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Review Article

A COMPREHENSIVE REVIEW ON COMORBID DEPRESSION IN PATIENTS WITH EPILEPSY

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ABSTRACT

Epilepsy is one of the common neurological disorders that are seen worldwide. It can also affect a person's social, mental, and physiological well-being and thus restricts and disables the common living of man. Depression as such has been well reported in patients with epilepsy, and also depression itself remains a factor that can lead to the development of epilepsy. Increased rates of suicidal tendencies are also associated with depression both in men and women. Depression is further extended in affecting the quality of life in epileptic patients. Depressive rates are found to have a higher value in epileptic patients when compared with the normal population. This article aims to produce a comprehensive review of the epidemiological considerations, clinical findings and management strategies for depression associated with epilepsy.

Keywords: Epilepsy, Comorbidity, Depression, Suicide, Anxiety.

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INTRODUCTION

Epilepsy is one of the common neurological disorders that is seen worldwide [1]. Epilepsy, anxiety, and depression are related disorders. It is, therefore, not a surprising issue that patients exhibit all of these together. About 55% lifetime prevalence for depression was found in epileptic patients which was tend to be high and that with temporal lobe epilepsy is estimated as 35% [2]. Depression directly increases seizure frequency through sleep deprivation. Failure to realize the patients with depression or a delay or inadequate treatment can lead them to suicide. Depression also reduces the compliance of the patient to antiepileptic medication [3]. People with epilepsy (PWE) will experience depression at a higher rate, mainly two-three fold when compared to a general population [4]. Depression is the psychiatric comorbidity which is seen more frequently in patients with epilepsy [2]. PWE and comorbid depression have reported lower quality of life [2]. Therefore, a study to determine the impact of depression and its related symptoms in epileptic patients is warranted to improve their quality of life.

The aim of this review is to bring into light the available evidence about the certain aspects of the comorbidity of depression in epileptic patients as the two are closely associated with one another.

DEPRESSION AND EPILEPSY- TWO WAY STREET

Depression is the psychiatric comorbidity which is seen more frequently in PWE [5,6]. The association between both has been well established in various studies. Studies have noted that rate of depression tends to be high among epileptic patients than in a normal population or in subjects with other chronic diseases such as diabetes and hypertension [7]. For a considerable time period, depression was thought to be a chain reaction of epilepsy [7]. Demonstration of depressive disorders in patients with epilepsy have been multifaceted, with many psychological and neurobiological interactions, which also includes various clinical characteristics of epilepsy and possible neurochemical mechanisms [8,9]. Not only epilepsy can cause depression, but also depressive episodes showed increased the risks of developing seizures.

Colin *et al*., in this study, have discussed about the relevance of a bi-directional relationship that exists between depression and epilepsy. In this observational study of a population-based primary cohort identified. We identified 10,595,709 patients in The Health Improvement Network of whom 229,164 (2.2%) developed depression and 97,177 (0.9%) developed epilepsy. Significantly more patients from the population with depression (144,373 [63%] were women and 84,791 [37%] were men; $p<0.001$) or epilepsy (54,419 [56%] were women and 42,758 [44%] were men; $p<0.001$) were female. It was also observed that incident epilepsy was related to an increased risk of developing depression (hazard ratio [HR], 2.04 [95% CI, 1.97-2.09]; $p<0.001$), and incident depression was associated with an increased risk of developing epilepsy (HR, 2.55 [95% CI, 2.49-2.60]; $p<0.001$) there was an incremental hazard according to depression treatment type and lowest risk was seen for those receiving counseling alone (HR, 1.84 [95% CI, 1.30-2.59]; $p<0.001$), an intermediate risk was seen for those receiving antidepressants alone (HR, 3.43 [95% CI, 3.37-3.47]; $p<0.001$), and the highest risk was seen for those receiving both (HR, 9.85 [95% CI, 5.74-16.90]; $p<0.001$). He concluded that treated depression is associated with worse epilepsy outcomes thereby suggesting that it may be a surrogate for more severe depression and that severity of both depression and epilepsy is inter-related [10].

Attarian *et al*., in this study, have concluded that PWE have a predominance of depression than in normal population. Seizure free patients for a period of more than 6 months were considered not intractable. Of the total number of patients, 36% were neither intractable nor depressed. 43% was found to have intractable epilepsy but were not depressed. The results indicate that 10% had both intractable epilepsy and depression and 11% did not have intractable epilepsy but was found depressed [11].

A study by Gilliam *et al*. have concluded by saying that presence of depression is considered as a strongest predictor of health status of the patient [12].

All these studies reveal that there is a considerable relation between epilepsy and depression and it also worsens with the increase in the severity of epilepsy.

PSYCHOLOGICAL DISORDERS IN PATIENTS WITH EPILEPSY

Acute psychological disorders (APDs) are a most prevailing problem faced by epileptic patients, with an approximate estimate varying from 2% to 16% as per the studied population [13]. Epileptic patients are very often confronted with mood disorders.

Cockerell *et al*. conducted a study using an ongoing prospective surveillance system to determine the epileptic patients who developed APDs. 64 cases were determined. Location-related epilepsy was found to be predominant in the subjects included. 31 (48%) patients presented with APD due to ictal or post-ictal activity [13].

Mula *et al*. conducted a study on 143 out-patients, only adults, with epilepsy comprising 83 females and 60 males. Of the total, 17 patients (11.9%) were diagnosed to have bipolar disorder (BD) according to DSM-IV criteria; moreover, 21 patients (14.7%) were screened positively for bipolar symptoms (BS) using mood disorder questionnaire (MDQ). This showed that a higher occurrence of psychological disorders is present in PWE [14].

A multistage random cluster sampling was done by Richard *et al*., against 1403 subjects of age 8-12 years old including all the households in two rural areas in Calicut district in Kerala. The screening interview was administered to the caretaker of every subject which included demographic data, expectation of parents' on children for participation in house works using a Malayalam version of Rutter's A2 questionnaire as a measure of child psychiatric disturbance and items indicating the social impact of child's disorder (adapted from the Ontario child health study). A poverty score was also designed from 8 equally-weighted items. 95% of the teachers in the sample completed Malayalam version of Rutter's B2 child behavior questionnaire [15,16]. 26 children were in accordance to the definition of epilepsy. The guardians/parents of these epileptic children had only lower expectations, and only 50% of them expect to continue education for their children beyond 16 years compared with 77% of controls (χ^2=6.83, p=0.009). School attendance was also found to be significantly lower in these children. Children with epilepsy were predominantly more disturbed than the normal population on the Rutter (parent) questionnaire. Thus, evidence was obtained that epilepsy severely interferes with the psychiatric well-being, cognitive and academic performance of children in the South Indian population and also their personal life [15].

Kogeorgos *et al*. assessed the presence of psychiatric comorbidity in 66 chronic epilepsy out-patients with the help of two self-rating psychopathology questionnaires which had established reliability, consistency and validity. His study showed that around half (45.5%) of the population was psychiatrically ill. When compared with a population of chronic neurological out-patients, patients with epilepsy showed higher rates of psychiatric comorbidities. Most predominant conditions were depression, anxiety, and hysteria [17].

Ettinger *et al*., in this study using a validated instrument, the MDQ which in conjugation with questions about prevailing health issues, was used against 127,800 adult subjects in the US. On comparison of patients diagnosed with epilepsy and those with migraine, asthma, and diabetes mellitus it was evident that BS presented high, approximately 1.6-2.2 times, in epileptic population than in patients with migraine, diabetes, and asthma [18].

Kathryn *et al*. conducted a cross-sectional, case–control survey among the children in Tanzania between the ages ranging from 6 to 14 years with active epilepsy. Comorbidities were assessed and compared with control groups. Comorbidities were very common among cases (95/112, 85%) and (62/112, 55%) cases showed multiple comorbidities. Comorbidities consisted of cognitive impairment, behavior disorder, motor difficulties, burns and other previous injuries and these complications were found to be common in these cases than in controls (odds ratio 14.8, 95% CI 7.6-28.6, p<0.001). Thus, he concluded that high level of comorbidity was seen in children's with epilepsy in Sub-Saharan Africa [19].

Psychological disorders hence are found mostly in epileptic patients. These conditions are often left unrecognized. Other than depression, anxiety psychosis is also found to be predominant in epileptic patients. Occurrence of such comorbidities needs to be assessed carefully in order for providing proper care. Other studies related to Psychological disorders in PWE are listed in Table 1.

PREVELANCE OF DEPRESSION IN EPILEPSY

Most of the studies have determined the predominance of psychiatric disorders in epilepsy which are characterized by considerable heterogeneity which is due to the differences in settings of the population and the study type underwent [20].

Jose *et al*., in this study to estimate the prevalence of mental disorders in those with epilepsy with the means of Canadian Community Health Survey 1.2, to identify numerous aspects of mental health in persons with epilepsy. The prevalence of epilepsy was seen as 0.6%. Prevalence of mental health disorders in those with epilepsy was also determined and was found to be 23.5 for 12 month period and 35.5 when checked for lifetime [21].

Occurrence of depression in epileptic patients and the associated factors were determined by Samart *et al*. in a cross-sectional study where 110 patients were enrolled overall, and among them, 60 patients only conformed to the inclusion criteria. Patients were screened using the Thai geriatric depressive scale. Prevalence of depression was obtained overall as 38.3%. Depression was diagnosed as 36.8% in males and 40.9% in females. No significant difference (p=0.75) was seen when male and female population was compared. Age group also showed no significant difference (p=0.77). Other variables such as duration of seizures, type of seizures and number of anti-epileptic drugs (AEDs) showed no significant difference among epileptic patients and thus concluded that they are not the risk factors associated with depression [22]. On the contrary, Ting Zhao *et al*. depicted that the strongest predictors of depression were the type of seizure (odds ratio = 3.773, p=0.049, β=1.328). Weaker predictors included the seizure worry scores (OR=0.947, p=0.030, β=−0.54), social function scores (OR=0.947, p=0.000, β=−0.10) and complex partial seizure score (OR=0.112, p=0.002, β=−2.187) [23]. Thus, two opinions have been raised when the factors that cause depression in epileptic patients were checked into.

Mohammadi *et al*. determined the lifetime prevalence of self-reported and relative informants-reported epilepsy among Iranian adult of age 18 years and above using a cross-sectional epidemiological study and identified the possible relation between epilepsy and lifetime psychiatric disorders. 25,180 individual were selected from all the Iranian households and interviewed face to face using epilepsy questionnaire. The response rate was observed as 90%. The prevalence rate of epilepsy was identified as 1.8%. Epilepsy was observed to be more predominant in females, unemployed people and people with higher educational status. Factors such as age group, marital status, and residential areas were not associated with epilepsy. The predominant psychiatric comorbidity which was seen in subjects with epilepsy were major depressive disorder and obsessive-compulsive disorder and the rate of lifetime suicidal attempt was observed to be as 8.1% [24].

A cross-sectional observational study where patients were evaluated by mini international neuropsychiatric interview by Sajjadur *et al*. conducted to see their psychiatric comorbidities and the sociodemographic and clinical factors. Psychiatric comorbidity was seen in 50% of the subjects with epilepsy. Depression 18%, psychosis 14%, and anxiety disorders 11% were the other most commonly found psychiatric comorbidities. Presence of partial seizures, frequent seizures, long duration of epilepsy, and poor compliance to AED are other major factors that were significantly associated with the presence of psychiatric comorbidity in persons with epilepsy [25].

Prevalence of depression in epilepsy has found its stand itself to be very high when it is compared with the normal population in the society. The severity of depression alters accordingly with the type of seizure undergone by the patient, age and type of therapy undertaken by the patient. On concluding, depression is a factor that requires proper medical care mainly in epileptic patients.

FREQUENCY OF DEPRESSION IN EPILEPSY

Depression is the considered to be the most expected psychiatric morbidity among people with epilepsy and also have an adverse effect on their quality of life [34]. It has also been noted that 30-50% of epileptic patients reported with clinical depression [35,36]. Among 50 million PWE worldwide, 15-60% are also likely to experience any forms of depression or anxiety disorders, and 80% of those people are from a low economic status where these comorbidities remain concealed and thus untreated [37,38].

Ettinger *et al*., [39] in this study assessed the frequency of depressive symptoms, quality of life and disability among a community-based sample comprising epilepsy, asthma, and health control groups. His results indicated that from the population selected, 36.5% with epilepsy, 27.8% with asthma, and 11.8% of health control group were positive on center for epidemiological studies-depression scale ($p<0.001$). These findings thus suggest that depression is much more prevalent in epileptic patients when seen in comparison to other groups.

Yousafzai *et al*., in this cross-sectional study on 100 patients in a clinical diagnostic center for epilepsy, diagnosed patients with depression using ICD-10 diagnostic criteria. 100 patients were included in the study. It showed that 60% of the population that were included showed symptoms of depression when the interview was conducted. Predictors of depression that have a significant association with depression were identified as male gender, married status, and low socioeconomic status [34]. Frequency was relatively seen to be high.

In an ongoing cross-sectional study in Campinas, a city to the south-east of Brazil, Sabrina *et al*. given a population of 171 individuals with epilepsy, estimated the periodicity of depression or anxiety in PWE. The prevalence of anxiety and depression was observed in 39.4% and 24.4%, respectively. Significant factors that were associated with depression and anxiety were low schooling (OR 3.8, 2.8), lifetime suicidal thoughts (OR 4.4, 3.6) and lifetime suicidal attempts (OR 9.3, 6.9) [40].

In a cross-sectional study conducted for a period over 9 months involving 100 cases of primary epilepsy Wazir *et al*. determined the frequency of depression among subjects who presented only with primary epilepsy using beck depression inventory (BDI). 46 male (46%) patients and 54 female (54%) patients were enrolled for the study. 62% of patients with primary epilepsy reported to have depression during their course of life [41]. This study is comparable to the study by Yousafzai *et al*. Who suggested that depression was found in 60% of the population under his study [34].

Ting Zhao *et al*. conducted a study on 140 outpatients attending an epilepsy center in Huashan Hospital for a period of about 6 months and the patients were asked to fill questionnaires which contained data in liaison with epilepsy. Depressive levels were rated using HAMD-17 scale, and QOLIE-31 was used to appraise the quality of life in epileptic patients. He detailed out the type of seizure presented by each patient. About one-fourth of the population presented with depression. He also suggested that the strongest predictors of depression were the seizure types (odds ratio= 3.773, $p=0.049$, $\beta=1.328$). Weaker predictors included seizure worry scores (OR= 0.947, $p=0.030$, $\beta=-0.54$), social function scores (OR=0.947, $p=0.000$, $\beta=-0.10$), and complex partial seizure score (OR=0.112, $p=0.002$, $\beta=-2.187$) [23].

Onwuekwe *et al*. conducted a cross-sectional cohort study in a population of 83 epileptic patients to determine the periodicity and the method of depression that occurs in epileptic patients who were assessed using BECKs inventory for depression. Depression was found in 71 (85.5%) of the patients. Minimal depression was seen in 57 (68.7%), mild in 10 (12%), and moderate in 4 (4.8%) patients. No cases of severe depression were observed. No other variables showed a significant relationship with degrees of depression and concluded that recurring rate of depression among epileptic patients was observed to be as high as 85.5% [42].

On concluding, depression is considered as a psychiatric comorbidity whose frequency tends to be high than any other comorbidity in the lives of people with epilepsy. The higher rates of depression and anxiety within the society have prioritized the need to comprehend and treat the mental disorders in those presenting with epilepsy [40].

SUICIDAL TENDENCY ASSOCIATED WITH EPILEPTIC PATIENTS

Suicide is believed to be the 13th leading cause of death when considered globally [43] and attempted suicides are one of the major causes that leads to injury [44]. Psychiatric disorders mainly the affective disorders can increase the risk of the patient to attempt suicide [45,46]. Epilepsy also increases the risk of attempting suicide among patients who undergo psychiatric illness [47] and concomitantly epilepsy can also jeopardize the life of the patient and exposes the patient to develop psychiatric illness [48].

Various studies which include people with epilepsy (PWE) have shown suicide as a main cause of death, and its prevalence rate is keep on elevating. Even though most of the studies have not reported an increased rate of danger due to suicide, some collective data have proofs of about 12% risk among people with epilepsy (PWE). The endangered population involves children's, adolescents as well as adults. Elevated suicide attempts are reported in those subjects with epilepsy [49].

Chirstensen *et al*. conducted a population-based case–control study by identifying 21,169 cases of suicide and 423,128 controls. Within that population 492 (2.32%) individuals who committed suicide had epilepsy compared with 3140 (0.74%) controls. Patients with epilepsy were identified as the ones to have a high rate of suicidal tendency even though they were adjusted for socioeconomic factors ($p<0.0001$). Epileptic patients showed dangers of attempting suicide in their first half year of diagnosis ($p<0.0001$), and it was especially seen high in those patients with a history of the comorbid psychiatric disease ($p<0.0001$) [47].

Natasa *et al*. conducted a study in 50 patients who were selected randomly with epilepsy to analyze the presence of suicidal ideation in such patients. General questionnaire, HAM-D-17 (Hamilton 1960), The Beck Hopelessness Scale, and Beck Scale for Suicide Ideation were the instruments employed for the study. 38% of subjects presented with thoughts of death and suicide. Half of the participants showed feelings of hopelessness and symptoms that were similar to that depression. A significant relationship was believed to exist between suicidal ideation and the presence of chronic pain ($p=0.49$), sexual/physical abuse history ($p=0.015$), level of hopelessness ($p=0.000$), and severity of depression ($p=0.000$) in patients with epilepsy [50].

A meta-analytical study using randomized trials which revealed that AEDs have a potency to cause a hike in the incidence of suicidal thoughts and behavior. A nested case–control cohort studies in 44,300 PWE who are under treatment with AEDs were studied to identify patients who have tendencies for suicide or cause self-harm. Andersohn *et al*. included 453 patients and 8,962 age and sex-matched controls. AEDs were categorized based on the potential to cause depression. His studies expedited that use of newer AED's that shows a high potential of causing depression was even related with an increase in suicidal/self-harm behavior. Conventional AED's, low-risk new AED's was found to have no association with suicidal tendencies [51].

Pompili *et al*. [52] in a meta-analytic study of 29 cohorts comprising 50,814 patients, out of which 187 committed suicides indicated that suicidal behavior in epilepsy patients are more prevalent when compared to other population. The Index Medicus through Medline and World Health Statistics Annual was thoroughly assessed to determine the suicide rates prevailed among different age groups during the specific period of time and country.

All in all, we can conclude that epileptic patients are often encountered with higher rates of suicidal thoughts. Use of AEDs has also been

Table 1: Studies showing prevalence of psychological disorders in epilepsy

Country	Author	Number of Patients	Instrument	Method	Psychiatric disorder	Depression	Anxiety	Psychosis
Iran	Asadi-Pooya and Sperling, 2006 [26]	200	Hospital anxiety and depression scale	Cross-sectional study	-	9.5%	24.5%	-
Kenya	Kiko, 2013 [27]	327	Beck depression inventory	Cross- sectional study	-	16.5%	-	-
USA	Victoroff, 1994 [28]	60	SCID–P, DSM-III-R	-	70%	58.3%	31.7%	13.3%
Brazil	de Araujo *et al*., 2007 [29]	106	DSM-IV	Cross- sectional, population based study	61.3%	30%	-	Inter-ictal-14%. Post-ictal-9.4%
-	Mensah *et al*., [30]	499	HADS	Population based study	-	16.6%- borderline, 11.2%- clinical	-	-
Montengaro	Vujisic *et al*. [31]	70	HAM-D, HAM-A	-	-	32.8%	21.4%	-
Ethiopia	Bifftu *et al*., [32]	405	Becks Depression Inventory	Institution based quantitative cross-sectional study	-	45.2%	-	-
Australia	Briellmann *et al*., [33]	34	DSM-IV (APA-1994)	Comprehensive epilepsy program	-	44%	-	-
Ethiopia	Tegegne *et al*., [4]	432	Pre-tested structured questionnaire, HADS	Institution based cross-sectional study	-	32.8%	33.5%	-

shown as a contributing factor toward suicidal behavior in epileptic patients. On the contrary, attempted suicides also have increased the risk of unprovoked seizures [53]. Thus, patients with epilepsy must be carefully evaluated for their behavior and other related risks.

TREATMENT OF DEPRESSION IN EPILEPTIC PATIENTS

When treating a patient who presents with the complaints of both epilepsy and depression, the aim should be focussed mainly on controlling the seizure and its frequency by the use of appropriate AED's [9]. Adherences toward AEDs occupy an indispensable role in maintaining the control of seizures in those presenting with epilepsy [54]. Some anticonvulsants have shown to improve moods in epileptic patients which include drugs such as sodium valproate, carbamazepine, levetiracetam, lamotrigine, and gabapentin. These drugs also have shown their potential in preventing acute maniac and depressive episodes in patients with BD [9]. Thus, these drugs may be beneficial for epilepsy patients with depression.

Before initializing the therapy for depression in epileptic patients, all possible ways should be scrutinized to make sure that the depressive episodes are not the result of a sudden change in anti-epileptic regimen. Drug of choice for treating depression in epileptic patients is decided based on the prominent symptom of the depression exhibited by the subject [55].

Intra-nasal midazolam and intra-venous diazepam were given as a treatment option to pediatric population for prolonged febrile seizures. Eli *et al*. in her prospective randomized study on 47 children's who are of age 6 months to 5 years with these drugs found that both the drugs showed equal efficacy but seizure control was found to be more fast with intravenous diazepam and the overall time for seizures for cessation was faster with intra-nasal midazolam. Hence, both were equally proven effective for controlling seizures [56].

Mary *et al*. in her double-blind study for determining the treatment options that are available for treating depression in those with epilepsy enrolled 42 patients who are epileptic and also undergone depressive episodes. An antidepressant trial of amitriptyline, nomifensine and placebo was initiated. 25 mg TID was the dose of the active drug, and it was doubled in non-responders after 6 weeks, serum antidepressants and anticonvulsant levels were assessed after 6 weeks follow-up. Results indicated that at the end of 6 weeks all patients showed a decline in their depression score and at the end of 12 weeks it was identified that nomifensine was superior to amitriptyline [57].

Devinsky *et al*. conducted a prospective multi-center study to understand the changes in depression and anxiety when the epileptic patient undergoes a respective surgery. Subjects were reviewed using Beck psychiatric symptoms scale (BDI, Beck Anxiety Inventory- BAI) and Composite International Psychiatric Interview-CIDI) for a period of 24 months. A total of 358 pre-surgical BDI and 360 BAI was reviewed during the study. Depression and anxiety were prevailing among these patients and were observed as 22.1% and 24.7%, respectively. Post-surgery rates of depression were found to be declined successively in the 3, 12, 24 months follow-up. At the end of 24 months follow-up, moderate to severe levels of depression and anxiety were found only in 17.6% and 14.7% of subjects who had episodes of seizure even after surgery and 8.2% in patients who were seizure free [58].

Studies have suggested that depressive episodes can be also related with AED. In a cohort study of 39 epileptic patients, David *et al*. indicated that depressive rates were seen high in patients treated with phenobarbital when they are compared to patients treated with carbamazepine or no anticonvulsants (38% vs. 0%, p=0.04) [59].

Santosh *et al*. in an experimental study on male Swiss albino mice using the methanolic extract of *Passiflora foetida* (MEPF) leaves, a traditional Mexican medicine, demonstrated that administration of different doses of MEPF was able to induce antidepressant effects in mice. Harmaline alkaloids present in MEPF acts as a reversible mono-amino oxidase inhibitor and thus causes a reduction in the metabolism of catecholamine's and result in a subsequent increase in its concentrations. Flavonoid components also may bind to adrenergic and serotonergic systems and mediate antidepressant effect. Even though the exact mechanism is unknown traditional medicines have earned its place in substantial cure of depressive symptoms [60]. Thus, many plant extracts and phytoconstituents are investigated by the researchers for the treatment of epilepsy [61,62].

Treatment for both epilepsy and depression should be carried out simultaneously to prevent further risks to the patients. Studies have shown that depression can develop as a result of therapy with AEDs. Hence, care-full evaluation of the drugs should also be carried out in order for a better outcome.

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