Chapter 7

Psychiatric Comorbidities and Quality of Life in Epilepsy

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Abstract

Epilepsy is a chronic disorder characterized by a spontaneous tendency to recurrent seizures which affects patients' cognitive, behavioral, psychological, and social functioning. Epileptic patients face various problems that result in a lower quality of life. Seizure frequency, drug side effects, psychological comorbidity, and stigma are the major factors affecting the quality of lives of patients with epilepsy. Depression, anxiety, psychosis, and cognitive impairment are some of the comorbid psychiatric problems accompanying the clinical picture in epilepsy. Also the role of antiepileptic drugs (AEDs) in psychopathology of epilepsy should not be underestimated. One of the most important reasons why health-related quality of life (HRQOL) has become important for epileptic patients is related with well-known characteristics of this disorder. Its chronic nature, presence of unexpected, intractable and frequent seizures, and stigma are some of these characteristics among others. With the review of the current literature, it can be concluded that there is still a need for further scientific research to find out more clear relation between epilepsy, comorbidities, and HRQOL.

Keywords: epilepsy, psychiatric comorbidities, quality of life

1. Introduction

Epilepsy is a chronic disorder characterized by recurrent seizures which impairs patient's quality of life through cognitive, behavioral, psychological, and social functioning [1]. It has been reported that the total lifetime risk for epilepsy and for any unprovoked seizure are 3.1 and 4.1%, respectively in industrialized countries. The estimation of annual incidence of epilepsy is reported as high as 43 cases per 100,000 of the population in so-called developed countries, and is almost double this figure in the developing world [2]. Another estimation points out that there are 50 million people who have epilepsy in the world [3, 4]. It was

suggested that more than 80% of people with epilepsy live in developing countries, where the condition remains largely untreated [5, 6].

The science of health-related quality of life (HRQOL) measurements rapidly evolved during the 1980s and 1990s within general health and in all medicine disciplines [7]. HRQOL has become so important for patients with epilepsy (PWE) because of well-known characteristics of this disorder. Among these characteristics, chronic nature, unexpectability, intractable and/or frequent seizures, stigma, and side effects of the antiepileptic drugs are acknowledged. Also, neurobiological, cognitive, psychological, and social consequences of epilepsy are very important [8].

Patients with epilepsy (PWE) encounter various problems due to this disorder which conduce a lower quality of life (QOL). Seizure frequency, side effects of the antiepileptic drugs, psychological problems, and stigma are the major factors determining severity of the disease and these factors may cause an important impact on life quality of PWE. Therefore, identifying the factors which mostly affect are important for improving epileptic patients' quality of lives [9].

2. Psychiatric comorbidities

2.1. Depression

Psychiatric disorders are frequent in epilepsy and they have a marked effect in QOL, morbidity, and mortality. Mood and anxiety disorders are the most frequent problems [10]. Depression is the most frequent psychiatric comorbidity in epilepsy, affecting one of every three patients with epilepsy in clinical studies [11] and lifetime prevalence rates of depression range between 30 and 35% in patients with epilepsy [10].

The International League Against Epilepsy (ILAE) has recognized the importance of comorbidities in the management of PWE. But, these comorbidities are usually ignored, unless they lead to a major disability. This may be related to several factors, such as patients not giving enough information about their psychiatric state or neurologists may not be specifically trained for these comorbidities [12]. In a recent study reported by Kanner et al., it was demonstrated that comorbid psychiatric problems affect the quality of life, so patients with subsyndromic depressive episodes (SSDEs), major depressive episodes (MDEs), anxiety disorders, and mixed MDEs (or SSDEs) with anxiety disorders have a significantly worse QOL than asymptomatic patients [13]. Authors also demonstrated that occurrence of mixed disorders resulted with unfavorable HRQOL than the occurrence of anxiety disorders alone. Another important finding of this study was that the comorbid occurrence of depression and anxiety disorders accompanied to epilepsy cause to important clinical results beyond their impact on HRQOL which include:

1. An increased suicidal risk.

2. A worse course and poorer response to treatment of a depressive disorder.

3. An increased risk of MDE recurrence; types of anxiety increased the probability of a new depressive episode.
4. Pharmacoresistant temporal lobe epilepsy patients encountered unsatisfied results including increased risk of failure to achieve seizure-free state after anterotemporal lobectomy [13].

Literature survey reveals enough evidence regarding the negative impact of mood disorders and anxiety symptoms on the quality of life of PWEs [14–20]. Symptoms of depression and anxiety are independently associated with reduced HRQOL; psychiatric comorbidity explains more variance in HRQOL than the combined groups of clinical seizure or demographic variables [18]. A study with a large sample included 435 PWEs aiming to investigate the relative impact of mood and anxiety symptoms as well as social- and seizure-related variables on HRQOL [21]; the presence of depressive symptoms was the strongest predictor of the composite and subscales of the Quality of Life in Epilepsy instrument used (QOLIE-31). In other studies conducted on patients with pharmacoresistant temporal lobe epilepsy (TLE), symptoms of depression were found to be the strongest independent predictors of poor QOL but (unexpectedly) not the seizure frequency or severity [14, 15, 17].

Kim et al. studied impact of depression and anxiety on adverse event profiles in Korean people with epilepsy. Consecutively, 453 patients who took antiepileptic drugs for at least 1 year completed self-reported questionnaires. They used Liverpool adverse events profile (LAEP), Beck Depression Inventory (BDI), and Beck Anxiety Inventory (BAI). In this study, it was reported that BAI, BDI scores, and the duration of antiepileptic drug treatment were significant predictors [22].

Another important point is the women with epilepsy of childbearing age. Increased risk of depression is a considerable problem for these patients. Lack of occupation, the presence of an underlying disabling condition (with treatment), and the severity of epilepsy are the significant properties accompanied to depression. Compared with the general population depressed women with epilepsy display greater impairment of HRQOL with epilepsy also images the physical, social, and emotional aspects of the disease [23].

Depressive disorders are associated with a worse response of seizures to antiepileptic drug treatment [24]. Hitiris et al. [25] retrospectively searched 780 patients with new onset epilepsy. Epileptic patients with a history of depression had two times more risk in developing refractory epilepsy.

Endocrine, neurotransmitter, and immunologic disturbances were found to be related with depression in patients with epilepsy. Especially, serotonin, glutamate, and GABA have an important role in epileptic seizures. Fluoxetine, a selective serotonin reuptake inhibitor (SSRI), has been shown to be effective in seizure prevention in a focal epilepsy model in rats [26]. Mazarati et al. studied an animal model of status epilepticus demonstrated abnormal 5-HT secretion in the raphe-hippocampal serotonergic pathway, lower serotonin concentrations in the hippocampus, and decreased serotonin release from the hippocampus following raphe stimulation [27]. Also, fluoxetine administration reversed the cortical hyperexcitability following status epilepticus. In animal models of depression, dysfunction of glutamate

transporter proteins was shown, causing neuronal hyperexcitability and neuronal death [28]. In humans with depression, reduced expression of several glutamate transporter proteins was found in the frontal cortex and striatum in postmortem brain tissue that resulted in elevated synaptic glutamate concentrations [29]. By depression decreased cerebrospinal fluid concentration of GABA [30] and intracortical GABA signal on MR spectroscopy (MRS) [21, 28, 31–34] arises as a result of decreased GABAergic activity. For example, Rajkowska et al. [35] determined a significant decrease in GABAergic interneurons in the dorsolateral prefrontal cortex of the brains of the major depressive disorder patients (MDD) in a postmortem study which included 14 MDD patients (nine of whom died because of suicide) and nine controls [36]. Studies designed with transcranial magnetic stimulation (TMS), as a treatment modality for resistant MDD, also display decreased GABAergic activity in patients with depression [24].

2.2. Anxiety

Clinical studies found that 11–25% of PWE suffered from anxiety, which are higher proportions than healthy people [37]. These rates of depression and anxiety were close to that of drug-refractory epilepsy in a long-term population-based study [38]. The prevalence of depression or anxiety is higher in refractory epilepsy, and especially temporal lobe epilepsy (TLE), than in the general population of PWE [39–41]. The amygdala is important for the fear sensation. The avoidance behavior associated with fear is related to the output of the amygdala to the peri-aqueductal gray matter. Symptoms of anxiety disorders image the activation of the fear circuit involving structures of the hippocampus which is related with re-experiencing fear [42, 43]. Both in anxiety and epilepsy neurons discharging excitatory currents are associated with similar mechanisms [44]. Therefore, the amygdala and hippocampus play a critical pathophysiological role in both anxiety and epilepsy. The orbitofrontal cortex, insula, and cingulate gyrus are also essential in the central mediation of anxiety [45]. Inhibition of γ-aminobutyric acid (GABA)is an important factor in the pathogenesis of anxiety [44]. The $GABA_A$ receptor has an important role in controlling fear. Drugs affecting on $GABA_A$ receptors (like benzodiazepines and barbiturates) may increase the seizure threshold and also control anxiety symptoms by reducing neuronal excitability [46].

Tellez-Zentano et al. studied anxiety disorders in PWE; they found that people without epilepsy reported a lifetime incidence of 11.2% for any anxiety disorder compared with 22.8% in the group with epilepsy [10]. Rai et al. reported increased prevalence of depressive and anxiety disorders in people with epilepsy [47, 48].

We may think that the prevalence of anxiety disorders should be higher in refractory patients than in well-controlled patients. Brandt and Mula displayed a prevalence of 19.6% in patients with refractory epilepsy which is not different than the ratios reported in general epilepsy population [47]. Another important point stated was that the people with shorter epilepsy duration and younger age were more likely to have an anxiety disorder. This could show that the PWE can learn how to cope with the disease as getting older or with increasing duration of the disease. Also, it has been shown that patients in younger age and shorter duration of epilepsy are more likely to have anxiety disorders. This may be explained by patients acquiring coping strategies as years go by Brandt and Mula [47].

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Depression and anxiety increase suicide risk, suicidal ideation, and stigmatization in PWE [37, 39]. Recent studies performed with newly diagnosed epileptic patients, identified depression, and anxiety as risk factors of drug-refractory epilepsy [13, 25]. These risk factors have also been associated with worse outcomes of epileptic surgery [49, 50]. In addition, depression and anxiety have been associated with increased adverse events in response to antiepileptic drugs (AEDs)in PWE [51]. Ultimately, the psychiatric and clinical effects of depression and anxiety can impair the quality of life (QOL)of PWE. Therefore, early detection and management of depression and anxiety are critical for the management of PWE.

2.3. Psychosis

There is a higher incidence of psychosis (9%) in PWE, when compared to the general population (1%) [52]. Psychoses in epilepsy have a complex psychopathology that is similar to the positive symptoms of schizophrenia and usually without negative symptoms [53]. Psychoses with seizure disorders can be classified as ictal, postictal, and interictal, depending on the onset of symptoms. Postictal psychosis most commonly appears within a week of the last seizure, whereas psychosis in forced normalization continues to manifest after normalization and with a clear state of consciousness [54]. Forced normalization can be defined by the emergence of psychosis after the control of seizures. The mechanism is unknown, but it can occur whether convulsions are controlled by medication, surgery, or neurostimulation [55]. Hilger et al. retrospectively analyzed 1434 patients with epilepsy, evaluated with prolonged EEG monitoring in order to estimate the prevalence of postictal psychosis (PP) and interictal psychosis (IP) [56]. They found that the overall prevalence of psychosis was 5.9%; prevalence of PP; and IP was 3.7 and 2.2%, respectively. They showed that the 97.6% of the patients with psychosis had localization-related epilepsy. Prevalence of psychosis was highest (9.3%) in patients with temporal lobe epilepsy [56].

2.4. Cognitive impairment

Cognitive impairment is a very important problem for PWE and their families. Memory impairment in epilepsy has been shown in neuropsychological studies and temporal lobe epilepsy (TLE) is an important risk factor. Brain training exercises in the form of activities such as reading, doing crosswords, and sudoku have been shown to improve memory function. Thompson et al. studied patients with temporal lobe epilepsy who had memory impairments. They showed that the traditional memory rehabilitation techniques can help to reduce the burden of memory impairment in temporal lobe epilepsy [57, 58].

Regarding the psychiatric comorbidities of epilepsy, Kanner highlighted some important points. First, he stated that the psychiatric disorders and epilepsy had a bidirectional relationship. The PWE have an increased risk of developing psychiatric comorbidities, but also patients with a primary psychiatric disorder have a greater risk of developing epilepsy. Second, he reported that the PWE with psychiatric comorbidities are less likely to become seizure-free with antiepileptic drugs (AEDs) and with epilepsy surgery. In addition, they are more likely to develop adverse events to AEDs. Finally, Kanner pointed out the importance of psychiatric evaluation of the patients with epilepsy especially who are being considered for surgery.

Because after epilepsy surgery, presurgical comorbid disorders may remit, recur, or be exacerbated [59].

2.5. Stigma

Stigma is associated with feared or perceived discrimination and an important psychosocial burden in people with epilepsy. Stigma among people with epilepsy brings out impairment in quality of life. Also, stigma is associated with aggravation of psychosocial burden like anxiety and depression for people with epilepsy [60]. Generally, prevention of seizures is not adequate in order to relieve the burden of epilepsy, also attenuating of perception of stigma matters for quality of life of individual with epilepsy [61]. Beside impact of stigma on quality of life of individual with epilepsy is frequently underestimated whereas stigma affects quality of life more than frequency of seizure and adverse effects of antiepileptic drugs.

Fisher demonstrated psychosocial symptoms like depression were quite important as initial reaction to the diagnosis of epilepsy and perceived stigma was associated with psychosocial symptoms [62]. A study which was intended to obtain certain demographic, clinical, and psychosocial traits associated with perceived stigma indicated that; being single, having poor quality of life, having difficulty in understanding the written information, and use of behavioral disengagement as a coping mechanism were enhancing factors for perceived stigma [63]. Previous studies demonstrated that low socioeconomic status compared with high socioeconomic status worsens the perception of stigma among PWE [61, 64]. Baker et al. published the largest population-based study to evaluate the stigma of epilepsy in 15 European countries [65]. Stigma data were collected from over 5000 PWE. Perception of stigma was correlated with anxiety, long-term health problems, injuries, and adverse effect of antiepileptic drugs [65]. Another study performed which the epilepsy-related stigma percentages were obtained from the previous largest population-based study. Results of the study suggested overall quality of health system, the health expenditure per capita, and the perceived quality of life have little effect on perceived stigma among individuals with epilepsy. Mentioned trail indicated the role of the public health system invests on awareness programs to increase public knowledge and reduce stigma [60]. Increasing the level of contact between PWE and people without epilepsy may lead changing negative public attitudes [66]. A trial aimed to investigate the relation between the level of knowledge about epilepsy and perception of stigma in adolescents and their mothers was performed. This trial demonstrated that the level of knowledge about epilepsy among adolescents with epilepsy was significantly related to their perception of stigma. As a result, knowledge of epilepsy can minimize the impact of perceived stigma, depressive feelings, and anxiety. This trial indicated also that correlation between the level of the maternal concealment behavior and adolescent with epilepsy's perception of stigma was more significant than maternal knowledge of epilepsy or maternal perception of stigma [67].

Stigma can be categorized into enacted stigma and perceived stigma [63]. Actual disapprobation and discrimination determined against individual with epilepsy is accepted as enacted stigma. However, perceived stigma is characterized as fear of encountering enacted stigma, feeling guilty, and shame about epilepsy. Epilepsy is not the only highly stigmatized illness but one of the most important of them like tuberculosis, leprosy, or HIV/AIDS [61].

In conclusion, epilepsy is a disease with many complications which lowers quality of life of PWE. Stigma, seizure frequency, drugs' adverse reactions, and neuropsychiatric issues are the major factors which are associated with the quality of lives of PWE.

2.6. Self-esteem

Self-esteem has been shown as the most important part of the ego and a major factor effecting psychosocial well-being [68]. The most important determinants of self-esteem are what we think of ourselves, how we assess ourselves when compared to others [68]. Literature analysis shows different results in the correlation between epilepsy and self-esteem [69–70]. Gauffin et al. studied self-esteem in young PWE and compared it with the earlier results [71]. They found that there was a decline in both sense of coherence and self-esteem overtime in young adults with epilepsy. On the other hand, Lee et al. reported that epilepsy in general has little impact on overall self-esteem in adolescents [71].

3. Antiepileptic drugs and suicidality

The pathogenesis of AED induced depressive symptoms is probably multifactorial. In which some of the factors are associated with the drug and other factors may be related to the patient. GABAergic properties, rapid titration of the drug, interaction with folate metabolism may be the drug-related factors. Whereas, poorly controlled seizures, structural abnormalities in the limbic system like small hippocampal volumes may be the patient-related factors [72].

May be the result of effects on the function of two types of receptor GABAergic and antiglutamatergic receptors are considered to be the two main receptors responsible from the psychotropic effects of AEDs but there may also be other possible mechanisms. Presumably, other neurochemical pathways especially a serotonergic mechanism should be considered in psychotropic effects of AEDs [73].

People with epilepsy seemed to have an increased risk for suicide. The risk increases with a history of a psychiatric illness. The AEDs may increase the risk of suicide in PWE, but it is not certain. Some AEDs shown to have negative effects on mood. Especially, barbiturates, vigabatrin, tiagabine, and topiramate were associated with depressive symptoms. In 2008, the Food and Drug Administration (FDA) drew attention on an increased risk of suicidality in people taking AEDs [74] and pharmaceutical companies had been asked to submit data from placebo-controlled trials of AEDs. Suicide-related adverse events occurring during double-blind treatment with an AED (concerning 11 AEDs) were searched. In this study, nearly 28,000 people taking AEDs and more than 16,000 people taking placebo were analyzed. In this analysis, the odds ratios for suicidality were increased for topiramate, but neither barbiturates nor vigabatrin were included in the analysis, and there were few suicidality events reported in the tiagabine trials. Carbamazepine, lamotrigine, and valproate are used as mood stabilizers. In the FDA analysis, carbamazepine and valproate were shown to have a nonsignificant protective effect against suicidality, whereas odds ratios of lamotrigine were significantly increased.

Further clinical prospective studies are needed to evaluate the relation between AEDs and suicidality because FDA analysis may have methodological concerns [72, 74].

Mood disorders, family history of a psychiatric illness, and risk of suicide must be carefully monitored in PWE. Psychiatry consultation must be organized for patients with such symptoms and it is very important to choose the AEDs according to both seizure type and the risk of possible drug induced depressive symptoms [72].

4. Quality of life in PWE

Previous researches regarding quality of life (QOL) in epilepsy showed many different results [75, 76]. Although most studies highlighted the negative effects of epilepsy on patients' quality of lives, there are still some other reports which showed minor or no effect [75, 76]. Some authors suggested that the impact of epilepsy might be minimal if the disease is stabile [75, 76]. On the other hand, epileptic patients living in Europe and North America were reported to have important impairment in HRQOL [77, 78]. The different results reported may be associated with the methodological and/or cultural factors. However, it can be easily noticed that especially in studies with larger samples, HRQOL is decreased in PWE [79, 80].

Baker et al. reported that epilepsy has the potential to negatively affect different aspects of quality of life [79]. They collected data from 3889 PWE from 10 different countries. In this multicenter study, it was shown that nervousness, headaches, and tiredness were the most frequent factors affecting the daily activities.

Short Form-36 (SF-36) was used in Baker et al.'s study and patients scored significantly lower in domains such as physical and social functioning, energy, and vitality [76]. In another multicenter study conducted by Baker et al., data from more than 5000 patients were analyzed and reported that epilepsy had a negative effect on patients' social and psychological well-being [80].

Kutlu et al. investigated the HRQOL, anxiety, and depression states of patients with epilepsy (PWE) [81]. The SF-36 scores were significantly lower in all subscales in PWE compared with the control group. Total scores for Beck Depression Inventory (BDI) were significantly higher in epilepsy patients. Hamilton anxiety scale was also significantly increased in PWE. It was concluded that epilepsy significantly effects with QOL of patients. In the patient group relationship between the seizure frequency and vitality was found to be statistically significant [81]. Birbeck et al. in their study evaluating ability of HRQOL measures to detect change overtime in people with epilepsy, suggested that SF-36 yielded responsiveness indices comparable to those of the epilepsy targeted measures [82].

Recently, Chen et al. studied factors affecting QOL in 260 PWE in Taiwan in a cross-sectional, correlational study. They used the Quality of Life in Epilepsy-31 (QOLIE-31) questionnaire for evaluating HRQOL [9]. In this study, scores for the QOLIE-31 were correlated with the demographic characteristics, sleep quality, symptoms of anxiety and depression, epilepsy-specific variables such as, seizure frequency; types, number, and frequency of AEDs; and

adverse events of AED and social support. They reported that seven factors were predictive for quality of life: anxiety, depression, adverse events of AEDs, social support, seizure frequency of at least once in 3 months, household income of male gender. Another recent study was conducted by Mutluay et al., which they investigated the HRQOL in 124 PWE in Turkey [83]. This study measured the QOL in epilepsy and determined associated demographic and clinical factors by means of the Short Form-36 health survey. They found that patients with epilepsy do not perceive impaired physical health status. However, their mental health appears vulnerable, especially in women. In this study, the major burden was in the mental health category. They also reported that a positive treatment response is an important determinant of the HRQOL in PWE. Temporal lobe epilepsy (TLE) is the most common type of medically intractable epilepsy and is accepted as a prototype for a surgically remediable epilepsy when hippocampal sclerosis is the pathological substrate [84]. A reduction in seizure frequency and an improvement in the HRQOL are expected for patients with intractable epilepsy after epilepsy surgery [85]. Several studies indicate that complete seizure freedom is a strongly associated with psychosocial adjustment [86]. However, others show a poor correlation with postoperative seizure freedom. After surgery even if the seizures are completely lost, patients may still suffer from comorbidities such as depression, anxiety, and stigma. This can be explained by the "burden of normality" concept [84]. Patients' status changes from chronically ill to cured state in which the patient has to face the responsibilities of a normal life like finding a job and learn to continue and adjust life without the "advantages" of a chronic illness. Aydemir et al. studied 20 patients with intractable temporal lobe epilepsy who were waiting for surgery and 21 patients who had surgery. They used SF-36, Beck Depression Inventory, State Trait Anxiety Inventory, stigma and impact of epilepsy inventories, and a form asking their own perspectives about epilepsy and surgery. They found that QOL of patients after surgery was found to be better than before surgery. They also reported that seizure frequency, comorbidity, and AEDs affected HRQOL negatively. Impact of epilepsy levels was found to be higher among the preoperative patients [84]. A very important study was conducted by Taft et al. [87]. In this prospective study, HRQOL, mood, and patient satisfaction in epilepsy surgery candidates before and 2 years after epilepsy surgery was studied. They used Short Form Health Survey (SF-36), the Hospital Anxiety and Depression scale (HAD) at baseline and after 2-year follow-ups and also operated patients answered patient satisfaction questions. In patients who were seizure-free after epilepsy surgery HRQOL improved and anxiety decreased. Operated patients found surgery beneficial. But a very important point noticed in this study was that only about half of the seizure-free patients showed HRQOL improvements, in which that seizure freedom does not always improve patients' quality of lives.

5. Conclusion

Psychologically, PWE may have feelings of worthlessness, fear, stigma, anger, and hopelessness, and may exhibit passive behavior [88]. Stigmatization leads to discrimination, and PWE have been the target of prejudicial behavior in many aspects of life, over many centuries and

in many cultures [89]. These factors decrease their psychosocial function, self-efficacy, and quality of life [90, 91] and even increase the suicide rate [90–92].

Recognition of the past and current comorbid psychiatric disorders needs to be incorporated into the evaluation of every PWE, including those with a newly diagnosed seizure disorder. Future research will need to determine whether an early remission of psychiatric disorders reverses the worse course of the seizure disorder. Finally, presurgical psychiatric evaluations must be conducted in all patients undergoing a presurgical evaluation.

Epilepsy, with its rich clinical features, is particularly important for HRQOL research. Epileptic patients may experience various problems which will result in a lower quality of life. Seizure frequency, side effects of the antiepileptic drugs, psychological comorbidity, and stigma are important factors associated with the severity of the disease and these factors may cause an important impact on life quality of epileptic patients. Stemming from a thorough review of the current literature, we can conclude that there is still a need for further scientific research with further validated instruments to find out more clear relation between epilepsy and HRQOL.

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