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FULL-LENGTH ORIGINAL RESEARCH

Understanding the burden of focal epilepsy as a function of seizure frequency in the United States, Europe, and Brazil

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Summary

Objective: **To understand the current burden of focal epilepsy (FE) as a function of seizure frequency.**

Methods: **Patients were identified from the United States (2011, 2012, and 2013), five European countries (EU; France, Germany, Italy, Spain, United Kingdom) (2011 and 2013), and Brazil (2011 and 2012) National Health and Wellness Survey (NHWS), a nationally representative, Internet-based survey of adults (18+ years). The NHWS collected data on respondents' quality of life (QoL), health utilities, productivity loss, and healthcare resource utilization. Indirect and direct costs were calculated from the literature. Altogether, 345 of 176,093 (U.S.A.), 73 of 30,000 (United Kingdom), 53 of 30,001 (Germany), 53 of 30,000 (France), 41 of 12,011 (Spain), 37 of 17,500 (Italy), and 71 of 24,000 (Brazil) respondents self-reported a diagnosis of FE.**

Results: **Many respondents (U.S.A.: 56.2%; 5EU: 41.6%; Brazil + 5EU: 40.5%) reported persistent seizures (≥1 per year). Over 60% to just over 71% of respondents with FE were treated with antiepileptic drugs (AEDs). In the United States, seizure frequency was associated with hospitalizations, indirect costs (ages 18–60), and total direct costs. For the 5EU and Brazil + 5EU, seizure frequency was associated with physical QoL, health utilities, activity impairment, and emergency room (ER) visits. Additional associations were observed for the 5EU on hospitalizations, indirect costs (ages 18–60), ER visit costs, and total direct costs and for Brazil + 5EU on absenteeism, overall work impairment, and provider visits. Costing was not performed for Brazil + 5EU.**

Significance: **Around half of the patients had persistent seizures despite most taking an AED in this 2011–2013 dataset. The results support the hypothesis that reducing seizures can improve productivity and reduce resource utilization and associated costs. Regional differences may reflect differences in healthcare systems and selected patient populations. Overall, the results suggest that additional treatment options are needed to improve seizure control and reduce related costs.**

KEY WORDS: **Quality of life, Health utilities, Productivity, Costs, Resource utilization.**

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The objective of this study is to provide recent data in adult, focal-onset epilepsy (FE) patients regarding the relationship between seizure frequency and health outcomes (quality of life [QoL; including health utilities], productivity, indirect costs, healthcare resource utilization [HRU], and direct costs) in multiple Western populations where pharmacoeconomic modeling is required by reimbursement decision makers and these data are useful as model inputs.

Focal epilepsy comprises about 55.7–61.1% of the overall epilepsy patient population.[1,2] Whereas multiple studies have evaluated the relationship between seizure frequency and QoL,[3] most have done so in the overall adult epilepsy

Key Points

- The burden of focal epilepsy (FE) by seizure frequency was examined
- Quality of life and costs were assessed for FE patients in the United States, EU, and Brazil
- Up to 56% of patients reported experiencing one or more seizures per year
- As seizure frequency increased, productivity decreased and costs increased
- Regional differences were observed on the exact outcomes associated with seizure frequency

population or the population with temporal lobe epilepsy,[3] and few have evaluated FE as a whole.[4] Few data regarding a specific type of QoL known as a health utility are available for FE. Health utilities are a key parameter in economic evaluations.

No recent studies (since 2000) of the effect of seizure frequency on productivity or indirect costs were identified. A 2009 study of Chinese patients reported indirect costs by nonnumerical approximations of seizure frequency: seizure remission, occasional seizures, active non-drug-resistant epilepsy, and drug-resistant epilepsy.[5]

Few studies have examined direct costs by seizure frequency.[6–9] Most previous studies did not present data among FE patients by seizure frequency. Hence, current knowledge about how seizure frequency influences both indirect and direct costs among FE patients is limited.

Methods

Dataset and sample selection

The National Health and Wellness Survey (NHWS; www.kantarhealth.com) is a self-administered, cross-sectional general health survey of adults (aged 18 and older) in the United States (U.S.), five European Union countries (5EU; United Kingdom, Germany, France, Italy, and Spain), Brazil, China, Japan, and Russia. The NHWS is not an epilepsy-specific survey. This study focused on the U.S., 5EU, and Brazil datasets because of the pharmacoeconomic data requirements in these countries. The survey was initially translated from the original U.S. English to Germany German, France French, Italy Italian, Spain Spanish, and Brazil Portuguese by Transperfect (certified to ISO 9001:2008 and EN 15038:2006 standards). The U.S. English version was utilized in the United Kingdom. These translations were then reviewed and edited by Absolute Translations (certified to ISO 9001 standards), returned to Transperfect for further review and editing, tested with potential respondents, and further revised to obtain final versions.

Potential survey participants were identified using Lightspeed Research, a market research company, and its affiliates, who maintain a survey community that has agreed to receive invitations to participate in online surveys. Unique members are verified through their Internet Protocol addresses, and participants are limited to 12 surveys per year. In each country, a stratified random sampling framework was utilized to match potential respondents on age and gender to the distributions of the country. U.S. demographic distributions were obtained from the U.S. Census Bureau, and for all other countries, from the International Database of the U.S. Census Bureau. Additional stratifications for race/ethnicity distributions were performed for the United States. Additional details regarding data collection and sampling procedures are available from a similar companion study for idiopathic generalized epilepsy.[10] The NHWS study protocol was approved by Essex IRB (Lebanon, NJ, U.S.A.). Informed consent was obtained from all participants, and participants' privacy rights were observed at all times.

Data from multiple years (U.S.: 2011, 2012, and 2013; five European countries [5EU; France, Germany, Italy, Spain, and the United Kingdom]: 2011 and 2013 (5EU data not fielded in 2012); and Brazil: 2011 and 2012) were included in this analysis. Response rates for the NHWS in each region and year were as follows:

U.S.: 13.10% (2011; 572,738 invited), 7.24% (2012; 1,035,617 invited), and 6.34% (2013; 1,183,287 invited)

5EU: 17.22% (2011): 18.22% (France; 82,320 invited), 17.30% (Germany; 86,728 invited), 25.09% (Italy; 29,895 invited), 21.78% (Spain; 23,007 invited), and 13.40% (United Kingdom; 111,948 invited)

15.65% (2013): 18.6% (France; 80,619 invited), 14.06% (Germany; 106,685 invited), 16.00% (Italy; 62,499 invited), 14.57% (Spain; 48,036 invited), and 15.26% (United Kingdom; 98,284 invited)

Brazil: 4.17% (2011; 287,699 invited) and 4.00% (2012; 300,247 invited)

Participants were included in the current study if they self-reported a diagnosis of FE (responded to: "What type of epilepsy have you been diagnosed with?" and selected "Symptomatic Partial Epilepsy [Focal epilepsy, Temporal lobe epilepsy, Frontal lobe epilepsy]" or "Idiopathic Partial Epilepsy [Benign Focal Epilepsy of Childhood/BFEC]"). On the basis of affirmative responses to the aforementioned item, the study included final deduped FE sample sizes of n = 345 of 176,093 who completed the NHWS (2011–2013 U.S.), n = 257 (2011 and 2013 5EU: n = 73 of 30,000 [United Kingdom], n = 53 of 30,001 [Germany], n = 53 of 30,000 [France], n = 41 of 12,011 [Spain], and n = 37 of 17,500 [Italy]), and n = 71 of 24,000 (2011 and 2012 Brazil). Although most BFEC patients' seizures will remit prior to adulthood, these patients were included in the analysis because a disproportionally high number of respondents selected idiopathic partial epilepsy, indicating that patients possibly had difficulty distinguishing between symptomatic and idiopathic epilepsy. The full list of response options

was: "Idiopathic Generalized Epilepsy (Myoclonic seizures, Absence seizures, or Grand Mal seizures)," "Idiopathic Partial Epilepsy (Benign Focal Epilepsy of Childhood/BFEC)," "Symptomatic Generalized Epilepsy (West syndrome, Lennox-Gastaut syndrome)," "Symptomatic Partial Epilepsy (Focal Epilepsy, Temporal lobe epilepsy, Frontal lobe epilepsy)," and "Don't know." All options were mutually exclusive, and respondents could choose only one.

Measures

Seizure frequency

The NHWS asked respondents: "How often do you experience a seizure (more than once a week, once a week, two or three times a month, once a month, every 3 months, every 6 months, once a year, or less than once a year)?" The primary independent variable (seizure frequency categories: once a week or more, 1–3 times a month, 1–4 times a year, and less than once a year) was created from these response options.

Health and economic outcomes

QoL was measured by the Short Form (mix of SF-12v2 and SF-36v2) questionnaire. The Physical Component Summary (PCS) and Mental Component Summary (MCS) scores and health utility (SF-6D) scores are reported here. Productivity was measured by the Work Productivity and Activity Impairment—General Health (WPAI-GH) questionnaire. HRU was assessed by asking participants to report the number of healthcare provider visits, emergency room (ER) visits, and hospitalizations they had in the prior 6 months for their medical condition. The results reported here are prorated to 1 year. Indirect costs were calculated from these productivity measures using wage data for each country (U.S. and 5EU) and excluded patients who were not employed. In addition to this variable, another indirect cost variable that factored in unemployment as 100% absenteeism was created for patients ages 18–60. Further details on these measures, patient demographics, health characteristics, health outcomes, and costing methods are available in the companion study publication.[10]

Statistical analyses

Unadjusted analyses

Unadjusted analyses of the association between seizure frequency and health outcomes (MCS, PCS, health utilities, productivity [absenteeism, presenteeism, overall work impairment, and activity impairment], indirect costs, HRU [physician visits, ER visits, and hospitalizations], and direct costs) were conducted using chi-square tests for categorical variables and analysis of variance (ANOVA) tests for continuous variables for each region (U.S., 5EU, and Brazil + 5EU). A Bonferroni-adjusted threshold was applied to adjust for the repetitions of global tests across the three datasets, and a $p < 0.01667$ was considered significant and marked with two asterisks in Table 3.

Adjusted analyses

Adjusted analyses of the association between seizure frequency and health and economic outcomes were performed by adding covariates from a two-phase confounder selection process. Phase 1 of the confounder selection process involved selecting covariates (demographic and health characteristic variables) that were associated ($p < 0.20$) with seizure frequency based on the unadjusted results. Phase 2 involved assessing generalized linear models (GLMs) to further reduce the covariate list by selecting the covariates that were associated ($p < 0.20$) with each outcome variable among patients in the seizure frequency reference group.[11]

For phase 2, separate multivariable GLMs were created for the following dependent variables for the U.S. and 5EU datasets: MCS, PCS, health utilities, activity impairment, indirect costs, and direct costs. Covariates selected for the indirect cost models were utilized for the models of absenteeism, presenteeism, and overall work productivity. Covariates selected for the direct cost model were utilized for the models of the individual components of HRU. Because costing will not be performed for the Brazil + 5EU dataset, separate GLMs were created for all dependent variables.

The final adjusted analyses were performed for each health and economic outcome variable using a GLM in the total subject population with the following as independent variables: seizure frequency, age, gender, and variables with a $p < 0.20$ in phase 2 of the confounder selection process.

GLMs for QoL outcomes utilized a normal distribution with an identity link function. GLMs for productivity, activity impairment, HRU, and costs utilized a log link function and a negative binomial distribution. Standard errors were automatically adjusted for model dispersion.

Adjusted means were reported for each seizure frequency group using a maximum likelihood algorithm. Additionally, all the GLMs from the final adjusted analyses were re-run with the same exact set of covariates with seizure frequency treated as a continuous variable. The omnibus p values are reported for these models. Where seizure frequency (continuous variable) was associated with a given health outcome in the adjusted model, subsequent pairwise multiple comparisons were conducted: (1) between the lowest seizure frequency group (<1 seizure/year) and all other categories and (2) between the highest seizure frequency group (≥1 seizures/week) and all other categories. Bonferroni-adjusted thresholds were applied to p values in Table 4: (1) global tests were significant if $p < 0.01667$ given their repetition across three datasets and were marked with two asterisks; and (2) the five unique pairwise tests were significant if $p < 0.01$ and were marked with three asterisks.

Special considerations for the Brazilian dataset

Owing to the small sample size of the Brazilian dataset (n = 71), the Brazil and 5EU samples were compared on demographics and health characteristics to evaluate whether it would be reasonable to combine the two datasets for the purpose of estimating Brazilian outcomes (Table 1). A two-tailed $p < 0.05$ was considered statistically significant. Because minimal differences were identified, the above multivariable analyses were conducted for Brazil using a combined Brazil + 5EU dataset. However, because some differences were observed, the covariate selection process was performed separately for the Brazil + 5EU dataset rather than using the covariates selected for the 5EU dataset. No costing was performed on this combined dataset.

Results

The proportions reporting focal epilepsy out of the epilepsy patients were 21% U.S., 20% United Kingdom, 18% Germany, 22% France, 36% Spain, 41% Italy, and 41% Brazil.

Table 1 demonstrates the similarities between the 5EU and Brazil datasets on patient characteristics and outcomes. Patient characteristics appeared to be qualitatively different between the U.S. and other datasets (5EU, Brazil + 5EU) on certain estimates (Table 2). The distribution of seizure frequencies for the U.S. dataset appears flatter (15.9%, 19.7%, 20.6%, 43.8%) than do the distributions for the 5EU (9.3%, 9.7%, 22.6%, 58.4%) and Brazil + 5EU (8.5%, 9.8%, 22.3%, 59.5%) datasets. Regarding epilepsy characteristics, the U.S. dataset had at least 9% more patients reporting epilepsy duration of more than 30 years, at least 7% more reporting current AED use, and more patients reporting use of two or more AEDs. The proportion of patients with persistent seizures (>1 per year) among AED users was higher in the U.S. (66.4%) than the 5EU (53.0%) and Brazil + 5EU (52.3%) datasets (data not reported in tables). Individual AED use varied somewhat between regions (Table 2).

Unadjusted analyses by seizure frequency

Unadjusted analyses examining the relationship between seizure frequency and outcomes demonstrated statistically significant associations between seizure frequency and almost all evaluated outcomes for the 5EU (except provider visits) and Brazil + 5EU datasets. In the U.S. dataset, less than half of tested associations were statistically significant. Significant associations were observed for MCS, health utility, presenteeism, activity impairment, provider visits, total indirect costs, and total direct costs with seizure frequency (Table 3).

Adjusted analyses, including pairwise comparisons between seizure frequency categories

In the adjusted analyses for the U.S. dataset, seizure frequency was statistically significantly associated with MCS, presenteeism, overall work impairment, hospitalizations, total indirect costs, total indirect costs (ages 18–60), hospitalization costs, and total direct costs (Table 4). Pairwise comparisons, however, met Bonferroni thresholds for differences between the highest and lowest seizure frequency groups only for hospitalizations, indirect costs (ages 18–60), and direct costs.

It should be noted that differences between the two highest seizure frequency groups compared with the lowest seizure frequency group on the MCS met the minimally important difference (MID) threshold of 3.[12] Average total indirect costs (ages 18–60) were approximately $8,500 higher per person per year with one or more overall seizures per week compared to the reference group. Average total direct medical costs were $25,000 more per patient per year for patients with one or more overall seizures per week compared to the reference group (Table 4).

For the 5EU dataset, seizure frequency continued to be statistically significant for most outcomes after adjustments, with the exception of provider visits, presenteeism costs, and hospitalization costs (Table 4). Pairwise comparisons supported global associations for PCS, health utilities, activity impairment, ER visits, hospitalizations, indirect costs (ages 18–60), ER visit costs, and total direct costs.

All statistically significant differences on the MCS, PCS, and health utilities met their respective MID thresholds (3 for MCS, PCS and 0.041 for health utilities).[12,13] Total indirect costs (ages 18–60) were about 6,200 EUR more per patient per year for the highest seizure frequency group compared with the lowest. ER visit costs were about 180 EUR more per patient per year for the highest seizure frequency group compared with the lowest. Total direct medical costs were 1,200 EUR higher per patient per year for the highest seizure frequency group compared with the lowest (Table 4).

In the Brazil + 5EU adjusted analyses, seizure frequency was statistically significantly associated with all outcomes (Table 4). The results of the pairwise comparisons were similar to those of the 5EU dataset with the exception of absenteeism, overall work impairment, and provider visits. For this dataset, both of the two highest seizure frequency groups reached the Bonferroni threshold ($p < 0.01$) when comparing against the lowest seizure frequency group on PCS, health utilities, absenteeism, and activity impairment. Overall work impairment, provider visits, and ER visits reached the Bonferroni threshold in showing a difference between the highest and lowest seizure frequency groups. Statistically significant differences on the MCS, PCS, and health utilities met their respective MID thresholds (3 for MCS, PCS and 0.041 for health utilities).[12,13]

Discussion

The NHWS self-reported epilepsy prevalence is fairly close to physician-diagnosed values in the literature

Table 1. Evaluation of whether 5EU and Brazilian data can be combined for FE

	Total (N = 328)	5EU FE (N = 257)	Brazil FE (N = 71)	p Value
Age (years)—mean ± SD	42.61 ± 14.00	44.14 ± 14.30	37.10 ± 11.33	<0.001
Female (%)	159 (48.48)	125 (48.64)	34 (47.89)	0.911
Married/living with partner (%)	193 (58.84)	149 (57.98)	44 (61.97)	0.545
College educated (%)	117 (35.67)	81 (31.52)	36 (50.70)	0.003
Employed (%)	195 (59.45)	143 (55.64)	52 (73.24)	0.008
Retired (%)	40 (12.20)	35 (13.62)	5 (7.04)	0.134
Long-term disability (%)	24 (7.32)	23 (8.95)	1 (1.41)	0.031
Body mass index				
Underweight (%)	15 (4.57)	10 (3.89)	5 (7.04)	0.712
Normal weight (%)	141 (42.99)	109 (42.41)	32 (45.07)	
Overweight (%)	101 (30.79)	81 (31.52)	20 (28.17)	
Obese (%)	69 (21.04)	55 (21.40)	14 (19.72)	
Decline to provide weight (%)	2 (0.61)	2 (0.78)	0 (0.00)	
Drink alcohol (%)	217 (66.16)	175 (68.09)	42 (59.15)	0.159
Smoking behavior				
Nonsmoker (%)	144 (43.90)	111 (43.19)	33 (46.48)	0.258
Former smoker (%)	95 (28.96)	71 (27.63)	24 (33.80)	
Current smoker (%)	89 (27.13)	75 (29.18)	14 (19.72)	
Exercise (%)	193 (58.84)	155 (60.31)	38 (53.52)	0.303
Charlson comorbidity index—mean ± SD	0.85 ± 2.30	0.82 ± 2.39	0.97 ± 1.99	0.626
Length of time diagnosed with epilepsy				
0–5 years (%)	58 (17.68)	49 (19.07)	9 (12.68)	0.827
6–10 years (%)	35 (10.67)	32 (12.45)	3 (4.23)	
11–15 years (%)	48 (14.63)	35 (13.62)	13 (18.31)	
16–19 years (%)	22 (6.71)	18 (7.00)	4 (5.63)	
20–30 years (%)	73 (22.26)	53 (20.62)	20 (28.17)	
31 years or greater (%)	92 (28.05)	70 (27.24)	22 (30.99)	
Using a prescription medication of epilepsy (%)	199 (60.67)	166 (64.59)	33 (46.48)	0.006
Total number of epilepsy prescriptions				
None (%)	129 (39.33)	91 (35.41)	38 (53.52)	0.016
One medication (%)	137 (41.77)	115 (44.75)	22 (30.99)	
Two medications (%)	42 (12.80)	37 (14.40)	5 (7.04)	
Three or more medications (%)	20 (6.10)	14 (5.45)	6 (8.45)	
MCS—mean ± SD	41.79 ± 11.06	41.60 ± 11.12	42.48 ± 10.91	0.554
PCS—mean ± SD	46.95 ± 9.86	46.62 ± 10.26	48.16 ± 8.21	0.244
Health utility—mean ± SD	0.65 ± 0.13	0.66 ± 0.13	0.64 ± 0.11	0.256
Absenteeism[a,b] (%)—mean ± SD	8.16 ± 20.75	7.80 ± 20.51	9.16 ± 21.60	0.693
Presenteeism[a,b] (%)—mean ± SD	26.01 ± 28.96	26.34 ± 29.21	25.10 ± 28.51	0.798
Overall work impairment[a,b] (%)—mean ± SD	30.28 ± 32.46	30.68 ± 32.76	29.14 ± 31.90	0.776
Activity impairment[b] (%)—mean ± SD	34.09 ± 31.88	36.34 ± 32.49	25.92 ± 28.31	0.014
Healthcare provider visits in past 6—mean ± SD months	7.69 ± 8.15	7.69 ± 8.36	7.68 ± 7.41	0.988
ER visits in the past 6 months—mean ± SD	0.53 ± 1.19	0.42 ± 0.95	0.93 ± 1.75	0.001
Hospitalizations in the past 6 months—mean ± SD	0.29 ± 0.69	0.27 ± 0.64	0.37 ± 0.83	0.288

ER, emergency room; FE, focal epilepsy; MCS, Mental Component Summary; PCS, Physical Component Summary; SD, standard deviation.

Overall p values are provided indicating at least one group is different from another. Lower scores on MCS, 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 (0–100%).

[a]Includes only employed respondents.

[b]Productivity measures are derived from the Work Productivity and Activity Impairment (WPAI).

(NHWS vs. NHWS sans "Don't Know" vs. literature [per 1,000]: U.S. 9.1 vs. 6.5 vs. 7.1, United Kingdom 12.2 vs. 8.3 vs. 8.6, Germany 10.0 vs. 5.4 vs. 9.1, France 8.2 vs. 5.0 vs. 5.4, Spain 9.5 vs. 6.2 vs. 4.8, Italy 5.2 vs. 3.7 vs. 4.6, and Brazil 7.3 vs. 4.5 vs. 10.7).[1,14–19] This is consistent with studies that indicate that self-reporting in epilepsy is typically reliable.[20]

Publications from physician-diagnosed, epilepsy studies report that FE comprises 61.1% and 55.7% of the total epilepsy population.[1,2] Among patients who knew their seizure type and etiology (i.e., removing the Don't Know patients), 30% (U.S.), 29% (United Kingdom), 33% (Germany), 36% (France), 55% (Spain), 57% (Italy), and 66% (Brazil) reported FE. Because the overall epilepsy estimates are close to the literature, it is possible that some FE patients with secondarily generalized seizures (SGSs) classified themselves as idiopathic generalized epilepsy (IGE) or "Don't Know." The proportions reporting IGE out of the

Table 2. Patient characteristics for FE

	U.S. values (N = 345)	5EU values (N = 257)	Brazil + 5EU values (N = 328)
Age (years)—mean ± SD	46.63 ± 15.17	44.14 ± 14.30	42.61 ± 14.00
Female (%)	185 (53.62)	125 (48.64)	159 (48.48)
Race/ethnicity			
Non-Hispanic white (%)	268 (77.68)	N/A	N/A
Non-Hispanic black (%)	24 (6.96)	N/A	N/A
Hispanic (%)	24 (6.96)	N/A	N/A
Other ethnicity (%)	29 (8.41)	N/A	N/A
Married/living with partner (%)	182 (52.75)	149 (57.98)	193 (58.84)
College educated (%)	135 (39.13)	81 (31.52)	117 (35.67)
Annual household income			
<$25K, <€20K/<£20K, <R$ 1,000 (%)	107 (31.01)	90 (35.02)	101 (30.79)
$25K–<$50K, €20–<50K/£20–<40K, R$ 1,001–R$ 6,500 (%)	107 (31.01)	106 (41.25)	132 (40.24)
$50K–<$75K, €50K+/£40K+, R$ 6,501+ (%)	57 (16.52)	34 (13.23)	62 (18.90)
$75K+ (%)	58 (16.81)	N/A	N/A
Decline to answer (%)	16 (4.64)	27 (10.51)	33 (10.06)
Employed (%)	155 (44.93)	143 (55.64)	195 (59.45)
Retired (%)	65 (18.84)	35 (13.62)	40 (12.20)
Long-term disability (%)	51 (14.78)	23 (8.95)	24 (7.32)
Insured (%)	292 (84.64)	N/A	N/A
Body mass index			
Underweight (%)	2 (0.58)	10 (3.89)	15 (4.57)
Normal weight (%)	133 (38.55)	109 (42.41)	141 (42.99)
Overweight (%)	87 (25.22)	81 (31.52)	101 (30.79)
Obese (%)	117 (33.91)	55 (21.40)	69 (21.04)
Decline to provide weight (%)	6 (1.74)	2 (0.78)	2 (0.61)
Consume alcohol (%)	182 (52.75)	175 (68.09)	217 (66.16)
Smoking behavior			
Nonsmoker (%)	183 (53.04)	111 (43.19)	144 (43.90)
Former smoker (%)	87 (25.22)	71 (27.63)	95 (28.96)
Current smoker (%)	75 (21.74)	75 (29.18)	89 (27.13)
Exercise (%)	222 (64.35)	155 (60.31)	193 (58.84)
Charlson comorbidity index—mean ± SD	0.85 ± 2.20	0.82 ± 2.39	0.85 ± 2.30
Length of time diagnosed with epilepsy			
0–5 years (%)	47 (13.62)	49 (19.07)	58 (17.68)
6–10 years (%)	47 (13.62)	32 (12.45)	35 (10.67)
11–15 years (%)	41 (11.88)	35 (13.62)	48 (14.63)
16–19 years (%)	26 (7.54)	18 (7.00)	22 (6.71)
20–30 years (%)	55 (15.94)	53 (20.62)	73 (22.26)
31 years or greater (%)	129 (37.39)	70 (27.24)	92 (28.05)
Using a prescription medication for epilepsy (%)	247 (71.59)	166 (64.59)	199 (60.67)
Total number of epilepsy prescriptions			
None (%)	98 (28.41)	91 (35.41)	129 (39.33)
One medication (%)	146 (42.32)	115 (44.75)	137 (41.77)
Two medications (%)	73 (21.16)	37 (14.40)	42 (12.80)
Three or more medications (%)	28 (8.12)	14 (5.45)	20 (6.10)
Antiepileptic medications (among those treating)			
Acetazolamide (%)	NR	NR	NR
Alprazolam (%)	0.00%	0.00%	1 (0.50)
Carbamazepine (%)	45 (18.22)	38 (22.89)	51 (25.63)
Clobazam (%)	NR	3 (1.81)	3 (1.51)
Clonazepam (%)	NR	6 (3.61)	8 (4.02)
Diazepam (%)	NR	NR	NR
Eslicarbazepine (%)	NR	NR	NR
Ethosuximide (%)	NR	NR	NR
Felbamate (%)	0.00%	1 (0.60)	1 (0.50)
Gabapentin (%)	12 (4.86)	6 (3.61)	7 (3.52)
Gamibetal (%)	NR	NR	NR
Lacosamide (%)	16 (6.48)	3 (1.81)	3 (1.51)
Lamotrigine (%)	66 (26.72)	35 (21.08)	42 (21.11)

Continued

Table 2. Continued.

	U.S. values (N = 345)	5EU values (N = 257)	Brazil + 5EU values (N = 328)
Levetiracetam (%)	73 (29.55)	37 (22.29)	37 (18.59)
Lorazepam (%)	NR	NR	NR
Oxcarbazepine (%)	26 (10.53)	8 (4.82)	14 (7.04)
Perampanel (%)	1 (0.40)	NR	NR
Phenobarbital (%)	NR	7 (4.22)	7 (3.52)
Phenytoin (%)	35 (14.17)	9 (5.42)	9 (4.52)
Pregabalin (%)	10 (4.05)	3 (1.81)	3 (1.51)
Primidone (%)	NR	NR	NR
Retigabine (%)	1 (0.40)	1 (0.60)	1 (0.50)
Rufinamide (%)	5 (2.02)	NR	NR
Stiripentol (%)	0.00%	1 (0.60)	1 (0.50)
Tiagabine (%)	4 (1.62)	2 (1.20)	2 (1.01)
Topiramate (%)	30 (12.15)	17 (10.24)	23 (11.56)
Valproate (%)	28 (11.34)	26 (15.66)	30 (15.08)
Vigabatrin (%)	2 (0.81)	0.00%	0.00%
Zonisamide (%)	20 (8.10)	5 (3.01)	5 (2.51)

FE, focal epilepsy; N/A, not applicable because these data were not collected; NR, not reported.

epilepsy patients were 49% U.S., 47% United Kingdom, 35% Germany, 35% France, 27% Spain, 24% Italy, and 20% Brazil. Physician-diagnosed estimates in the literature indicate that IGE should be 16% of the epilepsy population.[2] The proportions reporting "Don't Know" in the NHWS were 29% U.S., 32% United Kingdom, 46% Germany, 39% France, 35% Spain, 29% Italy, and 38% Brazil. Thus, reported outcomes may reflect a conservative or minimal estimate of the burden experienced by FE patients if there is a higher proportion of focal without SGSs in our FE population. A comparison with published epilepsy costs for the 5EU (adjusted for inflation), do suggest that our 5EU cost estimates are within range of individual country estimate (Table 5). The impact on the cost estimates is difficult to estimate and ranges between some country publications were fairly wide.

It is also interesting to note that the U.S. dataset had the lowest FE proportion out of the datasets analyzed (possibly the fewest FE with SGSs) and demonstrated a seizure frequency association with outcomes in less than half of the associations tested. The EU dataset had a mix of low (United Kingdom 29%) and higher (Italy 57%) FE proportions and demonstrated an association with all but three outcomes tested. Combining the Brazil (FE 66%) and 5EU datasets resulted in showing an association with all outcomes tested. The results appear to support the hypothesis that SGSs drive more associations with seizure frequency and outcomes.

Self-reporting of seizure frequencies is the standard for clinical trials. A limitation of this is that absence seizures and seizures occurring during sleep may be underreported. However, focal seizures and other generalized seizures would be captured for all other time periods. Partial seizures are often more frequent than SGSs and may quickly add to the total seizure count, but SGSs may have a larger impact on QoL, productivity, and HRU. This study did not collect seizure frequency separately for each seizure type. However, as discussed earlier, the variation in FE proportion across datasets (a proxy for SGS) provides insight into the importance of SGSs in demonstrating an association between seizure frequency and outcomes.

Epilepsy patient proportions reporting <1 seizure per year were 44% (U.S.), 58% (5EU), and 59% (5EU + Brazil). Data were not collected on total lifetime AED use; however, these values are close to those reported in a prior study of newly diagnosed patients showing seizure freedom rates of 49.5% with the first regimen and 13.3% with the second regimen (total: 62.8% seizure free by second regimen).[21] Thus, NHWS percentages may be consistent with patients who have tried fewer cumulative regimens. Conversely, NHWS data indicate the following persistent seizures rates: 56% (U.S.), 42% (5EU), and 41% (5EU + Brazil). These are consistent with other research for epilepsy patients on monotherapy regimens[22] and patients treated with multiple AEDs.[23,24]

Previous studies have demonstrated an association between SF-36 domain scores and having any seizures.[4,25–27] On the basis of pairwise comparisons, MCS results for all three datasets are consistent with studies in patients with uncontrolled seizures (studies lacking a seizure-free group) that found no relationship between seizure frequency and QoL,[28–30] whereas PCS and health utility results for the 5EU and Brazil + 5EU datasets supported a relationship. Differences in some of the results between this study and others may result from the use of the SF-36v2. Interestingly, studies that did not find an association used epilepsy-specific QoL scales. The differences observed between regions on the PCS and health utility results may be due to the differences in regions in FE proportions (a potential proxy for SGS).

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Table 3. Unadjusted outcomes values by seizure frequency group for FE

	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
U.S.						
Sample size (%)	345 (100)	55 (15.9)	68 (19.7)	71 (20.6)	151 (43.8)	
MCS—mean ± SD	44.68 ± 11.37	40.30 ± 12.23	42.01 ± 11.79	44.33 ± 8.67	47.65 ± 11.23	<0.001**
PCS—mean ± SD	46.79 ± 10.71	44.94 ± 11.08	45.60 ± 10.54	47.17 ± 11.32	47.82 ± 10.30	0.267
Health utility—mean ± SD	0.67 ± 0.14	0.63 ± 0.14	0.65 ± 0.15	0.67 ± 0.13	0.70 ± 0.14	0.006**
Absenteeism[a,b] (%)—mean ± SD	6.33 ± 18.07	11.68 ± 25.60	11.82 ± 21.82	6.72 ± 16.48	3.16 ± 14.58	0.111
Presenteeism[a,b] (%)—mean ± SD	24.38 ± 27.69	34.44 ± 32.03	36.36 ± 36.97	28.48 ± 27.51	16.44 ± 20.64	0.003**
Overall work impairment[a,b] (%)—mean ± SD	26.82 ± 30.37	40.32 ± 34.78	38.59 ± 39.24	30.78 ± 30.91	18.14 ± 22.92	0.003**
Activity impairment[b] (%)—mean ± SD	37.25 ± 32.59	48.00 ± 35.61	44.71 ± 33.88	38.87 ± 29.26	29.21 ± 30.54	<0.001**
Healthcare provider visits in past 6 months—mean ± SD	5.88 ± 8.28	8.87 ± 15.59	6.51 ± 7.50	5.69 ± 6.06	4.60 ± 4.73	0.010**
ER visits in the past 6 months—mean ± SD	0.66 ± 2.36	1.35 ± 3.87	0.91 ± 3.26	0.55 ± 1.79	0.35 ± 0.90	0.042
Hospitalizations in the past 6 months—mean ± SD	0.56 ± 2.48	1.24 ± 3.87	0.90 ± 3.33	0.52 ± 2.57	0.18 ± 0.59	0.030
Absenteeism costs[a,b] ($)—mean ± SD	1629.15 ± 6218.83	3545.33 ± 8803.34	1901.53 ± 3249.42	996.33 ± 2783.45	1329.83 ± 7118.04	0.507
Presenteeism costs[a,b] ($)—mean ± SD	6555.67 ± 8941.83	9917.84 ± 11447.82	6765.69 ± 8578.83	6461.60 ± 8910.81	5704.59 ± 8351.00	0.362
Total indirect costs[a,b] ($)—mean ± SD	8095.63 ± 11665.55	12941.18 ± 12667.41	8667.22 ± 10247.33	7457.93 ± 10155.36	6957.33 ± 12284.12	0.249
Total indirect costs[b] (age 18–60) ($)—mean ± SD	24247.30 ± 18107.30	28526.79 ± 15302.04	29921.28 ± 16226.06	22268.48 ± 19076.71	20852.01 ± 18697.40	0.005**
Provider visit costs ($)—mean ± SD	14651.60 ± 22160.55	22712.51 ± 43634.27	15175.26 ± 15681.02	13824.00 ± 16020.40	11868.82 ± 13384.21	0.020
ER visit costs ($)—mean ± SD	1903.86 ± 6615.47	3858.58 ± 10783.52	2621.06 ± 9093.04	1598.79 ± 5070.60	1012.33 ± 2663.71	0.036
Hospitalization costs ($)—mean ± SD	16599.12 ± 66924.96	37141.96 ± 109543.2	24189.62 ± 85064.05	13998.34 ± 61264.98	6921.28 ± 26265.43	0.025
Total direct costs ($)—mean ± SD	33154.58 ± 83305.53	63713.05 ± 147697.1	41985.94 ± 94603.80	29421.13 ± 71529.30	19802.44 ± 33361.65	0.006**
5EU						
Sample size (%)	257 (100)	24 (9.3)	25 (9.7)	58 (22.6)	150 (58.4)	
MCS—mean ± SD	41.60 ± 11.12	37.37 ± 10.36	40.24 ± 7.99	38.02 ± 9.98	43.88 ± 11.58	<0.001**
PCS—mean ± SD	46.62 ± 10.26	39.67 ± 8.05	38.26 ± 10.21	46.18 ± 9.16	49.29 ± 9.76	<0.001**
Health utility—mean ± SD	0.66 ± 0.13	0.57 ± 0.10	0.59 ± 0.11	0.62 ± 0.11	0.70 ± 0.13	<0.001**
Absenteeism[a,b] (%)—mean ± SD	7.80 ± 20.51	39.80 ± 42.27	24.75 ± 38.77	5.91 ± 11.77	2.29 ± 7.23	<0.001**
Presenteeism[a,b] (%)—mean ± SD	26.34 ± 29.21	51.25 ± 35.63	53.00 ± 27.10	34.69 ± 30.05	17.62 ± 24.38	<0.001**
Overall work impairment[a,b] (%)—mean ± SD	30.68 ± 32.76	65.40 ± 39.80	66.50 ± 24.19	36.97 ± 32.04	19.04 ± 25.60	<0.001**
Activity impairment[b] (%)—mean ± SD	36.34 ± 32.49	66.25 ± 23.56	59.60 ± 28.50	41.55 ± 29.61	25.67 ± 30.02	<0.001**
Healthcare provider visits in past 6 months—mean ± SD	7.69 ± 8.36	11.21 ± 8.11	9.32 ± 9.53	8.24 ± 7.95	6.65 ± 8.21	0.049
ER visits in the past 6 months—mean ± SD	0.42 ± 0.95	1.17 ± 1.76	0.92 ± 1.50	0.40 ± 0.79	0.23 ± 0.56	<0.001**
Hospitalizations in the past 6 months—mean ± SD	0.27 ± 0.64	0.67 ± 0.82	0.60 ± 1.08	0.22 ± 0.53	0.17 ± 0.50	<0.001**
Absenteeism costs[a,b] (€)—mean ± SD	1629.14 ± 5217.39	6422.86 ± 8203.55	6474.80 ± 12707.11	1242.25 ± 3151.49	513.61 ± 2245.91	<0.001**
Presenteeism costs[a,b] (€)—mean ± SD	4229.84 ± 5490.46	5106.43 ± 6213.36	10253.74 ± 6129.50	6168.93 ± 6693.58	2690.53 ± 3993.40	<0.001**
Total indirect costs[a,b] (€)—mean ± SD	5736.38 ± 7435.18	10508.01 ± 8401.32	15019.58 ± 10414.17	7411.18 ± 7903.22	3204.14 ± 4808.22	<0.001**
Total indirect costs[b] (age 18–60) (€)—mean ± SD	11178.69 ± 8712.33	15964.05 ± 6366.01	16439.21 ± 8535.06	12365.81 ± 8458.23	8980.79 ± 8500.57	<0.001**
Provider visit costs (€)—mean ± SD	458.84 ± 539.04	709.30 ± 423.28	572.73 ± 673.08	540.58 ± 611.61	368.19 ± 482.02	0.007**
ER visit costs (€)—mean ± SD	98.22 ± 234.45	294.85 ± 428.54	225.56 ± 382.32	84.13 ± 195.23	50.99 ± 129.20	<0.001**
Hospitalization costs (€)—mean ± SD	593.03 ± 1462.47	1275.80 ± 1509.98	1450.83 ± 2795.29	554.37 ± 1330.46	355.77 ± 1063.59	<0.001**

Continued

Table 3. Continued.

	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
Total direct costs (€)—mean ± SD	1150.10 ± 1839.05	2279.95 ± 2035.68	2249.12 ± 3453.65	1179.09 ± 1489.23	774.95 ± 1360.60	<0.001**
Brazil + 5EU						
Sample size (%)	328 (100)	28 (8.5)	32 (9.8)	73 (22.3)	195 (59.5)	
MCS—mean ± SD	41.79 ± 11.06	37.78 ± 9.78	41.73 ± 9.34	37.61 ± 9.83	43.94 ± 11.39	<0.001**
PCS—mean ± SD	46.95 ± 9.86	40.85 ± 8.24	41.14 ± 10.99	45.73 ± 8.74	49.24 ± 9.49	<0.001**
Health utility—mean ± SD	0.65 ± 0.13	0.57 ± 0.10	0.61 ± 0.12	0.61 ± 0.10	0.69 ± 0.13	<0.001**
Absenteeism[a,b] (%)—mean ± SD	8.16 ± 20.75	41.50 ± 43.96	19.00 ± 33.62	7.13 ± 13.86	3.39 ± 11.30	<0.001**
Presenteeism[a,b] (%)—mean ± SD	26.01 ± 28.96	50.00 ± 33.54	42.00 ± 30.05	35.56 ± 31.08	18.25 ± 24.61	<0.001**
Overall work impairment[a,b] (%)—mean ± SD	30.28 ± 32.46	66.17 ± 38.25	53.65 ± 31.74	37.98 ± 33.13	19.88 ± 26.02	<0.001**
Activity impairment[b] (%)—mean ± SD	34.09 ± 31.88	61.79 ± 25.68	50.63 ± 31.92	41.64 ± 30.09	24.56 ± 29.22	<0.001**
Healthcare provider visits in past 6 months—mean ± SD	7.69 ± 8.15	12.07 ± 8.82	8.47 ± 8.94	8.15 ± 7.69	6.76 ± 7.91	0.01**
ER visits in the past 6 months—mean ± SD	0.53 ± 1.19	1.07 ± 1.68	1.00 ± 1.57	0.62 ± 1.32	0.34 ± 0.91	<0.001**
Hospitalizations in the past 6 months—mean ± SD	0.29 ± 0.69	0.61 ± 0.79	0.69 ± 1.18	0.26 ± 0.55	0.19 ± 0.57	<0.001**

ER, emergency room; FE, focal epilepsy; MCS, Mental Component Summary; PCS, Physical Component Summary; SD, standard deviation.

Overall p values are provided indicating at least one group is different from another. Lower scores on MCS, 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 (0–100%).

[a]Includes only employed respondents.

[b]Productivity measures are derived from the Work Productivity and Activity Impairment (WPAI).

**Statistical significance at the Bonferroni threshold ($p < 0.01667$).

Table 4. Adjusted outcomes values and pairwise comparisons between seizure frequency group for FE

	Parameter	≥1 seizures/week	1–3 seizures/month	1–4 seizures/year	<1 seizure/year	Overall p value
U.S. outcomes values						
MCS	LSMeans (CI)	42.29 (39.48, 45.11)	42.54 (40.05, 45.03)	44.83 (42.38, 47.27)	46.45 (44.76, 48.15)	
	Pairwise p value	0.0146	0.0119	0.2883	Reference	0.0028**
	Pairwise p value	Reference	0.8957	0.1836	0.0146	
PCS	LSMeans (CI)	46.9 (44.3, 49.51)	45.83 (43.54, 48.12)	46.83 (44.6, 49.07)	47.16 (45.61, 48.71)	
	Pairwise p value	0.8701	0.3492	0.8156	Reference	0.5932
	Pairwise p value	Reference	0.5428	0.9688	0.8701	
Health utilities	LSMeans (CI)	0.66 (0.63, 0.7)	0.65 (0.62, 0.69)	0.68 (0.65, 0.71)	0.69 (0.66, 0.71)	
	Pairwise p value	0.3012	0.1167	0.655	Reference	0.1372
	Pairwise p value	Reference	0.7232	0.5727	0.3012	
Absenteeism %[a,b]	LSMeans (CI)	11.54 (2.65, 50.33)	13.89 (3.05, 63.28)	4.79 (1.17, 19.62)	3.1 (1.21, 7.91)	
	Pairwise p value	0.1562	0.1344	0.6594	Reference	0.0639
	Pairwise p value	Reference	0.8577	0.3823	0.1562	
Presenteeism %[a,b]	LSMeans (CI)	34.68 (20.15, 59.67)	34.61 (21.05, 56.92)	25.72 (16.95, 39.02)	16.97 (12.87, 22.36)	
	Pairwise p value	0.022	0.0162	0.112	Reference	0.0047**
	Pairwise p value	Reference	0.996	0.400	0.022	
Overall work impairment %[a,b]	LSMeans (CI)	40 (23.85, 67.09)	36.82 (22.47, 60.35)	26.58 (17.52, 40.3)	18.67 (14.24, 24.47)	
	Pairwise p value	0.0109	0.0207	0.174	Reference	0.0029**
	Pairwise p value	Reference	0.8181	0.2317	0.0109	
Activity impairment %[b]	LSMeans (CI)	38.53 (29.67, 50.04)	38.21 (30.36, 48.09)	36.88 (29.49, 46.13)	29.39 (25.04, 34.49)	
	Pairwise p value	0.0944	0.0758	0.1115	Reference	0.0527
	Pairwise p value	Reference	0.9612	0.8036	0.0944	
Provider visits	LSMeans (CI)	6.87 (5.15, 9.16)	5.64 (4.33, 7.35)	5.22 (4.03, 6.76)	4.77 (3.97, 5.73)	
	Pairwise p value	0.0399	0.3168	0.583	Reference	0.0411
	Pairwise p value	Reference	0.3149	0.1628	0.0399	
ER visits	LSMeans (CI)	0.78 (0.43, 1.41)	0.45 (0.25, 0.81)	0.32 (0.17, 0.59)	0.36 (0.23, 0.55)	
	Pairwise p value	0.0417	0.5551	0.7707	Reference	0.0447
	Pairwise p value	Reference	0.1808	0.0412	0.0417	
Hospitalizations	LSMeans (CI)	0.71 (0.37, 1.39)	0.35 (0.18, 0.69)	0.16 (0.08, 0.35)	0.16 (0.09, 0.29)	
	Pairwise p value	0.001***	0.0906	0.992	Reference	0.0005**
	Pairwise p value	Reference	0.1328	0.0039***	0.001***	
Absenteeism costs[a,b] ($)	LSMeans (CI)	4345.02 (1029.38, 18,340)	3060.29 (776.3, 12,064)	1223.17 (286.06, 5230.18)	735.26 (295.5, 1829.45)	
	Pairwise p value	0.0586	0.1064	0.6198	Reference	0.0231
	Pairwise p value	Reference	0.7219	0.1796	0.0586	
Presenteeism costs[a,b] ($)	LSMeans (CI)	10127 (5466.08, 18,762)	6862.87 (3900.37, 12,076)	6057.41 (3775.98, 9717.27)	5014.53 (3686.98, 6820.06)	
	Pairwise p value	0.0469	0.3438	0.5146	Reference	0.0401
	Pairwise p value	Reference	0.3531	0.2002	0.0468	
Total indirect costs[a,b] ($)	LSMeans (CI)	12,929 (7041.31, 23,740)	8946.54 (5017.33, 15,953)	6775.22 (4189.37, 10,957)	5715.46 (4178.22, 7818.29)	
	Pairwise p value	0.0206	0.1878	0.5666	Reference	0.0135**
	Pairwise p value	Reference	0.3812	0.1028	0.0205	
Total indirect costs[b] (age 18–60) ($)	LSMeans (CI)	28,079 (22,522, 35,008)	29,291 (23,894, 35,907)	20,687 (16,971, 25,218)	19,570 (17,022, 22,499)	
	Pairwise p value	0.0067***	0.0014***	0.6532	Reference	0.0004**
	Pairwise p value	Reference	0.7826	0.0434	0.0067***	

Continued

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Table 4. Continued.

	Parameter	≥1 seizures/week	1–3 seizures/month	1–4 seizures/year	<1 seizure/year	Overall p value
Provider visit costs ($)	LSMeans (CI)	16,400 (12,076, 22,272)	13,243 (10,057, 17,439)	12,545 (9625.88, 16,350)	11,486 (9533.83, 13,838)	
	Pairwise p value	0.0564	0.412	0.5949	Reference	0.0637
	Pairwise p value	Reference	0.3014	0.1955	0.0564	
ER visit costs ($)	LSMeans (CI)	2163.77 (1060.78, 4413.67)	1287.14 (689.67, 2402.21)	1080.23 (581.87, 2005.4)	951.98 (617.49, 1467.68)	
	Pairwise p value	0.0626	0.4486	0.7477	Reference	0.0661
	Pairwise p value	Reference	0.2716	0.1519	0.0626	
Hospitalization costs ($)	LSMeans (CI)	22,402 (8910.45, 56,321)	10,876 (4774.05, 24,779)	5650.54 (2557.63, 12,484)	5402.23 (3059.23, 9539.69)	
	Pairwise p value	0.0124	0.1917	0.9299	Reference	0.0073**
	p value	Reference	0.2453	0.0284	0.0124	
Total direct costs ($)	LSMeans (CI)	43,708 (28,420, 67,219)	28,978 (19,665, 42,701)	20,943 (14,497, 30,257)	18,600 (14,319, 24,162)	
	Pairwise p value	0.0012***	0.0723	0.6079	Reference	0.0008**
	Pairwise p value	Reference	0.1583	0.0115	0.0012***	
5EU outcomes values						
MCS	LSMeans (CI)	38.48 (34.3, 42.67)	40.16 (35.95, 44.38)	37.96 (35.26, 40.67)	43.74 (42.05, 45.43)	
	Pairwise p value	0.0231	0.1266	0.0004***	Reference	0.0033**
	Pairwise p value	Reference	0.5792	0.837	0.0231	
PCS	LSMeans (CI)	40.66 (37.01, 44.31)	39.62 (36.07, 43.17)	46 (43.7, 48.29)	48.97 (47.51, 50.43)	
	Pairwise p value	<0.0001***	<0.0001***	0.0364	Reference	<0.0001**
	Pairwise p value	Reference	0.6851	0.0129	<0.0001***	
Health utilities	LSMeans (CI)	0.58 (0.53, 0.62)	0.6 (0.55, 0.64)	0.62 (0.59, 0.65)	0.7 (0.68, 0.72)	
	Pairwise p value	<0.0001***	0.0001***	<0.0001***	Reference	<0.0001**
	Pairwise p value	Reference	0.5908	0.1225	<0.0001***	
Absenteeism %[a,b]	LSMeans (CI)	21.6 (3.45, 135.28)	28.77 (5.1, 162.34)	4.78 (1.77, 12.92)	2.1 (1.1, 3.98)	
	Pairwise p value	0.0252	0.009***	0.1976	Reference	0.0087**
	Pairwise p value	Reference	0.8061	0.1492	0.0252	
Presenteeism %[a,b]	LSMeans (CI)	51.79 (20.58, 130.3)	38.82 (16.11, 93.52)	33.81 (20.9, 54.68)	17.78 (13.16, 24.01)	
	Pairwise p value	0.0349	0.1155	0.0379	Reference	0.0127**
	Pairwise p value	Reference	0.6512	0.4086	0.0349	
Overall work impairment %[a,b]	LSMeans (CI)	59.18 (26.5, 132.16)	55.86 (25.74, 121.22)	36.12 (22.9, 56.97)	19.31 (14.41, 25.87)	
	Pairwise p value	0.0133	0.0177	0.0341	Reference	0.0031**
	Pairwise p value	Reference	0.9153	0.279	0.0133	
Activity impairment %[b]	LSMeans (CI)	62.34 (41.97, 92.58)	53.52 (36, 79.56)	40.8 (31.63, 52.63)	24.15 (20.59, 28.33)	
	Pairwise p value	<0.0001***	0.0003***	0.0007***	Reference	<0.0001**
	Pairwise p value	Reference	0.5945	0.0768	<0.0001***	
Provider visits	LSMeans (CI)	10.13 (6.58, 15.61)	8.11 (5.21, 12.62)	8.09 (6.1, 10.73)	6.23 (5.21, 7.46)	
	Pairwise p value	0.0422	0.2832	0.1292	Reference	0.022
	Pairwise p value	Reference	0.4807	0.3912	0.0422	
ER visits	LSMeans (CI)	0.99 (0.53, 1.86)	0.77 (0.41, 1.47)	0.37 (0.22, 0.62)	0.23 (0.16, 0.34)	
	Pairwise p value	0.0001***	0.0017***	0.1729	Reference	<0.0001**

Continued

Table 4. Continued.

	Parameter	≥1 seizures/week	1–3 seizures/month	1–4 seizures/year	<1 seizure/year	Overall p value
	Pairwise p value	Reference	0.5804	0.015	0.0001***	
Hospitalizations	LSMeans (CI)	0.53 (0.26, 1.05)	0.42 (0.2, 0.88)	0.2 (0.1, 0.37)	0.15 (0.1, 0.24)	
	Pairwise p value	0.0031***	0.0187	0.5475	Reference	0.0006**
	Pairwise p value	Reference	0.6671	0.0367	0.0031***	
Absenteeism costs[a,b] (€)	LSMeans (CI)	2898.03 (365.23, 22,995)	7144.29 (1004.7, 50,802)	1190.89 (395.44, 3586.39)	389.51 (194.12, 781.56)	
	Pairwise p value	0.0845	0.0096***	0.1121	Reference	0.0163**
	Pairwise p value	Reference	0.5116	0.4523	0.0845	
Presenteeism costs[a,b] (€)	LSMeans (CI)	5221.81 (1917.91, 14,217)	6878.08 (2579.64, 18,339)	6369.96 (3723.52, 10,897)	2630.32 (1894.03, 3652.82)	
	Pairwise p value	0.2114	0.0804	0.0103	Reference	0.0488
	Pairwise p value	Reference	0.6971	0.7243	0.2114	
Total indirect costs[a,b] (€)	LSMeans (CI)	9550.26 (3857.83, 23,642)	11,825 (4897.74, 28,552)	8014.82 (4800.29, 13,382)	3098.42 (2237.34, 4290.9)	
	Pairwise p value	0.0271	0.0083***	0.004***	Reference	0.0046**
	Pairwise p value	Reference	0.7285	0.734	0.027	
Total indirect costs[b] (age 18–60) (€)	LSMeans (CI)	14,263 (9758.41, 20,846)	13,408 (8872.71, 20,260)	12,798 (10049, 16,299)	8026.32 (6828.55, 9434.18)	
	Pairwise p value	0.0075***	0.0261	0.0022***	Reference	0.0011**
	Pairwise p value	Reference	0.8284	0.6336	0.0075***	
Provider visit costs (€)	LSMeans (CI)	632.39 (392.73, 1018.32)	522.47 (322.53, 846.34)	516.57 (379.9, 702.43)	333.27 (275.36, 403.37)	
	Pairwise p value	0.0147	0.0922	0.0179	Reference	0.003**
	Pairwise p value	Reference	0.5798	0.4847	0.0147	
ER visit costs (€)	LSMeans (CI)	232.36 (88.9, 607.33)	186.14 (71.2, 486.62)	94.23 (48.78, 182.06)	47.54 (31.95, 70.74)	
	Pairwise p value	0.0033***	0.0115	0.0981	Reference	0.0005**
	Pairwise p value	Reference	0.7469	0.1238	0.0033***	
Hospitalization costs (€)	LSMeans (CI)	1244.38 (326.53, 4742.3)	474.96 (115.66, 1950.4)	458.03 (184.04, 1139.95)	279.64 (160.36, 487.64)	
	Pairwise p value	0.0482	0.5092	0.4036	Reference	0.0443
	Pairwise p value	Reference	0.3526	0.2087	0.0482	
Total direct costs (€)	LSMeans (CI)	1894.32 (1032.48, 3475.55)	1431.71 (767.23, 2671.67)	1140.02 (766.86, 1694.76)	689.25 (538.41, 882.35)	
	Pairwise p value	0.0027***	0.0365	0.0401	Reference	0.0006**
	Pairwise p value	Reference	0.5319	0.165	0.0027***	
Brazil + 5EU outcomes values						
MCS	LSMeans (CI)	38.94 (35.09, 42.78)	41.46 (37.81, 45.11)	38 (35.63, 40.37)	43.67 (42.21, 45.13)	
	Pairwise p value	0.0243	0.2746	<0.0001***	Reference	0.0038**
	Pairwise p value	Reference	0.3518	0.6842	0.0243	
PCS	LSMeans (CI)	41.99 (38.66, 45.32)	42.09 (39.02, 45.15)	45.71 (43.68, 47.75)	48.92 (47.67, 50.18)	
	Pairwise p value	0.0002***	<0.0001***	0.0102	Reference	<0.0001**
	Pairwise p value	Reference	0.9655	0.0578	0.0002***	
Health utilities	LSMeans (CI)	0.58 (0.54, 0.63)	0.62 (0.57, 0.66)	0.61 (0.59, 0.64)	0.69 (0.67, 0.7)	
	Pairwise p value	<0.0001***	0.0018***	<0.0001***	Reference	<0.0001**
	Pairwise p value	Reference	0.3004	0.2257	<0.0001***	
Absenteeism %[a,b]	LSMeans (CI)	26.89 (6.51, 111.08)	18.35 (5.42, 62.15)	6.39 (2.88, 14.19)	2.76 (1.69, 4.53)	

Continued

Table 4. Continued.

	Parameter	≥1 seizures/week	1–3 seizures/month	1–4 seizures/year	<1 seizure/year	Overall p value
	Pairwise p value	0.0032***	0.0057***	0.0988	Reference	0.0002**
	Pairwise p value	Reference	0.6923	0.0794	0.0032***	
Presenteeism %[a,b]	LSMeans (CI)	49.92 (22.13, 112.62)	34.44 (17.89, 66.32)	32.38 (21.93, 47.79)	18.41 (14.41, 23.51)	
	Pairwise p value	0.0238	0.0914	0.0247	Reference	0.0067**
	Pairwise p value	Reference	0.4781	0.3344	0.0238	
Overall work impairment %[a,b]	LSMeans (CI)	61.09 (30.86, 120.93)	46.74 (25.66, 85.15)	33.89 (23.41, 49.07)	20.36 (16.02, 25.87)	
	Pairwise p value	0.0038***	0.0166	0.0351	Reference	0.0007**
	Pairwise p value	Reference	0.5522	0.1239	0.0038***	
Activity impairment %[b]	LSMeans (CI)	57.06 (39.13, 83.19)	45.46 (31.69, 65.22)	40.62 (32.09, 51.42)	23.02 (19.92, 26.61)	
	Pairwise p value	<0.0001***	0.0007***	<0.0001***	Reference	<0.0001**
	Pairwise p value	Reference	0.3953	0.1339	<0.0001***	
Provider visits	LSMeans (CI)	11.08 (7.61, 16.13)	7.44 (5.16, 10.73)	8.1 (6.38, 10.28)	6.43 (5.54, 7.45)	
	Pairwise p value	0.0082***	0.4692	0.1072	Reference	0.0073**
	Pairwise p value	Reference	0.1382	0.1667	0.0082***	
ER visits	LSMeans (CI)	1.12 (0.56, 2.23)	0.84 (0.43, 1.61)	0.52 (0.32, 0.86)	0.33 (0.23, 0.46)	
	Pairwise p value	0.0025***	0.0141	0.1407	Reference	0.0005**
	Pairwise p value	Reference	0.5457	0.0728	0.0025***	
Hospitalizations	LSMeans (CI)	0.47 (0.23, 0.94)	0.54 (0.29, 1.02)	0.24 (0.14, 0.42)	0.18 (0.12, 0.26)	
	Pairwise p value	0.0151	0.0026***	0.3741	Reference	0.001**
	Pairwise p value	Reference	0.7601	0.1505	0.0151	

CI, confidence interval (95% CI are presented); ER, emergency room; FE, focal epilepsy; MCS, Mental Component Summary; PCS, Physical Component Summary.
Lower scores on MCS, 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 (0–100%).
[a]Includes only employed respondents.
[b]Productivity measures are derived from the Work Productivity and Activity Impairment (WPAI).
**Statistically significant at Bonferroni threshold of $p < 0.01667$ for three datasets.
***Statistically significant at Bonferroni threshold of $p < 0.01$ for five unique pairwise comparisons.

Table 5. Comparison of direct cost estimates by seizure frequency

Direct costs PPPY (2013 Euros)	Current study	Berto (Italy)[6]	De Zélicourt (France)[7]	Hamer (Germany)[8]	Jacoby (United Kingdom)[9]
Daily		3,454.71	7,210.76	2,682.48	
Weekly	1,894.32	5,605.03	892.62	1,226.28	
Monthly	1,431.71	2,389.59		1,954.38	3,500.37
Annual	1,140.02	1,307.48		485.40	1,893.65
None	689.25		470.96		371.84

PPPY, per patient per year.

Values from original papers were converted to 2013 euros using the health-specific and country-specific Harmonized Index of Consumer Prices for Italy, France, and Germany and the health-specific United Kingdom Consumer Price Index (2001–2013) and overall Retail Prices Index (1993–2000).

Of the productivity measures, the U.S. dataset pairwise results did not support global tests for any of the measures except indirect costs (ages 18–60). For presenteeism and overall work impairment, global tests were significant, but pairwise tests were not at the Bonferroni threshold. Pairwise results in the 5EU dataset supported a relationship for activity impairment and indirect costs (ages 18–60). For the Brazil + 5EU dataset, pairwise results supported a relationship for absenteeism, overall work impairment, and activity impairment. Again, the higher FE proportion (and likely higher SGS proportion) in the Brazil + 5EU dataset may explain why a greater number of associations were demonstrated.

Of the HRU measures, pairwise results in the U.S. dataset supported relationships between seizure frequency with hospitalizations and direct costs. For the 5EU dataset, pairwise results supported relationships with ER visits, hospitalizations, ER visit costs, and total direct costs. For the Brazil + 5EU dataset, pairwise results supported relationships with provider visits and ER visits. Differences between regional datasets may be reflective of differences in patterns of care between regions. Unlike the other datasets, the U.S. dataset lacks universal healthcare coverage. About 15% of the U.S. dataset was uninsured, with the remaining covered by Medicare, Medicaid (managed separately by each U.S. state), Tricare (military), or a multitude of private insurers that each offers hundreds of different coverage plans. The other countries have universal or near universal coverage, which is a mix of mostly government coverage and private coverage.

Because the NHWS is an Internet-based survey, results may have been affected by selection bias. For example, some FE patients in the three regions examined may have had insufficient access to or experience with the requisite technology. Additionally, those more severely affected by their epilepsy seizures may have been more inclined to report their epilepsy. Alternatively, respondents hospitalized or highly impaired because of their epilepsy may not have been healthy enough to participate in the study. The overall direction of this potential selection bias is uncertain. Moreover, given that response rates for the NHWS varied by region, we cannot exclude the possibility that the results reflect cultural differences in the willingness to participate or other unmeasured variables, rather than actual differences in the prevalence of FE. Surgical status, which may influence patients' physical and mental health status, as well as epilepsy-related costs incurred, was not measured in this study, thereby potentially reducing the validity of the findings.

Causal inferences cannot be established because the data were cross-sectional. The estimates of indirect costs must be interpreted cautiously. Specifically, the small sample sizes used to perform these analyses limited the statistical power (i.e., very few respondents were employed and there were a disproportionately smaller number of respondents in the higher seizure frequency categories).

Conclusions

Overall, results from the current study highlight interesting differences between regions on QoL associations that may or may not be reflective of a higher or lower proportion of SGS patients. This study also updated the understanding of how seizure frequency relates to productivity and indirect costs and provided new findings about HRU and direct costs. Whereas the relationship between seizure frequency and QoL, productivity, and indirect costs may be driven primarily by the difference between having seizures and not having seizures in this and previous studies, it is possible that larger datasets may demonstrate more refined differences between seizure frequency categories. This particular study did demonstrate regional differences in the association between seizure frequency and health resource utilization. These differences may be reflective of differences in healthcare coverage between regions. Nearly, half of the patients in this study had persistent seizures, despite most taking at least one AED in this 2011–2013 dataset. These results suggest that additional treatment options are needed to both improve seizure control and reduce direct costs.

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Conflict of Interest

Shaloo Gupta is an employee of Kantar Health, which received funding from Eisai to conduct and report on this study. Wan Tsong is an employee of Eisai, which funded this study. Philippe Ryvlin, Patrick Kwan, and Edward Faught were not paid for their participation in this particular publication and study but are paid consultants to Eisai for other projects. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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