A COMPREHENSIVE REVIEW ON COMORBID DEPRESSION IN PATIENTS WITH EPILEPSY

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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 neuromolecular 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 94,791 [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 ($\chi^2$=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 conjunction with questions about prevailing health issues, was used against 127,900 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.

PREVALENCE 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 at 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, 95% CI 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=0.008, β=−0.10) and complex partial seizure score (OR=1.12, 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.

Mohammad 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 therapy 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 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].

Ettlinger 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, β=1.328). Weaker predictors included 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].

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 BECK’s 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].

Chistensen 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. Anderson 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
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 focused mainly on controlling the seizure and its frequency by the use of appropriate AEDs [9]. Adherences toward AEDs occupy an indispensable role in maintaining the control of seizures in those presenting with epilepsy [54-5]. Some anticonvulsants have shown to improve moods in epileptic patients including drug such as sodium valproate, carbamazepine, levetiracetam, lamotrigine, and gabapentin. These drugs also have shown their potential in preventing acute manic and depressive episodes in patients with BD [9]. Thus, these drugs may be beneficial for epilepsy patients with depression.

Before initiating 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].

Devisky 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 also be 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 been shown to be beneficial for epilepsy patients with depression.

### Table 1: Studies showing prevalence of psychological disorders in epilepsy

| Country | Author | Number of Patients | Instrument | Method | Psychiatric Depression disorder | 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% |
| Brazil  | de Araujo et al., 2007 [29] | 106 | DSM-IV | Cross-sectional, 61.3% population based study | - | 30% | - |
| -       | Mensah et al., [30] | 499 | HADS | Population based study | - | 16.6%- borderline, - 11.2%- clinical | - |
| Montengaro Ethiopia | Vujisic et al. [31] | 70 | HAM-D, HAM-A Becks Depression Inventory | - | - | 32.8% | 21.4% |
| 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% |
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.

REFERENCES

1. Mehta S, Tyagi A, Tripathi R, Kumar M. Study of inter-relation of depression, seizure frequency and quality of life of people with epilepsy in India. Ment Illn 2014;6(1): 5169.
2. Scévolta L, Saradiansky M, Lanzillotti A, Oddo S, Kochen S, D’Alessio L. To what extent does depression influence quality of life of people with pharmaco-resistant epilepsy in Argentina? Epilepsy Behav 2017;69:133-8.
3. Jackson MJ, Turkington D. Depression and anxiety in epilepsy. J Neurol Neurosurg Psychiatry 2005;76 Suppl 1:A45-7.
4. Tegegne MT, Mossie TB, Eshtetu DA. Depression and Anxiety disorder among epileptic people at amuelal specialized mental hospital, Addis Ababa, Ethiopia. BMC Psychiatry 2015;15:210.
5. Mendez MF, Cummings JL, Benson DF. Depression in epilepsy. Significance and phenomenology. Arch Neurol 1986;43(8):766-70.
6. Robertson MM, Trimble MR. Depressive illness in patients with epilepsy: A review. Epilepsia 1983;24(2):5109-16.
7. American Association for the Advancement of Science. Epilepsy and depression: A two way street? Science Daily. Washington, DC: American Association for the Advancement of Science; 2005.
8. Kanner AM. Depression in epilepsy: A complex relation with unexpected consequences. Curr Opin Neurol 2008;21(2):190-4.
9. Harden CL. The co-morbidity of depression and epilepsy: Epidemiology, etiology, and treatment. Neurology 2002;59:6 Suppl 4:S84-55.
10. Colin BJ, Mark L, Isabelle V, Tolulope TS, Scott P, Natalie J, et al. Association of depression and treated depression with epilepsy and seizure outcomes: A multicohort analysis. JAMA Neurology 2017;74:533-9.
11. Attarian H, Vahle V, Carter J, Hykes E, Gilliam F. Relationship between depression and intractability of seizures. Epilepsy Behav 2003;4(3):298-301.
12. Gilliam F, Kuzniecky R, Mula M, Schmitz B, Jauch R, Cavanna A, Cantello R, Monaco F, et al. Cockerell OC, Moriarty J, Trimble M, Sander JW, Shorvon SD. Acute neurology 2005;65(4):535-40.
13. Ettinger A, Reed M, Cramer J. Depression and comorbidity in epilepsy. Acta Neurol Scand 2004;110(4):207-20.
14. Nilsson L, Ahlbom A, Farahmand BY, Asberg M, Tomson T. Risk of chronic epileptics attending a neurological clinic: A controlled investigation. Br J Psychiatry 1982;140:236-43.
15. Burton K, Rogathe J, Whttaker RG, Mankad K, Hunter E, Burton MJ, et al. Co-morbidity of epilepsy in Tanzanian children: A community-based case-control-study. Seizure 2012;21(3):169-74.
16. Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. Acta Neurol Scand 2004;110(4):207-20.
17. Tellez-Zenteno JF, Patten SB, Jette N, Williams J, Wiebe S. Psychiatric co-morbidity in epilepsy: A population-based analysis. Epilepsia 2007;48(12):2363-44.
18. Siddhuraj D, Baluni SK, Srinivasan R, Bhatia S, Shekhar D, et al. Depression in epilepsy: A hospital based study. Epilepsia 2008;6(15):746-82.
19. Sajjadur R, Kalita KK, Aparajeepta B. A hospital based cross sectional study on comorbid psychiatric problems in persons with epilepsy from north eastern part of India. Int J Epilepsy 2017;4(1):31-5.
20. Asadi-Pooya AA, Sperlir MG. Depression and anxiety in patients with epilepsy, with or without other chronic disorders. Iran Red Crescent Med J 2011;13(2):112-6.
21. Kiko N, Prevalence and factors associated with depression among patients with epilepsy in a Kenyan tertiary care hospital. Nairobi, Kenya: Aga Khan University; 2013.
22. Victorof JF. DSS-III-R psychiatric diagnoses in candidates for epilepsy surgery: Lifetime prevalence. Cogn Behav Neurol 1994;7:287-97.
23. de Araujo GM, Rosa VP, Caboclo LO, Sakamoto AC, Yakubian EM. Prevalence of psychiatric disorders in patients with mesial temporal lobe seizures. J Epilepsy Clin Europhysiol 2008;13:658-61.
24. Mensah SA, Beavis JM, Thapar AK, Merr M. The presence and clinical implications of depression in a community population of adults with epilepsy. Epilepsy Behav 2006;8(1):213-9.
25. Vujisic S, Vodopic S, Radulovic L, Injaedic-Stevovic L. Psychiatric comorbidities among patients with epilepsy in Montenegro. Acta Clin Croat 2015;43(4):411-6.
26. Bitru BB, Dachew BA, Biruene BT, Biruhan Tepbeh N. Depression among people with epilepsy in Northwest Ethiopia: A cross-sectional study on the basis of a BMDM Notes 2001/2.
27. Briellmann RS, Hopwood MJ, Jackson GD. Major depression in temporal lobe epilepsy with hippocampal sclerosis: Clinical and imaging correlates. J Neurol Neurosurg Psychiatry 2007;78(11):1226-30.
28. Yousafzai AU, Yousafzai AW, Taj R. Frequency of depression in epilepsy: A hospital based study. J Ayub Med Coll Abbottabad 2009;21(2):73-5.
29. Barrowclough B. Suicide and epilepsy. In: Reynolds FH, Trimble MR, editors. Psychiatry and Psychology. Edinburgh: Churchill-Livingstone; 1981. p. 72-6.
30. Kanner AM, Nieto JC. Depressive disorders in epilepsy. Neurology 1999;53 Suppl 2:S262-32.
31. Mbewe EK, Uys LR, Nkwanyana NM, Birbeck GL. Apremial health care screening tool to identify depression and anxiety disorders among people with epilepsy in Zambia. Epilepsy Behav 2013;27(2):296-300.
32. Kanner AM, Schachter SC, Barry JJ, Heffner DC, Men J, Mula M, Trimble M, et al. Depression and epilepsy: Epidemiologic and neuropsychiologic perspectives that may explain their high comorbid occurrence. Epilepsy Behav 2012;24(2):156-68.
33. Ettinger A, Reed M, Cramer J. Depression and comorbidity in community-based patients with epilepsy or asthma. Neurology 2004;63(6):1008-14.
34. Stefanello S, Marin-Leon L, Fernandes PT, Li LM, Botega NJ. Depression and anxiety in a community sample with epilepsy in Brazil. Arq Neuropsiquiatr 2011;69(4):342-8.
35. Wazir A, Khosa NA, Amuliath S. To determine the frequency of depression in patients with primary epilepsy. Pak J Neurol Sci 1981;1(2):32-4.
36. de Leo D, Bertolote J, Lester D. Self-directed violence. In: Krug EG, Maris RW, editors. Suicide Prevention: Toward the Year 2000. New York: Guilford; 1985. p. 22-35.
37. Moscicki EK. Epidemiology of suicidal behaviour. In: Silverman MM, Maris RW, editors. Suicide Prevention: Toward the Year 2000. New York: Guilford; 1985. p. 22-35.
38. Moscicki EK. Epidemiology of attempted and completed suicide: Toward a framework for prevention. Clin Neurosci Res 2001;1:310-23.
39. Nilsson L, Alhomb A, Farahmand BY, Asberg M, Tomson T. Risk factors for suicide in epilepsy: A case control study. Epilepsia 2002;43(6):644-51.
40. Christensen J, Vestergaard M, Mortensen PB, Sidenius P, Agerbo E. Epilepsy and risk of suicide: A population-based case-control study. Lancet Neurol 2007;6(7):693-8.
41. Qin P, Xu H, Laursen TM, Vestergaard M, Mortensen PB. Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: Population based cohort study. BMJ 2005;331(7507):23.
42. Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ. Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. Epilepsy Behav 2003;4 Suppl 3:S31-8.
43. Andrijic NL, Alajbegovic A, Zec SL, Loga S. Suicidal ideation and attempts in patients with epilepsy: A hospital based study. BMC Psychiatry 2015;15:210.
44. Christensen J, Vestergaard M, Mortensen PB, Sidenius P, Agerbo E. Epilepsy and risk of suicide: A population-based case-control study. Lancet Neurol 2007;6(7):693-8.
45. Qin P, Xu H, Laursen TM, Vestergaard M, Mortensen PB. Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: Population based cohort study. BMJ 2005;331(7507):23.
46. Jones JE, Hermann BP, Barry JJ, Gilliam FG, Kanner AM, Meador KJ. Rates and risk factors for suicide, suicidal ideation, and suicide attempts in chronic epilepsy. Epilepsy Behav 2003;4 Suppl 3:S31-8.
47. Andrijic NL, Alajbegovic A, Zec SL, Loga S. Suicidal ideation and attempts in patients with epilepsy: A hospital based study. BMC Psychiatry 2015;15:210.
52. Pompili M, Girardi P, Ruberto A, Tarelli R. Suicide in the epilepsies: A meta-analytic investigation of 29 cohorts. Epilepsy Behav 2005;7(2):305-10.
53. Hesdorffer DC, Hauser WA, Olafsson E, Ludvigsson P, Kjartansson O. Depression and suicide attempt as risk factors for incident unprovoked seizures. Ann Neurol 2006;59(1):35-41.
54. Ahmad N, Othaman NI, Islahudin F. Medication adherence and quality of life in epilepsy patients. Int J Pharm Sci Res 2013;5(2):401-4.
55. Mebanga O, Allen SN. Treatment of depression in patients with epilepsy. US Pharm 2012;37(11):29-32.
56. Lahat E, Goldman M, Barr J, Bistritzer T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: Prospective randomised study. BMJ 2000;321(7253):83-6.
57. Robertson MM, Trimble MR. The treatment of depression in patients with epilepsy: A double-blinded trial. J Affect Disord 1985;9(2):127-36.
58. Devinsky O, Barr WB, Vickrey BG, Berg AT, Bazil CW, Pacia SV, et al. Changes in depression and anxiety after resective surgery for epilepsy. Neurology 2005;65(11):1744-9.
59. Brent DA, Cunnrime PK, Varma RR, Allan M, Allman C. Phenobarbital treatment and major depressive disorder in children with epilepsy. Pediatrics 1987;85(6):1086-91.
60. Santosh P, Venugop R, Nilakash AS, Kunjibihari S, Mangala LD. Anti depressant activity of methanolic extract of Passiflora foetida leaves in mice. Int J Pharm Pharm Sci 2011;3(1):112-5.
61. Singh P, Singh D, Goel RK. Phytoflavonoids: Anti-epileptics for the future. Int J Pharm Pharm Sci 2017;6(8):51-66.
62. Deka D, Chakravarthty P, Purkayastha A. Evaluation of the anticonvulsant effect of aqueous extract of Centella asiatica in Albino mice. Int J Pharm Pharm Sci 2017;9(2):312-4.