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# Understanding the burden of idiopathic generalized epilepsy in the United States, Europe, and Brazil: An analysis from the National Health and Wellness Survey

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ABSTRACT

The aim of this study was to understand the current burden of primary generalized tonic–clonic seizures (PGTCS) associated with idiopathic generalized epilepsy (IGE) as a function of seizure frequency. We analyzed data for (IGE) as a proxy measure of PGTCS. Little is known about the quality of life (QoL), health utility, productivity, healthcare resource utilization (HRU), and cost burden of PGTCS or IGE. Patients were identified from the US (2011, 2012, & 2013), 5EU (2011 & 2013), and Brazil (2011 & 2012) National Health and Wellness Survey, a nationally representative, internet-based survey of adults (18+ years). Patients that self-reported a diagnosis of IGE were categorized into seizure frequencies of: ≥1 seizure per week, 1–3 seizures per month, 1–4 seizures per year, or <1 seizure per year. QoL was measured using the SF-36v2 Mental (MCS) and Physical Component Summary (PCS) scores, health utilities with the SF-6D, productivity with the Work Productivity and Activity Impairment (WPAI) questionnaire, and HRU as reported in the past six months. Unit costs were estimated from the literature and multiplied against HRU values to calculate direct costs and WPAI values to calculate indirect costs. Generalized linear regression was utilized to examine the relationship between seizure frequency and each measure of burden with adjustment for covariates. Out of the general population surveyed, IGE was self-reported in 782 of 176,093 (US), 172 of 30,000 (UK), 106 of 30,001 (Germany), 87 of 30,000 (France), 31 of 12,011 (Spain), 22 of 17,500 (Italy), and 34 of 24,000 (Brazil). Persistent seizures (≥1 per year) were reported in over 40% of patients with IGE (10–15% with ≥1 seizure per week, 10–15% with 1–3 seizures per month, 20–25% with 1–4 seizures per year). Over 75% were treated with antiepileptic drugs (AEDs). Compared with those having <1 seizure per year (reference group), patients in the two most frequent seizure categories reported worse MCS and PCS scores. Patients in the three highest seizure frequency groups consistently reported worse health utility scores, and greater presenteeism (attending work while not physically or mentally capable of working), overall work impairment, activity impairment, HRU, indirect costs, and direct costs than the reference group. Despite the availability of AEDs during the year surveyed, a substantial number of patients experienced persistent seizures. Increasing seizure frequency was clearly associated with worse outcomes. The burden of PGTCS and IGE may be proportionally reduced by newer AEDs which may increase the proportion of seizure-free patients or shift more patients into lower seizure frequency categories.



## 1. Introduction

Very little research is published on primary generalized tonic–clonic seizures (PGTCS) associated with idiopathic generalized epilepsy (IGE) or genetic generalized epilepsy (GGE) [the current preferred terminology of the International League Against Epilepsy]. Although the majority of patients that would have been previously classified as IGE would now be classified as GGE, the term IGE will be used when it reflects that actual terminology used in original research. Seventy-four percent of children and adults with IGE have PGTCS as one of their seizure types [1]. The vast majority of studies include all patients with epilepsy where IGE comprises a mere 24% of the total population [2]. Of PGTCS and IGE/GGE publications, we are aware of only 1 burden study [3] that evaluates quality of life (QoL) in 19 patients with IGE. We are

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not aware of any studies that examine health utilities, productivity loss, healthcare resource utilization, or cost data for patients with PGTCS or IGE/GGE living in the US, 5EU (France, Germany, Italy, Spain, and United Kingdom), or Brazil in the public domain. Furthermore, we are aware of no other studies which evaluate these burden parameters as a function of actual seizure frequency. These data are vital to producing economic evaluations in PGTCS and IGE/GGE. Of published economic evaluations, we did not find any specifically for PGTCS or IGE/GGE.

This study of adults with epilepsy has substantial value in understanding the burden of illness of PGTCS and IGE/GGE overall and by seizure frequency. The results published here will be informative for both healthcare decision-makers and builders of economic evaluations in adult patients with PGTCS and IGE/GGE. Therefore, the objective of this study was to understand the association of IGE/GGE on QoL, health utilities, productivity loss, healthcare resource utilization, and indirect and direct costs as a function of seizure frequency among adults with IGE/GGE from the US, 5EU, and Brazil.

## 2. Methods

### 2.1. Sample and procedure

The current study includes data from the 2011, 2012, and 2013 (US), 2011 and 2012 (Brazil), and 2011 and 2013 (5EU: France, Germany, Italy, Spain, and the UK; the survey was not fielded in 2012) National Health and Wellness Survey (NHWS; www.kantarhealth.com). The NHWS is a self-administered, internet-based questionnaire from a sample of adults (aged 18 years or older) in the seven countries of interest: US, France, Germany, Italy, Spain, the UK, and Brazil. Potential NHWS participants were identified using Lightspeed Research, an opt-in online survey panel, and its affiliates. The NHWS is intended to represent the entire adult population of a given country by employing a stratified random sampling framework. The demographic distributions of each country were obtained from the US Census Bureau (for the US) or the International Database of the US Census Bureau (in the case of all other countries). Potential respondents were selected in such a way as to mirror these characteristics. Specifically, the age and gender distributions were matched in all countries. Additional matching for race/ethnicity distributions were performed for the US. The NHWS study protocol was approved by Essex IRB (Lebanon, NJ). Informed consent was obtained from all participants, and participants' privacy rights were observed at all times. Previous research has been published using data for the US, 5EU, and Brazil NHWS [4–6].

In all countries, the primary method of data collection was through the internet. For countries with suboptimal internet penetration (France, Germany, Italy, Spain, and Brazil), supplemental recruiting through computer assisted web interviews (CAWI) was performed, particularly among older age groups. In the cases of CAWI recruiting, potential respondents were recruited by telephone and had the choice to complete the interview on the phone while the interviewer entered the responses online or to complete the survey on their own and were e-mailed a link to the survey.

This study included combined data from the 2011, 2012, and 2013 NHWS. The current study pooled together multiple years of data to increase the sample size of respondents with IGE (the terminology used in the original survey). It is possible for a respondent to complete more than one survey across multiple years. In these instances, only the most recent data for a given respondent were kept.

Respondents were identified from adults who self-reported a diagnosis of epilepsy with IGE ("What type of epilepsy have you been diagnosed with?" and selected "Idiopathic Generalized Epilepsy [Myoclonic seizures, Absence seizures, or Grand Mal seizures]") on the NHWS.

### 2.2. Measures

#### 2.2.1. Seizure frequency

The NHWS asked respondents "How often do you experience a seizure?" with the following options: more than once a week, once a week, two or three times a month, once a month, every three months, every six months, once a year, or less than once a year. These responses were then used to create the categories representing seizure frequency for adult patients with IGE (once a week or more, 1–3 times a month, 1–4 times a year, or less than once a year). The assessment was not repeated by seizure type and represents the total of all IGE seizure types.

#### 2.2.2. Demographics

Survey respondents reported their age, gender, race/ethnicity (only US), marital status, education, annual household income, employment status, and insurance status (only US).

#### 2.2.3. Health characteristics

Body mass index (BMI) was calculated from self-reported height and weight. Alcohol consumption, smoking status, and exercise behaviors were also assessed. Self-reported comorbidity data were used to calculate a comorbidity burden score using the Charlson Comorbidity Index (CCI) [7]. The greater the total index score, the greater the comorbidity burden on the patient.

#### 2.2.4. Epilepsy-specific characteristics

Survey respondents provided information on the number of years diagnosed with epilepsy and the current prescription medications used to treat epilepsy.

#### 2.2.5. QoL

QoL was assessed using the Physical (PCS) and Mental Component Summary (MCS) scores from the Short Form (SF)-12v2 (2011 NHWS) and SF-36v2 (2012 and 2013 NHWS), as well as the health utility measure (SF-6D). The PCS and MCS scores are normed to the US population ($M = 50$, $SD = 10$), with higher scores indicating greater QoL [8,9]. The health utility score is a preference-based single index measure for health using general population values. A difference greater than 3 in PCS or MCS was regarded as a minimally important difference (MID) [10], and a difference greater than 0.041 on health utilities was identified as a MID [11].

#### 2.2.6. Work and activity impairment

The Work Productivity and Activity Impairment Questionnaire (General Health version; WPAIGH) [12] consists of six items measuring absenteeism, presenteeism (attending work while not physically or mentally capable of working), overall work productivity loss, and activity impairment. Only employed respondents provided data for the work-related items, but all respondents provided data for activity impairment. Scores can range from 0 to 100%, with higher scores representing greater impairment.

#### 2.2.7. Healthcare utilization

Resource use was defined by the number of traditional healthcare provider visits (e.g., general practitioner, internist, neurologist) in the past six months, the number of emergency room (ER) visits ("How many times have you been to the ER for your own medical condition in the past six months?"), and the number of times hospitalized ("How many times have you been hospitalized for your own medical condition in the past six months?").

#### 2.2.8. Direct costs

Total direct costs consisted of three components: cost of traditional provider visits, cost of ER visits, and hospitalization costs. For each respondent and visit type, the number of visits (in the past six months) was multiplied by two to project to the annual number of visits, and then multiplied by its average visit cost.

In the US, visit costs were calculated for an average provider visit, ER visit, and hospitalization using the 2011 Medical Expenditure Panel Survey data (http://www.ahrq.gov/research/data/meps/). In the 5EU, visit

costs were estimated from the literature [13] and adjusted for inflation to 2013 values using the Eurostat health-related Harmonized Consumer Prices Index. Because 5EU visit costs for a hospitalization were reported per diem in the literature, the per diem value was multiplied by three as this was the median length of stay (LOS) in the latest NHWS survey (2007) that assessed LOS.

#### 2.2.9. Indirect costs

Total indirect costs were estimated for each respondent using the human capital method. Specifically, wages were multiplied by the percentage of work productivity impairment and then annualized. The WPAI-GH [12] was used to calculate productivity loss.

In the US, average gender-specific and age-specific (i.e., 18–24, 25–34, 35–44, 45–54, 55–64, or 65 + years) wages were obtained from the US Bureau of Labor Statistics (2012). In the 5EU, median annual income (18 years or older) was obtained for each country from Eurostat 2012 annual net income figures [14]. Hourly wages were estimated by dividing annual income by the typical number of weeks worked per year and hours worked per week. Data on weeks and hours worked in 2012 were obtained from the European Foundation for the Improvement of Living and Working Conditions [15].

### 2.3. Statistical analyses

#### 2.3.1. Bivariate analyses to identify covariates for multivariable models

Individually for each region (US, 5EU, Brazil + 5EU), the relationships between seizure frequency categories (reference group = less than 1 seizure per year) and demographics (as listed earlier), health characteristics (as listed earlier), and epilepsy-specific characteristics (as listed earlier) were evaluated in bivariate analyses to identify covariates for multivariable regression models. Chi-square tests were used for categorical variables and ANOVAs for continuous variables.

#### 2.3.2. Multivariable models and pairwise comparisons

Scientifically relevant and data-informed variables were included as covariates in multivariable regression models predicting QoL, productivity loss, healthcare resource utilization, and indirect and direct costs, as a function of seizure frequency. These models controlled for age, gender, race/ethnicity (only US), education, employment status (not included in WPAI and indirect cost metrics), marital status, insurance status (only US and not included in WPAI and indirect cost metrics), length of time diagnosed with epilepsy, and the CCI. Adjusted means from these models were reported for each seizure frequency group using a maximum likelihood algorithm. Pairwise multiple comparisons were made between higher seizure frequency groups and the reference group (less than 1 seizure per year). There was no adjustment for multiple comparisons. For all analyses, a $p < 0.05$, two-tailed, was considered statistically significant. All analyses were conducted in SAS version 9.3 (SAS Institute, Cary, NC, USA).

#### 2.3.3. Special considerations for the Brazilian dataset

Due to the small sample size of Brazilian patient numbers (n = 34), the total Brazil and 5EU IGE samples were compared on demographics, health characteristics, and epilepsy characteristics to evaluate whether it would be reasonable to combine the two datasets for the purpose of estimating Brazilian outcomes. Because minimal differences were identified, the above multivariable analyses were conducted for Brazil using a combined Brazil + 5EU dataset. No costing was performed on this combined dataset.

## 3. Results

Out of the total NHWS population, 782 of 176,093 [0.44%] (US), 172 of 30,000 [0.57%] (UK), 106 of 30,001 [0.35%] (Germany), 87 of 30,000 [0.29%] (France), 31 of 12,011 [0.26%] (Spain), 22 of 17,500 [0.13%] (Italy), and 34 of 24,000 [0.14%] (Brazil) self-reported a diagnosis of IGE. These results suggest a self-reported prevalence of 0.4% for IGE among the entire study cohort.

Patient characteristics (Table 1) appeared to be qualitatively different between the US and other datasets (5EU, Brazil + 5EU) on certain estimates. Employment appeared lower and long-term disability higher in the US. There appeared to be more obese patients in the US, but fewer alcohol consumers and more nonsmokers. The overall CCI was higher in the US. There were fewer patients with 0–5 years of epilepsy and more with 31 + years of epilepsy in the US. There were fewer monotherapy patients and more taking 2 antiepileptic drugs (AEDs) in the US than other regions. The proportion of patients taking any AEDs was similar between regions (75% US, 77% 5EU, 76% Brazil + 5EU) (Table 1). The proportion of patients with persistent seizures (>1 per year) among AED users was slightly higher in the US (51%) than the 5EU (45%) and Brazil + 5EU (45%) [data not reported in tables]. Individual AED use varied somewhat between regions (Table 1).

Table 2 demonstrates the similarities between the 5EU and Brazil datasets on patient characteristics and outcomes. There were small but statistically significant differences on age, BMI, alcohol consumption, duration of epilepsy, absenteeism, and overall work impairment.

### 3.1. Bivariate results to determine covariates for multivariable outcomes analyses of the relationship between seizure frequency and outcomes

Analyses were performed separately by region (US, 5EU, Brazil + 5EU). In the US analyses, seizure frequency was statistically significantly associated with age, race/ethnicity, education, household income, employment status, long-term disability, BMI, smoking status, CCI, epilepsy duration, and total number of AEDs (Table 3). In the 5EU analyses, seizure frequency was associated with these same variables with the exception of: variables that were not assessed in the 5EU (race/ethnicity), variables not significant for the 5EU (education, long-term disability, BMI, and epilepsy duration), and variables significant for the 5EU (retirement) (Table 3). In the Brazil + 5EU dataset analyses, seizure frequency was associated with the same factors as the 5EU dataset with the exception of CCI which was marginally not significant for the combined dataset (Table 3).

### 3.2. Unadjusted and adjusted multivariable analyses of the relationship between seizure frequency and outcomes

#### 3.2.1. Unadjusted outcomes results

Unadjusted analyses examining the relationship between seizure frequency and outcomes demonstrated statistically significant associations between seizure frequency and all outcomes in all datasets with the exception of absenteeism in the Brazil + 5EU dataset. The directions of the associations were as expected. Decreasing seizure frequency was associated with improved QoL scores (MCS, PCS, utilities), less work and activity impairment (absenteeism, presenteeism, overall work impairment, activity impairment), and lower healthcare resource use (provider visits, ER visits, hospitalizations) (Table 4).

#### 3.2.2. Adjusted multivariable outcomes results

*3.2.2.1. US IGE.* After adjustments for covariates identified through the bivariate analysis, pairwise comparisons between the lowest seizure frequency group (<1 seizure per year) and all other seizure frequency groups indicated that patients reporting less than one seizure per year had higher MCS and PCS QoL scores than the ≥1 seizures a week and 1–3 seizures per month groups (all $p < 0.001$). Differences in MCS and PCS (>3) scores exceeded MIDs for these significant comparisons. Patients that reported having less than one seizure per year had better

**Table 1**
Patient characteristics.

| | US values (N = 782) | 5EU values (N = 418) | Brazil + 5EU values (N = 452) |
|---|---|---|---|
| Age (years) — mean ± SD | 45.27 ± 14.46 | 43.64 ± 13.75 | 43.00 ± 13.70 |
| Female (%) | 388 (49.62%) | 204 (48.80%) | 225 (49.78%) |
| Race/ethnicity | | | |
| Non-Hispanic white (%) | 592 (75.70%) | N/A | N/A |
| Non-Hispanic black (%) | 84 (10.74%) | N/A | N/A |
| Hispanic (%) | 60 (7.67%) | N/A | N/A |
| Other ethnicity (%) | 46 (5.88%) | N/A | N/A |
| Married/living with partner (%) | 400 (51.15%) | 244 (58.37%) | 263 (58.19%) |
| College educated (%) | 236 (30.18%) | 147 (35.17%) | 158 (34.96%) |
| Annual household income | | | |
| <$25K, <€20K/<£20K, <R$ 1000 (%) | 268 (34.27%) | 153 (36.60%) | 160 (35.40%) |
| $25K–<$50K, €20–<50K/£20–<40K, R$ 1001–R$ 6500 (%) | 220 (28.13%) | 165 (39.47%) | 184 (40.71%) |
| $50K–<$75K, €50K+/£40K+, R$ 6501+ (%) | 134 (17.14%) | 60 (14.35%) | 68 (15.04%) |
| $75K+ (%) | 123 (15.73%) | N/A | N/A |
| Decline to answer (%) | 37 (4.73%) | 40 (9.57%) | 40 (8.85%) |
| Employed (%) | 351 (44.88%) | 239 (57.18%) | 257 (56.86%) |
| Retired (%) | 101 (12.92%) | 57 (13.64%) | 58 (12.83%) |
| Long-term disability (%) | 117 (14.96%) | 39 (9.33%) | 39 (8.63%) |
| Insured (%) | 633 (80.95%) | N/A | N/A |
| Body mass index | | | |
| Underweight (%) | 27 (3.45%) | 11 (2.63%) | 15 (3.32%) |
| Normal weight (%) | 217 (27.75%) | 178 (42.58%) | 189 (41.81%) |
| Overweight (%) | 251 (32.10%) | 122 (29.19%) | 133 (29.42%) |
| Obese (%) | 274 (35.04%) | 91 (21.77%) | 99 (21.90%) |
| Decline to provide weight (%) | 13 (1.66%) | 16 (3.83%) | 16 (3.54%) |
| Consume alcohol (%) | 423 (54.09%) | 289 (69.14%) | 303 (67.04%) |
| Smoking behavior | | | |
| Nonsmoker (%) | 355 (45.40%) | 162 (38.76%) | 181 (40.04%) |
| Former smoker (%) | 230 (29.41%) | 136 (32.54%) | 143 (31.64%) |
| Current smoker (%) | 197 (25.19%) | 120 (28.71%) | 128 (28.32%) |
| Exercise (%) | 468 (59.85%) | 235 (56.22%) | 253 (55.97%) |
| Charlson comorbidity index — mean ± SD | 0.79 ± 1.91 | 0.63 ± 2.38 | 0.67 ± 2.68 |
| Length of time diagnosed with epilepsy | | | |
| 0 to 5 years (%) | 74 (9.46%) | 65 (15.55%) | 72 (15.93%) |
| 6 to 10 years (%) | 85 (10.87%) | 57 (13.64%) | 58 (12.83%) |
| 11 to 15 years (%) | 105 (13.43%) | 62 (14.83%) | 65 (14.38%) |
| 16 to 19 years (%) | 62 (7.93%) | 34 (8.13%) | 35 (7.74%) |
| 20 to 30 years (%) | 143 (18.29%) | 76 (18.18%) | 89 (19.69%) |
| 31 years or greater (%) | 313 (40.03%) | 124 (29.67%) | 133 (29.42%) |
| Total number of epilepsy prescriptions | | | |
| None (%) | 195 (24.94%) | 97 (23.21%) | 109 (24.12%) |
| One medication (%) | 380 (48.59%) | 237 (56.70%) | 252 (55.75%) |
| Two medications (%) | 155 (19.82%) | 59 (14.11%) | 62 (13.72%) |
| Three or more medications (%) | 52 (6.65%) | 25 (5.98%) | 29 (6.42%) |
| Antiepileptic medications (among AED-treated) | | | |
| Acetazolamide | NR | 0.62% | 0.58% |
| Carbamazepine | 16.70% | 21.18% | 22.16% |
| Clobazam | NR | 0.62% | 0.58% |
| Clonazepam | NR | 4.36% | 6.12% |
| Diazepam | NR | 1.56% | 1.46% |
| Eslicarbazepine | NR | 0.31% | 0.29% |
| Ethosuximide | NR | 1.25% | 1.17% |
| Gamibetal | NR | NR | 0.29% |
| Gabapentin | 5.96% | 2.18% | 2.33% |
| Lacosamide | 3.75% | 0.93% | 0.87% |
| Lamotrigine | 18.40% | 24.61% | 23.91% |
| Lorazepam | NR | 0.62% | 0.58% |
| Levetiracetam | 26.41% | 17.76% | 16.62% |
| Oxcarbazepine | 3.58% | 2.49% | 2.33% |
| Perampanel | 0.17% | NR | NR |
| Phenobarbital | NR | 5.92% | 5.54% |
| Phenytoin | 22.15% | 7.48% | 7.00% |
| Pregabalin | 1.19% | 2.18% | 2.04% |
| Primidone | NR | 0.62% | 0.58% |
| Rufinamide | 0.85% | NR | NR |
| Tiagabine | 0.68% | NR | NR |
| Topiramate | 11.07% | 4.98% | 4.66% |
| Valproate | 16.35% | 20.56% | 20.70% |
| Zonisamide | 3.75% | 0.93% | 0.87% |

N/A = not applicable as these data were not collected in these countries, NR = not reported.

**Table 2**
Evaluation of whether 5EU and Brazilian data can be combined.

| | Total (N = 452) | 5EU IGE (N = 418) | Brazil IGE (N = 34) | p-Value |
|---|---|---|---|---|
| Age (years) — mean ± SD | 43.00 ± 13.70 | 43.64 ± 13.75 | 35.18 ± 10.33 | <.001 |
| Female (%) | 225 (49.78%) | 204 (48.80%) | 21 (61.76%) | 0.146 |
| Married/living with partner (%) | 263 (58.19%) | 244 (58.37%) | 19 (55.88%) | 0.777 |
| College educated (%) | 158 (34.96%) | 147 (35.17%) | 11 (32.35%) | 0.741 |
| Employed (%) | 257 (56.86%) | 239 (57.18%) | 18 (52.94%) | 0.632 |
| Retired (%) | 58 (12.83%) | 57 (13.64%) | 1 (2.94%) | 0.073 |
| Long-term disability (%) | 39 (8.63%) | 39 (9.33%) | 0 (0.00%) | 0.062 |
| Body mass index | | | | 0.038 |
| Underweight (%) | 15 (3.32%) | 11 (2.63%) | 4 (11.76%) | |
| Normal weight (%) | 189 (41.81%) | 178 (42.58%) | 11 (32.35%) | |
| Overweight (%) | 133 (29.42%) | 122 (29.19%) | 11 (32.35%) | |
| Obese (%) | 99 (21.90%) | 91 (21.77%) | 8 (23.53%) | |
| Decline to provide weight (%) | 16 (3.54%) | 16 (3.83%) | 0 (0.00%) | |
| Drink alcohol (%) | 303 (67.04%) | 289 (69.14%) | 14 (41.18%) | <.001 |
| Smoking behavior | | | | 0.134 |
| Nonsmoker (%) | 181 (40.04%) | 162 (38.76%) | 19 (55.88%) | |
| Former smoker (%) | 143 (31.64%) | 136 (32.54%) | 7 (20.59%) | |
| Current smoker (%) | 128 (28.32%) | 120 (28.71%) | 8 (23.53%) | |
| Exercise (%) | 253 (55.97%) | 235 (56.22%) | 18 (52.94%) | 0.711 |
| Charlson comorbidity index — mean ± SD | 0.67 ± 2.68 | 0.63 ± 2.38 | 1.18 ± 5.14 | 0.257 |
| Length of time diagnosed with epilepsy | | | | 0.039 |
| 0 to 5 years (%) | 72 (15.93%) | 65 (15.55%) | 7 (20.59%) | |
| 6 to 10 years (%) | 58 (12.83%) | 57 (13.64%) | 1 (2.94%) | |
| 11 to 15 years (%) | 65 (14.38%) | 62 (14.83%) | 3 (8.82%) | |
| 16 to 19 years (%) | 35 (7.74%) | 34 (8.13%) | 1 (2.94%) | |
| 20 to 30 years (%) | 89 (19.69%) | 76 (18.18%) | 13 (38.24%) | |
| 31 years or greater (%) | 133 (29.42%) | 124 (29.67%) | 9 (26.47%) | |
| Using a prescription medication of epilepsy (%) | 343 (75.88%) | 321 (76.79%) | 22 (64.71%) | 0.113 |
| MCS — mean ± SD | 43.13 ± 12.09 | 43.21 ± 11.75 | 42.19 ± 15.89 | 0.637 |
| PCS — mean ± SD | 46.41 ± 10.48 | 46.20 ± 10.55 | 49.05 ± 9.40 | 0.128 |
| Health utility — mean ± SD | 0.67 ± 0.14 | 0.67 ± 0.14 | 0.68 ± 0.17 | 0.786 |
| Absenteeism[a,b] (%) — mean ± SD | 10.26 ± 23.44 | 9.30 ± 22.13 | 22.61 ± 34.94 | 0.020 |
| Presenteeism[a,b] (%) — mean ± SD | 24.42 ± 28.88 | 23.71 ± 28.49 | 34.38 ± 33.26 | 0.154 |
| Overall work impairment[a,b] (%) — mean ± SD | 29.97 ± 33.20 | 28.72 ± 32.56 | 45.94 ± 38.06 | 0.034 |
| Activity impairment[b] (%) — mean ± SD | 36.53 ± 32.26 | 36.51 ± 31.97 | 36.76 ± 36.07 | 0.964 |
| Healthcare provider visits in past 6 months — mean ± SD | 7.17 ± 9.57 | 7.15 ± 9.56 | 7.38 ± 9.87 | 0.891 |
| ER visits in the past 6 months — mean ± SD | 0.53 ± 1.39 | 0.51 ± 1.39 | 0.74 ± 1.48 | 0.374 |
| Hospitalizations in the past 6 months — mean ± SD | 0.37 ± 1.12 | 0.37 ± 1.14 | 0.38 ± 0.89 | 0.954 |

Note: Overall p-values are provided indicating that at least one group is different from another. Lower scores on Mental Component Summary (MCS), Physical Component Summary (PCS), and health utilities indicate a decrease in quality of life. Absenteeism, presenteeism, overall work impairment, and activity impairment scores represent impairment percentages, with higher scores indicating greater impairment. ER = emergency room, IGE = idiopathic generalized epilepsy, SD = standard deviation.
[a] Includes only employed respondents.
[b] Productivity measures are derived from the WPAI.

SF-6D health utility scores than the three more frequent seizure groups (all $p < 0.003$). Differences in health utility (>0.041) scores exceeded MIDs for patients that reported ≥1 seizures a week or 1–3 seizures per month, relative to patients that reported <1 seizure per year.

**Table 3**
Relationship between seizure frequency and patient characteristics for covariate selection.

| | US p-values for Seizure Frequency Association | 5EU p-values for Seizure Frequency Association | Brazil + 5EU p-values for Seizure Frequency Association |
|---|---|---|---|
| Age (years) — mean ± SD | 0.003 | 0.008 | 0.021 |
| Female (%) | 0.098 | 0.350 | 0.408 |
| Race/ethnicity | <.001 | N/A | N/A |
| Married/living with partner (%) | 0.378 | 0.137 | 0.314 |
| College educated (%) | 0.003 | 0.990 | 0.951 |
| Annual household income | <.001 | 0.005 | 0.003 |
| Employed (%) | <.001 | 0.019 | 0.032 |
| Retired (%) | 0.654 | 0.034 | 0.029 |
| Long-term disability (%) | <.001 | 0.153 | 0.128 |
| Insured (%) | 0.055 | N/A | N/A |
| Body mass index | 0.021 | 0.113 | 0.173 |
| Consume alcohol (%) | 0.061 | 0.362 | 0.129 |
| Smoking behavior | <.001 | 0.005 | 0.014 |
| Exercise (%) | 0.841 | 0.651 | 0.524 |
| Charlson comorbidity index — mean ± SD | <.001 | 0.006 | 0.061 |
| Length of time diagnosed with epilepsy | <.001 | 0.294 | 0.377 |
| Total number of epilepsy prescriptions | <.001 | <.001 | <.001 |

**Table 4**
Unadjusted outcomes values by seizure frequency group.

| | Total | ≥1 times a week | 1–3 times a month | 1–4 times a year | <1 time a year | p-Value for relationship to seizure frequency |
|---|---|---|---|---|---|---|
| *US* | | | | | | |
| Sample size | 782 | 85 | 100 | 172 | 425 | |
| MCS — mean ± SD | 44.60 ± 12.31 | 37.62 ± 13.59 | 39.13 ± 11.93 | 43.95 ± 12.38 | 47.56 ± 11.04 | <.001 |
| PCS — mean ± SD | 46.44 ± 10.93 | 41.69 ± 11.40 | 42.30 ± 10.32 | 45.53 ± 11.31 | 48.72 ± 10.20 | <.001 |
| Health utility — mean ± SD | 0.68 ± 0.15 | 0.60 ± 0.15 | 0.61 ± 0.12 | 0.66 ± 0.14 | 0.72 ± 0.14 | <.001 |
| Absenteeism[a,b] (%) — mean ± SD | 6.78 ± 17.43 | 30.18 ± 34.64 | 6.38 ± 12.31 | 9.07 ± 19.31 | 3.91 ± 12.58 | <.001 |
| Presenteeism[a,b] (%) — mean ± SD | 23.05 ± 28.16 | 47.73 ± 35.98 | 41.92 ± 30.86 | 29.50 ± 28.31 | 16.68 ± 24.12 | <.001 |
| Overall work impairment[a,b] (%) — mean ± SD | 26.17 ± 30.79 | 57.32 ± 38.76 | 44.00 ± 32.38 | 33.75 ± 30.64 | 18.97 ± 26.44 | <.001 |
| Activity impairment[b] (%) — mean ± SD | 33.67 ± 31.90 | 52.71 ± 32.64 | 47.50 ± 32.86 | 36.51 ± 29.81 | 25.46 ± 29.41 | <.001 |
| Healthcare provider visits in past 6 months (mean ± SD) | 6.36 ± 9.20 | 10.46 ± 11.89 | 10.17 ± 13.64 | 4.99 ± 5.91 | 5.21 ± 7.83 | <.001 |
| ER visits in the past 6 months (mean ± SD) | 0.71 ± 2.41 | 1.92 ± 4.10 | 0.97 ± 2.41 | 0.92 ± 3.25 | 0.31 ± 1.11 | <.001 |
| Hospitalizations in the past 6 months (mean ± SD) | 0.25 ± 0.89 | 0.85 ± 1.81 | 0.27 ± 0.74 | 0.35 ± 1.03 | 0.09 ± 0.41 | <.001 |
| *5EU* | | | | | | |
| Sample size | 418 | 43 | 44 | 84 | 247 | |
| MCS — mean ± SD | 43.21 ± 11.75 | 37.84 ± 10.84 | 41.47 ± 8.89 | 39.28 ± 10.17 | 45.79 ± 12.16 | <.001 |
| PCS — mean ± SD | 46.20 ± 10.55 | 39.74 ± 11.85 | 42.88 ± 9.07 | 44.75 ± 10.33 | 48.41 ± 9.97 | <.001 |
| Health utility — mean ± SD | 0.67 ± 0.14 | 0.58 ± 0.13 | 0.63 ± 0.10 | 0.62 ± 0.12 | 0.71 ± 0.14 | <.001 |
| Absenteeism[a,b] (%) — mean ± SD | 9.30 ± 22.13 | 15.65 ± 25.25 | 16.12 ± 22.45 | 15.12 ± 26.61 | 6.09 ± 19.73 | 0.024 |
| Presenteeism[a,b] (%) — mean ± SD | 23.71 ± 28.49 | 48.42 ± 36.40 | 37.65 ± 27.73 | 31.71 ± 30.98 | 16.67 ± 23.65 | <.001 |
| Overall work impairment[a,b] (%) — mean ± SD | 28.72 ± 32.56 | 52.80 ± 38.30 | 46.47 ± 31.25 | 37.64 ± 34.65 | 21.11 ± 28.42 | <.001 |
| Activity impairment[b] (%) — mean ± SD) | 36.51 ± 31.97 | 60.47 ± 29.35 | 48.86 ± 26.08 | 43.81 ± 31.04 | 27.65 ± 30.29 | <.001 |
| Healthcare provider visits in past 6 months (— mean ± SD) | 7.15 ± 9.56 | 9.70 ± 13.57 | 7.36 ± 9.30 | 9.89 ± 12.28 | 5.73 ± 7.19 | 0.001 |
| ER visits in the past 6 months (— mean ± SD) | 0.51 ± 1.39 | 1.37 ± 3.07 | 0.84 ± 1.33 | 0.69 ± 1.22 | 0.25 ± 0.78 | <.001 |
| Hospitalizations in the past 6 months (— mean ± SD) | 0.37 ± 1.14 | 1.07 ± 2.42 | 0.61 ± 1.24 | 0.65 ± 1.34 | 0.11 ± 0.37 | <.001 |
| *Brazil + 5EU* | | | | | | |
| Sample size | 452 | 47 | 45 | 92 | 268 | |
| MCS — mean ± SD | 43.13 ± 12.09 | 37.27 ± 11.57 | 41.53 ± 8.80 | 39.80 ± 10.98 | 45.57 ± 12.40 | <.001 |
| PCS — mean ± SD | 46.41 ± 10.48 | 41.08 ± 12.23 | 42.80 ± 8.99 | 45.14 ± 10.51 | 48.39 ± 9.86 | <.001 |
| Health utility — mean ± SD | 0.67 ± 0.14 | 0.58 ± 0.14 | 0.63 ± 0.10 | 0.62 ± 0.12 | 0.71 ± 0.14 | <.001 |
| Absenteeism[a,b] (%) — mean ± SD | 10.26 ± 23.44 | 14.23 ± 24.46 | 15.50 ± 21.94 | 16.07 ± 28.58 | 7.51 ± 21.54 | 0.085 |
| Presenteeism[a,b] (%) — mean ± SD | 24.42 ± 28.88 | 43.81 ± 37.48 | 38.89 ± 27.42 | 30.91 ± 30.33 | 18.34 ± 25.26 | <.001 |
| Overall work impairment[a,b] (%) — mean ± SD | 29.97 ± 33.20 | 48.00 ± 39.61 | 47.33 ± 30.53 | 37.91 ± 34.88 | 23.37 ± 30.15 | <.001 |
| Activity impairment[b] (%) — mean ± SD | 36.53 ± 32.26 | 56.81 ± 30.86 | 49.11 ± 25.83 | 43.70 ± 31.61 | 28.40 ± 30.98 | <.001 |
| Healthcare provider visits in past 6 months (— mean ± SD) | 7.17 ± 9.57 | 9.79 ± 13.11 | 7.33 ± 9.20 | 9.49 ± 11.91 | 5.88 ± 7.62 | 0.003 |
| ER visits in the past 6 months (— mean ± SD) | 0.53 ± 1.39 | 1.30 ± 2.96 | 0.84 ± 1.31 | 0.71 ± 1.26 | 0.28 ± 0.87 | <.001 |
| Hospitalizations in the past 6 months (— mean ± SD) | 0.37 ± 1.12 | 1.00 ± 2.33 | 0.60 ± 1.23 | 0.63 ± 1.29 | 0.13 ± 0.47 | <.001 |

Note: Overall p-values are provided indicating at least one group is different from another. Lower scores on Mental Component Summary (MCS), Physical Component Summary (PCS), and health utilities indicate a decrease in quality of life. Absenteeism, presenteeism, overall work impairment and activity impairment scores represent impairment percentages, with higher scores indicating greater impairment. ER = emergency room, IGE = idiopathic generalized epilepsy, SD = standard deviation.

[a] Includes only employed respondents.

[b] Productivity measures are derived from the WPAI.

Patients that reported having less than one seizure per year had less overall work and activity impairment than respondents that reported having seizures more often (all $p < 0.02$). Respondents that experienced <1 seizure a year had fewer provider visits than respondents that reported ≥1 seizures per week ($p < 0.001$) or 1–3 seizures a month ($p = 0.004$). For the more frequent seizure groups, the number of ER visits was significantly greater than those for the <1 seizure per year group (all $p < 0.04$). Hospitalizations in the past six months also increased with more frequent seizures (<1 seizure/year vs. ≥1 seizures/week, $p < 0.001$) (Table 5).

After adjustments, seizure frequency was positively related to indirect costs. Specifically, as seizures occurred more often, patients' indirect costs also increased. Assuming 100% missed work for the unemployed, working age respondents (aged 18–60 years), those with more frequent seizures had significantly higher indirect costs than patients reporting less than one seizure per year (all $p < 0.001$). The more frequent seizure groups additionally incurred significantly higher direct costs than participants who reported experiencing less than one seizure a year (all $p < 0.02$) (Table 5).

*3.2.2.2. 5EU IGE.* Differences in MCS and PCS (>3) QoL scores exceeded MIDs for patients that reported 1–3 seizures a month and ≥1 seizures per week, compared with patients that reported <1 seizure per year (all $p < 0.05$). Patients that reported having less than one seizure per year had higher SF-6D health utility scores than the three more frequent seizure groups (all $p < 0.001$).

Patients that reported having less than one seizure per year had less overall work impairment (all $p < 0.05$) and activity impairment (all $p < 0.001$) than respondents that reported having seizures more often, after controlling for covariates. The number of provider visits was significantly greater for the 1–4 seizures per year group than for the <1 seizure a year group ($p = 0.003$). The number of ER visits was significantly higher for the more frequent seizure groups than for the <1 seizure per year group (all $p < 0.001$). Furthermore, patients in the three frequent seizure groups had significantly more hospitalizations in the past six months than patients who experienced seizures less than once per year (all $p < 0.001$) (Table 5).

After adjustments, both direct and indirect costs increased, as seizure frequency increased. Assuming 100% missed work for the unemployed respondents, who were of an employable age (18–60 years),

**Table 5**
Adjusted outcomes values and pairwise comparisons to lowest seizure frequency group.

| | Parameter | ≥1 seizures/week | 1–3 seizures/month | 1–4 seizures/year | <1 seizure/year |
|---|---|---|---|---|---|
| *US outcomes values* | | | | | |
| Sample size | | 85 | 100 | 172 | 425 |
| MCS | LSMeans | 39.18 | 40.48 | 45.05 | 46.48 |
| | p-Value | <.0001 | <.0001 | 0.1787 | |
| PCS | LSMeans | 43.10 | 43.77 | 46.02 | 47.90 |
| | p-Value | <.0001 | 0.0002 | 0.0382 | |
| Health utilities | LSMeans | 0.619 | 0.628 | 0.673 | 0.711 |
| | p-Value | <.0001 | <.0001 | 0.0024 | |
| Absenteeism%[a,b] | LSMeans | 21.04 | 4.86 | 8.22 | 3.98 |
| | p-Value | 0.0444 | 0.7732 | 0.1231 | |
| Presenteeism%[a,b] | LSMeans | 39.23 | 37.62 | 26.88 | 17.05 |
| | p-Value | 0.0129 | 0.0055 | 0.0261 | |
| Overall work impairment%[a,b] | LSMeans | 48.14 | 39.72 | 30.71 | 19.39 |
| | p-Value | 0.0051 | 0.0087 | 0.0184 | |
| Activity impairment%[b] | LSMeans | 45.45 | 40.28 | 32.49 | 25.51 |
| | p-Value | <.0001 | 0.0001 | 0.013 | |
| Provider visits | LSMeans | 8.52 | 7.53 | 4.95 | 4.88 |
| | p-Value | 0.0005 | 0.0041 | 0.9107 | |
| ER visits | LSMeans | 1.30 | 0.52 | 0.69 | 0.28 |
| | p-Value | <.0001 | 0.0361 | 0.0002 | |
| Hospitalizations | LSMeans | 0.49 | 0.15 | 0.27 | 0.09 |
| | p-Value | <.0001 | 0.1998 | 0.0004 | |
| Absenteeism costs ($)[a,b] | LSMeans | 6592.64 | 1308.90 | 4544.76 | 1665.38 |
| | p-Value | 0.1257 | 0.7540 | 0.0616 | |
| Presenteeism costs ($)[a,b] | LSMeans | 9818.06 | 11,288 | 8327.59 | 5317.66 |
| | p-Value | 0.0710 | 0.0138 | 0.0431 | |
| Total indirect costs ($)[a,b] | LSMeans | 17,072 | 12,799 | 12,323 | 7114.65 |
| | p-Value | 0.0154 | 0.0592 | 0.0157 | |
| Total indirect costs (age 18–60) ($)[a,b] | LSMeans | 32,751 | 29,758 | 28,594 | 19,184 |
| | p-Value | <.0001 | <.0001 | <.0001 | |
| Provider visit costs ($) | LSMeans | 20,479 | 17,290 | 12,021 | 11,473 |
| | p-Value | 0.0007 | 0.0110 | 0.7272 | |
| ER visit costs ($) | LSMeans | 3844.83 | 1388.44 | 2227.64 | 775.91 |
| | p-Value | <.0001 | 0.0944 | 0.0002 | |
| Hospitalization costs ($) | LSMeans | 18,489 | 5004.86 | 8531.14 | 2475.20 |
| | p-Value | 0.0003 | 0.1638 | 0.0024 | |
| Total direct costs ($) | LSMeans | 43,086 | 24,309 | 24,518 | 15,978 |
| | p-Value | <.0001 | 0.0185 | 0.0041 | |
| *5EU outcomes values* | | | | | |
| Sample size | | 43 | 44 | 84 | 247 |
| MCS | LSMeans | 38.99 | 41.61 | 40.11 | 45.28 |
| | p-Value | 0.0008 | 0.0441 | 0.0003 | |
| PCS | LSMeans | 40.08 | 43.69 | 45.27 | 48.03 |
| | p-Value | <.0001 | 0.0041 | 0.0195 | |
| Health utilities | LSMeans | 0.589 | 0.634 | 0.627 | 0.707 |
| | p-Value | <.0001 | 0.0004 | <.0001 | |
| Absenteeism%[a,b] | LSMeans | 17.74 | 18.59 | 15.96 | 5.18 |
| | p-Value | 0.1134 | 0.104 | 0.0418 | |
| Presenteeism%[a,b] | LSMeans | 49.30 | 39.79 | 30.34 | 15.91 |
| | p-Value | 0.0009 | 0.0074 | 0.0088 | |
| Overall work impairment%[a,b] | LSMeans | 51.21 | 47.39 | 36.23 | 20.87 |
| | p-Value | 0.0033 | 0.0105 | 0.0141 | |
| Activity impairment%[b] | LSMeans | 55.87 | 46.89 | 40.52 | 26.65 |
| | p-Value | <.0001 | 0.0005 | 0.0008 | |
| Provider visits | LSMeans | 8.40 | 6.74 | 9.52 | 5.77 |
| | p-Value | 0.0889 | 0.465 | 0.0027 | |
| ER visits | LSMeans | 0.93 | 0.77 | 0.61 | 0.22 |
| | p-Value | <.0001 | 0.0006 | 0.0008 | |
| Hospitalizations | LSMeans | 0.58 | 0.56 | 0.52 | 0.11 |
| | p-Value | <.0001 | <.0001 | <.0001 | |
| Absenteeism costs (€)[a,b] | LSMeans | 2027.02 | 2069.08 | 2569.75 | 1244.03 |
| | p-Value | 0.5873 | 0.5492 | 0.2126 | |
| Presenteeism costs (€)[a,b] | LSMeans | 5187.53 | 5735.75 | 4595.81 | 2543.76 |
| | p-Value | 0.0624 | 0.0390 | 0.0380 | |
| Total Indirect costs (€)[a,b] | LSMeans | 6524.98 | 7659.03 | 6883.54 | 3847.49 |
| | p-Value | 0.1421 | 0.0705 | 0.0297 | |
| Total indirect costs (age 18–60) (€)[a,b] | LSMeans | 13,671 | 14,041 | 12,386 | 8264.54 |
| | p-Value | 0.0014 | 0.0016 | 0.0011 | |
| Provider visit costs (€) | LSMeans | 563 | 439.31 | 641.27 | 368.97 |
| | p-Value | 0.0777 | 0.4425 | 0.0024 | |
| ER visit costs (€) | LSMeans | 259.36 | 208.66 | 156.55 | 47.28 |
| | p-Value | 0.0012 | 0.0027 | 0.0022 | |
| Hospitalization costs (€) | LSMeans | 1258.74 | 1503.40 | 1228.28 | 234.13 |
| | p-Value | 0.0068 | 0.0011 | 0.0003 | |

**Table 5** (*continued*)

| | Parameter | ≥1 seizures/week | 1–3 seizures/month | 1–4 seizures/year | <1 seizure/year |
|---|---|---|---|---|---|
| Total direct costs (€) | LSMeans | 2233.52 | 2051.92 | 1922.06 | 708.21 |
| | p-Value | 0.0001 | 0.0001 | <.0001 | |
| *Brazil + 5EU outcomes values* | | | | | |
| Sample size | | 47 | 45 | 92 | 268 |
| MCS | LSMeans | 38.23 | 41.33 | 40.35 | 45.25 |
| | p-Value | 0.0001 | 0.0357 | 0.0005 | |
| PCS | LSMeans | 41.28 | 43.55 | 45.61 | 48.07 |
| | p-Value | <.0001 | 0.0027 | 0.0301 | |
| Health utilities | LSMeans | 0.593 | 0.630 | 0.631 | 0.706 |
| | p-Value | <.0001 | 0.0003 | <.0001 | |
| Absenteeism%[a,b] | LSMeans | 13.23 | 16.10 | 16.24 | 7.10 |
| | p-Value | 0.3384 | 0.2286 | 0.0726 | |
| Presenteeism%[a,b] | LSMeans | 44.58 | 41.37 | 29.80 | 17.20 |
| | p-Value | 0.0024 | 0.0068 | 0.0162 | |
| Overall work impairment%[a,b] | LSMeans | 47.19 | 48.44 | 37.02 | 22.84 |
| | p-Value | 0.0107 | 0.0132 | 0.0198 | |
| Activity impairment%[b] | LSMeans | 52.73 | 47.85 | 41.08 | 27.54 |
| | p-Value | <.0001 | 0.0005 | 0.0009 | |
| Provider visits | LSMeans | 8.73 | 6.74 | 9.31 | 5.86 |
| | p-Value | 0.0613 | 0.5102 | 0.0040 | |
| ER visits | LSMeans | 0.91 | 0.79 | 0.66 | 0.25 |
| | p-Value | 0.0001 | 0.0011 | 0.0006 | |
| Hospitalizations | LSMeans | 0.55 | 0.56 | 0.53 | 0.13 |
| | p-Value | 0.0001 | <.0001 | <.0001 | |

Note: Pairwise p-values are provided indicating one group is different than another. Lower scores on Mental Component Summary (MCS), Physical Component Summary (PCS) and health utilities indicate a decrease in quality of life. Absenteeism, presenteeism, overall work impairment and activity impairment scores represent impairment percentages, with higher scores indicating greater impairment. ER = emergency room, IGE = idiopathic generalized epilepsy, SD = standard deviation.

[a] Includes only employed respondents.

[b] Productivity measures are derived from the WPAI.

all three more frequent seizure groups had significantly greater indirect costs than the <1 seizure a year group (all $p < 0.01$). Total direct costs were also greater for the three more frequent seizure groups than for the <1 seizure a year group (all $p < 0.001$) (Table 5).

*3.2.2.3. Brazil + 5EU IGE.* Patients that reported having less than one seizure per year had better MCS, PCS, and health utility scores, compared with the other three seizure groups (all $p < 0.05$), after controlling for covariates. Differences in MCS and PCS QoL scores exceeded MIDs (>3) for patients that reported 1–3 seizures a month or ≥1 seizures per week, relative to patients that reported <1 seizure per year. Patients that reported 1–4 seizures a year also exceeded the MID on MCS, compared with patients reporting ≥1 seizures per week. Differences in health utility scores exceeded MIDs (>0.041) for patients that reported ≥1 seizures per week, 1–3 seizures per month, and 1–4 seizures a year, compared with patients that reported <1 seizure per year.

After adjustments, among the employed respondents, there were no significant differences between seizure groups on absenteeism. However, patients that experienced <1 seizure per year reported less presenteeism and overall work impairment than the three more frequent seizure groups (all $p < 0.05$). Patients that experienced ≥1 seizures per week reported over 100% more overall work impairment than the <1 seizure per year group ($p = 0.011$). Among all respondents, as the number of seizures decreased, activity impairment also decreased. Patients that experienced ≥1 seizures a week reported 92% more activity impairment than the <1 seizure a year group ($p < 0.001$).

After controlling for covariates, patients that reported 1–4 seizures per year had significantly more traditional provider visits in the past six months than patients that reported <1 seizure per year (59%, $p = 0.004$). As the number of seizures decreased, the number of ER visits and the number of hospitalizations in the past six months also decreased. Patients that had ≥1 seizures per week reported significantly more ER visits (261%, $p < 0.001$) and hospitalizations (336%, $p < 0.001$) than patients that reported less than one seizure per year. Patients that reported 1–3 seizures a month also reported significantly more ER visits (215%, $p = 0.001$) and hospitalizations (345%, $p < 0.001$) than patients that reported <1 seizure per year. Patients that had 1–4 seizures per year also reported significantly more ER visits (163%, $p < 0.001$) and hospitalizations (324%, $p < 0.001$) than patients that reported less than one seizure per year (Table 5).

## 4. Discussion

Over 50 million people worldwide currently have epilepsy, with over two million new cases of epilepsy diagnosed each year [16]. Epilepsy prevalence varies considerably by region (Table 6). Therefore, it is important to understand the patient burden of this condition by epilepsy type, and hence, the overall objective of this current study was to extend and update the literature with respect to the burden of PGTCS and IGE/GGE, among patients diagnosed with epilepsy in the US, 5EU (France, Germany, Italy, Spain, and UK), and Brazil. Overall, the results suggested a significant burden existed across all three regions for patients with IGE with insufficiently managed seizures. In the current study, nearly half of participants from each region reported experiencing seizures once per year or more often. These findings were consistent

**Table 6**
The prevalence estimates in the US, 5EU, and Brazil.

| Country | Epilepsy overall (per 1000) |
|---|---|
| United States | 7.1 (Hirtz et al.) [17] |
| France | 5.4 (Picot et al.) [18] |
| Germany | 9.1 (Hamer et al.) [19] |
| Italy | 4.57 (Giussani et al.) [20] |
| Spain | 4.79 (Garcia-Martin et al.) [21] |
| United Kingdom | 8.6 (Ferro) [22] |
| Brazil | 10.7 (Bruno et al.) [23] |

with research for the overall epilepsy population highlighting the large number of patients with uncontrolled disease, despite receiving one or more AEDs. Specifically, prior research for the overall epilepsy population reports that over half of patients who used monotherapy [16] and nearly three quarters of adult patients with focal epilepsy who were treated with two or more AEDs [24,25] were still unable to achieve disease control.

Across the US and 5EU, similar distributions of age and gender were observed. The Brazilian sample was slightly younger and more likely to be female than the US and 5EU samples. Between 51% and 58% of respondents were married/living with a partner, 30% to 35% of respondents were college educated, and on average, CCI scores were between 0.6 and 1.2 across all three regions. The patterns of QoL, health utilities, productivity loss, activity impairment, and resource utilization in Brazil and the 5EU were not statistically different. Hence, similar burden was observed in Brazil and the 5EU. Overall, the patient burden of IGE increased as seizure frequency increased in both the US and 5EU.

Seizure frequency matters for QoL. Patients with one or more seizures per week demonstrated statistically significant and meaningful decrements in mental and physical health and in health status (utility), compared with patients with less than one seizure per year. The majority of results also exceeded MIDs. These findings were consistent with research for the overall epilepsy population showing that seizure frequency was negatively related to patient QoL in adults [26] and opposed overall epilepsy population research that has indicated no association of seizure frequency with QoL [27]. Some QoL studies may have difficulty showing a relationship between QoL and seizure frequency as AEDs may improve QoL by providing improved seizure control while simultaneously worsening QoL through the potential addition of adverse events [28]. A prior study among adults treated with AEDs reported that decreased QoL was associated with continued seizures and adverse events (ages 5 years and older, 12.3% IGE) [29]. Additionally, a QoL study in Korean patients with epilepsy (ages 20–70 years) of which 19.5% had a generalized epilepsy syndrome demonstrated an independent association between seizure control (defined as: well-controlled, poorly controlled, uncontrolled) and QoL (measured by the QOLIE-10 domain: role functioning and mental health) [30]. The relationship between seizure frequency and other outcomes such as healthcare resource utilization and productivity may also be similarly impacted.

Among patients with IGE, ER visits and hospitalizations significantly increased, as the number of seizures increased (in many cases, these increases were over 100%). These findings were in line with adult focal epilepsy research suggesting that patients with uncontrolled epilepsy have higher healthcare resource utilization [24]. Particularly, these adult patients with uncontrolled epilepsy may make more frequent visits to ERs and have longer hospital LOS [31]. Furthermore, they may receive a larger number of medications and undergo medical testing more often [25]. Generally, healthcare provider visits also differ between the frequency seizure groups. These findings were similar to previous published literature. Specifically, prior research for the overall adult epilepsy population has found that patients with unmanaged disease have significantly more healthcare provider visits than those with effectively controlled seizures [31]. Although the annual costs for AEDs were not collected in the current study, prior research suggests that one of the biggest components of overall direct costs is AED-related costs (children and adults, 8.2% IGE) [32].

Overall work and activity impairment scores monotonically increased with increasing seizure frequency. It is important to note that the number of employed patients was relatively small, but their average age was, at less than 50 years, below the traditional retirement age. Patients with frequent seizures were more likely to be on disability or may have decided to retire, as a result of their disease. This finding may have considerable implications for indirect costs, as research for the overall epilepsy population has demonstrated that epilepsy-related absenteeism accounted for more than three-quarters of annual indirect per patient costs [33]. Additionally, reduced employment participation, due to epilepsy overall, can potentially result in thousands of euros (or dollars) in lost wages each year [34]. Particularly, over two-thirds of indirect epilepsy costs have been found to be due to early retirement or days taken off from work for seizures, and indirect costs accounted for almost 70% of the total annual per patient epilepsy-related costs [35]. Similarly, another study found that indirect costs were higher than direct costs in adults with active epilepsy (19.8% patients with IGE) [36].

Indirect (assuming employable age) and direct costs were significantly higher for patients that experienced more frequent seizures. Likewise, prior research for the overall epilepsy population shows that adult patients with inadequately managed disease have collective yearly costs that are almost double those incurred by patients that have achieved seizure control [31]. Direct costs among patients with drug-resistant epilepsy were more than twice those found for seizure-free patients [25].

The current study made a number of contributions to the literature. Specifically, few studies have investigated QoL among patients with IGE/GGE [3,37] alone, and even fewer recent studies have done so as a function of IGE/GGE seizure frequency [30]. Thus, findings increased the understanding of a broader array of QoL outcomes and how these outcomes may differ by the number of seizures experienced. Furthermore, by examining the indirect and direct costs associated with seizure frequency, the results provided a more comprehensive portrayal of the economic burden associated with IGE.

Our findings have meaningful implications for the financial burden of epilepsy on healthcare systems. For instance, research using claims data shows that annual costs associated with epilepsy were over three and a half times higher than costs estimated for matched controls [38]. Other data have demonstrated that epilepsy-related costs can account for anywhere from 0.2 to 1% of total national direct and/or indirect healthcare expenses [19,33]. Adequate disease management among patients will be important for curbing these costs at the national level. Despite the availability of existing AEDs in 2013, the results suggested that patients with IGE in the US, 5EU, and Brazil are in need of additional treatment options, for which newer AED may provide a solution.

A major advantage of this study was the ability to evaluate the effects of seizure frequency on different types of burden within one study, using a large, representative database. While claims data are a useful source of information for resource utilization and costs, they do not report seizure frequency or health utility values. Clinical cohort studies are helpful for determining seizure frequency and QoL, but they often do not report information on costs attributed to resource utilization or productivity loss. Additionally, past studies have emphasized the major dichotomy in many patient-related outcomes between being completely seizure-free and having occasional seizures or auras [39], but our results suggested that even lesser degrees of seizure reduction can have major impacts on QoL and economic outcomes.

### 4.1. Limitations

Some factors may limit the external validity of our findings. Self-reported data were collected to assess the relationships among the study variables without verification of diagnoses, treatment, or seizure frequency. As such, we cannot rule out the possibility that the metrics reported by respondents were influenced, at least to some extent, by recall biases. Additionally, it is possible that some patients misclassified their seizure type (e.g., complex partial seizures may be confused with absences, secondarily generalized tonic–clonic seizures with PGTCS). Patients were given the option to respond as “Don't know”, allowing them an option if they were not sure about their seizure type diagnosis. Nevertheless, the study IGE prevalence value of 4 per 1000 is fairly large compared with the overall epilepsy prevalence (Table 6). A French study estimated IGE to be 1.8 per 1000 [18] and a Spanish study estimated IGE to be 16% of all patients with epilepsy [40]. Given the high likelihood of other seizure types in this analysis and the fact that PGTCS tends to be more severe and less frequent than other seizure types, it is likely

that a more homogenous population with PGTCS would demonstrate a larger impact on QoL, productivity, and healthcare resource utilization at lower seizure frequency levels. The inclusion of other seizure types may also explain the high prevalence of carbamazepine and phenytoin use reported in this population (Table 1). Because of the internet-based study design, results may not be generalizable to all adult patients with IGE. Specifically, some adults in the US, 5EU, and Brazil with IGE may not have had access to a computer or may have been limited in their experience with such technology. Only adult patients mentally and physically capable of completing the questionnaire were included.

Additionally, there may also be some selection bias of the respondents included in the study. Those more severely affected by their epilepsy seizures may possibly be more inclined to report their epilepsy, or those who are seizure-free may no longer consider themselves as having epilepsy. This study of a prevalent adult cohort with IGE reports that over 40% of patients reported having persistent seizures (1 or more per year in the past year) while other reports of newly diagnosed patients estimate this to be 33% of patients with IGE (ages 9–93 years) [41], and 44% for the first AED and approximately 50% for the second AED among those who had seizures that failed to improve with their first AED (ages 5 years and older, 19% generalized-onset) [42]. Additionally, the questionnaire did not collect information specifically on whether patients were considered seizure-free by their physicians or how long they have been seizure-free.

Because the data were cross-sectional in nature, causal inferences cannot be made regarding the relationships of interest. Furthermore, some of the findings must be evaluated with caution, due to the low sample sizes used to perform a subset of the analyses. Adjustments for multiple pairwise comparisons were not performed. It is possible that some of the significant differences reported were due to chance. There were very few p-values between 0.05 and 0.0167 (Bonferroni threshold). A majority of these were in the comparison between 1 and 4 seizures per year and <1 seizure per year. Future research will be needed to verify these comparisons.

### 4.2. Conclusions

The core strength of this study was that it utilized patient-reported outcomes to determine seizure frequency, QoL, productivity, and HRU. Assessment from the patient's perspective is vital, especially for examining more subjective outcomes, such as QoL and productivity. A greater burden was consistently associated with an increased frequency of seizures. Given the number of patients reporting more than 1 seizure a year and the substantial differences between this and lower seizure frequencies (1–4 per year, 1–3 per month) on many outcomes, there is clearly a need for additional treatment options among patients with PGTCS and IGE/GGE to increase the number of individual patients reaching seizure freedom. Additional options for disease management may not only improve QoL for affected patients but may likewise reduce the direct and indirect costs resulting from inadequate seizure control.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2015.12.018.

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