

Healthcare Utilization in Patients with Uncontrolled Epilepsy: A Retrospective Study in a Commercially-Insured U.S. Population

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Abstract

Objective: To evaluate the healthcare and societal economic burden of adjunctively-treated patients with uncontrolled epilepsy.

Methods: A retrospective claims database (representative of the commercially insured US population) was used to analyze direct and indirect costs (Jan-2006 to Dec-2011) for patients with epilepsy. Patients had ≥ 1 diagnosis code for epilepsy (ICD-9 345.xx), ≥ 18 years of age, and had received ≥ 1 add-on Anti Epileptic Drug (AED) within 60 days of first-line treatment. Patients were grouped into: Well-controlled (no change in AED and no epilepsy-related Emergency Room (ER) or inpatient visits), Uncontrolled (≥ 2 AED changes in ≥ 30 days and ≥ 1 Epilepsy-Related ER or inpatient visits), and Intermediate-controlled (not grouped as Uncontrolled or Well-controlled). The groups were matched based on propensity scoring in a 1:1:1 ratio including age, sex, and Charlson comorbidities index score. A mixed-effects model was used to calculate the adjusted cost differences.

Results: From 141,173 patients, 6,785 triads were included in the analysis. Mean age was 48 ± 16.6 years (62% female). Uncontrolled patients had significantly higher direct costs: Uncontrolled vs. Well-controlled: \$32,077; Uncontrolled vs. Intermediate-controlled: \$14,855. Indirect costs were: Uncontrolled vs. Well-controlled: \$5,016; Uncontrolled vs. Intermediate-controlled: \$2,750. Differences were due to hospitalization costs (Uncontrolled/Well-controlled:

\$15,297; Uncontrolled/Intermediate-controlled: \$9,123), outpatient visits (Uncontrolled/Well-controlled: \$9,248; Uncontrolled/Intermediate-controlled: \$4,534), AED costs (Uncontrolled/Well-controlled: \$4,546; Uncontrolled/Intermediate-controlled: \$3,079), sick leave costs (Uncontrolled/Well-controlled: \$4,849; Uncontrolled/Intermediate-controlled: \$2,577), and total work loss (Uncontrolled/Well-controlled: \$5,016; Uncontrolled/Intermediate-controlled: \$2,750) (all $p < 0.01$). Adjusted costs were significantly higher for Intermediate-control vs. Well-controlled patients for all cost items (all $p < 0.01$), with the exception of non-AED costs and disability, which were not significantly different.

Conclusions: In this study, direct and indirect costs were highest for uncontrolled, and lowest for well-controlled epilepsy. These findings suggest the importance of improvements in control of seizure activity (either from uncontrolled to intermediate-controlled, or from intermediate-controlled to well-controlled), both from a societal cost and public health perspective.

Abbreviations: EEG: Electroencephalography; RLS: Restless Legs Syndrome; TMS: Transcranial Magnetic Stimulation; rTms: Repetitive Transcranial Magnetic Stimulation

Keywords: Anti-Epileptic Drugs; Database Analysis; Healthcare Resource Utilization; Seizure Control

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Introduction

Epilepsy is one of the most commonly observed neurological conditions [1], characterized by recurrent unprovoked seizures [2]. In the United States alone, epilepsy and seizures affect more than 3 million individuals, with between 150,000 and 200,000 new cases diagnosed every year [3, 4]. Epilepsy represents a considerable economic burden to society with some estimates suggesting as much as 0.12% to 1.12% of a country's GDP is devoted to the direct costs of epilepsy [5]. Direct annual costs are approximately \$7,000 higher for patients with epilepsy compared with patients without epilepsy [6]. While the direct costs of the disease are high, they only represent a small proportion of the total economic burden of epilepsy; studies have found that 12% to 85% of the total costs of epilepsy can be attributed to indirect costs [7]. In 2000, the total annual cost of epilepsy was an estimated \$12.5 billion (\$US, 1995 values) [3]. However, only 14% of this was attributable to direct costs, whereas 86%, totaling over \$10 billion was due to indirect costs [3].

Despite improvements in treatment, epilepsy is associated with considerable morbidity; estimates suggest that the aggregate burden of epilepsy contributes to 0.5% of the total disease burden worldwide [8]. The increased morbidity associated with epilepsy is largely due to an increased risk of physical harm directly resulting from experiencing seizures. In addition, epilepsy is associated with negative psychological and emotional effects and the condition may lead to reduced social interactions and lower employment rates compared with patients without epilepsy [9, 10]. The morbidity issues are further compounded by a high risk of premature mortality in patients with epilepsy, reported to be more than twice that of the general population, regardless of seizure control status [11].

Seizures in patients with epilepsy are commonly treated with Anti-Epileptic Drugs (AEDs), which allow many patients to maintain seizure control and reduce other negative outcomes of the disease [12]. The ultimate goal of epilepsy treatment is the total elimination of seizures, and treatment must be tailored to the individual patient to establish a balance between seizure control and drug tolerability [12].

While most patients with epilepsy are able to achieve some degree of seizure control with currently available AEDs, up to 40% of patients experience uncontrolled epilepsy (i.e. seizures that do not respond to treatment with one or more AEDs), and only half of the patient population become seizure free with their first AED [13]. Patients with uncontrolled epilepsy are predisposed to severe health risks, impaired quality of life, increased risk of premature death and higher healthcare costs [9, 14].

There is a large unmet need in epilepsy with many patients frequently switching medications, taking multiple AEDs, or experiencing uncontrolled symptoms despite treatment. Further, patients with uncontrolled epilepsy contribute disproportionately to the cost of treating the disease. In a previous analysis, patients with uncontrolled epilepsy contributed up to 86% of the total direct costs of epilepsy, despite representing only 25% of the total patient population [3].

Despite substantial interest in the burden of uncontrolled epilepsy, it is difficult to assess the exact proportion of patients with uncontrolled epilepsy, as the criterion used to define uncontrolled epilepsy varies across different publications [15]. Publications using claims data often classify patients with epilepsy as uncontrolled if they have failed three or more AEDs, [15, 16] whereas other publications (and the current analysis) require more than two consecutive changes in AED and one or more epilepsy-related Emergency Room (ER) or inpatient hospital visits [17]. Further, most studies do not consider patients with varying degrees of epilepsy control, despite this

group comprising the majority of the overall epilepsy patient population.

While previous studies have focused on the healthcare burden of adjunctively-treated patients with uncontrolled epilepsy, literature on the healthcare resource utilization of patients with varying levels of epilepsy control is lacking. Patients with intermediate epilepsy are not widely characterized in the literature, particularly with relation to economic burden. As such, in order to gain a fuller picture of the burden of illness among patients with epilepsy, it is important to understand the impact any loss of seizure control has on the economic burden of epilepsy.

The objective of this study was to identify differences in cost and resource utilization between patients with varying degrees of epilepsy control, to better characterize these patients and support the development of individualized treatment strategies. In order to achieve this objective, this study evaluated the economic burden and healthcare resource utilization of adjunctively-treated patients with uncontrolled and well-controlled epilepsy, in addition to those that fall in between (i.e., intermediately-controlled epilepsy).

Methods

Data sources

This study was conducted using data from the Thomson Reuters MarketScan® claims database, which contains data on healthcare resource consumption that is broadly representative of the commercially insured population of the United States (US). Claims databases are easily accessible and usually comprise large patient populations. They represent an important source of information on resource use, and such analyses can uncover important variations in healthcare patterns within specific disease populations. The database used in this analysis contains information on person-specific clinical utilization, expenditures, and enrolment across inpatient, outpatient, prescription drug, and services not covered by the insurance

plan from a selection of large employers, government health plans, and public organizations in the US.

The data extracted from the database to be included in this analysis were inpatient admissions, facility name, inpatient services, outpatient services, outpatient drug claims, and hospital discharge claims. In compliance with the Health Insurance Portability and Accountability Act (HIPAA), patient data included in the analysis are de-identified; therefore, this study is exempt from Institutional Review Board review. The database was searched for patients with a diagnosis of epilepsy between January 2006 and December 2011.

Study design and study population

A retrospective, longitudinal, propensity-matched-cohort design was used to classify patients into three mutually exclusive cohorts: 1) uncontrolled epilepsy: more than two consecutive changes (either adjunctive or AED switch) in AED therapy occurring at least 30 days apart and more than one epilepsy-related ER or inpatient visits; 2) well-controlled epilepsy: no change in AED therapy and no epilepsy-related ER or inpatient visits; and 3) intermediate epilepsy: all other patients with epilepsy, i.e. those who met neither the uncontrolled or well-controlled epilepsy definitions.

The baseline period was defined as the 180-day interval prior to the beginning of the observation period (i.e. the 180 days prior to the index date). The observation period began after the baseline period once the first AED had been dispensed, and continued for at least 365 days until the first occurrence of end of continuous enrolment, end of data availability, or death. The index date was taken as the date of an epilepsy-related inpatient or ER visit and denoted the start of uncontrolled epilepsy for patients in the uncontrolled epilepsy cohort, and also acted as an imputed diagnosis date for patients in the control cohorts (well-controlled and intermediate cohorts, respectively). Figure 1 illustrates this study design.

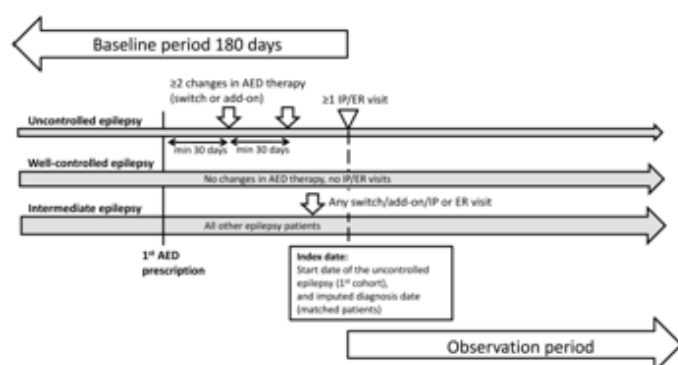


Figure 1: Overview of study design

AED: Anti-Epileptic Drug; ER: Emergency Room; IP: Inpatient

Propensity score matching

In observational studies, absence of randomization can lead to imbalance between groups, and thus lead to bias in the analysis. To overcome this problem, patients across the three cohorts were matched using propensity score matching, which limited any potential selection bias that may have occurred.

Patients were matched into the three cohorts in a 1:1:1 ratio using the nearest available neighbor without replacement method; therefore, once matched, patients were no longer available [18]. Propensity scores between any two cohorts were calculated using a logistic regression based on baseline age, gender, and the Charlson Co morbidities Index (CCI). The following steps were used: 1) patients in the uncontrolled and the well-controlled cohorts were propensity score-matched; 2) patients in the uncontrolled and the intermediate cohorts were propensity score-matched; and 3) well-controlled patients were then propensity score-matched with intermediate-control patients from step 2, above.

Matched cohorts were compared for healthcare resource utilization such as prescription drug use (AEDs and non-AEDs), hospitalizations, length of hospital stay, ER visits, neurologist visits, other healthcare services, total healthcare costs, and work days lost due to sick leave and short-term and long-term disability.

Outcome measures

The main outcome measures used to compare between matched cohorts were direct (health resource utilization and costs) and indirect (work loss) utilization and costs.

Direct healthcare utilization and costs included prescription drugs (AEDs and non-AEDs), hospitalizations, ER visits, neurologist visits, outpatient visits, use of other healthcare services (these included for example cardiologist visits and nephrologist visits), and total healthcare costs. Indirect utilization and costs were defined as short-term and long-term disability, sick leave, and total work days lost (due to disability and/or sick leave). Sick leave was imputed as 0.5 days for outpatient visits, and as the total length of stay for hospitalizations [17].

Statistical analysis

The statistical analysis was conducted using SAS[®] version 9.3 (SAS institute Inc., Cary, NC, USA), including study design, patient selection, data analysis, and propensity score matching. Descriptive statistics were used where data measured on a continuous scale were expressed as mean, Standard Deviation (SD), and compared using the Wilcoxon on rank sum test. Categorical data were expressed as percentages of patients in the category and evaluated using the Chi-square test.

Health Resource utilization and work loss were assessed using Incidence Rates (IRs), Incidence Rate Ratio (IRR) and adjusted costs. Incidence rates were defined as the number of new cases occurring over person-years and the IRR was defined as the relative difference between incidence rates. Adjusted IRRs were calculated using multivariate conditional Poisson regression models adjusted for matched pairs. Covariates included age, sex, CCI, Alzheimer's disease, brain tumor, meningitis, migraine, stroke, anxiety disorder, bipolar disorder, depression, psychosis, personality disorder, mental retardation, hypertension, and baseline resource use which should limit the effect of any baseline differences between the cohorts. The same regression was used to estimate the statistical differences between groups, as well as 95% Confidence Intervals (CI).

A mixed effect model was used to calculate Adjusted Cost Differences (ACD) of healthcare resource utilization and work days lost. The variables used in the final model to calculate adjusted cost differences were: age, sex, CCI score, Alzheimer's disease, brain tumor, meningitis, migraine, stroke, anxiety disorder, bipolar disorder, depression, psychosis, personality disorder, mental retardation, and hypertension. Baseline resource use was not used in the mixed model. All direct and indirect costs were calculated over the entire study duration and were adjusted using the US Consumer Price Index 2013. Adjusted cost differences between matched cohorts were calculated for each cost component.

Results

General search and baseline results

The study population comprised 745,504 eligible patients with epilepsy. Of these, 78,500 did not have continuous enrolment for 365 days; a further 339,189 patients with epilepsy were excluded based on age and prior AED treatment claims. Therefore, 141,173 (18.9% of the total diagnosed patients) met the inclusion criteria for this study and were included in the analysis (Figure 2).

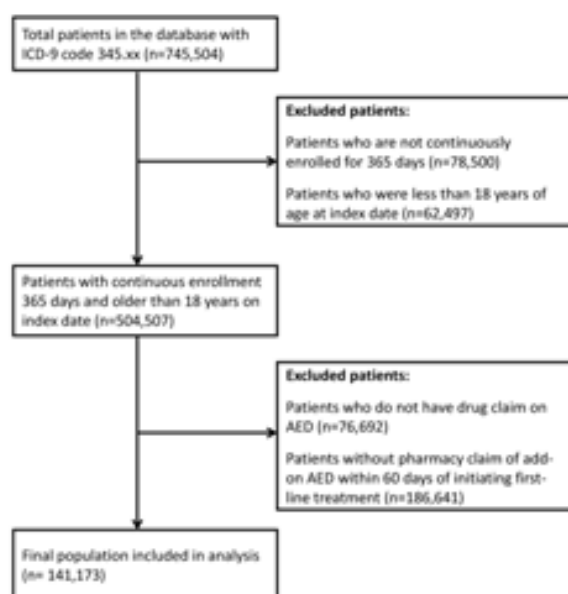


Figure 2: Flow of patient selection based on pre-specified inclusion and exclusion criteria. AED: Anti-epileptic drug; ICD: International Disease Classification

The final group of 141,173 included patients that were classified into the three cohorts according to pre-defined criteria. The vast majority of patients with epilepsy were classified in the intermediate cohort (i.e. neither uncontrolled nor well-controlled) (n=103,734; 73%), 8% were classified as uncontrolled (n=10,841), and 19% were classified as well-controlled (n=26,598).

The final analysis sample was comprised of 6,785 patient triads, matched on a 1:1:1 basis from each of the three cohorts. Table 1 compares the baseline characteristics of the matched cohorts. The number of hospitalizations, ER visits, neurologist visits, outpatient visits, and other healthcare visits between the matched cohorts were comparable to the unmatched population. After matching, no significant differences were observed between the three cohorts for age, gender, and CCI weight. The mean age was 48 years and 62% were female.

The number of early and Medicare retirees was higher in the uncontrolled cohort than the other two cohorts. Statistically significant differences in the average number of observation days between the cohorts were observed, with the uncontrolled cohort reporting the highest number of days (1,294 days), followed by the intermediate cohort (1,164 days) and the well-controlled cohort (1,047 days).

The average number of previously used treatments was significantly different between the cohorts ($p<0.001$). All the patients in the well-controlled cohort had previously used only two treatments, whereas 66% and 75% of the patients in the uncontrolled and intermediate cohorts, respectively, claimed two treatments before the index date. Similarly, region, number of hospitalizations, number of ER visits, number of neurologist visits, number of outpatient visits, other healthcare services, length of hospital stay, sick leave, and total work days lost were statistically significant across the cohorts. Short-term and long-term disabilities were not statistically significant due to missing values.

Table 1: Baseline characteristics of the matched populations

Characteristics	Total (n=20,355)	Well- controlled (n=6,785)	Uncontrol led (n=6,785)	Intermedia te (n=6,785)	p-value (well- controlled vs.uncontrol led)	p-value (well- controlled vs. intermedi ate)	p-value (uncontrol led vs. intermedi ate)
Age, years; mean, ($\pm$ SD)	48.2 (16.6)	48.2 (16.6)	48.2 (16.6)	48.2 (16.6)			
Female; N (%)	1,2546 (61.6)	4,182 (61.6)	4,182 (61.6)	4,182 (61.6)			
Employment status; n (%)					p<0.001[†]	p<0.001[†]	p<0.001[†]
Active full time	5,156 (25.3)	1,665 (24.5)	2,139 (31.5)	1,352 (19.9)			
Early retiree	1065 (5.2)	263 (3.9)	525 (7.7)	277 (4.1)			
Medicare retiree	2183 (10.7)	607 (8.9)	954 (14.1)	622 (9.2)			
Retiree (no status)	599 (2.9)	177 (2.6)	279 (4.1)	143 (2.1)			
Region n (%)					p<0.001[†]	p<0.001[†]	p<0.001[†]
Northeast	2202 (10.8)	838 (12.4)	682 (10.1)	682 (10.1)			
North central	4,240 (20.8)	1,455 (21.4)	1,549 (22.8)	1,236 (18.2)			
South	5,464 (26.8)	1,942 (28.6)	1,866 (27.5)	1,656 (24.4)			
West	2,460 (12.1)	760 (11.2)	998 (14.7)	702 (10.3)			
Missing	5,767 (28.3)	1,700 (25.1)	1,638 (24.1)	2,429 (35.8)			
CCI weight; mean, ($\pm$ SD)	0.7 (0.9)	0.7 (0.9)	0.7 (0.9)	0.7 (0.9)			
Observation period, days; mean, ($\pm$ SD)	1,168.5 (439.6)	1,047.4 (457.4)	1,294.0 (366.1)	1,164.1 (453.8)	p<0.001*	p<0.001*	p<0.001*
Previous AEDs; mean, ($\pm$ SD)	2.3 (0.6)	2.0 (0.0)	2.4 (0.7)	2.3 (0.6)	p<0.001*	p<0.001*	p<0.001*
Hospitalizations; mean, ($\pm$ SD)	2.1 (3.4)	1.1 (1.8)	3.2 (4.3)	2.1 (3.2)	p<0.001*	p<0.001*	p<0.001*
ER visits; mean, ($\pm$ SD)	6.5 (12.9)	3.1 (6.7)	9.7 (16.6)	6.6 (12.6)	p<0.001*	p<0.001*	p<0.001*
Neurologist visits; mean, ($\pm$ SD)	4.0 (6.1)	2.8 (4.3)	5.5 (7.3)	3.6 (5.9)	p<0.001*	p=0.078*	p<0.001*
Outpatient visits; mean, ($\pm$ SD)	122.2 (214.5)	102.5 (217.7)	130.8 (187.4)	133.3 (234.3)	p<0.001*	p<0.001*	p<0.001*
Other healthcare services; mean, ($\pm$ SD)	9.6 (18.8)	5.8 (14.0)	13.7 (22.7)	9.2 (17.8)	p<0.001*	p<0.001*	p<0.001*
Length of hospital stay, days; mean, ($\pm$ SD)	13.5 (31.0)	7.8 (20.2)	18.6 (37.2)	14.0 (32.0)	p<0.001*	p<0.001*	p<0.001*

AED: Anti-epileptic drug; CCI: Charlson Comorbidities Index; ER: Emergency room; SD: Standard deviation

*Wilcoxon sum rank test; Bold indicates statistical significance; [†]Chi-square test; Bold indicates statistical significance

Resource Use

The observed IRs and IRRs for healthcare resource utilization for the matched cohorts are displayed in Figure 3. Patients with uncontrolled epilepsy received 1.48 times more AEDs compared with patients with well-controlled epilepsy. Patients with intermediate epilepsy used a greater number of AEDs compared with the well-controlled cohort (IRR: 1.45 $p<0.001$), but a similar number compared with the uncontrolled cohort (IRR: 1.03) (Figure 3). Also, patients with uncontrolled epilepsy were hospitalized and admitted to the ER significantly more frequently than patients with well-controlled epilepsy (IRR: 1.31; $p<0.001$ and IRR: 1.45; $p<0.001$, respectively). Similarly, patients with intermediate epilepsy displayed higher rates of hospitalization and ER visits than the well-controlled cohort (IRR: 1.37; $p<0.001$ and IRR: 1.44; $p<0.001$, respectively), but similar rates compared with the uncontrolled cohort (IRR's: 0.95 and 1.01, respectively). Patients with uncontrolled epilepsy had similar levels of outpatient visits compared with the well-controlled cohort (IRR: 0.99; $p=0.061$). Conversely, patients with intermediate epilepsy had significantly increased rates of outpatient visits compared with both the well-controlled and the uncontrolled cohort (IRR: 1.05 $p<0.001$ and IRR: 1.06 $p<0.001$, respectively) (Figure 3). In terms of neurologist visits, patients with uncontrolled and intermediately-controlled epilepsy were both more likely to visit a neurologist compared to patients with well-controlled epilepsy (IRR's: 1.38 and 1.22, respectively, $p<0.001$ for both comparisons (data not reported). The adjusted cost difference for use of other healthcare services (such as visiting a cardiologist) was also higher in patients with uncontrolled and intermediately controlled epilepsy versus the well-controlled cohort (US\$ 2012; 1,526.83 and 560.21, respectively; $p<0.001$ for both comparisons) (Table 2).

Direct costs

Table 2 displays the adjusted cost difference of total direct costs for the matched cohorts based on the total costs observed throughout the duration of the study. Patients with uncontrolled epilepsy incurred \$32,077 higher total direct healthcare costs compared with those with well-controlled epilepsy. The main

cost drivers for patients with uncontrolled epilepsy were hospitalizations, outpatient visits, and AEDs. Similar cost drivers were observed for the intermediate cohort (Table 2). For every cost item reported, significantly greater costs were observed for the uncontrolled cohort compared with the well-controlled cohort (all $p<0.01$). The intermediate cohort also exhibited greater total direct costs (\$14,855) and, with the exception of non-AED drug costs, showed significantly greater costs for the remaining cost items compared with the well-controlled cohort(all $p<0.001$) (Table 2).

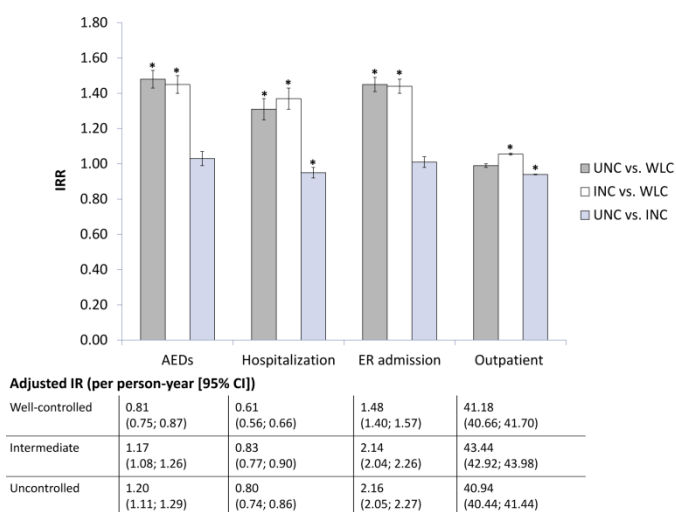


Figure 3: Adjusted incidence rate ratios for healthcare resource utilization between the different cohorts

AED: Anti-epileptic drug; CI: Confidence interval; ER: Emergency room; INC: Intermediate cohort; IRR: Incidence rate ratio; UNC: Uncontrolled epilepsy; WLC: Well-controlled epilepsy

*Indicates $p<0.001$

Average hospitalization costs were significantly higher in the uncontrolled cohort than in the well-controlled cohort (\$15,297) and the intermediate cohort (\$9,123).The intermediate cohort displayed higher incremental costs than the well-controlled cohort (\$6,173). The average outpatient visit costs observed for the uncontrolled cohort were approximately \$9,000 higher than in the well-controlled cohort and about \$4,000 higher than in the intermediate cohort. The adjusted difference in AED costs was

also significantly higher for the uncontrolled cohort compared with the well-controlled cohort (\$4,546). The intermediate

cohort displayed higher incremental AED costs than the well-controlled cohort (\$3,079).

Table 2: Adjusted cost difference for healthcare resource utilization between the different cohorts, US\$ 2012

Cost item	Uncontrolled vs. well-controlled		Uncontrolled vs. Intermediate		Intermediate vs. Well-controlled	
	ACD, (95% CI)	\$ p-value	ACD, (95% CI)	\$ p-value	ACD, (95% CI)	\$ p-value
AEDs	4,546 (4,230.61; 4,861.38)	p<0.001	1,466.7 (1,158.86; 1,774.53)	p<0.001	3,079.3 (2,774.41; 3,384.19)	p<0.001
Non-AEDs	56.02 (16.18; 95.85)	p=0.006	31.306 (-7.57; 70.19)	p=0.115	24.71 (-13.8; 63.21)	p=0.208
Hospitalizations	15,297 (12,801; 17,793)	p<0.001	9,123.86 (6,687.67; 11,560.00)	p<0.001	6,173.53 (3,760.61; 8,586.45)	p<0.001
ER visits	1,109.91 (964.9; 1,254.9)	p<0.001	762.76 (621.24; 904.28)	p<0.001	347.15 (206.98; 487.32)	p<0.001
Neurologist visits	293.86 (217.94; 369.77)	p<0.001	154.31 (80.20; 228.41)	p<0.001	139.55 (66.16; 212.94)	p<0.001
Outpatient visits	9,248.64 (6,964.4; 11,533)	p<0.001	4,714.32 (2,484.69; 6,943.96)	p<0.001	4,534.32 (2,325.98; 6,742.66)	p<0.001
Other healthcare services	1,526.83 (1,227.23; 1,826.42)	p<0.001	966.62 (674.17; 1,259.07)	p<0.001	560.21 (270.57; 849.84)	p<0.001
Total healthcare costs	32,077.00 (28,220.00; 35,934.00)	p<0.001	17,221 (13,457.00; 20,986.00)	p<0.001	14,855.00 (11,127.00; 18,584.00)	p<0.001

ACD: Adjusted cost difference; AED: Anti-epileptic drug; CI: Confidence Interval; ER: Emergency Room; US: United States
 Bold p-values indicate statistical significance

Indirect costs

Table 3 displays the adjusted IR, IRRs, and the adjusted cost difference of indirect costs for the matched cohorts. Patients with uncontrolled epilepsy were absent from work on average 1.01 times more than those with well-controlled epilepsy, but had 4% fewer days off due to epilepsy-related sickness ($p<0.0001$). The uncontrolled cohort had fewer days of absence from work, including 11% fewer sick leave days, than the intermediate cohort ($p<0.0001$). Patients in the intermediate cohort reported an 8% and 10% increase in sick leave and total

work days lost, respectively, compared with the well-controlled cohort (both $p<0.0001$). Both patients with uncontrolled epilepsy and patients with intermediate epilepsy had increased sick leave costs and greater total work days lost compared with the well-controlled cohort (Table 3). Despite having fewer missed days overall, patients with uncontrolled epilepsy incurred approximately \$2,500 higher sick leave costs and higher total work loss costs than the intermediate cohort (\$2,750).

Table 3: Adjusted incidence rate ratio and adjusted cost difference for total work-loss days between the different cohorts, US\$ 2013

	Adjusted IR per person-year (95% CI)		Adjusted IRR		Adjusted cost difference (US \$2013)	
	Uncontrolled	Well-controlled	IRR (95% CI)	p-value	ACD(\$) (95% CI)	p-value
Uncontrolled vs. Well-controlled						
Disability	3.38 (3.16; 3.59)	3.34 (3.08;3.60)	1.04 (0.90; 1.19)	p=0.578	1,235.85 (-3,495.31; 5,967.01)	p=0.608
Sick leave	3.30 (3.29; 3.32)	3.34 (3.32; 3.35)	0.96 (0.95; 0.97)	p<0.001	4,849.12 (3,672.52; 6,025.73)	p<0.001
Total work loss	3.44 (3.42; 3.45)	3.43 (3.42; 3.45)	1.01 (0.99; 1.02)	p=0.055	5,016.37 (3,834.09; 6,198.64)	p<0.001
Uncontrolled vs. Intermediate						
	Uncontrolled	Intermediate				
Disability	3.38 (3.16; 3.59)	3.45 (3.22; 3.68)	0.93 (0.82; 1.1)	p=0.257	1,138.41 (-3,338.61; 5,615.43)	p=0.617
Sick leave	3.30 (3.29; 3.32)	3.42 (3.40; 3.43)	0.89 (0.88; 0.90)	p<0.001	2,577.88 (1,429.45; 3,726.32)	p<0.001
Total work loss	3.44 (3.42; 3.45)	3.53 (3.51; 3.54)	0.92 (0.91; 0.93)	p<0.001	2,750.25 (1,596.29; 3,904.22)	p<0.001
Intermediate vs. Well-controlled						
	Intermediate	Well-controlled				
Disability	3.45 (3.22; 3.68)	3.34 (3.08;3.60)	1.12 (0.93; 1.3)	p=0.222	97.43 (-5,452.20; 5,647.07)	p=0.973
Sick leave	3.42 (3.40; 3.43)	3.34 (3.32; 3.35)	1.08 (1.07; 1.09)	p<0.001	2,271.24 (1,133.78; 3,408.71)	p<0.001
Total work loss	3.53 (3.51; 3.54)	3.43 (3.42; 3.45)	1.10 (1.09; 1.11)	p<0.001	2,266.11 (1,123.17; 3,409.06)	p<0.001

ACD: Adjusted cost difference; CI: Confidence Interval; IR: Incidence ratio; IRR: Incidence rate ratio; US: United States

Bold p-values indicate statistical significance

Discussion

It is important to ascertain the true economic cost of epilepsy in order to increase awareness of its burden on individuals and society, and the potential benefits of prevention and treatment. This retrospective, matched-cohort study demonstrated that patients with uncontrolled epilepsy and patients with intermediate epilepsy have an increased economic burden compared with patients with well-controlled epilepsy. Over the average follow-up period of 1,167 days, patients with uncontrolled epilepsy had over \$30,000 in additional total direct costs compared with patients with well-controlled epilepsy.

Similarly, patients with intermediate epilepsy had over \$10,000 in additional total direct costs compared with patients with well-controlled epilepsy over the follow-up period.

In this analysis, the definition of uncontrolled epilepsy included a requirement for hospitalization and ER visits; therefore, substantially increased hospitalization costs in the uncontrolled cohort compared with the well-controlled cohort were expected. In addition, patients with uncontrolled epilepsy displayed increased levels of utilization of other health care resources in addition to hospitalization and ER visits. After hospitalization costs, the main drivers of direct costs amongst patients with

uncontrolled and intermediately-controlled epilepsy were outpatient visits and AED costs, both of which had higher adjusted cost differences than ER visits. This is in line with currently available evidence, which supports the idea that the primary driver of direct costs in epilepsy is related to the heavy use of medical services. A review of a claims database determined that of a total expenditure of \$5,950,260, medical costs accounted for over 90% of these costs [19].

Previous studies have shown that the proportion of total costs represented by drug costs is highest in patients with well-controlled epilepsy and becomes less significant as epilepsy control is lost [20]. Therefore, improvements in seizure control that result in reduced use of medical services could have a considerable impact on reducing the total direct healthcare costs associated with epilepsy, even if at the expense of increased drug costs.

While the indirect costs associated with epilepsy are known to be substantial, it is difficult to find comparable estimates of such costs [3, 6, 7]. In this study, patients with poorly-controlled epilepsy (i.e. the uncontrolled cohort and the intermediate cohort) had higher costs related to work days lost compared with patients with well-controlled epilepsy. The higher indirect costs, however, were driven by disability-related absenteeism rather than sick leave, which led to increased costs overall in patients with uncontrolled epilepsy, despite fewer sick days overall [21]. Similar results have been observed in other studies evaluating the indirect costs of epilepsy as a whole. In one study, total work loss costs were higher in patients with epilepsy compared with employed controls (\$3,192 and \$1,242, respectively) [21]. Other estimates have shown the total work loss costs associated with epilepsy to be almost equal to the total lost work costs of diabetes, depression, anxiety, and asthma combined [22]. As a result of methodological differences in study design and differences in the choice of patient population, comparisons have not always been possible between individual studies [7, 20]; the findings of the current study, however, as it relates to disability-related absenteeism, are meaningful [7].

Patients with poorly-controlled epilepsy contribute disproportionately to the cost of treating the disease. A recent

study investigated the impact of loss of seizure control on direct costs. In this study, costs associated with treating a patient following an initial ER visit were assessed against the patient's pre-visit costs [23]. Both non-epilepsy-related (\$12,745.56) and epilepsy-related (\$2,013.62) direct medical costs of care prior to loss of control were significantly lower than the costs observed following loss of control (\$15,274.95 and \$7,087.53, respectively; $p < 0.001$) [23]. Together with the results of the present analysis, this highlights the substantial costs that arise from any deviation from optimum well-controlled epilepsy and demonstrates the potential cost utility associated with avoiding loss of control of epilepsy-related symptoms.

The current analysis is one of the first studies to characterize the healthcare resource utilization and costs for patients with varying degrees of epilepsy control. Patients with intermediate epilepsy displayed a unique pattern of resource utilization, which differed from both the well-controlled and uncontrolled cohorts. In particular, patients with intermediate epilepsy had an increased number of outpatient visits compared with both the well-controlled and uncontrolled cohorts, while AED use and ER visits were significantly higher than well-controlled patients and comparable to uncontrolled patients. Patients with intermediate epilepsy, therefore, represent a distinct subgroup of the overall epilepsy population, with a unique economic burden profile, which is suggestive of less than optimal seizure control.

The vast majority of patients in this study were classified within the intermediate cohort (73%). This suggests that the majority of patients with epilepsy experience some degree of seizure control loss. It is possible, therefore, that an increased focus on improving the treatment outcomes and seizure control of patients with intermediate epilepsy may have a substantial impact on reducing the overall economic burden of epilepsy. Further work is required to adequately characterize subgroups of patients within the intermediate control segment, particularly in relation to healthcare resource utilization. In this way, it may be possible to identify patients at risk of poor epilepsy control in clinical practice, and proactively deliver coordinated care and appropriate seizure management strategies.

This study should be interpreted with certain considerations in mind. The first is the conservative definition of uncontrolled epilepsy used in this analysis (i.e. adjunctive therapy, plus more than two consecutive changes in AED, plus one or more epilepsy-related ER or inpatient hospital visits). While this definition is in line with other studies in epilepsy research [17], many publications have used a less conservative definition for uncontrolled epilepsy that required failure of three different AEDs [13, 15]. The lack of a consistent definition for uncontrolled epilepsy, therefore, limits the comparability of studies investigating the economic burden of epilepsy in this patient population.

Secondly, hospitalization was identified as a key driver of the economic burden of patients with uncontrolled epilepsy. However, hospitalization was one of the key criteria used in our conservative definition of uncontrolled epilepsy, and therefore it is not surprising that this was found to be one of the biggest cost drivers. Despite the conservative definition, however, we observed that patients in the uncontrolled cohort had higher AED utilization compared to the well-controlled cohort, and that the intermediate cohort had an ER visit and AED utilization that was comparable to uncontrolled patients.

A third consideration is that the database used in this analysis did not allow the identification of absolute seizure counts. While a clear association between loss of seizure control and increased economic burden was established, it was not possible to identify a relationship between the intensity of seizure activity and increased economic burden.

In addition, another general consideration that should be noted with respect to claims databases is that they provide limited information on patient demographics such as race, ethnicity, education, and other socio-economic variables. It is therefore not possible to make any conclusions with respect to the effect these variables may have had on results or conclusions drawn.

Despite the limitations, the results presented in this analysis are in line with previously published literature, and provide a new perspective of the economic burden of epilepsy across patients with different levels of epilepsy control. The results of this study show that the intermediate-control patient population has

a burden of illness that is significantly greater than that of well-controlled patients, and a utilization of ER visits and AEDs comparable to that of uncontrolled patients.

Conclusions

In this study of the economic assessments of the burden of epilepsy, patients who were not well-controlled incurred significantly higher medical costs, healthcare service utilization, lower work productivity, and higher costs from lost productivity. This study shows that the impact of a lack of seizure control is not limited to patients with uncontrolled epilepsy, representing a significant disease burden for patients with intermediate levels of control. Overall, this research underscores the importance of optimal seizure control in the management of epilepsy. Additional research to better understand the drivers of healthcare service utilization and costs among well-defined segments of patients with epilepsy with varying levels of seizure control are needed, and may provide useful insights on the strategies that could make a difference in improving treatment outcomes.

Acknowledgements

The authors thank the team at HERON Evidence Development AB for their assistance with data analyses early in the study and Jasim Uddin and Kacey Goodrich at HERON Evidence Development, UK and KrithikaRajagopalan and Fred Grossman at Sunovion Pharmaceuticals Inc, for their assistance with preparation and review of the manuscript.

Author contributions

FV, VB, TP, and MM designed the search strategy and TP and MM conducted the data analysis and prepared the manuscript. FV and VB contributed to the design of the study and the preparation and review of the manuscript. All authors revised the manuscript for important intellectual content and approved the final version for publication. No other undisclosed groups or persons had a role in the study and/or in preparation of the manuscript.

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