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Review article

Causative factors and phenomenology of depression in EPILEPSY—A review

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ABSTRACT

It is a known fact that depression is the one of the leading causes of years lived with disability and the fourth leading cause of disability-adjusted life-years worldwide. Depression is often under-recognized among patients of epilepsy due to lack of awareness of depressive symptoms. Due to improper management of depression in epileptic patients, it can interfere with treatment outcomes and hence can impair the quality of life. Undermanaged depression in epilepsy is generally associated with work absenteeism and direct medical costs. Electronic bibliographic databases like PubMed and Google Scholar were searched using the format "(depression, epilepsy and symptoms)". Cross-linked searches were made taking the lead from key articles. Recent articles and those exploring the etiological factors & symptomatic presentation of depression were focused upon. The main purpose of this review was to study the causative association between epilepsy and depression and to discuss the varied symptomatic presentation.

Contents

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1. Introduction

With a prevalence rate of 8.2–12.9 per 1000 in general population, epilepsy is one of the most common chronic medical problems in the world.[1] While 30% of patients with epilepsy had medically refractory seizures (intractable epilepsy), fortunately, the other 70% become seizure free on antiepileptic drugs (AEDs).[2]

Psychiatric disorders (PD) occur in persons with epilepsy more frequently as compared to general population. Mood disorders occur in 11 to 62%, psychosis in 7 to 10% and personality disorders in 5 to 33%.[3–10] Most frequent PD in persons with epilepsy is depression.[11–13] The rate of depression ranges from 20 to 55% in patients with refractory epilepsy, especially with temporal lobe epilepsy caused by mesial temporal sclerosis (TLE-MTS). Depression remains underdiagnosed and undertreated in persons with epilepsy, despite its high prevalence, hence, increasing the personal and social cost. The most common psychiatric comorbidities in epilepsy include depression, anxiety, attention-deficit hyperactive disorder and psychosis.[14,15] Rates of depression are elevated above the general population in most community and clinic-based studies and these findings are comparable to studies with other chronic illnesses.[16,17] Depression is commonly associated with newly presenting patients with epilepsy.[18,19] and indeed may precede and constitute a risk factor for it also.[15]

Although, the prevalence of depression in epilepsy and its consequence in terms of mortality and morbidity has been a matter of debate among various researchers, but the mechanisms underlying this association — epilepsy and depression — has never been explored properly. For this reason, it is a common belief among many clinicians, patients and relatives that epilepsy and depression present as a – cause and consequence – a bidirectional relationship. This review was done to discuss in detail about the causative factors and phenomenology of depression in epilepsy.

1.1. Clinical evidence of depression and epilepsy as epiphenomena

Epilepsy may lead to depression was based on the hypothesis that epilepsy is a disabling and stigmatizing disease, but this hypothesis has been weakened by some clinical evidences that speaks against it. In addition, it has a clinical impact, as it keeps clinicians aware of the fact that depression may occur early in the course of epilepsy and sometimes can even precede its onset.

1.1.1. Depression In various seizure types and temporal lobe epilepsy (TLE)

Rodin et al. in 1970s reported higher depression scores in patients with temporal lobe epilepsy (TLE) than any other types of epilepsy.[20] Dikmen et al. in 1983 found that secondarily generalized complex partial seizures had more severe depressive scores than primarily generalized convulsive seizures.[21] There were also other study showing that patients with non-epileptic seizures have higher frequency of depression than those with epileptic seizures.[22] While In children, patients with focal complex partial seizures more likely to suffer from depression than patients with primarily generalized seizures.[23] It has been found that severity of depressive symptoms has been found to be related to seizure type, duration of epilepsy and response to the antiepileptic drugs instead of seizure frequency or intractability.[23–25] Patients with mesial TLE with psychiatric comorbidities have higher probability of secondarily generalized seizures than without psychiatric symptoms.[26] Kraeplinin 1923 described a pleomorphic affective disorder in epilepsy called “interictaldysphoric disorder” with a prevalence of 17% in TLE.[27] The term was first coined by Blumer et al. which includedirritability and outbursts of aggressive/euphoric behavior, labile depressive symptoms (depressive mood, lack of energy, pain, insomnia) and labile affective symptoms (fear, anxiety) as key symptoms.[28] Interictaldysphoriaas a symptom is moreclosely associated with bipolar disorder rather than depressive disorder with a prevalence of about 1.4% in classic bipolar disorder (type I), despite being seen more frequently in epilepsy.[29]

Depression is seen in about 50–60% of patients with temporal lobe epilepsy caused by mesial temporal sclerosis (TLE-MTS) than any other types of epilepsy.[30,31] Depression scores are higher in patients with TLE-MTS than patients with neocortical temporal lesions.Lateralization of the lesion has no relation to the severity of the depression score.[32] Persons with TLE-MTS have the highest rate of suicide and suicide attempts having approximately 25 times higher than general population, while the overall prevalence of suicide in all epilepsies range from 3 to 5%.[33,34] It was also found that persons with TLE-MTS have higher cognitive side effects and mood disturbances than patients without hippocampal sclerosis, while on antiepileptic drugs (AEDs).[35]

1.1.2. Depression In children with epilepsy

Similar findings were observed in children with epilepsy that there is high prevalence of Psychiatric Disorders, especially depressioneven during the erly course of illness.[36] The prevalence of depression ranges from 28% in children with uncomplicated epilepsy to 58% in children with refractory epilepsy.[37] Depression was the most frequent PD in children with refractory epilepsy, according to a study conducted in a Brazilian tertiary care facility.[38] Children with epilepsy often remain undertreated and underdiagnosed, especially those with depression, similar to adults.[5,39] High suicide rates areevident in children and adolescents with epilepsy.[40]

Few population based studies conducted in USA and UK gave a brief idea of prevalence of depression and anxiety in children with epilepsy, but there is a difference in the prevalence rates of anxiety and depression in various studies, as only two of the studies used DSM-IV criteria to identify depression and/or anxiety.[41,42] Davies et al.conductedchild and adolescent mental health survey using DAWBA (Development and Well-Being Assessment) and DSM-IV criteria in the age group of 5–15 years of children with a sample size of 67. Theyfound that 7 (16.7%) with ‘uncomplicated’epilepsy and 4 (16%) of those with‘complicated’ epilepsy met criteria for an ‘Emotional Disorder’.[41] He used the term ‘emotional disorder’ as a proxy for depression and/or anxiety. The authors also reported that there was no difference in the rates of ‘emotional disorder’ for children with ‘complicated epilepsy’ and those with ‘uncomplicated epilepsy’. ‘Complicated epilepsy’ included children with

severe learning difficulties (vocabulary quotient <60), speech or language difficulties, cerebral palsy, other physical impairments, and congenital conditions.[41] Hedderick and Buchhalter studied 134 patients of less than 16 years of age and, found that 16 (12%) of children with epilepsy had a DSM-IV 'Mood Disorder'. They used data from the Rochester Epidemiology project, which included all the incident cases of epilepsy in the Rochester area over a 15-year period.[42]

Berg et al. conducted a longitudinal study onchildren in Connecticut, which included 501 participants and found that 67 (13.4%) of children with epilepsy met criteria for 'Depression', 6 (1%) met criteria for 'Bipolar Disorder' and 25 (5%) met criteria for 'Anxiety'. The children and adolescents participated in the Connecticut Study of Epilepsy Children were originally diagnosed at an average age of 5.9 years and followed up to 9 years later.[43] Davies et al.,[41] Rodenburg et al.[44] and McDermott et al. [45]were also successful in showing that children with epilepsy have significantly higherdepression and/or anxiety problems compared to children with other health conditions and the general paediatric population. When compared to their siblings, children with epilepsy have similar incidence of difficulties on depression/anxiety domains, suggesting that family factors may have a major role in the elevated levels of symptoms of depression and anxiety in children with epilepsy.[44] McDermott et al. used the data from national health interview survey conducted in USA among 111 children in the age group of 5–17 years and found that 29 (24%) of children with epilepsy had significant 'Anxiety' compared with 16.5% of children with cardiac difficulties and 7.5% of general paediatric population.[45]

1.1.3. Bidirectional relationship

Depression and suicide attempt are considered asindependent risk factors for the onset of seizures and epilepsy according to some studies. The scientific studies showing the bidirectional view of epilepsy and depression were carried out in the last decade. One of the study established that a significant number of patients with new-onset epilepsy already had symptoms fulfilling criteria for depression prior to their first seizure.[46–48] The same studies also concluded that a history of depression preceding the onset of epilepsy was seven times more frequent among epilepsy patients than controls.[46–48] Another similar study found that history of depression preceding their initial seizure was 3.7 times more among people with epilepsy than the control group.[47]

Therefore, the high prevalence of the comorbidity of these two disorders in children and in patients with new-onset epilepsy suggests that depression and epilepsy may share common pathogenic mechanisms. Both of these disorders may be manifested with the involvement of the same brainstructures, although it is a common belief among neurologists and physicians that depression is due to consequence of long term effect of epilepsy and stigma related to it.[49]

1.2. Causation of depressive disorders in epilepsy – epilepsy as an etiological model for depression

The affective disturbances and depressive symptoms tend to be considered either as understandable psychological reaction to the stresses and challenges of living with epilepsy; or as neurobiological epiphenomena of the epileptic brain.[50] In addition, research interest has focused on two other 'causal arrows':[51]

i Psychiatric disturbances not only may result from epilepsy (via psychological and/or neurobiological pathways), but depression, may also contribute to the causation of epilepsy.
ii Shared causal factors (e.g. genes, traumatic brain injury, early-life stress) may give rise to both psychiatric illness and epilepsy.

Most of the depression research in the epilepsy field is 'either/or' – either psychosocial or neurobiological – and lacks a longitudinal perspective because of which a temporal relationship between epilepsy and depression can not be established effectively. Modern psychiatry research related to depression (non-epilepsy associated) is bio-psycho-social in nature, and includes genetics, epidemiology, psychology and neurobiology, based upon a diathesis–stress framework,[51] and adopts a lifespan perspective.[52]

1.2.1. Psychosocial etiological factors

Generally the neurological features of epilepsy are inconsistent predictors of psychopathology in depression, but some good-quality studies have shown associations between various factors such as seizure frequency and rates of depression.[53–57] In contrast to neurological factors, psychosocial factors such as life stress, coping style, social support, perceived stigma and personality have been more consistent predictors.[58] Different psychosocial factors were found as common factor in both the illness.

1.2.2. Stress

According to the diathesis stress model,[59] depression is viewed as the result of overwhelming life challenges (i.e., stress) in combination with an individual diathesis (i.e., a disadvantageous organic or psychological disposition or vulnerability). This concept was also addressed as allostatic load.[60] The burden of epilepsy may comprise seizure-related injuries and hospitalizations, cognitive and behavioral impairments, restricted mobility, reduced educational outcomes, lower socioeconomic and marital status, and humiliatingly social stigma.[61] Thus, epilepsy is a condition with unusual life demands from various aspects of life and hence heavy stress.

1.2.3. Learned helplessness

Learned helplessness has been most influential way of inciting depression like behaviors in experimental animals.[62] As per evidences, patients suffering from seizures (epileptic or non-epileptic) behave exactly like experimental animals.[63] Cognitively, helplessness translates into increased external locus of control attributions and loss of the sense of internal control. This causal attribution style alterations in epileptic patients have been confirmed by few studies.[64]

1.2.4. Loss of reinforcement

The impairment in the brain's reward system,i.e the meso-cortico-limbic dopamine system, could be correlated with intrinsic inability to experience pleasure.[65,66] However, experiences of embarrassing situations related to seizures (e.g., enuresis) may lead to social stigmatization and may reasonably result in withdrawn social activities in epileptic patients. This has a strong negative impact on their overall lifestyle as patients lose pleasant physical & social reinforcement, thus resulting in a socially withdrwnbehaviour.

1.2.5. Peri-ictal depression

Depressive mood alterations have been reported as a frequent precipitant of seizures.[67] It is also being reported as a symptom of prolonged (lasting over 2–3 days) postictal recovery.[68] Acute suicidal urge during postictal depression has been documented in a single case.[69] It is very difficult to distinguish interictal from *peri*-ictal depression in patients with mutiple seizures per month.[70] Similar electro-patho-physiological alterations have also been found in non-epileptic patients with major depressionas in those with epileptogenic abnormalities.[71]

1.2.6. Iatrogenic depression

Depression has been an important side effect of many drugs including phenobarbital[72] and primidone.[73] Symptoms comprising irritability and aggressiveness as psychiatric adverse effects have been reported for levetiracetam.[74] Black box warning issued by the FDA, listed an increased suicide risk among all antiepileptic drugs,[75] although this is still being debated.

1.3. Neuro etiological factors

Neurobiologically oriented studies gave more information related to etiological factors, employing structural[76–81] or functional imaging[82–85] or both[86–88] and, where available, histological, pathological or molecular pathological level study of excised temporal lobe tissue.[89] The findings related to mesial temporal lobe epilepsy has been most consistent, with evidences of enlarged amygdala, diminished hippocampal and neocortical volumes, the latter in both temporal and extra-temporal cortex.[77] The other findings such as diminished 5HT1A receptor binding in the hippocampus, possibly, raphe nuclei, insula and cingulate gyrus;[83] and a correlation between degree of hippocampal abnormality and depression on 1H-magnetic resonance spectroscopy imaging[82] has been a consistent finding related to epilepsy and depression. It has been found that severity of depression is associated with duration of epilepsy, irrespective of epilepsy variables such as seizure type, frequency or EEG alterations.[90] Various limbic and extralimbic structureswere found to have shown significant correlation between epilepsy and depression.

1.3.1. Limbic structures

Decreased volumes of the hippocampus have been found among individuals with TLE (Temporal Lobe Epilepsy) and depression in various MRI volumetric studies. By definition, it is expected that there is hippocampal volumes loss in TLE-MTS, especially related to the site of seizure origin– ictal onset zone.[91–93] But evidences suggest that there is more pronounced decrease, or bilateral decrease, in patients with TLE-MTS and depression.[92]

Richardson et al. in 2007 found that both right and left amygdala volumes are associated with depression severity among persons with TLE, indicating significant positive relationships between right and left amygdala volumes and depression.[94] It was also found that patients having depressive symptoms associated with TLE have increasing amygdala volumes measured by MRI.[94] Thus, during anxiety and mood disorders, there is amygdala hyperactivity and it has been found that amygdala may actually increase in size during acute depression in patients with TLE.[94,95] These findings overlie those previously demonstrated in patients with depression without epilepsy,[96] in which the transient amygdala enlargement can be because of two reasons:

1. Either secondary to enhanced regional blood flow and vascular volume as detected by positron emission tomography (PET)[97] or
2. Because of increased branching of amygdaloid neurons leading to dendritic remodeling.[98]

1.3.2. Extralimbic structures

Smaller volumes of frontal lobes have been seenin TLE as per MRI findings.[93] Woermann et al. in 2000 found decreased grey matter in patients with TLE with aggressive episodes, most markedly in the left frontal lobe, compared with the control group and with patients with TLE without aggressive episodes.[99] His work included automated segmentation of cerebral grey matter from T1 weighted MRI and he also suggested that the basic pathophysiology of aggression in TLE might be because of reduction of frontal neocortical grey matter volume.[99]

Later on, Salgado et al., 2010 conducted a study on 96 healthy controls and 48 TLE-MTS (24 with major depression and 24 without major depression) and revealed that the number of areas of gray matter volume (GMV) loss was significantly higher in the group with MTLE with depression.[79] They revealed significant group effect regarding GMV loss in some brain regions, suggesting that there was more widespread distribution of GMV loss in patients with depression compared to those without.[79] 1.3.3 Impact of impaired neurogenesis and neuronal integration in epilepsy on depression

1.3.3. Impact of impaired neurogenesis and neuronal integration in epilepsy on depression

During acute and chronic phases of epilepsy, altered neurogenesis and granule cell integration may have a significant impact on the course of depression. It is evident that neurogenesis is increased early in the epileptogenic process, but many of these new cells are abnormal in structure.[100–103] While the antidepressive therapy may increase the production of normal granule cells, which appears to be beneficial, but there is also increase in production of abnormal granule cells, which might have negative effects. Although, there is no clear evidence on the role of antidepressant therapy in the production of normal or abnormal granule cells, reduced neurogenesis could be a risk factor for depression.[104] Santarelli et al. in 2003 concluded that, similar to the limited utility of fluoxetine in rodents following radiation treatment, the utility of antidepressant treatments might also gets limited due to disruption of the neurogenic niche in the epileptic brain.[105] A recent study of depressive behavior in rodents rendered epileptic using the pilocarpine model (which produces significant cell loss) however, found fluoxetine to be ineffective.[106] But no such study on humans has been done till now which could provide important guidance for the treatment of depression in patients with epilepsy.

2. Patterns of depressive symptoms in epilepsy

2.1. Epilepsy and quality of life

Epilepsy can have a significant impact on the quality of life (QoL), as evident in various studies.[107–109] When various aspects of QoLwas evaluated, it was found that the performance of epileptic individuals is significantly inferior to those suffering from other chronic diseases[101,107]and also from that of the general population.[109,110,112,113]

A Study by Tedrus et al., in 2012 on 132 epileptic patients using the Quality of Life in Epilepsy Inventory (QOLIE-31) concluded that existence of psychiatric co-morbidity (cognitive function, seizure worry, emotional well-being, energy/fatigue, social function and total score) and a greater seizure frequency (energy/fatigue, cognitive function and total score) are important predictive factors for lower scores in the total QOLIE-31 score and in various other dimensions.[114] There are only few studies who have done a proper systematic evaluation on patients with stable epileptic seizures (ES),[110,118] while most of the QoL studies focused mainly on patients with refractory ES or with depressive outlooks[111,115–117] Since various cultural, ethnic and economic differences can have their impact on the QoL, a better understanding of the QoL in different countries can be an eye opener.

2.2. Fatigue in patients with epilepsy and its association with depression

Fatigue is one of the most common symptom being presented in day to day medical practice, but it is rarely evaluated properly among patients with epilepsy. It is a very common complaint

among patients with epilepsy, but very few researchers have examined it.[119,120–124] There is very less information about phenomenology of fatigue, severity and its impact among patients of epilepsy, as indicated by Hernandez-Ronquillo et al. in 2011.[119] In a study done by Tellez-Zenteno et al. in 2005, statistically significant association between epilepsy and chronic fatigue was demonstrated, in addition to associations with other medical conditions such as fibromyalgia, heart disease, back problems, asthma, and stomach/intestinal ulcers. It was also concluded that frequency of chronic fatigue among patients with epilepsy is four times more than the general Canadian population.[121]

Sometimes excessive daytime sleepiness is also being used instead offatigue by many clinicians,[125] and the term fatigue is often defined as the inability to stay awake and alert during the major waking periods of the day, thus resulting in unintended lapses into drowsiness or sleep (ICDS-2).[126] Unfortunately, fatigue has never been considered as a significant symptom among patients suffering from epilepsy and hence, has largely been overlooked by the clinicians in their management plan.[114]

2.3. Anger is a distinctive feature of epilepsy patients with depression

Blumer and colleagues in 1995 evaluated mood symptoms in patients with epilepsy and proposed “interictaldysphoric disorder” as one of the different type of mood disorder specific to epilepsy. The clinical presentation of Interictaldysphoric depression in epilepsy is characterized by recurrent episodes of dysphoria alongwith intermittent dysthmia.[127] Furthermore, Kanner and Palac in 2000 have emphasized the clinical significance of this epilepsy-specific mood disorder, demonstrating that almost three fourth of epilepsy patients with depressive symptoms have non-clinical depression according to the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV) criteria, and that anhedonia without sadness or irritability may predominate.[128] Some studies however negate the idea of an epilepsy-specific mood disorder and suggest that presentation of depressive symptoms is almost similar irrespective of epilepsy.[129–132] Overall, the general consensus is that the presentation of the depressive symptoms in epileptic patients mostly overlaps with that of patients with idiopathic major depression.[133]

From a pharmaco-therapeutic perspective, this presumed similarity has resulted in the widespread belief in the efficacy of antidepressants in epilepsy patients. Mood stabilizers such as lamotrigine (LTG) has significant effect on moods in epileptic patients in at least 11 studies, including 3 randomized control investigations.[134–143] Interestingly, Labiner et al. (2009) recently revealed that the effects of LTG on mood primarily affect anger or hostility rather than depression itself.[142] Thus, it seems that epileptic patients have variedpresentation of depression where anger or hostility is a distinctive feature.

2.4. Cognitive profile in patients of depression with epilepsy

Cognitive and emotional disturbances are commonly found in patients with all forms of epilepsy.[144] The cognitive functioning of an epileptic patient is significantly affected by various factors such as etiology of the disease, underlying neuropathology, frequency of seizures, side effects associated with antiepileptic drugs (AEDs), and other psychosocial factors.[145] Research involving cognitive functions in epileptic patients has mainly concentrated on the memory functions in patients with difficult to treat TLE, and new concept of “a complex of neuropsychological symptoms” related to the syndrome of mesial TLE was suggested, with material-specific memory disturbances playing the leading role.[146] Few studies on epileptic patients with frontal lobe involvement have revealed a more widespread disturbances in their cognitive functions (disturbances in psychomotor speed, poor attention span, impaired motor coordination, impairment in working memory, and response inhibition).[147] The disturbances of prefrontal functions, especially, conceptualization, abstract thinking, mental flexibility; cognitive speed, planning, and organization has been described by Piazzini et al. in 2008.[148]

Previous research has indicated that cognitive functions in epilepsy are influenced by several factors. Early age of onset, longer duration of epilepsy, a higher number of lifetime tonic-clonic epileptic episodes, history of status epilepticus, polytherapy, and symptomatic etiology of epilepsy are the variables that are linked to a greater risk for cognitive deficits.[149,150] Previous studies have found neuropsychological dysfunction to be present in newly diagnosed generalized tonic clonic and partial seizures,[151,152] while memory functions have been shown to decline with a longer duration of the illness.[153]

Neuropsychological studies have reported that depression can have a significant effect on various cognitive functions such as episodic memory and learning, verbal fluency, attention, and motor speed.[154] Paradiso et al. in 2001, demonstrated that cognitive performance related to measures of intelligence, language, visual perceptual ability, memory, and executive function was significantly poor in patients of TLE with depression compared to patients of TLE without depression.[155] It was also found that cognitive disturbance due to the effects of depression might be greater in patients with left TLE.[155] As depression is known to cause several disturbances in cognitive functioning, epileptic patients could therefore have a higher risk of double burden.

2.5. Suicidal ideation and thoughts of death in epilepsy patients

Epileptic patients have 5 times higher suicide rate than in general population including both adults and younger age groups. The epileptic patients possesshigher risk of suicidalbehavior (including suicidal thoughts and attempts) with an estimated lifetime prevalence rate that varies between 3.3% and 14.3% or even up to 32.5%.[151,152] It was also indicated that temporal lobe epilepsy (TLE)has 6 to 25 times higher suicidal rates[156,157] compared to 1.4%-6.9% in general population,[158] while patients with temporal lobectomyhave even higher suicide rates.[2] Suicide accounts for approximately 10% of deaths among epileptic patients compared to 1.4% in general population.[159]

Andrijic et al. in 2014 studied 50 epileptic inpatients and outpatients of both genders, aged 18 years and older and found suicidal ideation and thoughts of death to be present in 38% of epileptic patients. Symptoms of depression as well as feelings of hopelessness were found in half of the participants (52% and 48%), and was significantly more common in epileptic patients having suicidal ideation. There was a significant relation of suicidal ideation with the presence of chronic pain (3.86; $p = 0.49$), sexual/physical abuse history (5.95, $p = 0.015$), level of hopelessness (20.7; $p = 0.000$) and severity of depression (14.48; $p = 0.000$) in epilepsy patients. The study has shown that the level of hopelessness and unemployment have a predictive value for appearance of suicidal ideation in epilepsy patients.[168]

Suicidal behaviorin patients with epilepsy has complex and multifactorial etiologies. Several factors have been identified as risks which include: male sex, early age at onset, TLE, high frequency of primary generalized seizures, polymorphic seizures combination, severe epilepsy, lateralization of the epileptic focus, recent control of seizures, absence of seizures for a long time especially after being very frequent, cognitive deterioration, hypofrontality and comorbid psychiatric illness. It has been shown in various retrospective studies that most of the suicides (81%-100%) occuring in epileptic patients had some comorbid

psychiatric illnesses, depression being the most common with a risk of 15%-18.9%, even 50 times higher than the general population. Others include anxiety, mood disorders and epileptoid personality and past or family histories of psychiatric disorders.[159–162]

Recently, AEDs have been suggested as a risk of suicide with epilepsy.[163,164] The mechanisms of the negative psychotropic effects of AEDs are complex and vary from patient to patient and has been related to the direct (i.e., anticonvulsant action) and indirect mechanisms of the drug action, particularly with rapid dose titration, slow drug metabolism, polypharmacy, drug–drug interactions, drug toxicity, drug withdrawal and metabolic derangements (as folate deficiency).[165] Also non-pharmacological treatments as surgery[2] and vagus nerve stimulation[166] have been associated with increased risk of suicide up to 5-folds higher than pharmacological therapy. The concept of forced normalization (or alternative psychosis) in which a good control of seizures regardless control of EEG changes by pharmacological and non-pharmacological therapy results in appearance of behavioral abnormalities or psychosis, has been suggested as a cause of behavioral adverse effects or even suicide, although the exact mechanisms are not fully understood.[167]

3. Conclusion

Despite the above information, there is a vide variation in the findings related to prevalence of depression among epileptic patients and its effect on the life of a person. This reflects the heterogeneity of epilepsy and the differences in study designs and studied populations. Early recognition and possible modification of clinical and psychosocial variables will have significant impact on the quality of life of epileptic patients and in medical management. We need more research to understand the various aspects of mood disorders in epileptic patients, which will guide all clinicians to take a more holistic approach in management of epilepsy, although complete cessation of seizures remains the only goal of therapy in epileptic patients for every clinician. With further research, the significance of mood symptoms in epilepsy will be more evident and this will help in changing the outlook towards epilepsy management among clinicians i.e, to go beyond seizure control.

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