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Enlightening the Relationship Between Epilepsy and Depression

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ABSTRACT

The most common concomitant mental illness with epilepsy is depression. According to population-based research, its lifetime prevalence ranges from 6% to 30%, and among patients monitored at tertiary hospitals, it can reach 50%. According to estimates, the risk of suicide is ten times higher than that of the general population. No one disputes the link between epilepsy and depression, but new research has now shown that a history of depression is linked to a 4- to 6-fold increased risk of epilepsy. There is the possibility of a "bi-directional" interaction between these two illnesses or the existence of shared pathogenic pathways that make it easier for one to arise when the other is present. The emotional cost of chronic disease, genetic predispositions, and common neurobiological pathways including neurotransmitter dysregulation are some of the variables that contribute to this comorbidity. Antiepileptic medications (AEDs) can also affect mood, either making depression symptoms worse or making them better. Despite its relatively high prevalence, depression remains unrecognized and untreated, and unfortunately its treatment is based on empirical and uncontrolled data.

Keywords: epilepsy, depression, neurobiology, bidirectional relationship, antiepileptic drugs, quality of life.

1. INTRODUCTION

Epilepsy is a neurological disorder characterized by recurrent unprovoked seizures. Medicine has long known that people with epilepsy may suffer symptoms other than seizures. Epilepsy is a chronic disorder and as such it brings about social discrimination leading to demoralization, poor self-esteem, and a negative perspective toward life. Patients with epilepsy have the ever-ready risk of either becoming unconscious or falling and damaging themselves, and, in public, of social embarrassment. In addition, recent research has pointed out the involvement of the temporal lobes and the psychotropic effects of antiepileptic drugs. Comorbid depression represents an important issue in the management of people with epilepsy being associated with poor quality of life (QOL) and poor prognosis.

Depression may arise as a result of other mental or physical problems or as a side effect of the drugs used to treat such illnesses, or it could be caused by epilepsy-related structural abnormalities. Depression is the most important predictor of QOL, representing a more powerful predictor than the actual seizure frequency.

Comorbid depression also seems to represent a predictor of poor prognosis. People with epilepsy and depression are more likely to experience side effects of anti-epileptic drugs (AEDs), are more often drug-refractory, and have a poorer outcome

after epilepsy surgery compared with epilepsy patients without depression.

Epilepsy impairs quality of life in many ways and is related to seizure control. With more than 20 options of medications, up to 70% of newly diagnosed persons with epilepsy can be successfully managed. Drugs that are used to treat epilepsy work by decreasing brain electrical activity, improving potassium channel function, suppressing excitation mediated by glutamate, or promoting inhibition mediated by GABA. Depression also impairs the quality of life of epilepsy patients but is a curable illness [1,2].

2. DEPRESSION IN EPILEPSY

In patients with epilepsy, the most common affective disorder is inter-ictal depression. Various factors increase the risk of depression. It is more prevalent in patients with uncontrolled seizures than in seizure-free patients. Paradoxically, depression can follow both remissions of epilepsy either after epilepsy surgery or after the initiation of an antiepileptic drug. Interictal depression affects two-thirds of patients, especially those with severe and/or frequent seizures. It was used to describe a syndrome comprising eight symptoms, of which the patient must experience a minimum of three (3/8): Depressive moods, energy, pain, irritability, insomnia, anxiety, fear, and euphoric mood. In severe form, this disorder has been associated with sudden suicidal attempts during episodes of intense depressive mood.

All psychiatric comorbidities in general, and depression in particular is an under-recognized and under-treated psychiatric comorbidity. The major reasons for this are the failure to recognize or underestimation of the symptoms by the patients, limited access to treatment, and lack of health insurance for psychiatric illnesses [3].

3. EPIDEMIOLOGY OF DEPRESSION IN EPILEPSY

3.1. Prevalence of Depression in Epilepsy Patients

In epilepsy, depression is the most common psychiatric comorbidity. Depression affects around one-third of these cases and impacts the quality of life. It occurs in 14.1% of females and 14.8% of males worldwide. Depression is more frequent in patients with epilepsy compared to the general population. The reported prevalence of depression in patients with epilepsy (PWE) varies between 10.7 to 44%, and it can reach 54% in refractory epilepsy [4].

Within PWE, a recent meta-analysis of population-based studies in PWE found an overall pooled prevalence of 23.1% for depression, and significantly increased odds of depression in PWE compared to control samples.[5]

The prevalence of current depression in epilepsy patients varies depending on diagnostic criteria and the populations surveyed. Large epidemiological studies, such as the Canadian Community Health Survey, report a prevalence of 13.0% in patients with epilepsy compared to 7.2% in the general population. Other community-based studies show prevalence rates below 20%, while smaller community samples report slightly higher rates (22.0-27.6%). [6]

3.2. Demographic or Clinical Factors Influencing the Risk of Depression in Epilepsy:

Some epidemiological studies reported that major depressive disorder may precede and increase the risk of onset of epilepsy.

Depression in epilepsy can be influenced by several factors. Patients with more severe epilepsy or those in tertiary care settings show higher prevalence rates of depression, nearly 50% due to selection bias. Factors such as psychological stress, learned helplessness and chronic exposure to uncontrollable seizures play a significant role. Additionally, social support, family resources, and higher income are protective factors against depression in epilepsy. [6,7]

4. PATHOPHYSIOLOGY OF DEPRESSION IN EPILEPSY

Epilepsy in adults is associated with many known risk factors, including head trauma,

CNS infections, strokes (embolic and hemorrhagic), CNS malignant neoplasms, Alzheimer's disease, and other neurodegenerative disorders. A seizure can be understood as a disruption of the brain's normal balance of excitation (E) and inhibition (I). This E/I imbalance can be caused by changes in various aspects of brain function, ranging from genes and subcellular signaling cascades to extensive neural circuits. [1].

Biological and Neurological Mechanisms: Depression in epilepsy can be explained using the diathesis-stress model, which considers both neurobiological and psychological factors. Stressful life events and individual vulnerability contribute to mental health issues. Epilepsy can le ad to states of depressed mood on a purely neurobiological basis.

Shared neurochemical pathways and structural brain changes are implicated. For instance, the impact of recurrent seizures as unpredictable and uncontrollable events can induce a state of learned helplessness, contributing to depression. [6]

The pathophysiology of depression in epilepsy involves several biological and neurological mechanisms:

1. **Shared Neurochemical Pathways:** Both epilepsy and depression are associated with imbalances in neurotransmitters like serotonin, dopamine, and GABA, affecting mood and seizure regulation.
2. **Structural Brain Changes:** Structural abnormalities in brain regions such as the hippocampus and prefrontal cortex are common in both conditions. These changes can disrupt normal brain function and contribute to mood disorders.
3. **Inflammatory Processes:** Chronic inflammation in the brain is a common factor that can influence both seizure activity and depressive symptoms.

Other Factors:

1. **Genetic Predisposition:** Shared genetic factors may increase susceptibility to both conditions.
2. **Medication Effects:** Antiepileptic drugs can have side effects that contribute to depression. [1].

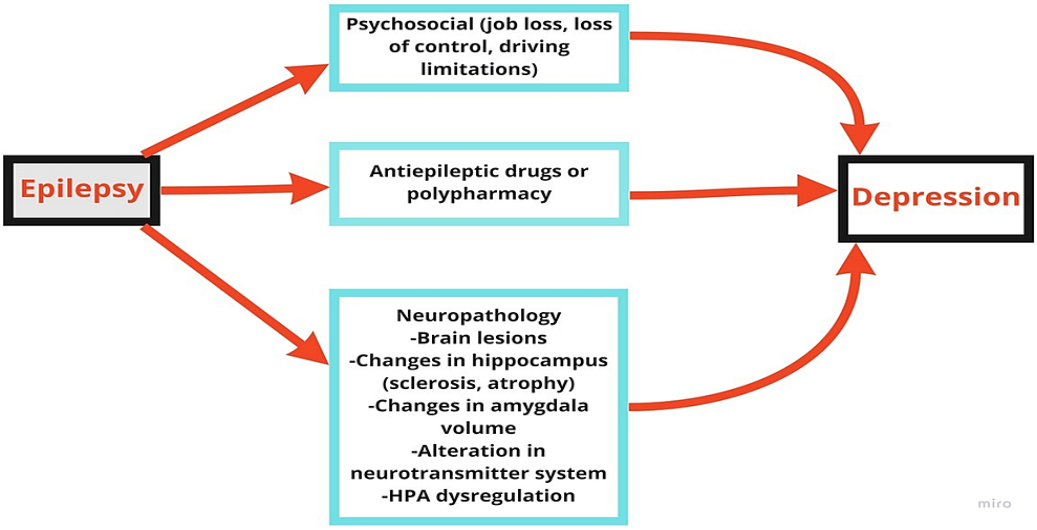

Figure 1: pathophysiology of depression in epilepsy

5. BIDIRECTIONAL RELATIONSHIP BETWEEN EPILEPSY AND DEPRESSION

Persons with epilepsy (PWE) have a higher risk of developing depressive disorders (DDs), and people with primary DD have an increased risk of developing epilepsy.

Depression is more frequent in patients with epilepsy compared to the general population. Epilepsy and depression both

can influent an individual's interpersonal communication, and social activities and can increase the risk of sudden attacks. Some studies indicate that epilepsy and depression are bidirectional.

Forty-three papers reported a prevalence estimate for depression with epilepsy. Among the 43 reports on the incidence rate of depression in epilepsy, 15 were based on a population survey, and 28 were clinical studies. In a population-based environment, the combined prevalence of epilepsy in depression patients was 27%, while the prevalence was 34% in the clinic. [4,8]

The bidirectional relationship between epilepsy and depression is well-documented in the literature, and it highlights the complex interplay between these two conditions.

- **Increased Risk in Both Directions:** A significant long-term bidirectional relationship between epilepsy and depression is identified. Specifically, individuals diagnosed with epilepsy have an increased risk of developing depression, and conversely, individuals diagnosed with depression have an increased risk of developing epilepsy. The adjusted hazard ratio (aHR) for developing depression after an epilepsy diagnosis is 1.88, while the aHR for developing epilepsy after a depression diagnosis is 2.35.
- **Timing of Risk:** The risk of developing depression is highest in the years immediately preceding and following an epilepsy diagnosis, and similarly, the risk of developing epilepsy is highest in the years around the diagnosis of depression. However, the elevated risk persists throughout the follow-up period for both conditions.
- **Impact on Clinical Outcomes:** Depression in individuals with epilepsy is associated with worse clinical outcomes, including higher frequency and severity of seizures, poor response to antiseizure medication, and increased hospital admissions for acute seizures. Conversely, having epilepsy can worsen depressive symptoms and outcomes, creating a detrimental feedback loop between the two conditions.
- **Common Underlying Factors:** The exact nature of the bidirectional relationship remains unclear, but several theories have been proposed. These include common neurobiological and genetic factors, psychosocial stressors, and the potential negative effects of treatments (e.g., antiseizure medications can have psychotropic side effects, and some antidepressants can have proconvulsant properties).
- **Comparison with Other Chronic Conditions:** The risk estimates for depression following epilepsy or vice versa were higher than those observed for other chronic conditions, suggesting a particularly strong association between epilepsy and depression compared to other chronic illnesses. [9]

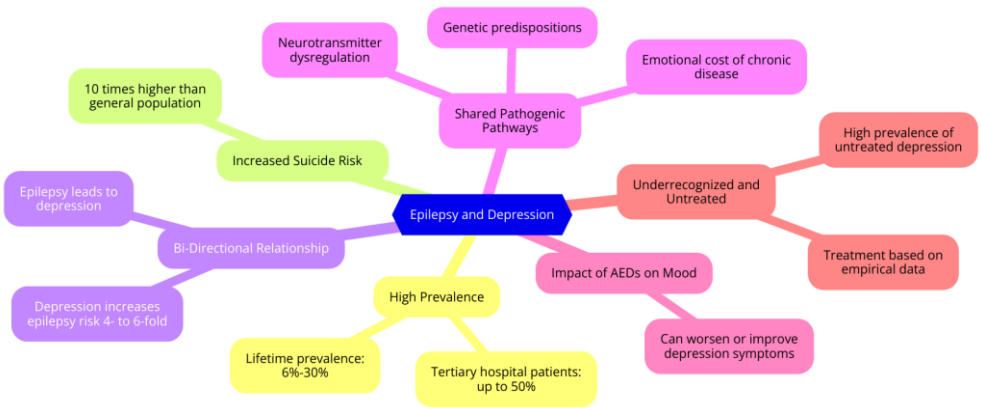

Figure 2: Bidirectional relationship between epilepsy and depression

6. CLINICAL PRESENTATION AND DIAGNOSTIC CHALLENGES

6.1. Typical symptom presentation: Patients with epilepsy often exhibit depressive symptoms that can mimic primary mood disorders. The symptoms commonly seen include:

1. Depressed mood
2. Anhedonia (loss of interest or pleasure)
3. Feelings of worthlessness or guilt
4. Decreased ability to concentrate
5. Recurrent thoughts of death
6. Neurovegetative symptoms such as weight loss or gain, insomnia or hypersomnia, psychomotor agitation or retardation, and fatigue.

6.2. Diagnostic challenges: Depression in epilepsy patients can present with unique or atypical features that complicate the diagnosis:

- **Pleomorphic Symptoms:** Some patients exhibit a pleomorphic pattern of symptoms including irritability, euphoric mood, fear, anxiety, anergia (lack of energy), pain, and insomnia.
- **Interictal Dysphoric Disorder:** This is a chronic course of depression with recurrent symptom-free periods and responds well to low doses of antidepressants. It includes affective symptoms such as prominent irritability intermixed with euphoric mood, fear, anxiety, anergia, pain, and insomnia.
- **Dysthymic-like Disorder of Epilepsy:** Characterized by anhedonia, fatigue, anxiety, irritability, poor frustration tolerance, mood lability, changes in appetite and sleep patterns, and concentration problems. Symptoms often have a waxing and waning course with intermittent symptom-free periods.
- **Sub-syndromic Depression:** Some patients exhibit symptoms that do not meet the full criteria for DSM-IV categories but still impact their quality of life. This can include mild-to-moderate depressive symptoms combined with anxiety, irritability, physical symptoms, and increased energy. [10]

7. SCREENING AND ASSESSMENT

7.1. **Diagnostic and Statistical Manual of Mental Disorders:** The DSM-5 defines a major depressive episode as follows: it lasts for at least two weeks, is accompanied by at least five of the nine suggested symptoms, and exhibits a considerably diminished interest in practically all living activities.

Table 1: Diagnostic criteria of major depressive disorder according to DSM-5. [7]

Criterion A	Five (or more) of the following symptoms have been present during the same two-week period and represent a change in previous functioning; at least one of the symptoms is: *a)* depressed mood, or *b)* loss of interest or pleasure:
	• Depressed mood most of the day, nearly every day; may be subjective or observed by others
	• Markedly diminished interest/pleasure in all (or almost all) activities most of the day, nearly every day; may be subjective or observed by others
	• Significant weight loss when not dieting or weight gain, or decrease or increase in appetite nearly every day
	• Insomnia or hypersomnia nearly every day
	• Psychomotor agitation or retardation nearly every day
	• Fatigue or loss of energy nearly every day
	• Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional)
Criterion B	Symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
Criterion C	Episode not attributable to physiological effects of a substance or another medical condition
Criterion D	Episode of major depression not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other psychiatric disorders

7.2. Neurological Disorders Depression Inventory for Epilepsy (NDDI-E): The NDDI-E is an epilepsy-specific self-rating inventory designed to quickly identify major depressive episodes in neurology clinics. It differentiates depressive symptoms from

antiepileptic drug side effects. Validated in various languages, the NDDI-E is frequently used due to its ease of administration and availability in the public domain. Its median sensitivity at the most common cut point (>15) is 80.5%, with a specificity of 86.2%.

7.3. Beck Depression Inventory (BDI): The BDI is a widely used self-reported inventory for assessing depressive symptoms over the preceding two weeks. It has multiple versions, including the original BDI, BDI-II, (based on DSM-IV criteria), and shortened forms like the BDI-FS (based on DSM-5 criteria). The BDI-2 is a self-rating questionnaire consisting of a 21-item scale with four severity ratings for each item. This tool measures both cognitive and somatic-affective symptoms of depression. It has been validated in epilepsy patients, underscoring its reliability for assessing treatment outcomes. These tools are validated in the general population and have been adapted for use in patients with epilepsy.

7.4. Patient Health Questionnaire – 9 (PHQ-9): The PHQ-9, a self-administered screening tool, used to evaluate the severity of depressive symptoms. Unlike other depression scales, the PHQ-9 consists of 9 items, this questionnaire evaluates how frequently subjects experienced each of the 9 symptoms over the past 2 weeks.

7.5. Hospital Anxiety and Depression Scale - Depression subscale (HADS-D): The HADS-D is another tool commonly used for detecting depression in various populations, including those with epilepsy. It is a 14-item tool that includes a 7-item depression subscale (HADS-D) and a 7-item anxiety subscale. It is designed for use in hospital settings to assess both anxiety and depression. It focuses on psychological rather than physical symptoms of depression, making it useful for distinguishing depressive symptoms from epilepsy or medication side effects. A cut point of 8 is recommended for detecting depression.

7.6. Major Depression Inventory (MDI): The MDI is a depression scale consisting of items corresponding to ICD-10 symptoms of depression over the preceding two weeks. It is validated in the general population and is increasingly used in neurological conditions.

7.7. Mini International Neuropsychiatric Interview (MINI): The MINI is often used as a reference standard in validating other depression screening tools. It has high concordance with the SCID, a gold standard for detecting depression. The MINI is widely used as a reference standard in validating other screening tools due to its reliability and practicality in clinical settings. It is a structured diagnostic interview used to identify major depressive episodes and other psychiatric disorders.

A comprehensive evaluation of depression in epilepsy patients is crucial due to the complex interplay between neurological and psychological factors. A multidisciplinary approach ensures that various aspects of the patient's condition are addressed, including medical, psychological, and social factors. [11,12,13]

8. TREATMENT APPROACHES

Treatment of depression using psychotherapy and pharmacological methods in patients with epilepsy has improved the quality of life and reduced admission rates, easing the disease burden [14].

8.1. PHARMACOLOGICAL THERAPIES

a. **Selective Serotonin Reuptake Inhibitors (SSRIs):** SSRIs are considered the first line of treatment for depression in epilepsy patients due to their safety and tolerability. Studies have shown positive outcomes with SSRIs like sertraline and citalopram. For instance, 59% of patients treated with sertraline experienced remission of depression symptoms. Another study demonstrated significant reductions in depression scores with citalopram. SSRIs are generally well-tolerated,

although there are limited controlled studies on their effectiveness specifically in epilepsy patients.

b. **Tricyclic Antidepressants (TCAs):** TCAs have been used in uncontrolled clinical trials but have less favorable safety profiles compared to SSRIs.
c. **Other Antidepressants:** Medications like mirtazapine and reboxetine have also been evaluated, showing some effectiveness, although with varying degrees of symptom reduction.
d. **Antiepileptic Drugs (AEDs):** Certain AEDs like carbamazepine, gabapentin, lamotrigine, pregabalin, and sodium valproate have better psychotropic profiles and are considered safer for patients with depression and epilepsy. It is recommended to avoid AEDs with negative psychotropic properties (e.g., benzodiazepines, barbiturates, topiramate, levetiracetam) in patients with a personal or family history of psychiatric disorders.

8.2. PSYCHOTHERAPEUTIC THERAPIES

a. **Cognitive Behavioral Therapy (CBT):** CBT is effective for treating depression in patients with epilepsy, especially for those who refuse or cannot tolerate antidepressants. It is beneficial for long-term depressive disorders and comorbid anxiety disorders in epilepsy patients.
b. **Neuromodulation Therapies:** Neuromodulation therapies, including electroconvulsive therapy (ECT) and vagus nerve stimulation (VNS), are also mentioned as potential treatments. These methods are considered particularly for patients who do not respond to conventional pharmacological or psychotherapeutic interventions.

Vagus nerve stimulation (VNS) and transcranial magnetic stimulation (TMS) are emerging treatments for refractory depression in epilepsy. These therapies target brain areas involved in mood regulation. [6.7]

8.3. EVALUATION OF EFFICACY AND SAFETY

Studies suggest that combining pharmacological treatments with psychotherapy improves outcomes. Neuromodulation therapies have shown a promising effect. [6]

a. Pharmacological Treatments:

Specific drugs mentioned include selective serotonin reuptake inhibitors (SSRIs) and other antidepressants that have shown efficacy in this population. However, the choice of medication needs careful consideration due to potential interactions with antiepileptic drugs (AEDs).

SSRIs: Demonstrated efficacy in controlled and uncontrolled studies, with sertraline and citalopram showing significant symptom improvement.

TCAs and other antidepressants: Limited evidence in controlled trials; safety and tolerability can be a concern.

AEDs: Some AEDs are preferred for their better psychotropic profiles, but close monitoring is necessary to manage potential adverse effects

b. **Psychotherapeutic Treatments:** Psychotherapeutic approaches such as cognitive-behavioral therapy (CBT) are recommended for treating depression in epilepsy patients. These therapies focus on altering negative thought patterns and improving coping strategies, which can help mitigate depressive symptoms without the risk of pharmacological interactions.

c. General Considerations:

The interplay between AEDs and antidepressants needs careful management to avoid adverse interactions and ensure efficacy. Individual patient history, particularly concerning psychiatric disorders, significantly influences the choice of treatment and its success. [7,12]

9. PROGNOSIS AND IMPACT

Comorbid depression can significantly impact seizure control, with depressive

symptoms potentially lowering the seizure threshold and worsening epilepsy management. Depression in epilepsy patients is also associated with poorer quality of life, increased disability, and higher healthcare utilization.

The presence of depression in epilepsy patients is linked to a substantial decline in quality of life. This includes impairments in daily functioning, social interactions, and overall well-being. Effective management of depression is crucial for improving these patients' overall disease outcomes.

The broader societal and economic implications of depression in epilepsy are significant. These include increased healthcare costs due to more frequent hospitalizations and doctor visits, as well as indirect costs related to lost productivity and the need for long-term care. Addressing depression in epilepsy patients is thus essential not only for individual health but also for reducing the economic burden on society. [12]

9.1. IMPACT OF DEPRESSION IN EPILEPSY

Depression is the most common psychiatric comorbidity in epilepsy and has significant impacts, including:

- **Quality of Life:** Persistent depression is an independent predictor of poor quality of life in epilepsy patients.
- **Suicidal Risk:** Increased risk of suicide.
- **Healthcare Utilization:** Greater use of health services and higher medical costs not related to psychiatric treatment
- **Postsurgical Outcomes:** A lifetime history of depression can predict poorer outcomes post-surgery, such as persistent auras and failure to achieve freedom from disabling seizures. [10]

10. CONCLUSION

There is a complex and reciprocal interaction between depression and epilepsy. When compared to the general population, the prevalence of depression is significantly greater among people with epilepsy. On the other hand, there is a complicated interaction between both conditions since depression can influence the frequency and intensity of seizures. A multidisciplinary approach is necessary for effective therapy, which involves routinely assessing patients for depression symptoms and taking the psychological effects of epilepsy into account when designing a treatment plan. In order to enhance patient outcomes, future research should concentrate on clarifying the specific processes underlying these disorders and creating integrated treatment strategies.

Declaration by Authors

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