Epilepsy & Behavior 32 (2014) 135–141

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Healthcare utilization and costs in children with stable and uncontrolled epilepsy☆

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ARTICLE INFO

Article history:
Received 12 November 2013
Revised 21 January 2014
Accepted 22 January 2014
Available online 19 February 2014

Keywords:
Epilepsy
Seizures
Antiepileptic drugs
Cost analysis
Economics
Medical care
Children
Pediatric epilepsy
Comorbidities

ABSTRACT

Objective: Epilepsy adversely affects childhood development, possibly leading to increased economic burden in pediatric populations. We compared annual healthcare utilization and costs between children (<12 years old) with stable and uncontrolled epilepsy treated with antiepileptic drugs (AEDs).
Methods: Children (<12 years old) with epilepsy (ICD-9-CM 345.xx or 780.39) in 2008 were identified in the MarketScan claims database from 2007 to 2009. Patients with "stable" epilepsy used the same AED for ≥12 months, and patients with "uncontrolled" epilepsy were prescribed additional AED(s) during that period. For patients with uncontrolled epilepsy, the study index date was the start of additional AED(s); for patients with stable epilepsy, the study index date was a random AED fill date. Epilepsy-related utilization included medical services with 345.xx or 780.39 in any diagnosis field and AED fills. Epilepsy-related costs included AEDs, medical claims with epilepsy in any diagnosis field, and certain tests. We adjusted for baseline cohort differences (demographics, region, usual-care physician specialty, and comorbidities) using logistic regression and analysis of covariance.
Results: Two thousand one hundred seventy patients were identified (mean: 7.5 years; 45.3% were female; Charlson comorbidity index: 0.3; 422 (19.4%) patients with uncontrolled epilepsy). Patients with uncontrolled epilepsy faced more hospitalizations (30.1% vs. 12.0%) and greater overall ($30,343 vs. $18,206) and epilepsy-related costs ($16,894 vs. $7979) (all $p < .001$). Adjusting for baseline measures, patients with uncontrolled epilepsy had greater odds of hospitalization (OR: 2.5; 95% CI: 1.9–3.3) and costs (overall: $3908, $p = .087$; epilepsy-related: $5744, $p < .001$).
Conclusions: Children with uncontrolled epilepsy use significantly more healthcare resources and have a greater economic burden than children with stable epilepsy. However, epilepsy accounted for only half of overall costs, indicating that comorbid conditions may add substantially to the disease burden.

1. Introduction

Epilepsy adversely affects people of all ages, affecting health, quality of life, and daily activities [1,2]. Importantly, seizures may lead to poor development of language and motor skills in children [1,2]. Affecting about 2.2 million people and 150,000 new cases annually in the United States [2,3], the incidence of epilepsy is highest in young children and older adults [2,4]. Although epidemiological data are limited, studies indicate that over 300,000 US children under the age of 15 may have epilepsy [5,6].

Because this disorder manifests differently in children and adults, healthcare utilization and costs can vary between these subpopulations [7,8]. A European review found that children with epilepsy require more hospitalizations compared with adults with epilepsy, raising direct costs, while adults with epilepsy generally face more indirect costs compared with children with epilepsy [7]. However, it is difficult to determine the burden of epilepsy in children because of limited available data on healthcare costs and utilization for this subpopulation [2]. Thus, it is an Institute of Medicine research priority to include children with epilepsy in population-based studies [2]. Our objective in this study was to examine overall and epilepsy-related healthcare utilization and costs between groups of pediatric patients (age: <12 years)

☆ Statistical analysis: All statistical analyses were completed by Eunice Chang, PhD at the Partnership for Health Analytic Research, LLC.

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http://dx.doi.org/10.1016/j.yebeh.2014.01.016

with epilepsy, particularly those identified as having stable or uncontrolled disease.

2. Material and methods

2.1. Study design and data sources

We conducted a retrospective cohort analysis of pediatric patients with epilepsy using a major Health Insurance Portability and Accountability Act compliant administrative claims database, the Truven Health Analytics MarketScan database. The database, which includes data on millions of patients across the US, contained deidentified adjudicated medical (inpatient and outpatient) and pharmacy claims submitted for payment by providers, healthcare facilities, and pharmacies. The database contained limited information on patient demographics or physician visits, medical procedures, hospitalizations, drugs dispensed in the outpatient setting, dates of services/prescriptions, number of days of medications supplied, and tests performed. Data covered the calendar years 2007–2009. Further details on this study design and data sources may be found in a recent study on adults with epilepsy [9].

2.2. Study population

Patients <12 years old, diagnosed with epilepsy and treated with at least one AED in the identification (ID) period, calendar year 2008, were included. We identified all patients with ≥2 medical claims with epilepsy (ICD-9-CM codes: 345.xx or 780.39; ≥30 days apart) in any diagnosis field in the ID period and who had either 1) the same AED (monotherapy or combination) for ≥12 months or 2) added additional AED(s) in the ID period. We defined additional AED therapy as ≥3 months of baseline therapy, followed by ≥3 months with both baseline and additional AED(s). Included AEDs were as follows: carbamazepine, clonazepam, divalproex, valproate, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, vigabatrin, and zonisamide. Patients were excluded if they were not continuously enrolled or had a diagnosis of chronic pain, fibromyalgia, bipolar disorder, or migraines in the study period. These diagnoses were excluded because AEDs may be prescribed for these conditions [10–12].

The identified study patients were classified into one of two cohorts: 1) "cohort with stable epilepsy", if they had no change in AED monotherapy or combination therapy for ≥1 year or 2) "cohort with uncontrolled epilepsy", if they added AEDs to an existing regimen during the follow-up period. We referred to "children with stable epilepsy" as CWSE[1] and to "children with uncontrolled epilepsy" as CWUE.[2] The term "uncontrolled" was used for patients who added an additional AED to their existing regimen since seizure frequency was not in the database. For each cohort, an index date was selected. This was the date an additional AED was started for CWUE and a randomly selected date during the ID period for CWSE, whose AED use (either single agent or combination) was unchanged in the prior year.

2.3. Study measures

The database contains every claim for an individual's enrollment period. There are no missing data since a payment is processed only if a claim exists. Study measures used enrollment files, medical claims, and pharmacy claims. We constructed baseline measures—age, gender, US census region, physician specialty, and burden of illness—using all claims in the 12-month preindex period. Physician specialty, labeled as "usual-care specialty", was assigned using a published algorithm [13] based on the largest number of office visits that carried evaluation and management (E&M) service codes during the year.

Three burden of illness measures were assessed during the preindex year: Healthcare Cost and Utilization Project (HCUP) Chronic Condition Indicator, Charlson Comorbidity Index (CCI), and central nervous system (CNS) specific comorbidities. In this study, the term "comorbid" means that diagnoses of these conditions and of epilepsy were cooccurring in the claims database and that conditions include both potential causes of epilepsy and potential consequences of the disease. The HCUP Chronic Condition Indicator [14,15] categorizes ICD-9-CM diagnosis codes as chronic or not chronic. Chronic conditions are defined as follows: lasting ≥12 months and either (a) place limitations on self-care, independent living, and social interactions or (b) result in the need for ongoing intervention with medical products, services, and special equipment [15]. The CCI is used to measure overall burden of illness in the general population [16,17]. We identified CNS-specific comorbidities that might complicate the management of epilepsy: head injury (ICD-9-CM: 854.x), brain tumor (ICD-9-CM: 191.x, 198.3, 225.x, 237.5, 239.6), cerebrovascular disease (ICD-9-CM: 430–438.xx, 997.02), tuberous sclerosis (ICD-9-CM: 759.5), and depression and other mood disorders (ICD-9-CM: 296.xx, 298.0, 300.4, 309.1, 311).

The main outcome measures were annual overall and epilepsy-related healthcare utilization and costs in the postindex year. Utilization measures included number of inpatient hospitalizations, days of stay among patients with inpatient hospitalizations, emergency department (ED) visits, and physician office visits. Additional measures included number of AEDs, number of vagus nerve stimulation devices implanted, and tests (electroencephalography [EEG] or brain imaging studies). Overall and epilepsy-related cost measures included medical costs (inpatient stays, ED visits, and outpatient/non-ED services) and pharmacy costs. Epilepsy-related utilization included AED fills and healthcare services associated with epilepsy claims (ICD-9-CM: 345.xx or 780.93) in any diagnosis field. Epilepsy-related costs encompassed costs reported on claims with epilepsy in any diagnosis field, epilepsy-related tests, and the cost of AEDs. We did not evaluate indirect costs, including informal or out-of-pocket expenses such as patient transport and time off work, in this study.

2.4. Analysis

Differences between patients with stable epilepsy and those with uncontrolled epilepsy were compared using chi-squared tests and t-tests. Analysis of covariance (ANCOVA) was used to estimate incremental increases in costs associated with uncontrolled epilepsy adjusted for baseline measures. Logistic regression was conducted to estimate the odds ratio for the risk of inpatient hospitalization and ED visit with the same adjustors. All statistical analyses were performed using SAS© version 9.2 (SAS Institute, Cary, NC).

3. Results

There were 25,033 patients with ≥2 claims for epilepsy (ICD-9-CM: 345.xx or 780.39) ≥30 days apart in the ID period and classifiable as having either stable or uncontrolled epilepsy. We excluded the following: 5799 patients who were not continuously enrolled in the baseline or postindex periods; 5063 patients with diagnoses of neuropathic or chronic pain, fibromyalgia, bipolar, or migraine in the baseline period; and 12,001 patients who were ≥12 years old. The final analytic sample included 422 (19.4%) CWUE and 1748 (80.6%) CWSE.

Children with uncontrolled epilepsy were younger than children with stable disease (mean age: 6.6 vs. 7.8.; standard deviation [SD]: 2.7 vs. 2.6; $p < .001$; Table 1). Similar proportions of each cohort were female (46.0% vs. 45.2%, $p = .774$). The cohorts did not differ in geographic distribution: 10.4% of all patients were from the Northeast, 31.0% from the North Central, 42.5% from the South, and 16.1% from the West. Both CWUE and CWSE received care most often from primary care physicians (56.2% vs. 53.6%; $p = .004$). Compared with CWSE, CWUE had higher levels of overall and CNS-related illness during the

[1] Children with stable epilepsy (CWSE).
[2] Children with uncontrolled epilepsy (CWUE).

Table 1
Demographics, usual-care physician specialties, and comorbidities in <12-year-old patients with epilepsy.

	Stable N = 1748; 80.6%	Uncontrolled N = 422; 19.4%	All N = 2170	*p*-Value[e]
Age, year, mean (SD)	7.8 (2.6)	6.6 (2.7)	7.5 (2.6)	<.001
Age group, year, n (%)				<.001
≤5	362 (20.7)	158 (37.4)	520 (24.0)	
6–11	1386 (79.3)	264 (62.6)	1650 (76.0)	
Female, n (%)	790 (45.2)	194 (46.0)	984 (45.3)	0.774
Region, n (%)				0.918
Northeast	184 (10.5)	41 (9.7)	225 (10.4)	
North Central	539 (30.8)	134 (31.8)	673 (31.0)	
South	741 (42.4)	182 (43.1)	923 (42.5)	
West	284 (16.2)	65 (15.4)	349 (16.1)	
Usual-care physician specialty, n (%)				0.004
Neurology	409 (23.4)	69 (16.4)	478 (22.0)	
Primary care[a]	937 (53.6)	237 (56.2)	1174 (54.1)	
Other[b]/unknown[c]	402 (23.0)	116 (27.5)	518 (23.9)	
Number of chronic conditions, mean (SD)	2.1 (1.4)	2.7 (1.8)	2.2 (1.5)	<.001
Charlson comorbidity index, mean (SD)	0.3 (0.8)	0.4 (1.0)	0.3 (0.8)	0.002
No. with ≥1 CNS comorbidity,[d] n (%)	110 (6.3)	50 (11.8)	160 (7.4)	<.001
Head injury	12 (0.7)	6 (1.4)	18 (0.8)	0.135
Brain tumor	15 (0.9)	11 (2.6)	26 (1.2)	0.003
Cerebrovascular disease	39 (2.2)	21 (5.0)	60 (2.8)	0.002
Tuberous sclerosis	19 (1.1)	9 (2.1)	28 (1.3)	0.088
Depression and other mood disorders	19 (1.1)	1 (0.2)	20 (0.9)	0.101

Central nervous system: CNS; E&M: evaluation and management; standard deviation: SD.
[a] Including family practice, internal medicine, and pediatrician.
[b] All individual specialties in "Other" are <2%.
[c] Specialty was reported as "unknown" if it could not be identified with E&M service claims or if it was recorded as "unknown" on the claim.
[d] Patients could have more than one comorbidity.
[e] Stable vs. uncontrolled epilepsy.

preindex year, more chronic conditions (2.7 vs. 2.1; $p < .001$), and a lower mean CCI score (0.4 vs. 0.3; $p = .002$). A greater proportion of CWUE than CWSE had a head injury (1.4% vs. 0.7%; $p < .135$), brain tumor (2.6% vs. 0.9%; $p = .003$), cerebrovascular disease (5.0% vs. 2.2%; $p = .002$), and tuberous sclerosis (2.1% vs. 1.1%; $p = .088$), but proportion of children with depression and other mood disorders was lower in CWUE (0.2% vs. 1.1%; $p = .101$).

In the postindex year, hospitalizations were more frequent in CWUE than in CWSE, both for any (30.1% vs. 12% had ≥1 hospitalization) and for epilepsy-related diagnoses (25.4% vs. 9.3% had ≥1 hospitalization) (all $p < .001$; Table 2). Children with uncontrolled epilepsy also had more physician office visits compared with children with stable epilepsy for any diagnosis (17.3 vs. 12.5) and epilepsy-related (4.7 vs. 2.8; all $p < .001$). Up to 40.3% of CWUE had ≥1 ER visit (for any reason) compared with 29.2% of CWSE; similarly, the proportion of epilepsy-related ER visits in CWUE (22.5%) was twice that in CWSE (12.1%; all $p < .001$). Among children with hospital stays, the two cohorts had a similar mean hospital length of stay—6.4 vs. 6.8 days ($p = .710$) for any diagnosis and 6.0 vs. 6.8 days ($p = .512$) for epilepsy-related diagnosis in CWUE vs. CWSE, respectively. The proportion of children who had ≥1 EEG (47.9% vs. 44.5%) or brain imaging study (29.1% vs. 14.6%) was greater in patients with stable epilepsy than in those with uncontrolled epilepsy (all $p < .001$). Vagus nerve stimulation was uncommon, and the rate was similar for both cohorts (0.9% CWUE vs. 0.3% CWSE; $p = .058$). Children with uncontrolled epilepsy (81.3%) used two AEDs most frequently, 15.2% used three, and 3.6% used four or more. About 80% of CWSE used AED monotherapy, 16.8% used a two-AED regimen, 2.7% used a three-AED regimen, and 0.3% used a four-AED or more AED regimen.

Annual medical and pharmacy costs were significantly higher in CWUE than in CWSE (all $p < .01$; Table 3). Overall mean costs were more than $12,000 higher in CWUE than in CWSE: $30,343 (SD: $49,330) vs. $18,206 (SD: $42,638) per patient-year (PPY) ($p < .001$). There was a similar result for epilepsy-related costs—$16,894 (SD: $37,034) in CWUE vs. $7979 (SD: $24,136) in CWSE PPY ($p < .001$). Of the epilepsy-related costs, $12,926 (SD: $36,615) PPY for medical services and $3968 (SD: $3494) PPY for AEDs in CWUE as compared with $5524 (SD: $23,514) were for medical services and $2456 (SD: $3183) were for AEDs in CWSE (all $p < .001$).

Adjusting for baseline factors, the risk of hospitalization (odds ratio [OR]: 2.48; 95% CI: 1.88–3.27), ED visit (OR: 1.34; CI: 1.06–1.69), epilepsy-related hospitalization (OR: 2.58; CI: 1.93–3.45), and epilepsy-related ED visit (OR: 1.81; CI: 1.36–2.39) were all greater in CWUE than in CWSE (Table 4). Similarly, adjusted mean costs were greater in CWUE than in CWSE. Adjusted overall costs were $3908 (standard error [SE]: $2282; $p = .087$) greater, and adjusted epilepsy-related costs were $5744 (SE: $1471; $p < .001$) greater in CWUE than in CWSE, although the cost difference was only statistically significant for epilepsy-related costs.

4. Discussion

Although the highest incidence of epilepsy is among children and older adults [2,4], there is limited burden of illness information on epilepsy in the US pediatric population. This study provides detailed information on annual adjusted and unadjusted overall and epilepsy-related healthcare utilization and costs incurred by children with epilepsy in the US. The data reveal that epilepsy-related costs represent only approximately half of overall healthcare costs for children—44% for CWSE and 56% for CWUE. In addition, AED costs represented only about 13% of overall healthcare costs for both CWSE (13.49%) and CWUE (13.08%). Our study demonstrates a substantial economic burden beyond the cost of treating epilepsy, particularly in children with uncontrolled seizures.

A third of CWUE are hospitalized annually, with over a quarter of these hospitalizations related to epilepsy. Significantly fewer CWSE are hospitalized per year as compared with CWUE. Up to 40% of CWUE have emergency visits annually compared with a third of CWSE, and in CWUE, more than half of these visits (55.8%) may be epilepsy-related compared with 41.4% in CWSE. Children with uncontrolled epilepsy have significantly more physician office visits, although the majority of visits are not epilepsy-related. The large proportion of healthcare use

Table 2
Annual overall and epilepsy-related healthcare utilization in <12-year-old patients with epilepsy.

	Stable N = 1748; 80.6%	Uncontrolled N = 422; 19.4%	All N = 2170	p-Value [b]
Annual overall healthcare utilization				
Inpatient hospitalizations, n (%)				<0.001
0	1538 (88.0)	295 (69.9)	1833 (84.5)	
1	139 (8.0)	89 (21.1)	228 (10.5)	
2+	71 (4.1)	38 (9.0)	109 (5.0)	
Days of stay among patients with inpatient hospitalizations, mean (SD)	6.8 (11.5)	6.4 (10.1)	6.6 (11.0)	0.710
ED visits, n (%)				<0.001
0	1238 (70.8)	252 (59.7)	1490 (68.7)	
1	324 (18.5)	86 (20.4)	410 (18.9)	
2+	186 (10.6)	84 (19.9)	270 (12.4)	
Office visits, mean (SD) [median]	12.5 (16.7) [7.0]	17.3 (21.0) [10.0]	13.5 (17.7) [8.0]	<0.001
Annual epilepsy-related[a] healthcare utilization				
Inpatient hospitalizations, n (%)				<0.001
0	1586 (90.7)	315 (74.6)	1901 (87.6)	
1	106 (6.1)	78 (18.5)	184 (8.5)	
2+	56 (3.2)	29 (6.9)	85 (3.9)	
Days of stay among patients with inpatient hospitalizations, mean (SD)	6.8 (10.1)	6.0 (10.2)	6.5 (10.1)	0.512
Epilepsy-related ED visits, n (%)				<0.001
0	1536 (87.9)	327 (77.5)	1863 (85.9)	
1	148 (8.5)	56 (13.3)	204 (9.4)	
2+	64 (3.7)	39 (9.2)	103 (4.7)	
Vagus nerve stimulation, n (%)	5 (0.3)	4 (0.9)	9 (0.4)	0.058
Office visits, mean (SD) [median]	2.8 (5.0) [2.0]	4.7 (9.4) [3.0]	3.2 (6.2) [2.0]	<0.001
EEG, n (%)				<0.001
0	971 (55.5)	220 (52.1)	1191 (54.9)	
1	587 (33.6)	115 (27.3)	702 (32.4)	
2+	190 (10.9)	87 (20.6)	277 (12.8)	
Brain imaging, n (%)				<0.001
0	1493 (85.4)	299 (70.9)	1792 (82.6)	
1	202 (11.6)	87 (20.6)	289 (13.3)	
2+	53 (3.0)	36 (8.5)	89 (4.1)	
AEDs, n (%)				n/a
1	1403 (80.3)	0 (0)	1403 (64.7)	
2	293 (16.8)	343 (81.3)	636 (29.3)	
3	47 (2.7)	64 (15.2)	111 (5.1)	
4+	5 (0.3)	15 (3.6)	20 (0.9)	

AEDs: antiepileptic drugs; ED: emergency department; EEG: electroencephalographic; SD: standard deviation.
[a] Claims with a diagnosis of epilepsy in any diagnosis field.
[b] Stable vs. uncontrolled epilepsy.

attributed to nonepilepsy care alludes to the general poor state of health. Even after adjusting for baseline differences, CWUE are twice as likely to be hospitalized, and have a 34% increased odds of having an ED visit compared with CWSE.

Epilepsy manifests differently in children as compared with adults; thus, it is important to examine healthcare resource utilization in each group to further understand the disease impact. The pediatric patients in the current study use more healthcare resources compared with commercially insured adults (≥18 years old) with epilepsy described in a recent study [9]. This is particularly true in patients with uncontrolled epilepsy, who had a 64% increased risk of having at least one hospitalization and up to a 44% increase in mean number of physician visits

Table 3
Annual overall and epilepsy-related healthcare costs in <12-year-old patients with epilepsy.

	Stable N = 1748; 80.6%		Uncontrolled N = 422; 19.4%		All N = 2170		p-Value[b]
	Mean [median]	SD	Mean [median]	SD	Mean [median]	SD	
Overall healthcare cost, $	18,206 [6465]	42,638	30,343 [14,329]	49,330	20,768 [7809]	44,398	<.001
Medical cost, $	14,045 [2941]	39,471	24,231 [8465]	47,375	16,194 [3555]	41,461	<.001
Inpatient hospitalization cost, $	4405	25,141	10,200	35,073	5532	27,443	<.001
ED visit cost, $	297	782	539	1112	344	862	<.001
Outpatient (non-ED) service cost, $	8716 [2473]	23,233	12,951 [5909]	25,491	9610 [2866]	23,783	0.003
Pharmacy cost, $	3930 [2326]	6234	6035 [4670]	6271	4339 [2624]	6295	<.001
Epilepsy-related[a] overall healthcare cost, $	7979 [2851]	24,136	16,894 [7355]	37,034	9713 [3424]	27,348	<.001
Medical cost, $	5524 [739]	23,514	12,926 [2241]	36,615	6963 [914]	26,723	<.001
Inpatient hospitalization cost, $	3449	22,190	8400	33,483	4412	24,860	0.004
ED visit cost, $	126	486	295	820	159	571	<.001
Outpatient (non-ED) service cost, $	1949 [652]	4999	4231 [1476]	11,606	2393 [764]	6862	<.001
AED cost, $	2456 [1471]	3183	3968 [3088]	3494	2750 [1702]	3299	<.001

AED: antiepileptic drug; ED: emergency department; SD: standard deviation.
[a] Claims with a diagnosis of epilepsy in any diagnosis field.
[b] Stable vs. uncontrolled epilepsy.

Table 4
Regression model adjusted healthcare costs and utilization in <12-year-old patients with epilepsy.

	Overall cost			Epilepsy-related cost			Risk of inpatient hospitalization		Risk of ED visit		Risk of epilepsy-related inpatient hospitalization		Risk of epilepsy-related ED visit	
	β	(SE)	p	β	(SE)	p	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age group, year														
≤5 vs. 6–11	**6,955**[a]	(2166)	0.001	**3,971**[a]	(1375)	0.004	**1.54**[a]	(1.17–2.02)	**1.46**[a]	(1.18–1.81)	**1.66**[a]	(1.24–2.23)	**1.41**[a]	(1.08–1.86)
Female vs. male	−981	(1837)	0.593	−1260	(1143)	0.271	0.92	(0.71–1.18)	0.84	(0.70–1.02)	1.01	(0.77–1.33)	0.82	(0.64–1.05)
Region														
North Central vs. West	−2034	(2862)	0.477	−952	(1769)	0.591	0.98	(0.66–1.46)	**1.44**[a]	(1.07–1.93)	0.90	(0.59–1.37)	1.03	(0.70–1.52)
Northeast vs. West	−272	(3653)	0.941	1142	(2282)	0.617	1.37	(0.84–2.22)	1.12	(0.77–1.64)	1.17	(0.70–1.98)	1.16	(0.71–1.88)
South vs. West	−3489	(2762)	0.207	−1371	(1681)	0.415	0.92	(0.63–1.35)	1.02	(0.77–1.35)	0.90	(0.60–1.35)	0.99	(0.69–1.43)
Usual-care physician specialty														
Neurology vs. other/unknown	**−7,386**[a]	(2824)	0.009	−2271	(1717)	0.186	**0.60**[a]	(0.39–0.92)	**0.59**[a]	(0.44–0.79)	0.70	(0.44–1.11)	**0.58**[a]	(0.39–0.87)
Primary care vs. other/unknown	**−5573**[a]	(2266)	0.014	−1269	(1420)	0.372	0.93	(0.69–1.25)	0.87	(0.69–1.09)	0.96	(0.69–1.33)	0.90	(0.67–1.20)
Number of chronic conditions	**10,974**[a]	(682)	<.001	**3,658**[a]	(438)	<.001	**1.57**[a]	(1.44–1.71)	**1.23**[a]	(1.14–1.31)	**1.45**[a]	(1.32–1.58)	**1.16**[a]	(1.07–1.27)
Charlson comorbidity Index	**3,042**[a]	(1302)	0.020	68	(855)	0.937	1.01	(0.86–1.19)	1.12	(0.98–1.29)	0.95	(0.80–1.13)	0.97	(0.81–1.15)
Head injury, yes vs. no	13,989	(9727)	0.151	−7039	(6298)	0.264	0.92	(0.27–3.06)	1.28	(0.48–3.37)	0.55	(0.12–2.57)	0.00	(0.00)
Brain tumor, yes vs. no	−689	(8350)	0.934	6957	(5555)	0.211	0.99	(0.35–2.78)	0.52	(0.20–1.33)	1.64	(0.59–4.54)	0.83	(0.26–2.66)
Cerebrovascular disease, yes vs. no	2665	(5694)	0.640	50	(3722)	0.989	0.62	(0.31–1.23)	0.72	(0.40–1.29)	0.65	(0.31–1.38)	0.80	(0.38–1.69)
Tuberous sclerosis, yes vs. no	−4412	(7638)	0.564	3284	(5084)	0.518	0.86	(0.30–2.43)	1.48	(0.67–3.25)	0.81	(0.26–2.49)	1.11	(0.41–3.04)
Depression and other mood disorders, yes vs. no	−11,946	(9212)	0.195	−4416	(5976)	0.460	**3.11**[a]	(1.14–8.53)	0.89	(0.33–2.41)	1.85	(0.57–5.99)	0.69	(0.16–3.03)
Uncontrolled vs. stable	3908	(2282)	0.087	**5,744**[a]	(1471)	<.001	**2.48**[a]	(1.88–3.27)	**1.34**[a]	(1.06–1.69)	**2.58**[a]	(1.93–3.45)	**1.81**[a]	(1.36–2.39)

β: regression coefficient; CI: confidence interval; ED: emergency department; OR: odds ratio; SE: standard error.
[a] Estimate is statistically significantly different from zero.

during a year in children compared with adults with uncontrolled epilepsy [9]. It is possible that the high proportion (37.4%) of children with uncontrolled epilepsy in the ≤5-year-old age group represent catastrophic epilepsies [18], which lead to high resource consumption. In contrast, a study of Medicaid populations reported that the frequency of hospital admissions, ED visits, and physician office visits were greater in adults (≥18 years) than in children (<17 years), although this pediatric population was older than patients in our study [8].

The annual cost burden is considerable in both pediatric cohorts, although overall and epilepsy-related costs are about twice as high in those with uncontrolled epilepsy. In our study, the majority (>69%) of overall and epilepsy-related costs in both cohorts were associated with medical, not pharmacy, claims, consistent with the high frequency of hospitalization and ED visits, suggesting that costs of epilepsy in children could be greatly decreased by achieving control of the disease.

Despite the substantial economic burden seen in the pediatric population, only a few prior cost-of-illness studies have included children [7,8,19]. Our findings are consistent with the recent population study conducted in the United Kingdom, which reported that hospital care followed by costs of AEDs were the largest contributors to total direct medical costs in children newly diagnosed with epilepsy [19]. This study also confirms that younger children incur higher costs [19]. A review of six European studies reported that childhood epilepsy has greater costs than other more prevalent or chronic conditions, including moderate asthma, atopic dermatitis or eczema, or insulin-dependent (type-1) diabetes [7]. This review also revealed that direct costs vs. indirect costs represent more than 80% of total costs in children, with annual cost per patient being much lower in children without seizures than in those with treatment-resistant epilepsy. Another study compared pediatric and adult patients, reporting that direct medical costs in Medicaid patients were $10,669 (18.4% epilepsy-related) for a pediatric patient and $29,886 (17.7% epilepsy-related) for an adult patient [8]. A recent study of commercially insured patients reported lower estimates both for overall and epilepsy-related costs in adults with stable and uncontrolled epilepsy as compared with the cost estimates reported in the current study of commercially insured children [9]. Overall, prior studies confirm that the cost burden is high in pediatric epilepsy. Studies also indicate that costs are higher in children than in adults except one study showing substantially lower costs in children with Medicaid.

Our study suggests that comorbid conditions may contribute to additional healthcare utilization and costs in children since approximately 44% and 56% of overall costs were from epilepsy-related costs in patients with stable epilepsy and in patients with uncontrolled epilepsy, respectively. Children with uncontrolled epilepsy in our study had a greater burden of illness, as measured by the Charlson comorbidity index and the CCI. Children with uncontrolled epilepsy also had more CNS comorbidities, with significantly higher proportions of patients with brain tumor and cerebrovascular disease. Prior studies reported that youth affected by epilepsy have higher rates of emotional, behavioral, social, and academic difficulties compared with youth with other chronic conditions or youth in general [1]. The impact of comorbidity on children with epilepsy is highlighted by the decrease in the difference of mean costs between two cohorts from before to after adjustment for chronic conditions and central nervous system comorbidities: decreasing from $12,137 to $3908 in overall costs and from $8915 to $5744 in epilepsy-related costs. Our findings emphasize the importance of timely surveillance and treatment of comorbid conditions in children with epilepsy, since cooccurring conditions can cause seizures or be exacerbated by epilepsy. Poor control of comorbidities may further complicate overall disease management, leading to an increased economic burden [2,20–23]. Although not examined in this study, some comorbidities, such as head injury, brain tumor, and tuberous sclerosis, are more likely to be proximal causes of epilepsy, so the observed higher healthcare utilization and costs may imply that epilepsy secondary to injury, tumor, or infections is associated with higher costs compared with "idiopathic" epilepsy. Overall, these results indicate that better management of seizures and comorbidities in childhood epilepsy is beneficial for improving the well-being of these children and also possibly significantly decreasing their use of healthcare resources.

4.1. Strengths and limitations

We analyzed a large analytic sample of pediatric patients identified in a major commercial insurance database. The availability of a comprehensive analytic dataset allowed us to detect statistically significant group differences in measures of burden of illness, utilization, and costs. The breadth of the claims database used also allowed us to compare and report recent experience of children with stable and

uncontrolled epilepsy on a number of key economic outcomes. For the first time, we produced age, gender, geographic region, and CNS comorbidity adjusted estimates of pediatric epilepsy cohort differences on multiple measures of utilization and costs.

This study has limitations. The claims database used only includes commercially insured patients; results may not be generalizable to other populations. The use of this particular claims database only allowed analysis of direct costs, although epilepsy may be associated with considerable social and emotional burden [2,24–28]. Administrative claims databases are designed for payment, not research, and lack clinical detail. Our definition of "uncontrolled" reflected this issue. Changes from one AED to another may represent either treatment intolerance or uncontrolled seizure activity, and these cases cannot be reliably distinguished using claims. We, therefore, excluded patients who switched AEDs, focusing instead on patients who added an AED to an existing regimen, assuming that this represented a need for increased intensity of treatment, rather than intolerance. Manjunath et al. presented a different algorithm to identify "uncontrolled" epilepsy, requiring both an AED therapy change (switch or addition) and ≥1 epilepsy-related ED visit or hospitalization [29]. This algorithm would not have been appropriate to use here, as it requires, by definition, greater utilization in the uncontrolled group and would have biased our utilization and cost results toward a positive finding. Neither definition is validated for use with administrative databases. Future research should entail the validation of an algorithm such as the one we used and other varied inclusion and cohort identification criteria. Future studies should also examine longitudinal outcomes in children with epilepsy in the US. A recent analysis of trends in resource use of adult patients with epilepsy in Germany revealed a shift in distribution of direct costs with increased hospital costs and cost neutral increase in prescription of AEDs [30]. It would be of interest to assess whether such trends are also present in the US.

5. Conclusions

Our results reveal not only that children with uncontrolled epilepsy have a higher economic burden compared with children with stable epilepsy but also that comorbidities may account for a large proportion of cost. Epilepsy comprised about half of overall costs. These findings highlight the impact of comorbidities on costs, showing the continuing need for better diagnosis and AEDs for difficult-to-treat epilepsy. These findings also suggest that better diagnosis and treatment of comorbidities may reduce overall healthcare utilization and associated costs in children with epilepsy.

Authorship contributions

Ms. Cramer: contributed substantially to conception and design and interpretation of data; drafting of the manuscript or revising it critically for significant intellectual content; and final approval of the manuscript submitted.

Dr. Wang: contributed substantially to conception and design and interpretation of data; drafting of the manuscript or revising it critically for significant intellectual content; and final approval of the manuscript submitted.

Dr. Chang: contributed substantially to conception and design and interpretation of data; drafting of the manuscript or revising it critically for significant intellectual content; and final approval of the manuscript submitted. Dr. Chang also acquired the data and performed statistical analysis.

Dr. Powers: contributed substantially to conception and design and interpretation of data; drafting of the manuscript or revising it critically for significant intellectual content; and final approval of the manuscript submitted.

Dr. Copher: contributed substantially to conception and design and interpretation of data; drafting of the manuscript or revising it critically for significant intellectual content; and final approval of the manuscript submitted.

Dr. Cherepanov: contributed substantially to conception and design and interpretation of data; drafting of the manuscript or revising it critically for significant intellectual content; and final approval of the manuscript submitted.

Dr. Broder: contributed substantially to conception and design and interpretation of data; drafting of the manuscript or revising it critically for significant intellectual content; and final approval of the manuscript submitted.

Funding

Funding for this study was provided by Eisai Inc.

Disclosures

Ms. Cramer is a consultant for Eisai Inc.

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