-rated versions available) was developed to evaluate the severity of illness and the effectiveness of psychopharmacological and psychotherapy treatments. It has been applied in double-blind placebo-controlled and other clinical trials [37,38]. The American Psychiatric Association (APA) provides the Severity Measure for Panic Disorder – Adult for free, which is an easy-to-use 10-item instrument to determine the severity of panic disorder [39].

In general, it is recommended to conduct structured clinical interviews, such as the Mini International Neuropsychiatric Interview (M.I.N.I.) [40], preferably with epilepsy-specific adaptations [41], to provide a valid diagnostic assessment of anxiety disorders [9], while avoiding underestimation and undertreatment of these comorbid disorders [23].

3. Pharmacologic treatment considerations

The APA Practice Guideline for the Treatment of Patients with panic disorder [42] provides recommendations for drug treatments in panic disorder. The APA recommends continuing panic disorder pharmacotherapy for at least 12 months after symptom remission. Long-term or maintenance treatment with medication may be necessary for patients experiencing multiple relapses or chronic symptoms.

First-line pharmacotherapy: Selective serotonin reuptake inhibitors (SSRIs) such as sertraline have been shown to be effective in reducing the frequency and severity of panic attacks. We recommend sertraline as the initial drug for treating panic disorder in epilepsy. This recommendation is based on its proven effectiveness in treating panic disorder, its generally well-tolerated side effect profile, low pharmacokinetic and pharmacodynamic interactions, and approval by the U. S. Food and Drug Administration (FDA) for panic disorder.

A common titration schedule for sertraline might look like this:

1. **Week 1–2:** Initiate treatment with a low dose, such as 25 mg once daily, usually given in the morning (to prevent overstimulation and insomnia).
2. **Week 3–4:** Increase the dose to 50 mg once daily.
3. **Week 5 and onward:** Since sertraline has a flat dose–response curve, approximately 75 % of patients respond to the initial dose of 50 mg once daily. Depending on individual response and tolerability, the dose may be further increased by 50 mg increments at intervals of at least one week. The target therapeutic dose for most conditions is in the range of 50–150 mg per day [43].

Second-line pharmacotherapy: As second-line option, we recommend the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine due to its dual mechanism of action, potentially offering a broader spectrum of action for individuals with symptoms related to both serotonin and norepinephrine. It is important to note that side effects, particularly blood pressure changes, may be more prevalent compared to sertraline. Nevertheless, venlafaxine is an FDA-approved medication for the treatment of panic disorder.

A common titration schedule for venlafaxine might look like this:

1. **Week 1:** Initiate treatment with a low dose, such as 37.5 mg once daily, usually given in the morning (to prevent overstimulation and insomnia), typically taken with food. The immediate-release form may be used initially.
2. **Week 2–3:** Increase the dose to 75 mg once daily. The extended-release (XR) formulation may be considered which allows for once-daily dosing.
3. **Week 4 and onward:** Since venlafaxine has a flat dose–response curve, approximately 75 % of patients respond to the initial dose of 75 mg once daily. Depending on individual response and tolerability, the dose may be further increased by 37.5 or 75 mg increments at intervals of at least one week. The target therapeutic dose for most conditions is in the range of 75–225 mg per day [43].

Nota bene: It can be helpful to inform patients about the possibility of experiencing activation symptoms, such as jitteriness, increased anxiety, or insomnia, during the initial stages of treatment. Such activation is not dangerous and may indicate that the diagnosis of panic disorder is correct, which can aid in patient adherence during early treatment.

Combining sertraline or venlafaxine with a benzodiazepine for a brief period (usually a few weeks) may be considered in certain situations, such as when rapid symptom relief is necessary. Benzodiazepines are effective in rapidly reducing anxiety symptoms and panic attacks. However, they are generally recommended for short-term use due to the risk of dependence, tolerance, and withdrawal symptoms. Once symptoms are under control, the benzodiazepine is usually tapered and discontinued while maintaining sertraline or venlafaxine.

3.1. Effective versus failed trial

Given the lack of standardized criteria for treatment resistance in panic disorder, treatment resistance commonly refers to an inadequate response to what is typically considered sufficient treatment [44]. Symptoms should show some reduction in intensity and frequency within the first 3–4 weeks of treatment at an adequate dose. After a minimum of 6 weeks of treatment with an adequate dose, a failure to achieve a 50 % reduction on a standard rating scale (such as the PAS) can be considered as nonresponse to drug treatment [45]. For patients with panic disorder who still have symptoms after the initial treatment, a re-evaluation of the diagnosis, treatment intensity, adherence, and comorbidities is necessary. Substance/alcohol abuse or underlying personality disorders should also be considered.

3.2. Most common adverse events of the psychotropic medications

Patients should be informed that the effects of antidepressants typically begin with a latency of about 2 weeks (range 1–6 weeks). The potential side effects, especially serious or common ones, should be discussed. In particular, the following should be mentioned:

- For treatment with sertraline or venlafaxine: Restlessness and insomnia in the first days of treatment; sexual dysfunctions; discontinuation symptoms.
- For treatment with benzodiazepines (if used in justified exceptional cases): Development of dependence, tolerance, prolonged reaction time, and the risk of falls.

Nota bene: Before initiating antidepressant treatment, a discussion with adult patients is essential to consider the potential risk of suicidal behavior, especially when dealing with panic disorder and other anxiety disorders [46]. Asking about suicidal thoughts requires sensitivity and empathy. It is essential to approach the subject with genuine care, ensuring a safe and non-judgmental environment for the person's well-being. Here is on example of how one might delicately broach the topic: "*I've noticed that you've been going through a tough time lately. Sometimes, when people feel this way, they may have thoughts of self-harm. Have you been thinking of suicide or do you ever feel like you're at a point where you don't want to go on?*" If someone discloses suicidal thoughts, it is critical to take their disclosure seriously and facilitate connections with mental health professionals or crisis resources. For neurologists seeking additional resources on how to approach or discuss the topic of suicidal behavior, the American Psychiatric Association (APA) and the World Health Organization (WHO) offer valuable guidelines and resources.

3.3. Safety for use in people with epilepsy

The use of antidepressants in PWE has raised concerns due to reported seizures during treatment with tricyclic antidepressants (TCAs) [47]. However, evidence suggests that SSRIs/SNRIs pose a low risk of seizures and can generally be recommended for PWE, with moderate to low evidence indicating neither an increase nor exacerbation of seizures in the latest Cochrane *meta*-analysis on antidepressants for PWE and depression [48]. In some cases, SSRIs and SNRIs have even shown potential to decrease seizure frequency in patients with frequent seizures [49]. Moreover, these medications have demonstrated promising therapeutic outcomes for the treatment of a depressive and/or anxiety disorders regardless of the frequency of seizures. Therefore, treatment of panic disorder with an SSRI or SNRI poses a low risk of seizures and can be safely prescribed for PWE.

3.4. Iatrogenic and therapeutic phenomena of pharmacokinetic interactions with antiseizure medication

Considering pharmacokinetic interactions is crucial when treating epilepsy and psychiatric disorders. Knowing the major metabolic pathways enables to predict pharmacokinetic interactions. Sertraline and venlafaxine have a low to moderate potential for drug-drug interactions. See Table 3 for examples of pharmacokinetic interactions between ASMs and psychiatric drugs.

3.5. Antiseizure medication as a treatment option for panic disorder

While many ASM have been tested for the treatment of anxiety disorders, it is difficult to find studies dedicated to their use in panic disorder. A placebo-controlled trial of gabapentin for the treatment of panic disorder failed to demonstrate a significant improvement compared with placebo, although post hoc analyses of severely ill patients showed an improvement [53]. For lamotrigine, there is only a case series of four patients with panic disorder in which it showed some efficacy [54], and for VPA and levetiracetam there are small-scale open studies which showed some benefit [55,56].

Table 3
Examples of pharmacokinetic interactions between antiseizure medication and psychiatric medication.

	May decrease the serum concentration of:	May increase the serum concentration of:
Carbamazepine, phenytoin, phenobarbital, and primidone [50]	■ Tricyclic antidepressants ■ Selective serotonin reuptake inhibitors ■ Selective serotonin and noradrenaline reuptake inhibitors	–
Cenobamate [51,52]	■ Citalopram, escitalopram, mirtazapine, bupropione, haloperidol, clorazepate, alprazolam, and buspirone	■ Sertraline ■ N-desmethyl-clobazam
Valproate [50]	–	■ O-desmethylvenlafaxine
Fluoxetine, norfluoxetine, and fluvoxamine [50]	–	■ Phenytoin
Fluoxetine [50]	–	■ Valproate
Sertraline [50]	–	■ Valproate and lamotrigine

On the other hand, it has to be asked whether ASM lead to panic attacks. There are single case reports on the development of panic attacks under topiramate [57]. Generally, around 8 % of PWE develop psychiatric problems while receiving ASM, which seems to be more related to a history of psychiatric disorders than to a specific ASM [58]. Thus, no specific ASM has to be avoided, but treatment changes have to monitored carefully.

3.6. The benefits of a psychotherapeutic modality for the clinical scenario

It is important to note that medication alone should not be considered the sole treatment for panic disorder independent of the presence of epilepsy. Psychotherapy, particularly cognitive-behavioral therapy (CBT), is a proven and effective treatment for panic disorder [42]. CBT helps individuals identify and modify thought patterns and behaviors that contribute to panic attacks, providing coping strategies and techniques to manage anxiety. CBT, in particular, is recommended by the Clinical Practice Guidelines for treatment of interictal anxiety [42]. According to Mula [25], CBT plus SSRIs is recommended for acute treatment of panic attacks in PWE, while CBT with or without SSRIs is suitable for long-term treatment. In general, psychological strategies can be useful to support coping in PWE [59,60].

3.7. Indication for psychiatric treatment

No definitive rule can be given in this regard: It certainly depends on the experience and certification of the treating epileptologist. In some countries, psychiatrists care for PWE. When the panic disorder diagnosis has been established in a PWE, the patient should be referred to a psychologist/psychotherapist. Anxiolytic drug therapy may be initiated by the epileptologist. The patient should be referred to a psychiatrist in case of failure of the first medication.

4. Summary and recommendations

This case report highlights the importance of recognizing and effectively managing anxiety disorders in PWE. Distinguishing between *peri*-ictal fear and panic attacks is crucial for an accurate diagnosis and appropriate treatment. Various anxiety-related symptoms may occur in relation to seizures, making a differential diagnosis necessary to avoid misdiagnosis and iatrogenic effects. Misdiagnosis and inappropriate treatment approaches can lead to worsened symptoms and diminished quality of life. Accurate assessment using reliable psychometric tools can help identify anxiety-related symptoms and guide clinicians in providing appropriate care for PWE and comorbid anxiety disorders.

The use of sertraline/venlafaxine in PWE poses a low risk of seizures and can generally be recommended. However, TCAs may have a higher risk of seizures and should be used with caution. Benzodiazepines should be used cautiously, and treatment resistance should prompt a thorough re-evaluation. Psychotherapy, particularly CBT, can further enhance the treatment outcome. Overall, personalized treatment plans should be devised, considering the individual patient's response, side effect profile, and comorbid conditions.

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Declaration of competing interest

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