The impact of comorbidity in epilepsy on quality of life

Epilepsy is a neurological disorder that disrupts normal brain activity and results in an individual experiencing a convulsion or seizure. Seizures can consist of foaming at the mouth, uncontrollable jerking movements of the arms and legs, and/or blank moments where the individual wanders off from their current task without being aware. According to the International League Against Epilepsy (ILAE), epilepsy is defined as having at least two seizures occurring over 24 hours apart. While epilepsy is categorized by unprovoked seizures, many individuals experience non-epileptic seizures that can be attributed to psychological disorders that mimic epileptic seizures. Due to this, the first step in treatment decisions is to determine whether the episode was, in fact, an epileptic seizure. The next question is whether the seizure was provoked or unprovoked. Provoked seizures occur within seven days after an acute medical or neurologic illness, such as fever, alcohol withdrawal or drug use, systemic or central nervous system infection, traumatic brain injury, or stroke. The cause of unprovoked seizures is unknown (Herman S, et al. 2004).

According to the Centers for Disease Control and Prevention, as of 2012, 2.3 million adults were classified with currently having epilepsy, 4.1 million were reported with being told they had epilepsy, and 1.7 million adults had inactive epilepsy. Because of the high numbers of people diagnosed with epilepsy, resources, neurologists, equipment, etc. are restricted in amount which affects the quality and level of care of the patient and while epilepsy affects more people than those with multiple sclerosis, Parkinson's disease, or autism, patients with epilepsy receive less research funding (www.epilepsytalk.com). The lack of funding for epilepsy is not due to a lower prevalence or mortality, but could be due to several factors involved in the processes of reviewing and funding such as consistently poorer scientific quality of epilepsy grant proposals, inequality in epilepsy representation and expertise on the NIH review panels in a process that pits one disease against another, allocation of funding by Congress, more effective lobby activities to promote research funding for other diseases, and a poorer, more disadvantaged patient population (Meador et al., 2011). Another issue is that the family members of people with epilepsy and even the patients themselves will often try to hide their epilepsy which alters their treatment and care-taking (Theodore W et al., 2006).

There are two major categories of seizure types in epilepsy: focal seizures and generalized seizures. The brain is divided into two sections and four lobes and when abnormal

activity begins in one of these sections, the seizure is considered focal. Most of the time, the person is conscious, but will experience a twitching or jerking movement in their face, arms, etc. but can't control it. One example of a focal seizure would be a frontal lobe seizure which originates in the frontal lobe of the brain. Unlike focal seizures, generalized seizures involve the entire brain, or at least a larger part of the brain than focal seizures. In a generalized seizure, the person is rarely aware of what's going on and therefore has no control over their body. One example would be a generalized tonic-clonic seizure, also known as a grand mal seizure. In some cases, focal seizures can spread to the rest of the brain (i.e., a secondary generalized seizure). While both of these seizure types can be dangerous, generalized seizures tend to be more dangerous. This is due to the fact that a person is unconscious of their surroundings during a generalized seizure which leads to a greater risk of injury or danger to himself or others. An example of this danger would be if a person was driving and experienced a generalized seizure (http://www.cdc.gov/).

There are various forms of treatment for epilepsy patients, but antiepileptic drugs (AEDs) are most common. While AEDs suppress the patient's seizures, these medications can also cause many side effects that negatively impact the patient's life. For example, sleepiness and dizziness are common. Some patients have even reported that the side effects of their AEDs are more of a burden on them than the seizures themselves (Karceski, 2007). Perucca, et al., showed in a study that up to 90% of patients with epilepsy experience side effects from their AEDs (2009). Hitiris N, et al., in 2007 has also shown that there's a strong link between epilepsy and depression, and that a history of depression is associated with a higher risk of epilepsy. It is possible that some of the anxiety, depression, and suicidality that is associated with epilepsy is due to the emotional burden of having epilepsy or to some of the side effects of the AEDs (Hesdorffer, et al. 2012).

Another form of epilepsy treatment is surgery. Epilepsy surgery requires a large team of well qualified and experienced specialists performing together. Usually surgery occurs while the patient is unconscious under anesthesia. The surgery is targeted to the location within the brain and specific characteristics of the abnormality. The procedure usually involves removing the part of the brain that causes the seizure or to block the nerve pathways that the seizure impulses use. A large percent of procedures require a few hours in the operating room and a few days of hospital care post-surgery (Engel, J., 1996). The after-effects of surgery are temporary or minor

enough that in a few months they are completely gone and death and permanent implications are very rare (Haeder et al., 2013).

Another alternative form of treatment is the ketogenic diet which has been around since the early 1900's and is most popular amongst drug-resistant childhood epilepsy (Neal, et al., 2008). This dieting method revolves around consuming foods high in fat and low in carbohydrates and proteins. Even though it is a very strict dieting plan, it has been known to be a very successful form of treatment (Henderson, et al., 2005). Another alternative form of treatment for those who continue to have seizures despite medication is vagus nerve stimulation (VNS). Almost like a pacemaker for the brain, it's designed to prevent seizures through stimulation via a programmable generator which sends pulses to the brain through the vagus nerve, allowing variation in current, pulse, and frequency (DeGiorgio, et al., 2005). The most common result reported is improved seizure control with an increasing duration of VNS therapy (Elliott, et al., 2011).

Comorbidities are when an individual has two or more simultaneous chronic disorders and are common in epilepsy. Persons with epilepsy report a significantly higher lifetime prevalence of comorbid somatic conditions such as asthma, high blood pressure, high cholesterol, heart disease, stroke, arthritis, and cancer (Elliott, et al., 2009). Moreira, et al., in 2013 found that epilepsy patients are at greater increased risk of experiencing comorbidities than patients with other chronic disorders such as asthma or depression. Many of the comorbidites that patients experience can be attributed to the AEDs that they take to suppress their seizures and can be due to the side effects of the medication (Hesdorffer, et al., 2012). The burden of these comorbidities on people with epilepsy depends on its effect on the quality of life of the patient as well as other factors such as the financial cost (Wiebe, et al., 1999). The general impact of a specific condition on the quality of life of the patient is associated with the frequency, duration, severity, and treatment of comorbid conditions when present with epilepsy (Gaitatzis A, et al. 2012).

Comorbidities are categorized as being either psychiatric or somatic. Psychiatric events happen to be more frequent in people with epilepsy (PWE) than in the general population; The most prevalent psychiatric disorders seen in association with epilepsy are mood disorders such as major depression (MD), anxiety disorders and personality disorders (Gaitatzis, et, al. 2004). Many studies on epilepsy and comorbid psychiatric disorders have found that around half of the

patients with epilepsy have a psychiatric disorder (Swinkels WAM, et al., 2005). In a study by Gulpek D, et al., in 2011, more psychiatric disorders were observed among epileptic patients than in healthy controls.

Most of the time, diagnosis and treatment are not the most important aspects of epilepsy management. Improving Health Related Quality of Life (HRQOL), rather than just suppressing seizures, should be an important goal in managing patients epilepsy (Clary, et al., 2010). Reilly, et al., in 2015 found that persons with epilepsy who have the right resources available to help them manage and control their seizures have an increased HRQOL. Later work has shown that an early psychiatric evaluation and diagnosis can help improve QOL in epilepsy patients (Shanmukhi, et al., 2014). In 2014, Adebayo et al., performed a study to determine the frequency of somatic comorbidity and its impact on the HRQOL of persons with epilepsy (PWE) by comparing those with somatic comorbidities and those without. The results of the study showed that somatic comorbidities were prevalent in the cohort of PWE and that PWE with multiple comorbid conditions had a lower QOL than those with one comorbidity.

The focus of this study is to examine HRQOL as an outcome of new-onset epilepsy in relation to several predictors, including socioeconomic status (SES), burden of comorbidity, ethnicity, gender and age at onset over a two year period. An increased burden of comorbidity and low SES was hypothesized to be associated with a poorer HRQOL. The study focused on predictors of HRQOL. This is important because in past community-based studies, there has never been a focus on the outcomes of epilepsy in relation to burden of comorbidity as a predictor of quality of life in epilepsy. This study has the potential to establish a pathway from comorbidity burden to HRQOL and lead to future interventions that can improve outcomes for patients.

Methodology

Patients with a first unprovoked seizure or newly diagnosed epilepsy were recruited from an impoverished community in New York City to participate in this study. They were seen in the emergency room, neurology clinics and doctors' private offices in six hospitals throughout the communities of NYC. Screening for potential cases occurred over a two-and-a half year period. Methods used to find cases were specific to each site due to differences in local practice, but all methods were designed to find cases with incident unprovoked seizure or newly diagnosed epilepsy who resided in the zip codes previously mentioned. Individuals in the study were

identified with a study ID to maintain anonymity. There was no control group. Health related quality of life (HRQOL) was assessed with the data collected at the beginning of a study (baseline). All eligible potential incident cases received a neurological evaluation. For this study, parents of the children or the adult individuals themselves completed questionnaires about the index seizure, seizure history, demographics, medical history, and lifetime history of comorbidities. A trained physician abstracted the medical records of the index seizure for all cases in order to collect the features of the seizure, body temperature (to rule out febrile seizure in children), associated illnesses (to rule out acute symptomatic seizure), and age at seizure. Discharge diagnoses were also recorded.

First the incidence of first unprovoked seizure and newly diagnosed epilepsy in participants was examined. Outcomes in the first two years after being diagnosed were looked at. Age, gender, ethnicity, seizure type, socioeconomic status (SES), and the burden of comorbidity were examined. The age at incidence was categorized as child (<18 years) or adult ($\geq$18 years). Cases were classified as non-Hispanic compared to Hispanic. Annual household income was categorized as either < \$15,000 or ≥ \$15,000. The Elixhauser Index is a way of categorizing comorbidities based on the International Classification of Diseases (ICD) diagnosis code. The comorbidities taken from the Elixhauser Index were categorical variables, with ‘yes’ or ‘no’ answers. The total score of these comorbidites was a continuous variable, counting all the comorbidities for each individual. The Elixhauser Index was used to assess psychiatric and somatic comorbidities, using the total scores for each person. The Elixhauser Index score was out of a total of 45.

A HRQOL survey was completed by the individuals themselves or by the parents. A scale of smiley faces ranging from happy (one) to sad (seven) were used to measure health related quality of life (HRQOL) and were analyzed with the predictors to determine the HRQOL. The survey asked questions that assessed quality of life. The participants answered based on a scale of smiley faces, choosing the face that most closely matched how they felt about their quality of life (Figure 1). Smiley faces numbered one to three were associated with a high HRQOL and numbers four to seven were associated with a poor HRQOL.

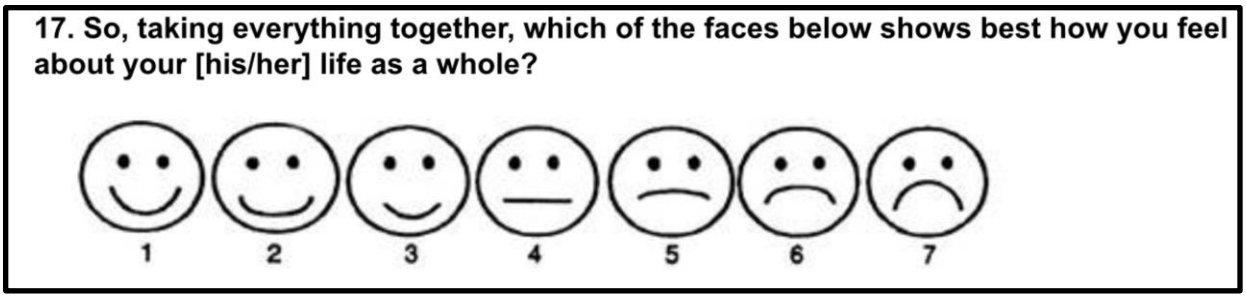

Figure 1: Smiley face scale used to assess quality of life

Predictors of HRQOL included whether someone was a child or an adult, SES (<$15K vs ≥$15K, ethnicity (Hispanic or non-Hispanic), as well as forty-five comorbidities in the Elixhauser Index. These predictors were summed for each subject overall and separately for psychiatric and somatic conditions, and separately for psychiatric and somatic indices. Models used first unprovoked seizure (N = 151) and epilepsy (N = 111) together and separately. Data were analyzed using SAS 9.4 statistical analysis software.

For categorical variables, a frequency analysis was run to determine the number and percentage in different categories (e.g., children and adults) . A univariate linear regression was performed as well as a multivariable analysis for the HRQOL outcome. Continuous and categorical predictors were entered in the model for Table 4. Variables were considered statistically significant if they had a p-value of <0.05.

Table 1. Multivariate analysis for predictors of QOL

Analyses for HRQOL	**Variables Compared**
Model 1 (Epilepsy and single unprovoked seizures)	Elixhauser Index, Ethnicity
Model 2 (Epilepsy)	Elixhauser Index, Age group
Model 3 (Epilepsy)	Elixhauser Index, Annual income

Model 4 (Epilepsy)	Psychiatric, Age group
Model 5 (Epilepsy)	Psychiatric, Annual income
Model 6 (Epilepsy)	Psychiatric, Age group, Annual income
Model 7 (Epilepsy)	Somatic comorbidity, Age group
Model 8 (Epilepsy)	Somatic comorbidity, Annual income
Model 9 (Single unprovoked seizures)	Elixhauser Index, Ethnicity

Demographics - Table 2.

All of the demographic information was taken for the eligible participants that filled out the questionnaire. Missing values are present due to the participants not required to completely fill out the HRQOL survey.

Factors	**First Unprovoked Seizure (n=151)***	**Epilepsy (n=111)****	**All seizures (n=262)**
Age Group at Incidence	**N(%)**	**N(%)**	**N(%)**

Children	57 (37.75)	40 (36.04)	97 (37.02)
Adults	94 (62.25)	71 (63.96)	165 (62.98)
Gender	**N(%)[1]**	**N(%)[2]**	**N(%)[3]**
Male	35 (55.56)	18 (37.50)	53 (47.75)
Female	28 (44.44)	30 (62.50)	58 (52.25)
Ethnicity	**N(%)[1]**	**N(%)[2]**	**N(%)[3]**
Non-Hispanic	42 (66.67)	30 (62.5)	72 (64.85)
Hispanic	21 (33.33)	18 (37.5)	39 (35.14)
SES	**N(%)[4]**	**N(%)[5]**	**N(%)[6]**
< $15K	32 (51.61)	20 (42.55)	52 (47.71)
≥ $15K	30 (48.39)	27 (57.45)	57 (52.29)
Elixhauser Index	**N(%)[1]**	**N(%)[2]**	**N(%)[3]**
Psychiatric	42 (66.67)	24 (50.00)	66 (59.46)
Somatic	21 (33.33)	31 (50.00)	45 (40.54)

Missing Values

1- Missing 88 in the total N
2- Missing 63 in the total N
3- Missing 151 in the total N
4- Missing 89 in the total N
5- Missing 64 in the total N
6- Missing 153 in the total N

Univariate analysis of the variables - Table 3.

Table 3 shows the benefits of the univariate estimate in the analysis of epilepsy and single unprovoked seizure. The univariate estimate represents the increase or decrease in quality of life based on the presence of the variable being looked at. A positive univariate estimate leads to a decrease in the total GHQ17 score which is the smiley face score predicting QOL. A negative univariate estimate leads to an increase in the total GHQ17 score. The Elixhauser Index alone was the only statistically significant variable (p=0.04) showing an inverse relationship between

the Elixhauser Index score and QOL. The Elixhauser Index score showed an increased QOL with an increased score. In a model for people with epilepsy only, age group (p=0.00) and psychiatric (p=0.02) were the variables statistically significant. Age group showed that a decrease in age results in a decrease by 1.17 in QOL score. An increased score of psychiatric indices was associated with a 1.29 increase in QOL score. In a model for people with single unprovoked seizure only, the Elixhauser Index and ethnicity (Hispanic vs non-Hispanic) has no statistically significant correlation.–For epilepsy and single unprovoked seizures, there was no significant association found between any of the variables and the GHQ17 score. This score was based on the patient's choices regarding the smiley face question, where a one to three was categorized as a happy QOL and four to seven as a low QOL. This means that a one point increase in the Elixhauser Index score would lead to a 0.724 increase in the GHQ17 score showing that the more comorbidities a person with epilepsy has leads to a lower QOL.

Variable	**Univariate Estimate**	**95% Confidence Interval**	**p-value**
Epilepsy & single unprovoked seizure			
Elixhauser Index	-0.724	-7.43 – 5.98	0.04
Gender (Male vs Female)	15.34	-15.28 – 45.95	0.32
Annual Income (<15k vs ≥15k)	14.47	-16.86 – 45.80	0.39
Ethnicity (Hispanic vs non-Hispanic)	-21.74	-53.42 – 9.93	0.17
Age Group (child vs adult)	4.11	-9.12 – 17.33	0.54

Psychiatric (yes vs no)	14.81	-16.39 – 46.01	0.40
Somatic (yes vs no)	-2.16	-9.67 – 5.35	0.42
Epilepsy			
Elixhauser Index	0.17	-0.07 -- 0.41	0.16
Gender (Male vs Female)	-0.29	-1.45 – 0.88	0.62
Annual Income (<15k vs ≥15k)	-0.56	-0.23 -- 1.72	0.13
Ethnicity (Hispanic vs non-Hispanic)	-0.85	-2.00 – 0.30	0.22
Age Group (child vs adult)	-1.17	-1.84 -- -0.51	0.00*
Psychiatric (yes vs no)	1.29	0.21 – 2.36	0.02*
Somatic (yes vs no)	0.11	-0.15 – 0.38	0.41
Single unprovoked seizure			
Elixhauser Index	-3.45	-16.18 -- 9.28	0.59
Gender (Male vs Female)	30.35	-22.47 – 83.16	0.26
Annual Income (<15k vs ≥15k)	26.41	-27.31 – 80.14	0.34
Ethnicity (Hispanic vs non-Hispanic)	-45.11	-92.80 -- 2.59	0.17
Age Group (child vs adult)	8.03	-14.34 – 30.39	0.48
Psychiatric (yes vs no)	41.86	-35.08 – 78.80	0.45
Somatic (yes vs no)	-6.37	-20.58 – 7.83	0.38

Multivariate analysis of the variables - Table 4.

The most statistically significant predictors from Table 3 were selected and linear regression analyses were performed for epilepsy, single unprovoked seizure, and both epilepsy and single unprovoked seizure together to see whether adjustment for other variables would change the relationship between the psychiatric part of the Elixhauser Index and HRQOL. In Model 4 for Epilepsy alone, both psychiatric and age group were statistically significant in a multivariable analysis. When the variables were put into a multivariable analyses for epilepsy, only Model 4

(P=0.03), Model 5 (P=0.03) and Model 6 (P=0.04) were statistically significant when adjusted for the psychiatric variable. In Model 4 for epilepsy alone, psychiatric comorbidity was significantly associated with a 1.19 decrease in HRQOL when adjusted for age group. In Model 5 for epilepsy alone, psychiatric comorbidity had a significant association with a 1.24 decrease in HRQOL when adjusted with annual income in the multivariable analysis. In Model 6 for epilepsy alone, psychiatric comorbidity had a significant association with a 1.6 increase in the HRQOL, when adjusted for age group and income together in a multivariable analysis. For both epilepsy and single unprovoked seizure and single unprovoked seizure alone there were not any further analyses because the other variables in the univariate analysis were not statistically significant.

Variable	**Estimate (95% CI)[1]**	**P-Value**
Model 1	**Epilepsy and single unprovoked seizure**	
Elixhauser Index	-0.36 (-7.03, 6.31)	0.18
Ethnicity (Ref: Non-Hispanic)	-21.60 (-53.38, 10.17)	0.92
Model 2	**Epilepsy**	
Elixhauser Index	0.14 (-0.10, 0.38)	0.26
Age group (Ref: Children)	2.14 (-1.56, 5.84)	0.26
Model 3		
Elixhauser Index	0.61 (-0.53, 1.75)	0.15

Annual Income (Ref: <15k)	0.17 (-0.07, 0.41)	0.29
Model 4		
Psychiatric	1.19 (0.11, 2.27)	0.03
Age Group (Ref: Children)	1.95 (-1.58, 5.48)	0.27
Model 5		
Psychiatric	1.24 (0.12, 2.35)	0.03
Annual Income (Ref: <15k)	0.36 (-0.76, 1.48)	0.53
Model 6		
Psychiatric	1.6 (0.04, 2.27)	0.04
Age Group(Ref: Children)	1.81 (-1.80, 5.42)	0.32
Annual Income	0.27 (-0.85, 1.39)	0.64
Model 7		
Somatic	0.08 (-0.18, 0.35)	0.54
Age Group(Ref: Children)	-2.38 (-6.10, 1.33)	0.21
Model 8		
Somatic	0.12 (-0.14, 0.39)	0.36
Annual Income (Ref: <15k)	0.61 (-0.55, 1.77)	0.30
Model 9	**Single unprovoked seizure**	
Elixhauser Index	-2.38 (-15.02, 10.26)	0.71
Ethnicity (Ref: Non-Hispanic)	37.19 (-18.01, 92.39)	0.19

[1] beta estimate and confidence intervals

The hypothesis was that an increased burden of comorbidity and low SES would be associated with a poorer HRQOL. The results regarding the inverse association between comorbidity and QOL supported the hypothesis, but the results regarding SES did not support the hypothesis. They were unexpected due to the fact that in past literature on comorbidities in patients with epilepsy, a high SES is associated with a higher QOL and a low SES is associated with a poorer QOL, but the results in this study showed that a low SES had no significant association with

QOL. Another unexpected result was that when analyzed for epilepsy alone and for single unprovoked seizure alone, the Elixhauser Index had no significant association with the HRQOL meaning that the burden of comorbidity has no impact on the QOL in the patient.

The findings of this study support the association between an increased score on the Elixhauser Index, indicating more comorbidities overall and separately for psychiatric comorbidities than somatic as well as an increase in HRQOL. In a similar study by Hesdorffer et al., in 2008 that looked at the first unprovoked seizure and epilepsy in a low-income urban community of New York City, it was found that a majority of the cases were hispanic which was the same as the findings in this study. In the Hesdorffer et al., study the findings indicated a small difference in epilepsy incidence across different groups defined by race and ethnicity in a poor urban community.this findings were very similar to the findings in this study because not a lot of the variables were associated with a lower QOL showing that there was a small gap between epilepsy and unprovoked seizures impact on quality of life throughout the different groups in an impoverished NYC community.

One limitation of this study was the inability to use many of the HRQOL categories as an outcome. This is due to the fact that in the analysis, there was no statistical significance for any of the variables. Further work should be performed to see if the lack of association between annual income and a HRQOL (sadder) is found in other studies of epilepsy. Also further work is needed to support the findings that for epilepsy alone and single unprovoked seizure alone there is no significant association with QOL. Including prevalence of seizures, age at onset and race could help increase the validity of the study. Further analyses would also be needed to support the findings of which variables have a positive association with a low QOL such as the Elixhauser Index score and psychiatric comorbidity score. Future studies should use a larger group of cases and more variables so that the information found is more reliable as well as do more multivariable analyses with predictors using more HRQOL categories as an outcome as well.

The findings indicate that as the Elixhauser Index score increases, the HRQOL score will increase which indicates a lower QOL as the number of comorbidities increases. More specifically, psychiatric comorbidities show a very significant association to having a low HRQOL in PWE.