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Healthcare utilization and costs in adults with stable and uncontrolled epilepsy

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ABSTRACT

Despite the availability of numerous antiepileptic drugs (AEDs), some epilepsies remain resistant to treatment. We compared utilization and costs in patients with uncontrolled epilepsy to those with stable epilepsy. Claims data (2007–2009) were used to identify adults with epilepsy requiring additional AED therapy (having uncontrolled epilepsy) and those not requiring additional AED therapy (having stable epilepsy). The date in 2008 on which an additional AED was started was the index date for patients with uncontrolled epilepsy, and a randomly selected date was used for patients with stable epilepsy, whose AED use was unchanged in the preceding year. In the postindex year, all pharmacy and medical claims were used to estimate overall utilization and costs; claims with epilepsy in any diagnosis field were used to estimate epilepsy-related outcomes. Outcomes were adjusted using multivariate analyses. We identified 1536 patients with uncontrolled epilepsy and 8571 patients with stable epilepsy (mean age: 42.8 years; female: 48%). Patients with uncontrolled epilepsy had higher comorbidity rates ($p < .02$). A greater proportion of patients with uncontrolled epilepsy had ≥1 hospitalization or emergency department visit ($p < .001$). Patients with uncontrolled epilepsy had a greater mean length of hospital stay and more physician office visits ($p < .034$). After adjustment, the odds of hospitalization (OR: 1.8, any diagnosis; 2.2, epilepsy-related) and emergency department visit (OR: 1.6, any diagnosis; 1.9, epilepsy-related) were greater for patients with uncontrolled epilepsy. Annual overall ($23,238 vs. $13,839) and epilepsy-related ($12,399 vs. $5511) costs were higher in patients with uncontrolled epilepsy and remained higher after adjustment ($p < .001$). Patients with uncontrolled epilepsy use more services and incur higher costs compared with those with stable epilepsy. Epilepsy-related costs accounted for <50% of the total costs, suggesting that comorbid conditions and/or underidentification of utilization may substantially contribute to costs.

1. Introduction

Epilepsy, the fourth most common neurological disorder in the United States after migraine, stroke, and Alzheimer's disease, is characterized by recurrent seizures and affects about 2.2 million people in the United States [1–3]. For people whose seizures are not fully controlled, the burden of epilepsy is immense both on an individual and a societal level. It adversely affects multiple aspects of life including physical and mental health, quality of life, and activities of daily living [3]. Although a variety of antiepileptic drugs (AEDs) and other therapies may be used to treat epilepsy, many patients continue to have seizures that may lead to a significant increase in healthcare resource use [3–8]. The estimated economic impact of epilepsy in the US includes $9.6 billion of direct medical care costs and additional indirect care costs [3,8,9]. Moreover, indirect costs associated with epilepsy, such as those resulting from productivity loss, can be considerably higher than direct medical costs associated with this disorder [3,9–11]. Although the economic burden of epilepsy has been studied, there are few studies comparing the burden of illness in patients with stable epilepsy to patients with uncontrolled epilepsy [12]. We compared overall and epilepsy-related healthcare utilization and costs between groups of adult patients (aged ≥18 years) identified as having stable or uncontrolled epilepsy.

2. Methods

2.1. Study design and data sources

We conducted a retrospective cohort study using data from the Thomson Reuters MarketScan Commercial database, a Health Insurance

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Portability and Accountability Act compliant administrative claims database of millions of covered lives, representing all major regions of the United States. The database contained de-identified adjudicated pharmacy and medical claims submitted for payment by providers, healthcare facilities, and pharmacies. The database contained information on physician visits, medical procedures, hospitalizations, drugs dispensed in the outpatient setting, dates of services/prescriptions, number of days of medications supplied, and tests performed. Paid amounts were recorded for medical, inpatient, and pharmacy claims. Member enrollment and limited patient demographic information were also available. Data used covered a study time period from 1/1/2007 to 12/31/2009. This was an analysis of a Health Insurance Portability and Accountability Act compliant secondary database; hence, no Institutional Review Board review was required for this study.

2.2. Study population

Study patients were ≥18 years old, diagnosed with epilepsy, and treated with at least one AED in the identification (ID) period (calendar year 2008). The included AEDs were carbamazepine, clonazepam, divalproex, valproate, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, vigabatrin, and zonisamide. To identify the patients, we first identified all patients with ≥2 medical claims, ≥30 days apart, with epilepsy (ICD-9-CM codes: 345.xx or 780.39) in any diagnosis field in the ID period, and who either 1) continued on the same AED (either monotherapy or combination) for ≥12 months or 2) added additional AED(s) in the ID period. Additional AED therapy was defined as ≥3 months of baseline therapy, followed by ≥3 months with both baseline and additional AED(s). We excluded patients if they were <18 years old in the baseline period, if they were not continuously enrolled in the baseline and follow-up periods, or if they had diagnoses of neuropathic or chronic pain or evidence of pregnancy, fibromyalgia, bipolar disorder, or migraines in the baseline or follow-up periods since the AEDs may have been used for these conditions rather than epilepsy [13–15].

Study patients were classified into two cohorts and labeled as either "having stable epilepsy" if they had no change in AED monotherapy or combination therapy for at least 1 year or as "having uncontrolled epilepsy" if they added AEDs to an existing regimen during the year of observation. An index date was selected for each group: the date on which an additional AED was started for patients with uncontrolled epilepsy and a randomly selected date during the ID period for patients with stable epilepsy, whose AED use (either single agent or combination) was unchanged in the preceding year.

The definition of "uncontrolled" reflected the lack of clinical detail in claims. Specifically, AEDs can be changed for different reasons. Changes from one drug (or regimen) to a different drug (or regimen) may represent either intolerance to treatment or uncontrolled seizure activity, but these cases cannot be reliably distinguished using claims and, therefore, were excluded from the study. In contrast, the addition of an AED to an existing regimen was felt to more likely represent a need for a greater intensity of treatment (e.g., lack of seizure control), since intolerance of the regimen would be expected to lead to a change in the offending agent.

2.3. Study measures

We used enrollment files, medical claims, and pharmacy claims to derive study measures. The claims database contains every claim for an individual's period of enrollment. No missing data are assumed since a payment is processed only if a claim exists. Baseline measures were determined by reviewing all pharmacy and medical claims in the 12-month preindex period and included patient demographics, physician specialty, and burden of illness. Patient demographics included age, gender, and US census region and were identified in enrollment records. Using a published algorithm, the physician specialty with the largest plurality of office visits that carried evaluation and management (E&M) service codes was assigned as the "usual care specialty" [16]. That is, if a patient had 6 E&M visits during the year, 4 of them with a neurologist, the patient would be assigned "neurology" as the usual care specialty. Three measures were used to describe burden of illness. First, we used the widely validated Healthcare Cost and Utilization Project Chronic Condition Indicator to calculate the number of chronic conditions experienced by each patient [17,18]. The indicator categorizes ICD-9-CM diagnosis codes as chronic or not chronic, defining a chronic condition as one that lasts ≥12 months and either (a) places limitations on self-care, independent living, and social interactions or (b) results in the need for ongoing intervention with medical products, services, and special equipment [18]. Second, we included the Charlson comorbidity index (CCI). Although initially developed as a predictor of in-hospital mortality, the CCI has been adapted and widely used to measure overall burden of illness in the general population [19,20]. Finally, to account for burden of illness due to central nervous system (CNS) specific comorbidities, we identified the presence of head injury (ICD-9-CM: 854.x), brain tumor (ICD-9-CM: 191.x, 198.3, 225.x, 237.5, or 239.6), cerebrovascular disease or stroke (ICD-9-CM: 430-438.xx, or 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, or 311) in the preindex period.

Outcome measures included annual overall healthcare utilization and costs, estimated using pharmacy and medical claims in the postindex (follow-up) year. Other outcomes were epilepsy-related utilization, estimated using AED fills and services associated with claims with epilepsy (ICD-9-CM: 345.xx or 780.93) in any diagnosis field and epilepsy-related costs, estimated using claims with epilepsy in any diagnosis field or epilepsy-related tests. Measures of overall and epilepsy-related utilization included number of inpatient hospitalizations, number of days of stay among patients with inpatient hospitalizations, number of emergency department (ED) visits, and number of physician office visits. Measures of epilepsy-related utilization also included treatments (number of AEDs and number of vagus nerve stimulation devices implanted) and tests (electroencephalographic [EEG] or brain imaging). Measures of overall and epilepsy-related costs included medical costs (inpatient hospitalization cost, ED visit cost, and outpatient/non-ED service cost) and pharmacy costs. Indirect costs, including informal or out-of-pocket expenses such as patient transport and time off work, were not evaluated in this study.

2.4. Analysis

Descriptive statistics were reported for all study measures and were reported separately for patients with stable epilepsy and for patients with uncontrolled epilepsy. We compared differences between the two cohorts using Chi-square tests and t-tests, where applicable. Multivariate analyses were conducted to adjust for relevant baseline measures, including age, sex, US census region, usual care physician specialty, number of chronic conditions, CCI, and CNS comorbidities. Analysis of covariance (ANCOVA) was used to estimate the incremental increase in overall and epilepsy-related costs associated with uncontrolled epilepsy and logistic regression to estimate the incremental increase in risk of overall and epilepsy-related inpatient hospitalization and ED visits. All data transformations and statistical analyses were performed using SAS© version 9.2 (SAS Institute, Cary, NC).

3. Results

There were 243,484 patients with at least one medical claim for epilepsy (ICD-9-CM: 345.xx or 780.39) in the ID period. Of these, 99,438 patients had at least two claims ≥30 days apart, and 62,132 patients used AED therapy in the ID period. From the 25,033 patients who both had ≥2 claims with epilepsy diagnoses and used AEDs, we

excluded 5799 who were not continuously enrolled in the baseline or postindex periods, 5063 who had diagnoses of neuropathic or chronic pain, pregnancy, fibromyalgia, bipolar, or migraine in the baseline period, and 4064 who were <18 years old. Our final analytic sample included 10,107 patients, of which 8571 (84.8%) were classified as having stable epilepsy and 1536 (15.2%) were classified as having uncontrolled epilepsy.

The average age was 43 years (standard deviation [SD]: 13.7) in patients with stable epilepsy and 41.8 years (SD: 13.7) in patients with uncontrolled epilepsy (Table 1). A smaller proportion of patients with stable epilepsy compared with patients with uncontrolled epilepsy were female (47.6% vs. 50.7%, $p = .025$). Patients were from all regions in the US: 11.4% from the Northeast, 29.9% from the North Central, 42.3% from the South, and 16.5% from the West; the cohorts did not differ in geographic distribution. Patients with stable epilepsy received care most often from primary care physicians (40.6% vs. 32.1% for patients with uncontrolled epilepsy), while patients with uncontrolled epilepsy received care most often from neurologists (39.4% vs. 32.8% for patients with stable epilepsy) ($p<.001$). Patients with stable epilepsy had a lower mean number of chronic conditions (2.2 vs. 2.7) and mean CCI score (0.5 vs. 0.7) than patients with uncontrolled epilepsy ($p < .001$). Compared with patients with uncontrolled epilepsy, a lower proportion of patients with stable epilepsy had a head injury (0.7% vs. 1.3%), brain tumor (3.5% vs. 6.2%), cerebrovascular disease/stroke (6.3% vs. 12.7%), and depression and other mood disorders (6.3% vs. 10.9%) ($p<.02$).

Patients with stable epilepsy were hospitalized less often than patients with uncontrolled epilepsy both for any diagnosis (9.8% vs. 18.3% had ≥1 hospitalization) and for epilepsy-related diagnoses (7% vs. 15.7%) ($p<.001$; Table 2). Patients with stable epilepsy had a lower mean length of hospital stay (any diagnosis: 7.1 vs. 10.9 days; epilepsy-related: 5.6 vs. 8.9 days) ($p < .05$). They also had fewer physician office visits than patients with uncontrolled epilepsy (mean number of visits associated with any diagnosis: 9 vs. 12; and mean number of visits associated with epilepsy-related diagnoses: 2.2 vs. 3.6) ($p < .001$). Frequency of emergency department (ER) visits was also lower in patients with stable epilepsy than in patients with uncontrolled epilepsy, both for any diagnosis (25.5% vs. 37.4% had ≥1 ER visit) and for epilepsy-related diagnoses (12% vs. 21.2%) ($p<.001$). The percentage of patients who had had ≥1 electroencephalographic (14.9% vs. 28.5%) or brain imaging (18.5% vs. 34.4%) study was smaller in patients with stable epilepsy than in those with uncontrolled epilepsy ($p<.001$). Most patients with stable epilepsy used AED monotherapy (71.5%), 22.7% used a two-AED combination therapy, 5.1% used a three-AED combination therapy, and 0.7% used a ≥4-AED combination therapy. The majority of patients with uncontrolled epilepsy used two (73%) AEDs, 21.4% used 3 AEDs, and 5.6% used 4 or more AEDs.

Comparing patients with stable epilepsy with patients with uncontrolled epilepsy, the total costs were $13,839 (SD: $31,355) vs. $23,238 (SD: $42,894) per patient-year (PPY) and epilepsy-related costs were $5511 (SD: $11,730) vs. $12,399 (SD: $25,773) PPY ($p<.001$; Table 3). Of epilepsy-related costs, $2751 (SD: $11,029) vs. $7257 (SD: $25,202) PPY were for medical services and $2760 (SD: $3361) vs. $5142 (SD: $4110) PPY were for AEDs in patients with stable epilepsy vs. in patients with uncontrolled epilepsy ($p < .001$), respectively. Overall, patients with stable epilepsy had statistically significantly lower annual overall and epilepsy-related costs, in terms of medical costs (inpatient hospitalizations, ED visits, or outpatient non-ED services) and AED costs, compared with patients with uncontrolled epilepsy ($p<.001$).

After adjusting for baseline measures, the odds of hospitalization (odds ratio [OR]: 1.82; 95% CI: 1.56–2.13), emergency department visit (OR: 1.64; 95% CI: 1.46–1.84), epilepsy-related hospitalization (OR: 2.2; 95% CI: 1.87–2.60), and epilepsy-related emergency

Table 1
Patient demographics, usual care physician specialty, and baseline comorbidity measures in adult patients with epilepsy.

	Stable n = 8571; 84.8%	Uncontrolled n = 1536; 15.2%	All N = 10,107	*p*-Value[e]
Age, y, mean (SD)	43.0 (13.7)	41.8 (13.7)	42.8 (13.7)	0.003
Age group, y, n (%)				<.001
18–34	2517 (29.4)	493 (32.1)	3010 (29.8)	
35–44	1591 (18.6)	328 (21.4)	1919 (19.0)	
45–54	2290 (26.7)	356 (23.2)	2646 (26.2)	
55+	2173 (25.4)	359 (23.4)	2532 (25.1)	
Female, n (%)	4076 (47.6)	778 (50.7)	4854 (48.0)	0.025
Region, n (%)				0.224
Northeast	994 (11.6)	157 (10.2)	1151 (11.4)	
North Central	2573 (30.0)	446 (29.0)	3019 (29.9)	
South	3609 (42.1)	662 (43.1)	4271 (42.3)	
West	1395 (16.3)	271 (17.6)	1666 (16.5)	
Usual care physician specialty, n (%)				<.001
Neurology	2815 (32.8)	605 (39.4)	3420 (33.8)	
Primary care[a]	3483 (40.6)	493 (32.1)	3976 (39.3)	
Other[b]/unknown[c]	2273 (26.5)	438 (28.5)	2711 (26.8)	
Number of chronic conditions, mean (SD)	2.2 (1.5)	2.7 (1.7)	2.3 (1.6)	<.001
Charlson comorbidity index, mean (SD)	0.5 (1.3)	0.7 (1.5)	0.6 (1.3)	<.001
No. with ≥1 CNS comorbidity[d], n (%)	1304 (15.2)	400 (26.0)	1704 (16.9)	<.001
Head injury	61 (0.7)	20 (1.3)	81 (0.8)	0.017
Brain tumor	298 (3.5)	95 (6.2)	393 (3.9)	<.001
Cerebrovascular disease/stroke	537 (6.3)	195 (12.7)	732 (7.2)	<.001
Tuberous sclerosis	14 (0.2)	6 (0.4)	20 (0.2)	0.065
Depression and other mood disorders	544 (6.3)	167 (10.9)	711 (7.0)	<.001

SD: standard deviation.
[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.

Table 2
Annual overall and epilepsy-related healthcare utilization in adult patients with epilepsy.

	Stable n = 8571; 84.8%	Uncontrolled n = 1536; 15.2%	All N = 10,107	*p*-Value[b]
Annual overall healthcare utilization				
Inpatient hospitalizations, n (%)				<0.001
0	7727 (90.2)	1255 (81.7)	8982 (88.9)	
1	627 (7.3)	179 (11.7)	806 (8.0)	
2+	217 (2.5)	102 (6.6)	319 (3.2)	
Days of stay among patients with inpatient hospitalizations, mean (SD)	7.1 (11.0)	10.9 (29.5)	8.0 (17.6)	0.034
ED visits, n (%)				<0.001
0	6389 (74.5)	962 (62.6)	7351 (72.7)	
1	1422 (16.6)	327 (21.3)	1749 (17.3)	
2+	760 (8.9)	247 (16.1)	1007 (10.0)	
Office visits, mean (SD) [median]	9.0 (9.6) [6.0]	12.0 (11.6) [9.0]	9.4 (10.0) [7.0]	<0.001
Annual epilepsy-related[a] healthcare utilization				
Epilepsy-related[a] inpatient hospitalizations, n (%)				<0.001
0	7969 (93.0)	1295 (84.3)	9264 (91.7)	
1	494 (5.8)	171 (11.1)	665 (6.6)	
2+	108 (1.3)	70 (4.6)	178 (1.8)	
Days of stay among patients with epilepsy-related[a] inpatient hospitalizations, mean (SD)	5.6 (8.6)	8.9 (21.1)	6.5 (13.5)	0.018
Epilepsy-related ED visits, n (%)				<0.001
0	7541 (88.0)	1211 (78.8)	8752 (86.6)	
1	795 (9.3)	218 (14.2)	1013 (10.0)	
2+	235 (2.7)	107 (7.0)	342 (3.4)	
Vagus nerve stimulation, n (%)	14 (0.2)	10 (0.7)	24 (0.2)	<0.001
Epilepsy-related[a] office visits, mean (SD) [median]	2.2 (2.1) [2.0]	3.6 (3.0) [3.0]	2.4 (2.3) [2.0]	<0.001
EEG, n (%)				<0.001
0	7294 (85.1)	1098 (71.5)	8392 (83.0)	
1	982 (11.5)	256 (16.7)	1238 (12.2)	
2+	295 (3.4)	182 (11.8)	477 (4.7)	
Brain imaging, n (%)				<0.001
0	6983 (81.5)	1007 (65.6)	7990 (79.1)	
1	1109 (12.9)	300 (19.5)	1409 (13.9)	
2+	479 (5.6)	229 (14.9)	708 (7.0)	
AEDs, n (%)				n/a
1	6130 (71.5)	0 (0)	6130 (60.7)	
2	1947 (22.7)	1122 (73.0)	3069 (30.4)	
3	433 (5.1)	328 (21.4)	761 (7.5)	
4+	61 (0.7)	86 (5.6)	147 (1.5)	

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

department visit (OR: 1.91; 95% CI: 1.66–2.20) were greater in the group with uncontrolled epilepsy than in the group with stable epilepsy (Table 4). After adjusting for the same demographic and risk factors in the cost analyses, both overall and epilepsy-related costs were greater in the patients with uncontrolled epilepsy than in patients with stable epilepsy by $7187 (standard error [SE]: $967) and $6023 (SE: $4069), respectively ($p < .001$).

4. Discussion

These results provide new information about the excess costs attributable to uncontrolled epilepsy, including both overall and epilepsy-related healthcare utilization costs. The large database provided evidence that patients with uncontrolled disease (i.e., those who may have had seizures or drug intolerance and, thus, required additional AEDs during the yearlong study period) had significantly higher burden of illness, higher utilization of healthcare services, and greater incurred healthcare costs than patients with stable disease (i.e., those who may have had seizures but required no change in AED therapy during the study period), even after controlling for baseline differences between groups.

Patients with uncontrolled epilepsy had a greater mean length of hospital stay and more physician office visits. Even after adjustment for baseline differences in patient characteristics and CNS comorbidities, patients with uncontrolled epilepsy were about twice more likely than patients with stable epilepsy to be hospitalized and to have an emergency department visit. Annual healthcare costs were about twice as high in the group with uncontrolled epilepsy than in the group with stable epilepsy and remained about $6000 to $7000 higher in the patients with uncontrolled epilepsy even after adjustment. Our findings are consistent with the substantial economic burden of epilepsy documented in earlier studies [4–6,8,11,13,21–25]. Although previous studies have examined patients with refractory epilepsy, we found no recent studies comparing overall and epilepsy-related healthcare resource use and costs between patients with stable epilepsy and patients with uncontrolled epilepsy in the US [4,6,7,12].

Patients with epilepsy tend to suffer from serious comorbidities that can impact the diagnosis and treatment of the disease, impair quality of life and productivity, and increase mortality and economic burden [2,26–29]. Seidenberg et al. summarized data from six large studies from different countries and reported that up to 26.8% to 84% of patients with epilepsy had at least one comorbid condition [29]. Studies have shown that the prevalence of many common psychiatric and somatic conditions is higher in patients with epilepsy than in patients without epilepsy, with psychiatric disorders, for example, occurring about twice as often in patients with epilepsy [11,23,27,28]. Lee et al. reported that the presence of comorbidities, especially depression, was associated with increase in healthcare use and costs in patients with refractory epilepsy with partial seizure disorder [6]. These findings emphasize the importance of monitoring and treating comorbid conditions in patients with epilepsy, since cooccurring conditions

Table 3
Annual overall and epilepsy-related healthcare costs in adult patients with epilepsy.

	Stable n = 8571; 84.8%		Uncontrolled n = 1536; 15.2%		All N = 10,107		p-Value[b]
	Mean [median]	SD	Mean [median]	SD	Mean [median]	SD	
Overall healthcare cost, $	13,839 [6789]	31,355	23,238 [11,380]	42,894	15,414 [7481]	33,746	<0.001
Medical cost, $	9214 [2457]	30,075	15,842 [4286]	40,999	10,324 [2684]	32,257	<0.001
Inpatient hospitalization cost, $	2818	20,329	6196	28,167	3332	21,736	<0.001
ED visit cost, $	316	1007	542	1455	350	1090	<0.001
Outpatient (non-ED) service cost, $	5379 [2024]	14,864	8458 [3347]	23,059	5895 [2189]	16,561	<0.001
Pharmacy cost, $	4349 [2814]	5085	7247 [5708]	6411	4789 [3228]	5408	<0.001
Epilepsy-related overall healthcare cost, $	5511 [2647]	11,730	12,399 [6256]	25,773	6558 [3128]	14,956	<0.001
Epilepsy-related[a] medical cost, $	2751 [348]	11,029	7257 [1003]	25,202	3436 [399]	14,221	<0.001
Epilepsy-related[a] inpatient hospitalization cost, $	1543	10,047	4610	23,529	2009	13,073	<0.001
Epilepsy-related[a] ED visit cost, $	142	622	295	970	166	689	<0.001
Epilepsy-related[a] outpatient (non-ED) service cost, $	1065 [312]	3095	2352 [748]	5305	1261 [349]	3551	<0.001
AED cost, $	2760 [1591]	3361	5142 [4072]	4110	3122 [1929]	3588	<0.001

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

can be the cause (e.g., cerebrovascular disease) of seizures or can be exacerbated by epilepsy (e.g., psychiatric disorders and brain degenerative diseases) complicating the overall management of the disease [2,3,27–29]. Patients who achieve better management of their seizures and comorbidities are likely to significantly decrease their use of healthcare services, though we also noted that even those with stable disease may still have ED visits and readmissions because of consequences of seizures, such as from lacerations and fractures [30].

A related finding was that epilepsy-related costs were only about 40% of the overall costs in patients with stable epilepsy and 50% in patients with uncontrolled epilepsy, suggesting that comorbid conditions may contribute to additional healthcare utilization and costs in those patients. Patients with uncontrolled epilepsy had more chronic conditions and a greater overall burden of illness (acute and chronic) as measured by the CCI. Central nervous system comorbidities were more prevalent among patients with uncontrolled epilepsy, with a significantly higher percentage of patients with head injury, brain tumor, cerebrovascular disease or stroke, depression, and other mood disorders. Our findings are consistent with current literature, indicating that management of epilepsy extends beyond seizure control to achieving improvement in overall burden of this disease [2,26–29].

4.1. Strengths and limitations

A primary strength of this study is the large analytic sample achieved by using a major commercial insurance database, allowing us to detect statistically significant group differences in estimates of burden of illness measures, utilization, and costs. The breadth of the claims database allowed us to compare and report recent experience of patients with stable and uncontrolled epilepsy on a number of

Table 4
Regression models of overall and epilepsy-related healthcare costs and utilization in adult 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	
	Coefficient	(SE)	p	Coefficient	(SE)	p	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Age group, y														
18–34 vs. 55+	**3691**[a]	(1015)	<.001	**2565**[a]	(415)	<.001	0.87	(0.72–1.03)	**1.40**[a]	(1.24–1.60)	1.03	(0.84–1.27)	**1.67**[a]	(1.41–1.98)
35–44 vs. 55+	−337	(1112)	0.762	703	(454)	0.122	**0.73**[a]	(0.59–0.89)	**1.16**[a]	(1.01–1.34)	0.87	(0.70–1.10)	**1.38**[a]	(1.15–1.67)
45–54 vs. 55+	−24	(991)	0.981	407	(411)	0.322	**0.81**[a]	(0.68–0.96)	1.03	(0.91–1.17)	0.97	(0.80–1.19)	**1.21**[a]	(1.02–1.44)
Female vs. male	−958	(718)	0.183	−508	(292)	0.082	0.93	(0.82–1.06)	0.97	(0.88–1.06)	**0.84**[a]	(0.73–0.98)	**0.81**[a]	(0.72–0.91)
Region														
North Central vs. West	**−2226**[a]	(1124)	0.048	−499	(448)	0.265	**1.30**[a]	(1.06–1.60)	1.08	(0.94–1.24)	1.23	(0.98–1.55)	0.96	(0.80–1.15)
Northeast vs. West	−2651	(1382)	0.055	−1062	(560)	0.058	1.24	(0.97–1.60)	1.01	(0.85–1.20)	1.25	(0.95–1.66)	0.91	(0.73–1.14)
South vs. West	−1995	(1090)	0.067	**−1015**[a]	(425)	0.017	1.18	(0.97–1.44)	1.11	(0.97–1.26)	1.13	(0.90–1.40)	1.07	(0.90–1.26)
Usual care physician specialty														
Neurology vs. other/unknown	−1207	(938)	0.198	679	(381)	0.075	**0.84**[a]	(0.71–0.99)	**0.85**[a]	(0.76–0.96)	0.94	(0.78–1.13)	**0.81**[a]	(0.70–0.94)
Primary care vs. other/unknown	**−2160**[a]	(894)	0.016	**−1032**[a]	(368)	0.005	**0.85**[a]	(0.73–0.99)	1.04	(0.93–1.16)	0.86	(0.72–1.03)	0.90	(0.78–1.04)
Number of chronic conditions	**3419**[a]	(271)	<.001	**813**[a]	(113)	<.001	**1.26**[a]	(1.20–1.31)	**1.11**[a]	(1.07–1.15)	**1.18**[a]	(1.12–1.24)	1.00	(0.96–1.05)
Charlson comorbidity index	**3569**[a]	(320)	<.001	**411**[a]	(138)	0.003	**1.11**[a]	(1.06–1.16)	**1.08**[a]	(1.04–1.12)	**1.09**[a]	(1.04–1.15)	1.05	(0.99–1.10)
Head injury	3639	(3746)	0.331	2412	(1638)	0.141	1.47	(0.84–2.59)	1.22	(0.77–1.94)	1.34	(0.72–2.51)	1.09	(0.60–1.97)
Brain tumor	**10,291**[a]	(1807)	<.001	**4713**[a]	(799)	<.001	1.11	(0.84–1.47)	0.94	(0.74–1.18)	1.23	(0.90–1.67)	1.02	(0.75–1.38)
Cerebrovascular disease/stroke	−2383	(1425)	0.095	**1340**[a]	(615)	0.030	0.99	(0.79–1.24)	1.16	(0.97–1.38)	1.09	(0.85–1.39)	1.15	(0.91–1.45)
Tuberous sclerosis	9945	(7426)	0.181	3748	(3270)	0.252	1.26	(0.40–3.95)	0.97	(0.38–2.49)	1.28	(0.36–4.56)	0.87	(0.25–3.03)
Depression/other mood disorders	−2030	(1385)	0.143	−66	(587)	0.910	**1.26**[a]	(1.02–1.57)	1.18	(0.99–1.40)	**1.36**[a]	(1.07–1.73)	1.20	(0.96–1.50)
Uncontrolled vs. stable	**7187**[a]	(967)	<.001	**6023**[a]	(409)	<.001	**1.82**[a]	(1.56–2.13)	**1.64**[a]	(1.46–1.84)	**2.20**[a]	(1.87–2.60)	**1.91**[a]	(1.66–2.20)

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

key healthcare utilization and cost measures. We were also able to produce age, gender, geographic region, and CNS comorbidity adjusted estimates of epilepsy cohort differences in utilization and cost.

This study has limitations typical of claims studies as well as some specific to the condition being studied. The database included only commercially insured patients, and our findings may not be generalizable to other populations. Claims-based studies provide an overview of costs in patients with epilepsy, but epilepsy-specific costs may be more challenging to highlight given that the data source lacks clinical context. Indirect costs cannot be examined using insurance claims, and epilepsy may result in considerable social and emotional burden [3,9–11,23,31]. Hence, we urge future research in this area. Although we defined "epilepsy-related" costs broadly, including claims with an epilepsy diagnosis in any position on the claim, epilepsy-related costs accounted for <50% of total observed costs, suggesting that epilepsy-related utilization may have been underidentified [32].

Finally, claims data are collected for the purpose of payment, not research, and have limited ability to capture disease severity or to precisely identify categories of conditions that are part of a spectrum disorder, such as epilepsy. Specifically, current literature lacks a validated claims-based epilepsy patient identification algorithm to identify patients with stable and uncontrolled epilepsy. Manjunath et al. used a different algorithm to identify "uncontrolled" epilepsy, requiring both an AED therapy change (switch or addition) and ≥1 epilepsy-related ED visit or hospitalization [12], while Tetto et al. defined epilepsy manifesting with occasional seizures not requiring changes in treatment as "in remission for 1–2 years" [33]. Our study was designed to compare utilization and cost between patients with stable epilepsy and patients with uncontrolled epilepsy, and requiring greater utilization imposed in patients with uncontrolled epilepsy (e.g., inpatient admission) would have biased our results toward a positive finding. Our approach allowed only patients who filled an additional AED to ongoing treatment as having uncontrolled seizures, under the assumption that the primary reason for adding medications would be lack of seizure control. Including patients whose regimens were changed in ways other than the addition of AEDs (e.g., a regimen switch) may result in the inclusion of patients whose epilepsy was well controlled, but who experience adverse treatment effects. The validation of an algorithm such as the one we used would be valuable for future research, as could the use of varied inclusion and cohort identification criteria.

4.2. Conclusions

These results confirm not only that uncontrolled epilepsy is associated with a higher economic burden than stable epilepsy but also that patients with uncontrolled epilepsy use significantly more nonepilepsy-related healthcare services and incur more costs compared with those with stable epilepsy. These detailed analyses revealed the impact of comorbidities on cost of care, showing the continuing need for better diagnosis and treatment in order to reduce the burden of epilepsy and comorbidities. It is important that healthcare systems extend care for epilepsy in order to reduce overall healthcare utilization and costs.

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Ms. Cramer is a consultant for Eisai Inc.

Dr. Wang is an employee of Eisai Inc.

Dr. Chang is an employee of Partnership for Health Analytic Research, LLC.

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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.

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